PSYCHIATRIC ASPECTS OF MIGRAINE

Diana Patricia Morrison, MB ChB, MRCPsych.

M.D. submission to the University of Glasgow on the basis of research conducted in the Department of Psychiatry, Western General Hospital, Edinburgh.

February 1988.

ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 – 1346

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Contents

Acknowledgements

First and foremost I should like to thank the patients with migraine who took part in the study and without whose help it would have been impossible to carry out the study.

Dr Bill Price, Senior Lecturer in Medicine and Consultant Physician at the Western General Hospital supplied the original clinical observation that complaints of mood change were not uncommon in migraine and also provided access to his patients. His support and constructive comments were of value throughout.

Dr Lawrence Whalley, Senior Lecturer, Department of Psychiatry, University of Edinburgh, encouraged to me write the thesis and made me believe I could complete it. His advice and critical comments have undoubtedly helped me to improve the quality of the work.

Mr Dave Peck, Senior Lecturer in Psychology, University of Edinburgh was always available to provide guidance on the statistical analysis of the data and also helped to make this an enjoyable task.

Dr Malcolm Merrick, Department of Nuclear Medicine, Western General Hospital and the staff in his department, despite being extremely busy, still managed to fit in scans for the migraine patients and were friendly and helpful throughout.

Mrs Ann Schering, Clinical Research Associate, without whose patience in teaching basic computing I would never have been initiated

into the complexities of the SPSSX computer package.

Mrs Margaret Robb, Miss Linda Wallace, Mrs Dorothy Hume - together the secretarial staff at the Department of Psychiatry, Western General Hospital were immensely helpful in obtaining case records, writing letters and organising patients during the course of the study.

Last, but by no means least, I should like to thank Mrs Patricia Rose, who typed the manuscript, for her tolerance and good humour in the face of multiple revisions of the text and for her constant encouragement and reassurance that the thesis really was progressing.

SUMMARY

Psychiatric aspects of migraine

Literature review

This section provides a survey of the literature on the multiple factors implicated in the aetiology of migraine and the links between migraine and psychiatric disorder.

The historical development of current concepts of migraine is outlined and the main controversies in the present-day classification of the condition are critically reviewed.

General characteristics of migraine clinic populations are described and contrasted with the results of community surveys.

Studies of the genetics of migraine suggest that genetic factors are important in only a subgroup of migraineurs.

No evidence is found for a specific personality type in migraine although patients may be rather obsessional and more sensitive to minor stresses. Recurrent headaches are associated with mild depressive illness, somatisation and anxiety, the extent of which is directly related to the frequency and severity of the pain.

Mind-body interaction is a difficult philosophical issue. A

variety of models are briefly reviewed and the dualist-interactionist model is suggested as the most relevant to migraine.

It is suggested that a neural event, the Spreading Depression of Leao (S.D.), initiates classical migraine attacks, possibly due to light-induced changes in potassium ion concentration in the visual cortex. This underlies the prodrome and aura. Cerebral blood flow changes may be secondary to this. The headache could be a direct consequence of SD or may be vascular in origin.

Kindling may provide a mechanism for the periodicity in migraine, affective disorder and epilepsy. Limbic system involvement could explain the emotional symptoms common to the three conditions.

Migraine can be associated with persistent neurological dysfunction and is a risk factor in cerebral infarction.

The relationship between epilepsy and migraine is reviewed. Olfactory auras in epilepsy are associated with depression.

Cocaine abuse is suggested as a model for migraine hallucinations and the precipitation of psychiatric illness by stress. Endorphins are released along with stress hormones and are likely to play an, as yet, unspecified role in the production of stress-related psychiatric and physical illness. They are clearly involved in the experience of pain in migraine and possibly also in mood changes.

Menstrual migraine is accepted as a subgroup of migraine although it can be defined objectively much less frequently than it is subjectively complained of.

Finally cerebral asymmetry in physiology and cognition is discussed as it applies to migraine.

Research conducted

A consecutive series of 46 new, female referrals to a Migraine Clinic was obtained for a three part study of the association of affective changes and migraine.

The initial psychiatric interview was used to obtain details of the family history of migraine and psychiatric illness, the patient's own migraine history and the factors involved in precipitating migraine attacks. A specific enquiry was made about presence or absence of mood changes in association with migraine and their frequency. The Structured Clinical Interview for DSM-III was used to provide DSM-III diagnoses of psychiatric disorder. The Clinical Anxiety Scale, the Montgomery and Åsberg Depression Rating Scale and the Manic Rating Scale were also completed to provide estimates of the severity of anxiety, depression and hypomania respectively.

Thirty-seven patients then completed Irritability-Depression-Anxiety rating scales and visual analogue scales over a six week

prospective period.

Finally 27 patients attended for regional cerebral blood flow monitoring while migraine was absent and five also had scans when migraine was present.

Results

Complaints of mood change and DSM-III diagnoses of affective disorder were present in just under half the sample. The initial self report of mood changes, the presence or absence of DSM-III diagnoses of affective disorder and the data from the prospective rating scales were all used to define 'affective' and 'non-affective' groups. Differences between the groups were then examined. The main factor related to complaints of mood change was the presence of a DSM-III diagnosis of affective disorder. Self reports of mood change at the initial interview did not correlate with the changes in mood components rated in the six week prospective period. Twelve of the 37 patients had significant associations between changes in mood components and days when migraine was present. There was no evidence of a change in any mood component in the period just before or just after a migraine attack in the group as a whole although this was seen ocasionally in individual patients. Olfactory hallucinations as part of migraine attacks were significantly associated with complaints of mood change. Classical and common migraine patients had differences in symptoms and anxiety levels which were likely to be a secondary consequence of their condition.

The regional cerebral blood flow data did not discriminate between affective and non-affective groups in the absence of migraine. There were too few scans in the presence of migraine to permit analysis. However when scans were performed in the presence and absence of migraine they did show a trend towards differences between common and classical migraine and this would merit further examination. No evidence for an excess of weekend headaches was found in this sample. Weekend headaches were unrelated to employment status or type of migraine. An association between migraine, mood change and menstruation was found in only one of a subgroup of six patients.

Conclusions

Patients' initial self reports of the association of migraine and mood change did not agree with the prospective data. These complaints and diagnoses of affective disorder were probably more common than expected in this sample, although in the absence of a control population this can only be a tentative conclusion.

There was no evidence of an affective prodrome to migraine or of affective change subsequent to migraine attacks. Changes in mood components were related to the presence of migraine in a third of subjects.

There was no evidence in this sample that migraine attacks clustered at weekends or that the day of the week that attacks

occurred was related to employment status or type of migraine.

A statistically significant association between migraine, menstruation and changes in mood components was found in only one patient of a small subgroup of six. This could be due to chance alone. Further investigation of the association of migraine, menstruation and changes in mood components is required to explore this area properly.

I hereby declare that except for that help specified in the acknowledgements this thesis is entirely my own work.

Psychiatric Aspects of Migraine

Introduction

Approximately 10% of patients who consult a doctor because of migraine complain of mood changes which they associate with the migraine attack. These may occur before, during or after the migraine. This figure for the incidence of mood disturbance is quoted in both specialist texts on migraine and reference works on organic psychiatry. It is based on clinical observation as although mood changes were recognised as a feature of migraine as early as the 1860s there have been few studies of this aspect of the condition. This may be due to the fact that physicans, rather than psychiatrists, are primarily involved in the treatment of migraine. By contrast the visual, sensory and motor prodromal symptoms have been extensively described.

Migraine is particularly interesting because it is a physical condition which has a close association with many psychiatric disorders. As such it can be used to examine the interplay of psychological and physical factors in the production of illness e.g. personality variables interact with genetic constitution to determine predisposition to migraine. Social status and intelligence also play a major part in deciding which patients with migraine present themselves to the medical services.

From a philosophical point of view migraine provides a model for the study of mind-body and brain-mind relationships. The patient and the lay population generally have difficulty conceptualising migraine as it

does not fit neatly into either a psychiatric or physical illness model but lies somewhere between the two.

Migraine has the advantage of being a cerebral disorder with clear diagnostic criteria which is generally benign and recurrent. It has parallels with recurrent affective disorder, for which it can provide a medical model. Vascular and neural components are intertwined in the pathogenesis of migraine. A better understanding of this type of interaction is relevant to both psychiatry and medicine. Changes in cerebral blood flow are found in both classical migraine and affective illness. The spreading oligaemia seen in migraine has been compared to Leao's spreading depression of cortical electrical activity.

The neural component to migraine has similarities with epilepsy. Disturbances in the electroencephalogram are found in both conditions. Temporal lobe epilepsy is closely connected anatomically with the limbic system and through this with emotional disorder. Paroxysmal disorders such as temporal lobe epilepsy, affective disorder and migraine may all be linked pathogenetically by a kindling mechanism similar to that found in limbic epilepsy.

Migrainous visual hallucinations are similar to those found with cocaine abuse. Consequently cocaine effects can help in understanding both the visual hallucinations in migraine and the aetiology of visual hallucinations generally.

Stress can lead to both physical and psychiatric illness and is also

an important factor in the production of endogenous analgesia. Migraine provides an opportunity to examine these relationships. As pain and depression are also closely linked the episodic pain in migraine can be used to study the interaction between depression and endorphin concentrations.

Ovarian hormones have a major influence on migraine in a subgroup of patients. This may be related to their effects on central opiate receptors. The mood changes found in the premenstrual syndrome can be used as a model for the association of migraine with affective disorder.

Migraine is unusual in its tendency to be unilateral. Not only that but the pain can vary from one side of the head to the other between one attack and the next. This is associated with cerebral asymmetry and possibly with difficulties in cognitive processing.

In summary migraine provides a medical model which can help in understanding the interaction of psychological and physical factors in the production of psychosomatic illness and affective disorder.

CHAPTER 1

Historical Review

The psychiatric aspects of migraine have largely been ignored. Instead the main debate over the last 200 years has been over whether neurogenic or vascular factors are more important in the aetiology of the condition.

The prodromata, especially the visual ones, have lent a particular status to classical migraine since they were first described in the 5th Century A.D. by Caelius Aurelianus. The fact that it was a common condition with a repetitive pattern presumably contributed to the ease with which it could be studied and to the extensive clinical descriptions which were published in the medical literature.

Galen ascribed migraine to an excessive upward thrust of corrupted vapours, humors or both from the body to the brain. These substances were then driven out into the scalp causing pain and tenderness.

The Swiss physicians Johann Jakob Wepfer (1620-95) and Johann Caspar Anhalt (1720s) both thought that migraine and epilepsy were due to vascular congestion. Anhalt believed in humoral involvement but differed from Galen in suggesting that the deteriorated chyle affected not the brain itself but also the blood vessels. It caused vasoconstriction or vasodilatation which in turn led to pain. He explained the unilateral pain on the basis of congenital weakness of one side of the head.

The neural hypothesis originated with Robert Whytt (1767) who considered migraine as a nervous disorder because it depended on "sympathy" between various parts of the body - in this case the head and the stomach (1).

By contrast John Fothergill (1778) had very definite views that the headache proceeded from the stomach rather than the reverse and that migraine generally arose from inattention to diet. He believed that only self control and strict adherence to a dietary regime with laxatives and stomach bitters over an extended period could relieve the condition. He recognised that the medical profession had been unsuccessful in treating the disorder - (the patients) "who are yet, sometimes, not much less sufferers by the means frequently made use of to remove it, than by the disease itself". However he blamed this on the patients' errors in diet and conduct. He neatly avoided alienating his customers totally by absolving them on the grounds that eventually their behaviour weakened the powers of digestion, the secretions of the digestive juices, and the organs themselves. The 'morbid piquancy' of the juices inevitably led the patient to overeat and defeated the best efforts of the physician. The main foods implicated were butter, fat meats and spices, especially black pepper. Wine, beer and spirits, together with tea and coffee were all acceptable in moderation. Bile was seen as the causal agent echoing Galen's earlier humoral theory (2).

Du Bois Reymond (1859) was first to suggest that migraine was caused by the vasomotor effect of the cervical sympathetic nerves. He drew an analogy between pain emanating from the blood vessels and pain produced by stimulating striated or smooth muscle. He attributed the pain of

migraine to 'increased lateral blood pressure against the blood vessel wall' and illustrated this with examples of increased headache when blood pressure increased within the head.

The visual phenomena associated with migraine attracted considerable interest in the 19th Century because of their inter-relationship with optics and perception. Astronomers and physicists who suffered from the condition themselves contributed their self- observations to the medical literature. William Hyde Wollaston reported his own two single attacks of hemianopic scotoma in 1824 and extrapolated from them to the first description of the 'semi-decussation' of optic fibres in the optic chiasm. George Airy (1865) was the first to put forward the view that 'the seat of the disease in in the brain; that the disease is a species of paralysis; and that the ocular affection is only a secondary symptom'. Sir Hubert Airy (1870) thought the condition originated in either the optic tract or the corresponding optic thalamus. He combined vascular and neural theories to postulate a temporary suspension of function, propagated by contiguity, among the nerve cells of the visual sensorium which was due to vascular congestion. He later suggested that the headache might be due to propagation of this nervous disturbance into other parts of the brain where it could cause pain. This propagation could also explain the aphasias seen in the prodrome (1).

Edward Liveing (1873) wrote a carefully researched volume 'On megrim, sick-headache and some allied disorders', illustrated with case histories and observations of groups patients. His insight into the condition was so penetrating that more recent studies have served only to confirm his original work.

His work is worth studying in detail because he went beyond simple description of the symptoms of migraine and into an examination of the interplay of external and internal factors in the production of the illness. He also took the major step of attempting to integrate migraine into a general theory of aetiology of neurotic illness (neurotic in the sense of having its basis in neural tissue). He noted that if the onset of the condition occurred in childhood there was generally a hereditary predisposition to it. If there was no family history of migraine the onset tended to be later. The attacks generally decreased when the patient was approximately 50 and ceased completely before old age. They often increased perimenopausally in women and decreased after the menopause. He described 'hereditary transformations' in which a child might suffer not from the same 'neurosis' as the parent but a 'kindred affection'. Epilepsy, insanity and neuralgia were all found in relatives of migraineurs. He quoted Sir Henry Holland's observation of a periodicity in attacks of migraine even when the intervals between them extended to 2-3 weeks. This seemed to denote 'a cause specific in nature and uniform in operation'. A kind of compensation was sometimes observed between the severity of a seizure and the degree of immunity which preceded or followed it (i.e. the more severe the seizure the longer the interval till the next one). He clearly appreciated that external and internal events influenced the disorder and differentiated exciting and accessory causes on the basis of the time period involved. (Exciting causes were much briefer than accessory ones.)

'Where the constitutional predisposition is present in a fully-developed form and of a well-marked hereditary type these accidental

circumstances are not at all essential to its manifestation and the seizures will occur whether they are present or not; but when this is not the case, when the predisposition is originally feeble or latent, and when it is waning or declining in force, the influence of these secondary agencies becomes much more apparent and important and may make all the difference to the patient between frequent suffering and comparative immunity.'

Gastric disorder, menstruation and emotional disturbance were the main exciting causes. There was no particular relationship between the migraine and the phase of menstruation. 'Mental emotion' was recognised not only by Liveing but also by Romberg & Tissot as 'among the more influential of the occasional causes of migraine'. The passions, especially anger and vexation, were particularly linked with the condition. The character of the emotion did not seem to matter provided it was strongly felt.

Sleep and waking were associated with migraine attacks as well as other neurosal affections. Dr Marshall Hall, as quoted by Liveing, indicated that 'the transitions from sleeping to waking, and from waking to sleeping are peculiarly apt to determine the accession of nervous disorders.'

Sensory impressions could also trigger attacks e.g. glaring lights, loud noise and strong odours. Liveing cited M. Labarraque as saying that 'The sense of smell, so highly developed in some persons, often becomes an occasion of migraines. Nothing is more common than to see the odours of spirits of turpentine, of lilies, of the essence of roses, of anise,

or musk, of valerian and so forth, determine violent attacks of this malady; flowers, especially those which exhale a strong odour, sweet or not, often produce the same effect'. Where there was a marked visual prodrome to the attack anything which strained vision could produce the migraine. Interestingly, Sir John Herschel remarked that his own, purely visual, migraines could be induced by allowing his mind to dwell on his visual symptoms. This supported the idea that 'the same kind of impression on the sensorium, whether arriving through channels of sense of idea, may be followed by the same result.'

Accessory causes had 'a more prolonged operation in consequence of which the nervous system's latent morbid tendencies are developed or those already in action are intensified'. The main factors identified were:-

(1) exhausting circumstances of any kind - both physical and mental exertion if too close or continuous and especially if accompanied by anxiety,

(2) puberty and the climacteric.

The clinical symptoms of attacks were meticulously described and the 'natural succession' of symptoms documented. 'The affection of sight when it occurs is always or almost always first, next come disorders of touch and of the muscular sense in the extremities which are quickly followed by impairment of speech and disordered ideation; the headache then sets in, and as it increases nausea is gradually developed; actual vomiting is always later and may terminate the attack, but more frequently the paroxysm ends in sleep'. Liveing noted that, in most cases, if the headache was unilateral so were the other symptoms and if

bilateral then both sides were affected. Disturbances of touch and sight when unilateral were almost as likely to occur on the opposite as on the same side of the body. In most well differentiated unilateral cases one side of the body suffered far more than the other. This unilateral, bilateral or intermediate character was seen as analogous with other functional disorders of the nervous system, particularly epilepsy where the convulsions frequently exhibited a more or less one-sided character. The tingling and centripetal progress of sensory phenomena were similar to the 'aura epileptica'. Disorders of speech were found in approximately 25% of a series of Liveing's patients. These could be persistent - 'It is certain that transient disorders of ideational consciousness, a sense of intellectual confusion and inability to attend or recollect, occur in many severe attacks of migraine, and that frequently repeated and severe seizures occasion a less temporary form of the same mental impairment'.

Liveing recognised close links between migraine and epilepsy. Migraineurs often had a family history of epilepsy and some patients who developed migraine during their teens went on to have epilepsy in adult life. The prodrome and aura of classical migraine had much in common with minor epilepsy.

'Psychical disorder' was frequently a part of severe attacks. In exceptional cases the whole migraine attack could be replaced by temporary mental derangement. The psychical disturbance could be either intellectual or emotional:

(1) intellectual - loss or impairment of memory; confused, incoherent or tumultuous ideation; very rarely hallucination.

(2) emotional - this affected approximately 25% of Liveing's patients and usually preceded the headache although in a few cases it could continue into, or not start until, the later stages of the attack. The emotional symptoms were depression or vague subjective feelings of anxiety or dread. Irritability could occur before attacks.

Liveing emphasised the importance of self report in this aspect of the condition: 'Autograph accounts of which the value can hardly be overestimated where the phenomena under consideration are those of the patient's own consciousness and do not come within the range of ordinary observation'.

Liveing believed in neurosal equivalency and transformations. He was convinced that neuroses frequently changed in character when they were inherited. Occasionally one form of seizure could be replaced temporarily or permanently by another. This happened in a range of disorders including epilepsy and mania. He thought that there was a continuum of nervous disorders - epilepsy, mania, vertigo, chorea, transient amaurosis and somnambulism were all regarded as closely allied and interchangeable conditions. These were all the result of 'a determination of blood' in different degrees in different parts of the brain. Brown-Sequard (as cited by Liveing) thought that many conditions resembled epilepsy in being 'due to an irritation starting from a centripetal nerve' that is, peripheral irritation with vaso-motor reflection. The explanation for the close connection and conversion of disorders was embedded in the constitution of the central nervous system. Tissot (also as cited by Liveing) proposed that metamorphosis in migraine was due to the transfer of morbid activity from one set of nerves to

another. Epilepsy was the neurosis most closely connected to migraine - occasionally one disease replaced the other and intermediate forms also occurred.

The fundamental cause of all neuroses was a primary and often hereditary morbid disposition of the nervous system itself. The nerve centres irregularly accumulated and discharged 'nerve-force' causing disruptive and uncoordinated action. The particular regions affected determined the type of neurosis. The illness was preceded by a condition of unstable equilibrium and gradually accumulating tension. The paroxysm was like a storm which dispersed the condition and temporarily restored equilibrium. The seizures were complicated by disruption of the function of the affected parts which caused various degrees of anaesthesia and paralysis. The positive features were direct expressions of the neural areas involved.

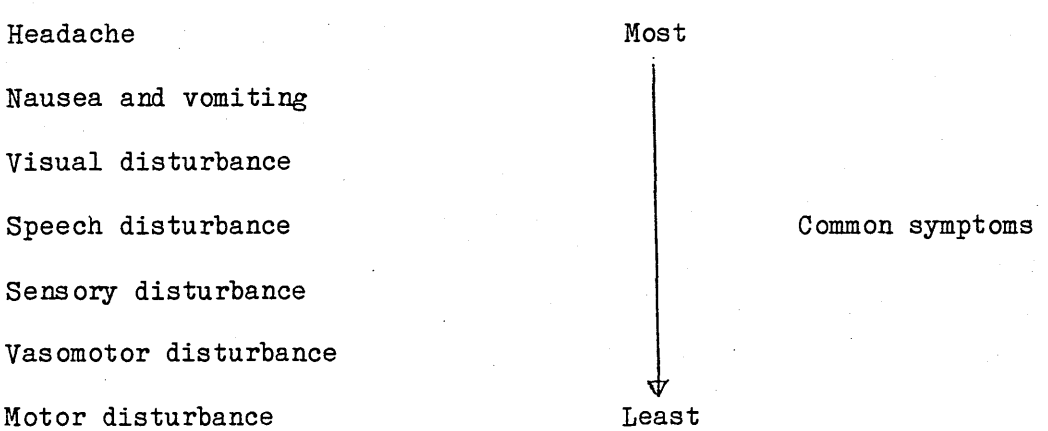
Liveing described 'nerve-storms' which were (i) paroxysmal and explosive, e.g. epilepsy and (ii) intermittent with healthy intervals. The mechanism was an accumulation and discharge of morbid material which was thought to be the 'nerve-force' itself. This also occurred in paroxysms of pain and delirium and explained the exhausting effects of pain or any strong sensation. Sir Henry Holland felt this was the explanation for the periodicity of migraine and epilepsy as it correlated with the increased irritability prior to the attack and the immunity afterwards.

Over a period exciting causes gradually led to increasing disability in the nervous system.

Liveing acknowledged that others thought that a disorder of cerebral circulation was the principal cause of migraine but felt that even they must assume a minor degree of morbid irritability or explosive tendency in the nervous system.

He thought that migraine could be triggered or exacerbated by 'excessive brainwork'. This could be intellectual or could be due to 'strain of the affective or emotional part of our nature, which is the result of prolonged mental anxiety, vexation and disappointment, whether associated with the former or independently and which is far more rapidly exhaustive of nervous power than any intellectual efforts which are free from such emotional complications.' (3)

Gowers (1888) included a chapter on migraine in his 'Manual of Diseases of the Nervous System'. He commented particularly on the resemblance between epilepsy and migraine with respect to sex distribution and age of onset. In order of frequency the common symptoms were



He noted that occasionally a visual impression such as watching

moving objects or seeing a peculiar kind of motion could induce migraine as could over-use of the eyes or a sudden change of light. This could also happen with loud noise or peculiar odours. 'A peculiar habit may become established by which a sensory impression will always induce a paroxysm'.

Emotional changes (depression, restlessness or confusion) could occur either as the earliest symptoms of the attack or after the development of sensory symptoms. Occasionally there was transient loss of memory, double-consciousness (a vivid recollection of things past) or brief stupor.

Movement, light and noise all increased pain during the migraine.

The most common vasomotor disturbance was pallor of the face at the onset of the migraine and often throughout its course. This could be followed by flushing. Rarely flushing was present from the beginning. The extremities were usually cold.

Gowers quoted two theories of aetiology:

(1) Vascular

(a) Spasm of the cerebral arteries as proposed by Whyte.

(b) Vascular dilatation as suggested by Mollendorf.

(c) Two varieties of migraine - (i) sympathetico-tonic

(ii) sympathetico-paralytic.

(d) The early symptoms of migraine were due to spasm and the headache to dilatation of the vessels (Latham).

The sympathetic nervous system was implicated in the production of all the vascular changes.

(2) Primary derangement of nerve cells

The vasomotor disturbance was secondary to the 'nerve-storm' which was a combination of inhibition and discharge of sensory centres. The vascular system was influenced by the cerebral centres, e.g. the blush of emotion and the pallor of fear. Therefore the vascular changes in migraine could be the result of disturbance in the sensory centres.

The sensory symptoms were linked to functional disturbance in the nerve cells of the cerebral cortex whereas the headache was more closely affiliated with vascular changes.

The prognosis for the condition given by Gowers could be repeated today - that the prospect of recovery was never considerable but there was a fair chance that attacks could be reduced in frequency and severity by continued treatment. Stress was laid on absolute rest and avoidance of all strong sensory impressions during the acute attack. (4)

John Hughlings Jackson initially (1876) described migraine as a sensory epilepsy. (1) In a footnote to a lecture on convulsive seizures given later (1890) he explained that he had used the term epilepsy to describe conditions in which any part of the cerebral cortex might become highly unstable and discharge excessively but henceforward he wished to restrict the term to convulsive seizures. (5)

Ergotamine was first isolated in 1925 and its benefits in the

treatment of migraine supported the vasomotor theory of causation.

The major treatise on migraine in this century has been Harold Wolff's 'Migraine and Other Head Pain' (1948). Wolff experimentally confirmed the classical hypothesis that a dilated temporal artery gave rise to a throbbing headache. He also postulated, but did not prove, a transient spasm of the occipital artery which preceded this vasodilatation and was responsible for the visual aura. In the most recent edition (1972) migraine was described 'as a form of relatively benign vasospasm, an episodic disorder of an integrative nature produced by the interaction of the cerebral vasomotor centres, the extracranial and intracranial blood vessels and the microcirculation. It involves both central and peripheral vasomotor mechanisms, as well as a sterile inflammatory reaction, evoked by the activity of the nervous system.' (6)

Sacks (1970) portrayed the primary disturbance in migraine as neurophysiological disturbance of brainstem activity. Local vascular disturbances and systemic upsets were variable in occurrence, intermediary in role and secondary to this. Migraine was seen as 'both eloquent and effective in providing an oblique expression of feelings which are denied direct or adequate expression in other ways.' (7)

1.1 Summary

The characteristic visual, sensory and motor symptoms prior to the migraine headache and the unilateral pain have always differentiated migraine from other types of headache. They distress the patient and

concern their physician. As a consequence they have been extensively described. This led to the delineation of the anatomical pathway of the optic fibres. The unilateral pain has suggested cerebral asymmetry in the production of symptoms. The prominence of nausea and vomiting caused initial confusion about the site of origin of migraine and interest in dietary factors as part of aetiology and treatment.

There has been longstanding controversy over whether the pathogenesis is neural or vascular. The convention has been to assume that the sensory and motor symptoms have a neurological origin whereas the headache has a vascular basis. The orderly progression of migraine symptoms is also seen in epilepsy. Different types of neurogenic illness may be inter-related.

Migraine has a multifactorial aetiology. This was recognised early and there has been interest in the interplay of internal and external factors for a long time. The main external factors implicated have been emotional and intellectual stress. The main internal ones have been the condition of the stomach, the phase of the menstrual cycle and emotional disturbance. The fact that so many factors are involved makes an explanation of the pathogenesis of the condition both challenging and difficult. On one hand migraine provides an opportunity to use multiple models to develop understanding of the condition and to look at the relative contributions of the variables concerned but on the other hand it makes it difficult to concisely summarise the roles of these factors in a simple way.

CHAPTER 2

Syndromes included under the general heading of migraine

2.1 Problems in the definitions of illnesses

The two main problems are achieving a diagnosis which is both reliable and useful.

The reliability of a diagnosis can be determined by:
(i) observer agreement i.e. the frequency with which two independent raters make the same diagnosis on the same patient,
(ii) frequency agreement i.e. a comparison of the range of diagnoses given to two comparable series of patients,
(iii) consistency or stability of the diagnosis over a period of time. (8)

A consensus of opinion may only reflect conformity to traditional ideas about a condition.

The concordance of diagnosis using two separate classification systems does not necessarily imply that either or both is valid. Different systems may be based on standard symptoms or signs elicited on examination of the patient.

The longitudinal development of an illness can produce changes in diagnosis which can only be avoided by introducing an arbitrary hierarchy. The prognosis of a condition can circularly justify its original diagnosis. (9)

The most satisfactory criteria are operational definitions particularly if these are based on aetiological factors e.g. inheritance.

The usefulness of a diagnostic system will depend partly on its purpose e.g. clinically useful systems may not be stringent enough for certain kinds of research. Clinical utility depends on:
(i) the relative homogeneity of groups - this is achieved best if the classification is based on differences in symptoms,
(ii) prediction of response to treatment - new, effective treatment can lead to the revision of diagnosis,
(iii) good separation between the groups - unfortunately overlap of symptoms between categories is very common
(iv) prediction of prognosis. (10)

2.2 Classifications of migraine

The two classification systems most commonly referred to in the literature on migraine are (1) that of the World Federation of Neurologists' Research Group on Migraine and Headache, and (2) that of the Ad Hoc Committee on the Classification of Headache.

The two systems have similar criteria. The World Federation of Neurologists consider migraine to be a familial disorder characterised by recurrent attacks of headache widely variable in intensity, frequency and duration. Attacks are commonly unilateral and are usually associated with anorexia, nausea and vomiting. In some cases they are preceded by, or associated with, neurologic and mood disturbances. Not all of these

characteristics are necessarily present in each attack or in each patient.

Conditions which are generally accepted as falling within this definition are classic migraine and non classic (common) migraine.

Conditions which may or may not fall within the category of migraine are 'cluster' headache, 'facial' migraine, 'opthalmoplegic' migraine and 'hemiplegic' migraine. (11)

The classification proposed by the Ad Hoc Committee on the Classification of Headache is mainly descriptive but is also based on pain mechanisms as these were conceptualised when the classification was introduced in 1962. It is made up of fifteen categories with definitions for each one.

Categories

(I) Vascular headache of migraine type

(a) 'Classic' migraine

(b) 'Common' migraine

(c) 'Cluster' headache

(d) 'Hemiplegic' and 'opthalmoplegic' migraine

(e) 'Lower-half' headache.

(II) Muscle-contraction headache

(III) Combined headache: vascular and muscle-contraction

(IV) Headache of vasomotor reaction

(V) Headache of delusional, conversion or hypochondriacal states

(VI) Non migrainous vascular headaches

(VII) Traction headache

(VIII) Headache due to overt cranial inflammation

(IX)-(XIII) Headache due to disease of ocular, aural, nasal and sinus, dental or other cranial or neck structures

(XIV) Cranial neuritides

(XV) Cranial neuralgias

2.3 Key definitions

For the purposes of this review of the literature the following key definitions will be adhered to throughout:

(I) Vascular headaches of the migraine type

Recurrent attacks of headache, widely varied in intensity, frequency and duration. The attacks are commonly unilateral in onset; are usually associated with anorexia and sometimes with nausea and vomiting; in some cases are preceded by or associated with conspicuous sensory, motor and mood disturbances; and are often familial. Cranial arterial distention and dilatation are importantly implicated in the pain phase but cause no permanent changes in the vessel involved.

(A) 'Classic' migraine

Vascular headache with sharply defined, transient visual and other sensory or motor prodromes, or both.

(B) 'Common' migraine

Vascular headache without striking prodromes and less often unilateral than (A) and (C). Synonyms are 'atypical' migraine or 'sick' headache. Attention is called to the relationships of this type of headache to environmental, occupational, menstrual or other variables by such terms as 'summer', 'Monday', 'weekend', 'relaxation', 'premenstrual' and 'menstrual' headache.

(C) 'Cluster' headache

Vascular headache, predominantly unilateral on the same side, usually associated with flushing, sweating, rhinorrhea, and increased lacrimation, brief in duration, and usually occurring in closely packed groups separated by long remissions.

(II) Muscle-contraction headache

Ache or sensations of tightness, pressure or constriction, widely varied in intensity, frequency and duration, sometimes long-lasting and commonly sub-occipital. It is associated with sustained contraction of skeletal muscles in the absence of permanent structural change, usually as part of the individual's reaction to life stress. The terms 'tension', 'psychogenic' and 'nervous' headache refer largely to this group. (12)

Diamond & Medina (1976) have suggested a simpler nosology categorising headache under three major headings including psychogenic. (13)

Traction & Inflammatory	Vascular	Psychogenic
Mass lesions	Migraine	Depression
	Classic	
	Common	Conversion
Diseases of eye, ear, nose & throat	Cluster	Delusion
Cranial neuralgias	Facial	
Allergy	Opthalmoplegic	Anxiety
Infection	Hemiplegic	
Arteritis	Toxic	
Temporomandibular joint dysfunction	Hyperextensive	
Cervical osteoarthritis		
Chronic myositis		

(Diamond and Medina 1976)

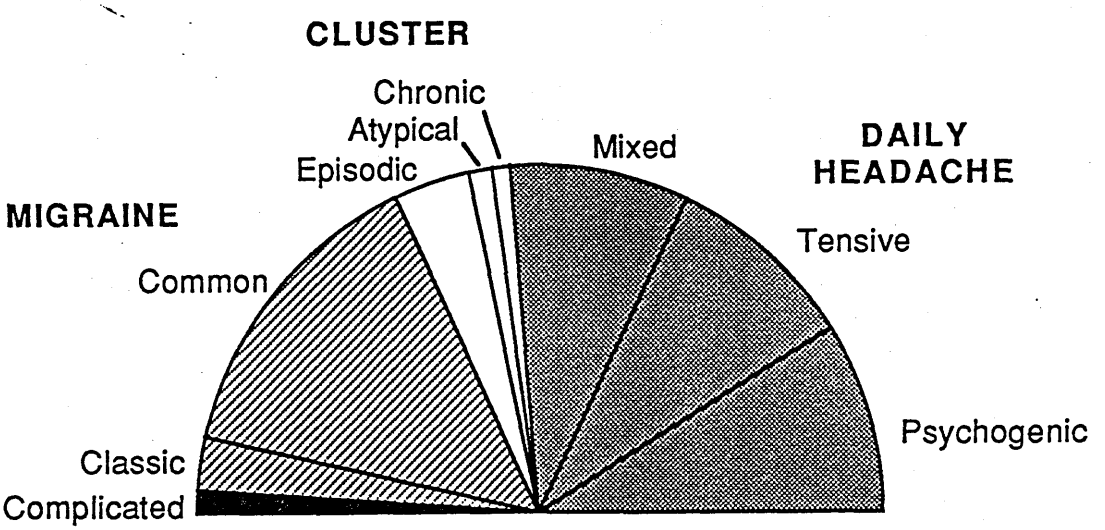
More recently chronic daily headache has been defined as a daily vascular headache without concomitant neurological symptoms. (14) The majority of these daily headaches are on a continuum with episodic migraine (15) and subsume migraine with inter-paroxysmal headache. This last form starts as a common migraine, but there is a progressive increase in the frequency of attacks and a reduction in pain-free intervals until the latter disappear altogether. (16)

2.4 Controversial issues in classification

(i) Migraine versus muscle-contraction headache

The main issue is whether migraine and muscle-contraction headache are separate categories or points on a continuum of headache severity.

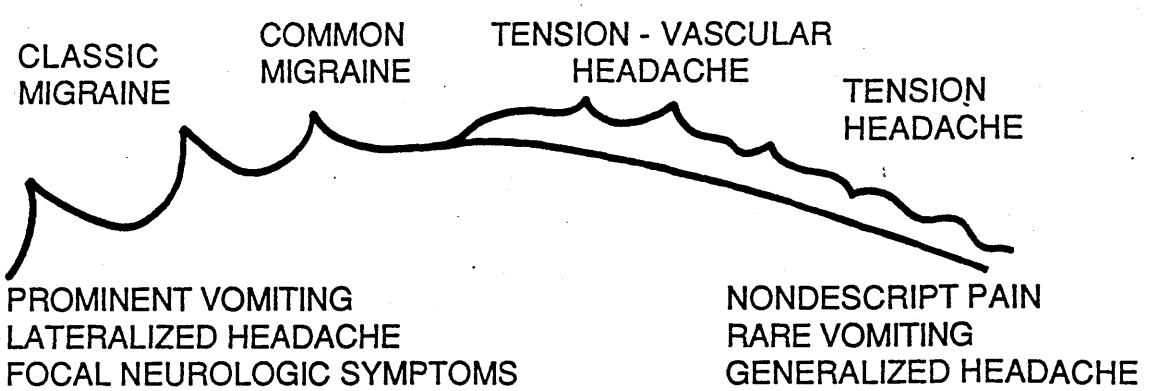
FIG 1 - The headache spectrum Nappi et al, 1985 (14)



According to the severity continuum model the headaches experienced most frequently would cluster at a point which would give the diagnosis of migraine, tension or mixed (migraine and tension) headache. However patients could also experience other headaches which were more or less severe. The accessory symptoms and the type of pain would correlate with the severity of the headache. (17)

FIG 2 - The continuum of benign recurrent headache

Raskin & Appenzeller 1980 (17)



Reproduced from Raskin N H, Appenzellor O, Headache. W.B. Saunders, Philadelphia 1980, p.182 with permission of the publishers.

Although there is variation within each type of headache and an individual can have both migraine and muscle-contraction headache (MCH) they differ on a number of variables:

(a) family history of the disorder - this is more frequent in migraine than MCH,

(b) age of onset - the majority of MCH cases developed after age 30, migraine begins earlier,

(c) prodomata - more frequent in migraine,

(d) frequency - 50% MCH versus 3% of migraine cases reported daily occurrence,

(e) duration - 35% of the migraine group versus 10% of the MCH group reported a duration of 1-3 days,

(f) type of pain - 80% reported throbbing pain in migraine versus 10% in MCH,

(g) location of pain - unilateral: 80% migraine versus 10% MCH,
bilateral: 90% MCH versus 20% migraine,

(h) associated symptoms - vomiting was present in 50% of migraine cases versus 10% of MCH.

These findings come from a very large study of 1,000 migraineurs and 1,000 tension headache sufferers. Although the characteristics of each group are described it is not clear what criteria were used to differentiate between them. All patients attended a headache clinic but beyond that there is no information on how they were selected. Migraine patients were not divided into common and classical groups. (18)

(II) Muscle-contraction headache versus daily chronic headache

As was noted in the preceding section increased frequency and duration of headache are likely to produce a diagnosis of MCH rather than migraine. By definition, migraine has been an episodic disorder. However 70% of patients with daily headaches had been found to have a previous history of episodic migraine. This was hormone-dependent (eg menstrual migraine) in more than half. Several years elapsed before the transformation from episodic to daily headache. (Mean age of onset of episodic headache was 17 years, mean number of years of episodic migraine was 19 years, and the mean age at which transformation occurred was 30.8 yrs.) Excluding these patients from a diagnosis of migraine might deprive them of the advantages of specific treatment. (15)

(III) Classical versus common migraine - are these the same or different entities?

Vasospasm and cerebral ischaemia followed by cerebral and extracerebral vasodilatation and hyperaemia are generally believed to form the common pathophysiology of the various subtypes of migraine. Common migraine is at the mild end and classical migraine the severe end of a continuum of severity. Because of this view virtually all drug trials and many pathophysiological studies have included both types of migraine. However regional cerebral blood flow studies have shown marked pathophysiological differences between the two conditions. Spreading oligaemia which originates posteriorly and progresses anteriorly has been found in patients with classical migraine, but not in patients with common migraine. This closely resembles the Spreading Depression of Leaõ. (19,20)

However, the conclusions from this work on cerebral blood flow have been challenged on both clinical and experimental grounds:

(1) Clinical

(a) The differentiation between classical and common migraine is made on the basis of the patient's self report. This is a notoriously unreliable source of information. It is also common for the same patient to have episodes of both classical and common migraine (20,21). However the vast majority of migraine patients never experience an aura, i.e. they have common migraine. Since the incidence of common migraine is approximately 20% one would expect a similar percentage of patients with classical

migraine to coincidentally have common migraine. However, as the percentage actually found is higher than this there is some indication of a relationship between the two conditions. (23)

(b) Headaches are the same whether or not they are preceded by an aura. (21)

(c) Classical and common migraine are both treated with the same types of medication. (21) Despite this it has never been shown in controlled trials that they respond equally well to them. (23)

(2) Experimental

(a) The topographical relationship between blood flow changes and symptoms is poor. However spreading oligaemia is not an all or none phenomenon but can differ in intensity and therefore in symptom production. (23)

(b) There has been controversy over whether:
(i) spreading depression (S.D.) can be elicited in man,
(ii) S.D. is the same as the spreading oligaemia demonstrated in regional CBF studies,
(iii) S.D. is followed by vasodilatation and reactive hyperaemia. (21)
In fact spreading depression has now been well described in humans but the short-lasting and very narrow band of hyperperfusion which follows it is difficult to see with external flow monitoring. (23)

(iv) Conclusions

The considerable differences between migraine and muscle-contraction headache suggest that they are separate entities. Both conditions are common and it is therefore likely that they will often occur together.

Duration alone is insufficient evidence to differentiate muscle contraction headache and daily chronic headache. The latter appears to be closely related to migraine and a past history of migraine in these patients may be an indication for specific anti-migraine drugs. There is a need for clinical trials to ascertain the most suitable type of medication for this group.

There is insufficient evidence to definitely say that classical and common migraine are different entities. However the differences between the conditions are sufficient to indicate a need to study them separately.

2.5 Description and definition of the migraine attack

(1) Prodrome

The prodrome comprises symptoms with an insidious onset, which last several hours and involve mood, behaviour, wakefulness, gut motility and fluid balance. It has been hypothesised that these symptoms and signs indicate dysfunction, either diffusely in the cerebral hemispheres or focally in the hypothalamus. The prodrome is not always followed by either the aura or the headache.

(2) Aura

This begins suddenly, lasts minutes and commonly affects vision or, less frequently, somatic sensation, motor, speech or brainstem function. It arises from stimulation or inhibition of a restricted area of cerebral cortex or, in basilar migraine, of the brainstem. It may occur independently from the headache.

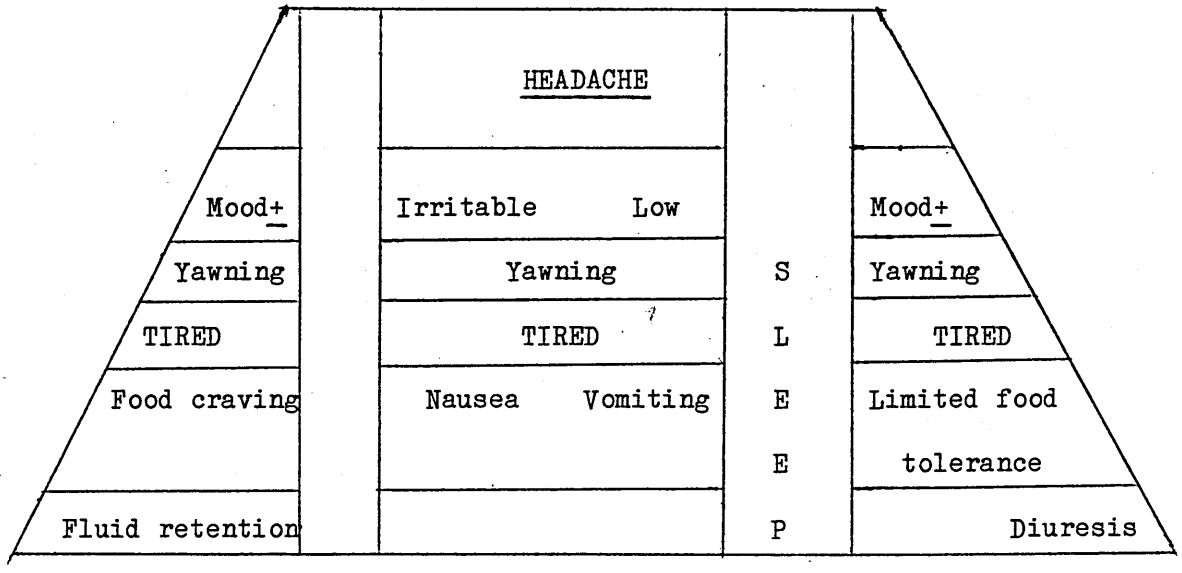
(3) Headache phase

Headache is accompanied by nausea, vomiting, photophobia and phonophobia and is thought to arise from extracranial vasodilation or from a vasomotor instability of the meningeal circulation. The mechanism of photophobia or phonophobia remains uncertain. (24)

(4) Sleep resolution

The most efficient relief for the headache in migraine is sleep. Normal sleep is thought to have a restorative function and in migraine could be a non-specific response to stress, pain, vomiting or lack of food. Alternatively somnolence, yawning and sleep may be integral to the altered physiology. Supportive evidence for this hypothesis is found in the observations that migraine can be precipitated by lack of sleep, becoming excessively tired or sleeping too long. Yawning and tiredness are prodromal symptoms that may continue during, as well as after, the headache phase. The sleep-waking cycle is affected by hypothalamic disturbances. Other cyclical changes implicating the hypothalamus are

mood variations, fluid retention, diuresis, hyperphagia, nausea and vomiting followed by restricted food tolerance. (25) Nocturnal migraine has been shown to be temporally related to REM sleep. It has been hypothesised that daytime migraine may be 'triggered' by a recurrent CNS physiological state resembling the REM stage of sleep although the subject is awake. There is a relationship between the adrenergic state (REM stage) of sleep and the decline of peripheral platelet-bound serotonin which places the peripheral level of serotonin in phase with what is thought to occur in the brainstem reticular activating system. (26)



Prodromal	Aure	Headache	Sleep	Recovery
Phase (34)	(16)	Phase (50)	Resolution (34)	Phase (47)
12 hours	40 mins	21 hours	7 hours	28 hours

Diagram illustrating phases, average duration and symptoms in migraine attacks from 50 subjects with uncomplicated migraine. (25)

CHAPTER 3

Social and Demographic Factors in Migraine

Three independent epidemiological studies in the British Isles reported the prevalence of migraine as 24-29% for women and 15-20% for men (27-29). Migraine is more common in women than in men but the exact extent of the sex difference is controversial. The figures quoted have varied widely between studies. Most of the epidemiological studies have been done in England and Australia and cross-cultural differences may account for some of the variance in the reported incidence. (30) However since women with migraine have a greater propensity to deny life problems and focus on physical symptoms they may report the condition more than men.

Approximately 50% of migraine sufferers do not consult their GP or any other doctor about their condition (31). This causes obvious problems in obtaining a representative sample of migraine patients.

The typical age of onset is approximately 20 years although migraines become relatively frequent as early as 10 years of age. After the age of 30 the probability of developing vascular headaches is greatly decreased and continues to decline through to the age of 60 for both men and women. (30)

Lennox (1941) thought migraine affected 'brain-using more than muscle-using persons'. (32) This view has subsequently been reformulated as the hypothesis that migraine sufferers are more

intelligent than the general population. However a comparison of intelligence in migraine sufferers and a matched comparison group without migraine failed to support this. Distributions of intelligence scores were similar in both groups. (27)

Fothergill (1784) found 'sick headache' mostly in the 'middle and upper ranks of life'. Migraine is said to be commoner in the professional classes. Again there is no definite evidence to confirm this though there is a tendency for more intelligent individuals with migraine and those in social classes I and II to consult a doctor because of their headaches. Migraine patients consulting their doctors are a therefore selected group and may well not be typical of all migraine sufferers in the community. (27)

CHAPTER 4

Genetic Influences on Migraine

Liveing (1873) stressed that migraine was a familial condition. Most published work confirms that migraine tends to run in families. However there are two problems in interpreting this work (1) the lack of a consistent definition of migraine (2) possible bias in the selection of patients with migraine or in the collection of data from their families. Selection is important as only half of migraine sufferers consult a doctor. Bias is almost inevitable when migraine patients are asked about the family history of the condition and relatives are often not questioned directly about their headaches. (27)

There is no diagnostic test for migraine nor is there a biological marker. A positive family history is sometimes included in the diagnostic criteria for migraine. There are several clinical varieties of migraine which may have different pathophysiological mechanisms. Different triggering factors for migraine may be genetically influenced, e.g. personality type. Questionnaires have been used to reach a diagnosis when large numbers of people are surveyed but this is not as accurate as the doctor- patient interview. Patients are usually correct in self reports of migraine but under report the condition. It may be particularly difficult to differentiate common migraine and tension headache.

Information on genetic influences in migraine comes from two sources - family studies and twin studies.

4.1 Family studies

In studies of family history the incidence of two or more migraine sufferers within a family has varied from 46-91%. Lance & Anthony found that 46% of parents and siblings of migraineurs also had migraine. Positive family histories of tension headache were found in only 18% of parents and relatives of tension headache sufferers. In a monograph by Bille 79.5% of children with severe migraine had parents or siblings with similar headaches. In 72.6% of these cases the mother had migraine; in 20.5% the father. Dalsgaard-Nielson found a positive family history in 75-90% of adult migraineurs. Again the mother was affected in 50- 70% of cases, the father in 16- 19%. For both sexes there was an inverse correlation between the age of onset of classical or common migraine and the strength of the family history. Although the mother was the most commonly affected parent involvement of the father was associated with earlier onset of migraine.

Waters, basing his results on questionnaires, found migraine occurred in 6% of first degree relatives of non-headache probands and in 10% of migraine probands. This difference is not statistically significant.

Although most studies confirm a strong familial component in migraine there is no simple pattern of inheritance. Both recessive inheritance with 70% penetrance and polygenic inheritance have been suggested.

4.2 Twin studies

Joel-Nielsen reported concordance in 3 of 5 pairs of monozygotic (MZ) twins reared apart; two of these were concordant for age of onset. Lennox reported 100% concordance in 5 pairs of MZ twins. However the results were biased by epilepsy in three of the pairs. A large study by Lucas used a strict definition of migraine and determined zygosity and personality by questionnaire. The concordance rate for migraine in MZ twins was 26% overall. Dizygotic (DZ) twins of the same sex had 16% concordance for migraine. When both same-sex and different sex DZ twin pairs were considered together the concordance rate was 13%. Rates of concordance in male and female twins did not differ significantly. No particular symptom had a markedly higher genetic loading. The personality questionnaire showed no evidence of increased neuroticism in the affected twin of a pair discordant for migraine.

Conclusion

Twin studies, like family studies, suggest that there is more than one migraine syndrome. In some cases there is a powerful genetic component, but in others environmental factors are more important. (33)

CHAPTER 5

The role of personality factors

5.1 Assessment of personality

Personality has been defined as the characteristic patterns of behaviour and thinking which determine a person's adjustment to the environment. (34)

Personality can be assessed by:

(i) observation of an individual in ordinary circumstances,

(ii) a clinical interview

(iii) self-report using personality inventories e.g. Minnesota Multiphasic Personality Inventory (MMPI) (35).

Constitution, social and cultural factors all affect the composition of personality. As a consequence personality does not lend itself readily to objective assessment. Investigator bias can thus be an important confounding factor in studies of the role of personality in illness.

The major sources of bias in subjective testing are:

(i) overinterpretation of information to derive expected or significant conclusions,

(ii) emphasising subject characteristics in accordance with the tester's biases,

(iii) simplifying data to fit the hypothesis being tested,

(iv) drawing conclusions from insufficient data,

(v) failure to externally verify conclusions (36).

Psychological tests improve objectivity and resist bias compared to unstructured interviews. The subject's behaviour can also invalidate the test results - the three main problems are:

(i) unwillingness to cooperate,

(ii) inability to cooperate,

(iii) extreme test-taking attitudes or unusual styles of self presentation. Difficulties can arise because of a tendency to conform with what the subject thinks is expected, or a need to present him/herself in an excessively favourable or unfavourable way or finally because of a wish to confirm or contradict the hypothesis being researched.

The concept of a personality profile which is specific to migraine assumes that:

(i) people with migraine have common traits

(ii) these traits are specific, measurable personality characteristics,

(iii) these traits can differentiate between migrainous and non-migrainous people.

The main difficulty in studies of personality in headache is the lack of a suitable control group. In practice different types of headache sufferers are used to control for each other. All findings have to be viewed in the context of wide variations in personality within non-

headache sufferers. Even when differences are found between patients with headache and the general population they could be the consequence rather than the cause of the illness - either as a direct result of the symptoms or indirectly through coping mechanisms developed by the individual concerned.

5.2 Personality factors in migraine

There is a specific migraine personality characterised by rigidity of thought, ambitiousness, an exaggerated sense of responsibility, intellectualism with a tendency to excessive worry, perfectionism, meticulousness, obsessional traits and inhibitions. This, at least, was the view of early psychoanalytic writers. The major conflict for patients was ambivalence about expressing hostility especially towards those close to them. Guilt then led to the repression of these feelings and their partial resolution through introjection and physical symbolism.

However there is little objective evidence that classical migraine is associated with increased hostility or aggression. One study, using an administered adjective checklist, found migraine patients were more inhibited in the expression of aggression, more likely to experience anxiety, guilt or both after anger and felt angry for longer. As children these patients were punished for, or prevented from, expressing anger. Unfortunately the checklist used was developed for the study and no information is available about findings in a normal control group.

Blaszcynski examined the question of increased obsessionality in migraine by comparing four groups of patients - classical migraine,

tension headache, normal controls and non-headache physical pain - using the Hysteroid-Obsessional Questionnaire, the Eysenck Personality Questionnaire, the Buss-Durkhee Hostility-Guilt Inventory and the Hostility and Direction of Hostility Questionnaire. No evidence for increased obsessionality in the migraineurs was found on any of these measures. The number of patients in each group was small (15) and the migraine patients had fairly mild illnesses (in terms of frequency of migraine). The patients had all attended general practitioners or clinics because of their complaints but were not directly comparable with the population attending a specialised migraine clinic. Only one study by Rogardo et al has found objective evidence of an obsessional component in migraine and Kudrow & Sutkus were unable to replicate these findings using the same measures in a larger sample. They argued that differences in diagnostic specificity in the two studies explained the results.

There are two factors which may explain the discrepancies in the results of studies of obsessionality.

(1) Pollock has argued that the obsessional personality is commonly found in Western cultures where it embodies the Protestant work ethic and is prevalent in professional and managerial workers. Waters has shown that this type of person is more likely to consult doctors with migraine than the general population. These patients will therefore be over-represented in clinic populations and this will bias clinical studies.

(2) The validity of the categorisation of 'obsessional personality' is doubtful and no satisfactory instrument is available to measure it. The differences between the studies quoted may therefore be due to the

inadequacy of existing measurements. (37)

More recently the MMPI, the Beck Depression Inventory, the State-Trait Anxiety Inventory and Eysenck's Personality Inventory have all been used to demonstrate abnormalities in migraine patients. It remains uncertain whether these are the cause or the effect of the migraine.

Henryk-Gutt and Linford Rees (1973) used a questionnaire to identify classic migraine sufferers in the staff of two Government departments. Twenty-five men and 25 women were randomly selected and matched for age, sex, marital status and civil service grade with controls with common migraine, non migrainous headache and no headache. In addition, 18 women were matched with patients who had either classical or common migraine and were attending a migraine clinic. Subjects with migraine experienced significantly greater emotional distress than controls although their life stresses did not differ. Migraineurs seem to be constitutionally predisposed to a greater than average reaction to a given amount of stress. (38)

Crisp et al (1977) also used a questionnaire method to identify migraineurs in a general population sample and asked respondents to complete the Middlesex Hospital Questionnaire. Female migraine sufferers were significantly more anxious and depressed but also more sociable. They complained more about other functional somatic disturbance. A smaller sample of men showed similar tendencies with respect to anxiety and somatic complaints. The profile found, especially in women was of undefended dysphoria coupled with a definite tendency to be outgoing and engaging in the world. (31)

Kudrow & Sutkus (1978) reported finding some specificity of MMPI patterns among types of headache.

(A) Migraine and cluster headache patients had normal test profiles.

(B) Muscle-contraction headache and mixed migraine-muscle contraction headache patients showed moderate somatisation patterns with borderline depressions.

(C) Post-traumatic cephalgia and conversion headache patients had mild to moderate depressions with somatisation features.

Group (A) differed from groups (B) and (C) in showing less elevation on the neuroticism scales.

The diagnostic criteria used in the study are open to criticism - one or two year minimal durations were specified for all categories except migraine for which no minimal duration was given. Additionally the only discriminating factor between chronic muscle contraction headache and 'conversion cephalgia' was the severity of pain. This is an extremely unreliable index. (39) Sternbach et al (1980) attempted to replicate these findings using the three most common diagnostic categories: vascular, muscle-contraction and mixed (vascular and muscle-contraction). All patients came from a pain treatment centre but it is not clear how they were selected. On the MMPI the vascular headache patients were less anxious and depressed than the muscle-contraction headache and mixed groups. However although statistically significant

differences were found there were no clinically significant findings - all three groups could be described as having mild masked depressions with somatisation and anxiety. Women were inclined to deny life problems and focus on physical symptoms. This was more marked in the muscle contraction headache and mixed groups. It was hypothesised that the lower MMPI scores in the vascular group might be due to the greater frequency and length of pain-free intervals in these patients. When all the groups of headache patients were compared with the MMPI scores of 50,000 general medical patients the former obtained markedly greater scores on most scales than the latter. This may reflect the greater duration and severity of subjective distress in the headache patients. However the data on which the authors base this last conclusion is not well presented and very little information is given about the general medical population used. (40)

Cuypers et al (1981) compared personality profiles of 40 patients with cluster headache with 49 patients with migraine. No details of the selection procedure are given. The diagnostic criteria used were those of the Ad Hoc Committee on the Classification of Headache. The personality measure employed was the Freiburg Personality Inventory. This is a multidimensional personality inventory with comparable validity to the MMPI.

No differences were found between the cluster headache and migraine groups nor was there any indication of neuroticism in the group as a whole. The authors comment that male cluster headache patients have limited interest in the masculine role and that this may reflect their chronic disease status. However no reasons are given for this view and

it does not accord with the intermittent nature of the disease and the long pain- free intervals.

Migraine patients are noted to have frequent gastric complaints. Cluster headache patients do not and yet they have an increased incidence of peptic ulcer. As nausea, vomiting and diarrhoea are frequently an integral part of migraine this observation is probably not significant.

Both migraine and cluster headache patients have been found to have a tendency towards psychosomatic reactions but no important or specific neurotic disturbances. (41)

Andrasik et al (1982) used a sample of 99 consecutive patients with chronic severe headache and 30 non-headache controls. Approximately half the headache patients were physician-referred. The other half were self-referrals. Diagnosis was made using a combination of the criteria of the Ad Hoc Committee on the Classification of Headache and those of Diamond & Dalessio. Migraine patients were not classified by diagnostic category (i.e. classical, common etc.) A continuum of increasing distress was found from cluster headache (minimal distress) through migraine and combined migraine muscle-contraction headache to muscle contraction headache (maximal distress). None of the headache groups could be characterised by marked elevations on any of the psychological tests.

Cluster headache patients were not significantly different from controls although there was a tendency to somatisation under stress. Migraine patients were preoccupied with somatic symptoms and bodily concerns of a vague or diffuse nature. The combined migraine muscle-

contraction group showed mild depression, worry and pessimism although there was uncertainty as to whether this was situational or a stable trait. The muscle contraction group were overly sensitive, resentful and hostile, perfectionistic, rigid and orderly, self-critical and aloof.

The muscle contraction group was the only one which differed significantly from Mayo Clinic medical outpatients.

All groups were equivalent on the Holmes & Rahe Social Readjustment Rating Scale which the authors felt ruled out differential exposure to stressful life events as a cause of the group differences in personality characteristics.

The pattern of test findings is directly related to the frequency with which the headache groups are subject to pain but is inversely related to the severity of pain experienced during the headaches.

The psychological distress is directly related to 'pain density'. However this does not imply that all the distress is a consequence of the pain. The MMPI has been applied to migraine patients before and after successful treatment with minimal changes suggesting that certain psychological characteristics are an integral part of the migraine. (42)

In conclusion migraine patients do not appear to have a specific type of personality. Likewise there is little evidence that they have particular difficulty in expressing anger. There may be a genuine increase in obsessionality in migraineurs but this could be artefactual. It may only reflect the characteristics of the patient population which

presents for treatment or be a consequence of inadequacies in the methods available to assess obsessionality.

Patients with migraine seem to react excessively to ordinary life stresses. Although it has been claimed that specific MMPI profiles are associated with different types of headache these results are statistically, rather than clinically significant. In fact recurrent headaches are associated with mild depressive illness, somatisation and anxiety. This profile is not altered by treatment, suggesting it is a trait rather than a state phenomenon. The degree of distress is directly proportional to the frequency and severity of the pain but is not related to external stress in the form of major life events.

5.3 Emotional specificity and migraine

One explanation for the specificity of psychophysiologic disorders (i.e. they occur in a single organ system) is that specific emotional patterns elicit specific types of physiologic response patterns. Continual emotional stimulation causes over-reaction and eventual disruption in the organ system concerned. In migraine unexpressed anger results in an overreactive cephalic vasomotor system which eventually becomes dysfunctional. However most of the evidence from studies of psychophysiology does not support this hypothesis. (30)

Migraineurs have higher 'N' scores on the Eysenck Personality Inventory (EPI) together with increased emotional reactivity. 'N' scores on the EPI are thought to be directly related to the degree of activation of hypothalamic centres and the autonomic nervous system response of the

individual. The 'N' score is also largely determined by hereditary factors. The association of high 'N' scores and increased autonomic sensitivity may predispose the individual to develop migraine. (38)

In a study of male students and patients attending the Institute of Psychiatry for psychological testing a significant association was found between high neuroticism and a family history of migraine and hypertension. The autonomic nervous system is labile in both conditions. (43)

A second study showed that migraineurs have higher levels of trait anxiety and also inhibit expression of feelings. Again this pattern is not specific and has also been found in hypertension. (44)

5.4 Pain and personality

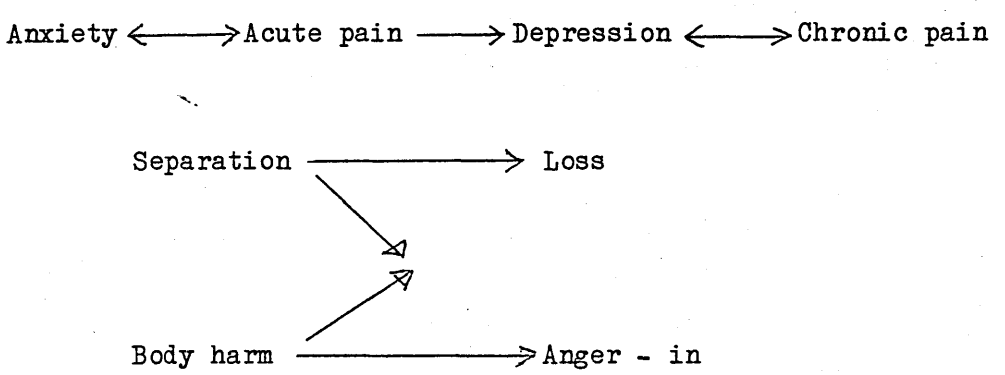
Pain lacks a clear definition and there are difficulties in making introspective distinctions between sensation and emotion.

Merskey (1964) has given an operational definition of pain as 'an unpleasant experience which we primarily associate with tissue damage or describe in terms of tissue damage or both.' There is no subjective difference between organic and psychogenic pain. Psychogenic pain can be defined as either pain which is independent of peripheral stimulation or damage to the nervous sytem and due to emotional factors or pain in which any peripheral change is a consequence of emotional factors. Organic pain can then be regarded as pain which is largely dependent upon irritation of nerves, or else due to a lesion of the central nervous

system. The terms 'organic' and 'psychogenic' in this context indicate what the principal cause of a pain is likely to be. (45)

Sternbach found that both organic and psychogenic pain patients had neurotic patterns in which hypochondriasis and depression were significant features. Pain may be substituted for anxiety and depression with greater use of somatisation, denial and repression as defenses. Some patients can be described as 'pain-prone' - they suffer from excessive guilt and pain serves them as a punishment. Pain and aggression feature prominently in their families of origin. Pain may also result from a perception of threat to the integrity of the body.

5.5 Psychodynamic aspects of pain



Chronic pain should hypothetically be associated with increased depression. The MMPI indicates that increased scores for depression, hysteria and hypochondriasis are associated with pain complaints. Pain is not associated more with depression than other psychiatric conditions but is present more often than in healthy controls. Pain occurs in slightly more than half of general medical and psychiatric populations. In psychiatric patients pain is equally likely to accompany a diagnosis

of anxiety, hysteria or reactive depression. Pain may 'mask' depression and in this sense is associated more with reactive than endogenous depression. In psychotic depression somatic disorders are related to the underlying neurochemical disturbance. Here the relationship between pain and depression may lie in the balance of brain monoamines. Norepinephrine decreases the analgesia-mediating properties of serotonin and dopamine in the mesencephalic gray matter. This may be the reason that antidepressants are not always effective in controlling pain. (46)

CHAPTER 6

Philosophical issues raised by migraine - mind-body and brain-mind relationships in psychiatry and medicine.

Practical problems in developing a hostilic approach to psychosomatic illness.

There is a major difference between people and ordinary objects: human beings have minds (or souls or selves) whereas things do not; people have both mental and physical events. (47)

The discovery of the consciousness of self and the knowledge that death is inevitable dates back to prehistoric times where it probably followed the acquisition of language. The burial customs of Neanderthal man indicate both a consciousness of death and a belief in survival. This entails some concept of dualism of mind and body.

Mind-body dualism was frequently referred to in Homer where mind and body were seen as polar opposites which could, however, interact. This interaction was seen in terms of animistic causation bordering on divine intervention.

In Greek philosophy soul and mind were equivalent. Together they were an entity which summed up the conscious experience of the self. Alcmaeon of Croton was the first to locate sensation and thought in the brain.

The Hippocratic school maintained that the brain was responsible for

bodily movements and was also the 'interpreter of consciousness'.

Democritus, a materialist, explained all natural and psychological processes mechanically by the movement and collision of atoms and their composition or dissociation. The atoms of soul were distributed throughout the body.

In Pythagorean theory the hidden essences of all things were abstract and based on the relations between numbers such as 'ratios' or harmonies'. There were two hypotheses concerning the soul - the first that it was a harmony or attunement of abstract numbers which preceded and survived the body and the second that the soul was a harmony or attunement of the body and therefore must perish with the body in death. The latter provided a model of mind-body interaction.

For Plato the soul was similar to ideas and was almost the essence of the living body. He regarded the body as the prison of the soul and accepted interactionism as inevitable. The mind was the pilot of the body. Plato believed the soul to be constant whereas for Aristotle it was always striving towards perfection. Socrates developed the concept of a responsible moral self for which there was no purely physical explanation.

Aristotle and the members of his school accepted that the mind was incorporeal, and that the relationship between mind and body was a non-mechanical interaction.

Descartes was an essentialist and argued for the existence of a

perfect God who guaranteed the validity of clear and distinct perceptions which became criteria of truth. He believed that mind and the consciousness of self were non-corporeal. Human beings were automatons except for the immaterial human mind which could cause movements in the human body and become conscious of mechanical impressions made by physical agencies on the body.

By contrast with Aristotle's cosmos which was always striving towards an end Descartes' world was filled with mechanical contrivances and only man was truly animate or alive. The soul was located mainly within the pineal gland, which it could move to act on the animal spirits and through them the movement of the body. The great difficulty of Cartesian mind-body interaction lies in the theory of physical causality according to which all physical actions must be by mechanical push. Descartes' critics objected that if soul and body were substances with different natures there could be no interaction between them, particularly if that interaction was due to physical causation. The latter objection is the major problem. Some Cartesians dealt with this by introducing 'occasionalism' - i.e. all causation is miraculous and God intervenes on every occasion of causal action or interaction. Psychophysical interactionism was rejected and replaced by psychophysical parallelism. There was no interaction between mind and body but a parallelism which created an appearance of interaction which was in fact due to the intervention of God.

Spinoza maintained that there could be only one substance (i.e. God) and that the only two attributes of him which the human intellect could grasp were mind and body. They ran parallel because they were

different aspects of one and the same thing.

Leibniz's explanation for mind-body parallelism was the doctrine of pre-established harmony. God, at the time of Creation, ensured that minds and bodies, though independent, would continue to run together without the need for constant readjustment. Minds and bodies were sharply distinguished - minds were real substances and bodies appearances. All minds were essentially individual because that was the way God made them.

In monism there were two systems for ordering things - a physical system and a mental one. Elements were neutral because they could become parts of either physical or mental complexes. Elements could be impressions, feelings or sensations. Interaction was avoided and the relation between the mental and the physical was parallelistic. (48)

Identity theory asserts that mental processes and physical processes are identical. Concepts of separate minds and bodies have arisen only because human beings are consistently looked at from two differing points of view. Identity theory forms an integral part of the holistic approach and is thus particularly relevant to psychosomatic medicine.

Behaviourism reduces mental events to publicly discernible behaviour. In its mildest form (methodological behaviourism) introspection is rejected as a valid method of study in favour of the investigation of physical phenomena only. Logical behaviourism is more stringent and defines mental phenomena only in terms of behaviour and physiology while in radical behaviourism the concept of mind and of other

hypothetical constructs or intervening variables is felt to be irrelevant. (47)

Most recently Popper & Eccles have together put forward a dualist-interactionist philosophy of mind-body relationships. They conceive the self-conscious mind as an independent entity which is actively engaged in reading out from a multitude of centres in the modules of the liaison areas of the dominant cerebral hemisphere. The self-conscious mind selects from these centres in accordance with its attention and interests and integrates its selection to give conscious experience. It also acts back upon the neural centres. Primacy is given to the self-conscious mind which during normal life is engaged in searching for brain events that are in its present interest and of integrating these into a unified conscious experience. (48)

CHAPTER 7

Neural and Vascular Hypotheses in Migraine

Both neural and vascular components are involved in the production of migraine but there is controversy over which is the primary phenomenon.

7.1 Vascular hypothesis

H.G. Wolff concluded from his clinical and laboratory investigation of migraine that the pre-headache phenomena were due to cerebral vasoconstriction; that the headache was produced by distension of the external carotid arteries and that pain was enhanced by vasoactive polypeptides in the tissues surrounding the blood vessels - causing a sterile inflammation. (49)

The vascular hypothesis agrees with the pulsatile, throbbing nature of the pain and explains the correspondence between the localisation of the pain and the branches of the external carotid artery in the face and scalp. It is consistent with the observation that digital compression of the neck arteries decreases the pain while pressure is maintained and with the dilation of conjunctival vessels occasionally seen during attacks. The relief of pain by α-adrenergic drugs (e.g. ergot) and the worsening with vasodilators (e.g. alcohol), the alleged prolongation of the aura by ergot and its resolution with nitrites all support a first phase of extracranial vasodilation. Reduced cerebral blood flow has been demonstrated in the aura followed by hyperaemia during headache. It has been claimed that oligaemia and hypoperfusion are directly related to the

symptoms of the aura. (50) A recent study measured CBF using an intracarotid injection of ^{133}Xe in 11 patients. All had attacks of classical migraine which had been induced by the procedure. Focal decreases in CBF were found in the occipital, parietal and temporal areas and these spead to central and frontal regions within 30 minutes. Cerebral blood flow levels known to be insufficient for normal cortical function were found in 7 of these patients during the attack. (51)

Objections

Blood vessels are certainly involved in the production of migraine headache. The headache itself appears to be mainly a painful dilatation of scalp and facial arteries. Arterio-venous shunting has also been implicated by Heyck but there is no evidence that these shunts are present in fronto-temporal or temporal regions and also uncertainty as to whether changes in arterio-venous oxygen content difference are reliable indicators of changes in the proportion of blood flow shunting through the anastomoses. (52) However the fact that symptoms of the disorder are related to the blood vessels does not necessarily imply a vascular cause for the condition. Reduced regional cerebral blood flow (rCBF) often precedes the aura by hours and there is no evidence that the oligaemia is caused by vasoconstriction. Prolonged major arterial constriction would result in infarction far more commonly than is reported. Regional CBF changes are also often bilateral during the attack when the pain is unilateral. Although visual cortical symptoms dominate the aura and are commonly bilateral the oligaemic phase seen with CBF monitoring is usually found mainly in part of one occipital lobe and spreads anteriorly across anatomical arterial territories rather than

across the midline. Headache and focal symptoms may occur on the same side. There are therefore many inconsistencies between the distribution of symptoms and the observed changes in rCBF - the symptoms are not adequately explained by sequential constriction and dilatation of major arterial trunks. (49)

Blau re-examined the vascular hypothesis of migraine by looking in turn at each phase of the attack. He concluded that:

(1) prodrome - this was not explicable on a vascular basis.

(2) aura - (i) the gradual spread of the visual or other sensory auras taking 10-30 minutes is not seen in cerebrovascular disease.

(ii) the slow progression of sensory symptoms would require sequential spasm of successive branches on the posterior aspect of the middle cerebral artery without altering the blood supply anteriorly. This is untenable.

(iii) migrating teichopsiae are not explicable on the basis of vasospasm or ischaemia.

(iv) arteriographic evidence obtained during migraine attacks is conflicting.

(3) headache phase - this has both vascular and neurological symptoms.

(4) sleep resolution - this, plus drowsiness and yawning in the prodrome and during the headache phase, implies a neurological substratum to migraine. (53)

7.2 Neural hypothesis

According to the neural hypothesis migraine is caused by a primary

disturbance of brain function. This is the periodic derangement of function called a 'nerve-storm' by Liveing (1873). From then till relatively recently, however, the concept of a primary cerebral cause for the condition has been neglected.

Evidence for the neural hypothesis:

(1) The clustering of patients attacks suggests a basic rhythmicity of a central threshold which falls for a time allowing the attacks to emerge and then rises with consequent remission. Both Pearce and Blau have suggested the hypothalamus as the initiating site for the condition.

A periodic disturbance of hypothalamic activity could acount for the periodicity of migraine attacks, and could also be related to emotional disturbances mediated by pathways from the limbic system to the hypothalamus. An instability of central control might be inherited in a similar way to the low convulsive threshold found in familial idiopathic epilepsy. (54)

(2) Altered neuronal metabolism causes changes in calibre in the microcirculation rather than the other way round. (49)

(3) The oligaemia demonstrated by rCBF studies does not correlate temporally with the symptoms seen, nor is it confined to the distribution of the major cerebral arteries. (49)

(4) An analogy can be drawn between between migraine and epilepsy. The sensory symptoms of both can be qualitatively similar as can the psychic phenomena of Hughlings Jackson's dreamy state, metamorphopsia, language

disorders and vegetative symptoms of mood and appetite. The disorders co-exist in a greater number of patients than expected by chance. The much briefer duration of symptoms in epilepsy and their abrupt onset separate the two conditions clinically but epilepsy occurs in 2-11% of migraine patients. In some patients epilepsy ceases ter many years and is replaced by migraine; in others the reverse occurs. An excess of migraine is also seen in families of epileptics. (49)

(5) Sleep is recognised as an integral part of the attack and a means of terminating it. The precipitating role of fatigue, excitement and stress suggest a cerebral rather than a vascular basis. (55)

7.3 Conclusion

There is good evidence for a vascular aetiology in the headache phase of migraine. The origin of the prodromal symptoms and the aura is much more controversial. The correlation between oligaemia and these symptoms is poor - both anatomically and temporally. A neural basis for these preliminary symptoms and therefore for the initiation of migraine attacks could explain:

(i) the periodicity of migraine

(ii) similarities in the prodromal symptoms in migraine and epilepsy and the higher than expected frequency with which migraine and epilepsy are found together in the same patient.

(iii) the precipitation of attacks by fatigue and their resolution with sleep.

CHAPTER 8

Cerebral blood flow in migraine

The development of a safe biotechnology for the measurement of cerebral blood flow and the interest in vascular changes during migraine attacks have combined to allow dynamic studies in patient volunteers. These have produced interesting information about the link between vascular and neural dysfunction in migraine.

8.1 Physiology of cerebral vasoconstriction

Brain arterioles have a tremendous capacity for dilatation as illustrated by the autoregulatory response i.e. constancy of cerebral blood flow is maintained even when there is reduction of arterial pressure. Arterial blood flow can be dropped to about 60% of normal values before brain blood flow begins to decrease. The constancy of blood flow is maintained by progressive arteriolar dilatation. If blood pressure is further decreased blood flow also decreases but oxygen uptake and cerebral metabolism continues undisturbed because the brain can increase its extraction of oxygen. Finally when the brain can increase this no further a continued decrease in blood pressure results in impaired cerebral metabolism and function.

Initially only an increase in regional cerebral blood volume can be observed. As constriction increases and cerebral blood flow begins to fall measurements of rCBF are of value although sometimes difficult to interpret. In the final phase when rCBF and metabolism are reduced

measurements of rCBF are more reliable.

Brain blood flow is closely linked to metabolism which, in turn, is connected with cerebral function. Reduced function results in decreased metabolism and decreased CBF. It can be difficult to decide whether reduced CBF is due to vasospasm or is a natural adaptation to decreased function and reduced metabolic needs.

The criteria used to make this distinction are:-

(1) Reduced cerebral blood flow secondary to vasospasm is likely to be located within one or more regions of supplied by the large cerebral arteries.
(2) To elicit clinical symptoms vasospastic CBF reduction must be marked whereas a primary metabolic disturbance may cause symptoms with lesser CBF reduction.
(3) In an ischaemic area autoregulation is usually lost. Only severe ischaemia will result in abnormal reactivity to changes in arterial carbon dioxide pressure (PCO2). Normal regulation or different patterns of disturbance suggest non-ischaemic mechanisms.

8.2 Methods used to measure regional cerebral blood flow

(i) Intra-arterial injection of a γ-emitting diffusible tracer has been the most commonly used method. The main tracer has been ^{133}Xenon (^{133}Xe). A bolus of this inert, radioactive gas is delivered into one internal carotid artery. It is distributed to the carotid artery territory and immediate diffusion equilibrium is established. Wash-out of radioactivity is then followed by external stationary γ detectors.

The initial slope analysis (where the slope of the first 1-2 mins of the clearance curve is used for flow calculation) mainly represents flow in gray substance. Using initial slope analysis has the advantage that it is easier to maintain a steady state during the short measurement period. The spatial resolution of the method is not optimal, however, because it is two-dimensional. Only areas which receive tracer from the internal carotid artery can be studied and this usually excludes primary visual cortex. Compton scatter also smooths out differences between regions. The advantages are that a high count rate gives good measurement accuracy and allows measurements from many channels. Contamination from extracerebral tissues is almost non- existent and the input function is a true bolus delivery. The method has been more sensitive in exposing functional activation and deactivation than any other method except positron emission tomography (PET).

(ii) Inhalation or intravenous (iv) bolus injection of ^{133}Xe and external stationary detection.

The immediate advantage is the avoidance of carotid puncture. A problem with inhalation or IV injection is that most of the tracer is in the respiratory air since Xenon has a low affinity for blood. Protracted inhalation over a minute or two is necessary and thus tracer arrives gradually in the brain. This can be corrected for by computation but at the expense of increased uncertainty over the input function. Recirculation of ^{133}Xe is considerable and must be corrected for. Extracranial tissues are labelled, as well as brain, causing confusion and the count rate is much lower than with intra-arterial injection and therefore does not allow the use of a large number of detectors.

(iii) Inhalation of ^{133}Xe and single photon emission computerised tomography (SPECT)

When ^{133}Xe inhalation or IV injection is used, tomographic detection can reduce the problem of radiation from extracerebral tissues. It provides a three dimensional view and thus gives much better spatial resolution than external stationary detectors. It also visualises deep structures as well as cortex. However there are still problems with the input function, an unsatisfactory count rate and much Compton scatter. Overall whilst single photon emission tomography is superior to ^{133}Xe inhalation and stationary detectors, the cerebral cortex is still studied more accurately with intracarotid injection.

(iv) Positron emission tomography

This uses detection of very short-lived tracers emitting positrons. The technique gives rCBF as well as regional oxygen consumption, the oxygen extraction fraction and the determination of regional glucose metabolism. (56)

8.3 Studies of regional cerebral blood flow during migraine attacks

Skinhøj used intracarotid ^{133}Xe with 35 detectors in four patients, all of whom had classical migraine using the accepted diagnostic criteria (although this was not specified in the paper). All patients had reduced perfusion to a level critical for adequate oxygenation in some areas during the prodrome. Further studies on six patients during the headache

phase showed increased blood flow. No distinction was made between classical and common migraine and patients were not studied between attacks for comparison. (50)

Olesen et al examined rCBF in headache-free intervals and after the induction of a migraine attack with red wine. No significant focal or global reduction in cerebral blood flow was found at either time. All six patients had common migraine. Three different techniques were used in the study. Although induced attacks were clinically identical with spontaneous migraines, this does not necessarily imply that the underlying physiological changes were the same. (19)

Lauritzen & Olesen used the ^{133}Xe inhalation method combined with single photon emission tomography. Twelve patients had common and 11 patients had classical migraine. During migraine attacks all patients with common migraine had normal rCBF whereas most patients with classical migraine had unilateral hypoperfusion. There was a focal decrease in blood flow of 17% on average compared to the symmetrical contralateral region. The low flow regions were always on the side opposite to the focal neurological symptoms. They persisted through the headache period for 4-6 hours. Regions of relative or absolute hyperaemia were not seen and between attacks rCBF was normal for both groups. (57)

In a further study of the regulation of rCBF during and between migraine attacks the same group used intracarotid ^{133}Xe with 254 stationary detectors in 14 patients suffering from classical migraine. Nine patients had migraine attacks induced by the procedure and 4 were examined without an attack developing. The regulation of rCBF was

impaired during provoked migraine attacks and the abnormalities were confined to the hypoperfused areas. This suggested that a local factor underlay the oligaemia and the regulation abnormalities. Blood pressure autoregulation was preserved but there was a reduced response to hypocapnia and functional activation procedures. There was thus an uncoupling of function, metabolism and CBF. No abnormalities of brain blood flow or its regulation were found between attacks. Again these attacks were not spontaneous and the intracarotid technique can only ethically be used in patients for whom carotid arteriography is clinically indicated for diagnostic purposes - this was therefore a selected group. (58)

The 9 patients who developed a migraine during the procedure were examined by a series of rCBF studies at intervals of 5-10 minutes. A wave of reduced blood flow originating in the posterior part of the brain and spreading anteriorly was observed in eight of the nine patients. The oligaemia advanced at a speed of 2mm/min over the hemisphere, progressing anteriorly but not crossing the rolandic or sylvian sulcus. Typically the spreading oligaemia reached the primary sensorimotor area after symptoms from that area had begun and persisted there long after the focal symptoms had disappeared. The time course suggested that focal symptoms were not secondary to the oligaemia. (59)

Summary of data obtained from rCBF studies

(1) rCBF data strongly indicate that common migraine attacks are not preceded by or associated with focal or global alterations of CBF.

(2) There is agreement that CBF is focally or even globally reduced during the prodrome in classical migraine.

(3) Although older studies described hyperaemia during the headache phase of classical migraine more recent studies have found no change in blood flow.

(4) On balance the CBF studies do not at present support the vasospastic theory of migraine but rather indicate a gradual spread of disturbed function located in the cortex. (56)

As yet there are very few studies in migraine which use positron emission tomography. However Sachs et al have used this technique in a group of five migraine patients (a mixture of classical and common migraine) and found that in the preheadache phase induced migraine is associated with decreased regional cerebral glucose metabolism. This appeared to be the initial event and was compatible with a primary derangement of brain function. There was no difference in laterality and both classical and common migraine patients were affected. (60)

8.4 The relationship between regional cerebral blood flow changes and Leaõ's spreading depression

The results of the rCBF studies outlined have indicated that a primary disturbance of neuronal function is more likely to be the cause of cerebral blood flow changes than Wolff's vasospastic theory. The most probable source of this disturbance is the spreading depression (SD) of Leaõ - a slow-moving suppression of electrical activity that propagates

across the cortex at a rate of 2-5mm/min. It is a transient phenomenon which is accompanied by severe disruption of ion homeostasis, depolarisation of nerve cells and increased energy metabolism. (61)

During the prodromal phase in classical migraine visual, sensory or motor symptoms develop in a way which suggests an underlying disturbance in the brain moving slowly in the cerebral cortex. The process causes a transient 'dysfunction' (scotoma, anaesthesia or paralysis) often preceded by enhanced function (fortification spectra, paraesthesiae or twitching). Lashley described his own scintillations (zig-zag pattern) which began near the centre of vision and propagated to the periphery of the field followed by dimming in the zig-zag area (scotoma). He mapped the scintillation-scotoma at brief intervals. The disturbances were symmetrically placed in the visual fields indicating a cortical origin for the symptoms. He calculated that they were caused by a process moving at 3mm/min in the visual cortex. Leaõ himself connected spreading depression with migraine without knowledge of Lashley's work. (61,62)

There is considerable uncertainty as to whether, and how, spreading depression could be initiated spontaneously in man. The three main candidates for the role of trigger factor are potassium ions, glutamate and neurotransmitters.

8.5 Neurotransmitter changes associated with Spreading Depression

A local increase in potassium ion concentration causes depolarisation of pre-synaptic terminals with the release of both excitatory and inhibitory transmitters. This leads to the opening of ion

channels in the post synaptic membrane which in turn causes an increase in potassium ions and a decrease in sodium, chloride and calcium ions analogous to the situation found in ischaemia. The diffusion of potassium ions to adjacent nerve cells leads to a repetition of the process. The ensuing recovery is an energy-requiring process which involves increased blood flow and local glucose metabolism. The brain cortex is refractory for a period after the passage of spreading depression possibly due to enhanced clearance of potassium ions. Attacks of classical migraine start most frequently in the visual cortex in the area corresponding to the macula where there is a very high neuronal density. This area is liable to have the greatest increase in potassium ion concentration when stimulated. Adequate light stimuli could increase the potassium ion concentration to the threshold for elicitation of spreading depression. It may be possible to condition the brain by exposing it to any agent which will evoke S.D. thereby lowering the threshold for it. (62)

8.6 Migraine, rCBF changes and Spreading Depression

Classic migraine attacks are initiated by a cortical spreading depression originating in the posterior part of the brain. The blood flow changes are not the prime event in migraine but are secondary to disturbed neuronal function.

The generation of pain in the head from intracranial sources requires activation of pain-sensitive fibres that are located on the ventral surface of the brain. SD may activate these fibres through changes in the extracellular fluid (high potassium ion concentration, low

pH) and thus produce pain. If this is so the latent period between the onset of the prodrome and headache may reflect the time it takes SD to propagate from the initiating site to the region where pain is triggered. Migraine headache would therefore be a specific response of pain-sensitive fibres to SD. The prodrome and headache could be separate effects of SD affecting different brain regions and this might explain the occurrence of different forms of migraine in the same patient. (61)

8.7 The hypoxic hypothesis

A patient suffers migraine attacks either because (s)he is more susceptible to the development of brain hypoxia for some reason and/or because s(he) reacts in an exaggerated or an abnormal manner to the presence of brain hypoxia.

There is some evidence that migraineurs may be more susceptible to hypoxia than other people. Subjects with a past history of migraine who are exposed to high altitudes simulated in a decompression chamber are much more susceptible to scotomata and subsequent headache than controls. The induction of migraine by cerebral angiography may also be a reaction to a transient reduction of oxygen availability to the brain shortly after the injection of contrast medium although this is not proven.

Hypoxia in the brain results from an imbalance between oxygen supply and oxygen consumption. The latter part of this equation receives little attention in the vasospastic theory.

Factors involved in decreased oxygen supply

(a) Evidence of vasospasm is scarce although it is difficult to exclude the role of diffusely decreased cerebral blood flow.

(b) The potential role of biogenic blood-borne constrictors depends on disruption of the blood-brain-barrier. The most likely candidates are 5HT and catecholamines.

(c) Exogenous substances such as tyramine lower CBF via the release of norepinephrine.

(d) Autonomic nervous system overactivity, as shown by a persistent degree of vasoconstriction in headache-free intervals, indicates excessive sympathetic tone. Migraine sufferers may show a supersensitivity to adrenoceptor stimulation during attack-free intervals or at the time of the attack.

(e) Anterio-venous shunting - there is no evidence that these shunts are involved in the initiation of an attack. If shunting is secondary to the migraine attack it may be caused by a sudden drop in blood levels of 5HT at the beginning of the headache phase.

(f) Reduced CBF without vasospasm. It is unlikely that the prodromal decrease in cerebral blood flow is enough to cause neurological symptoms due to ischaemia except in a small minority of cases.

Factors related to increased oxygen consumption

(i) Autonomic nervous system overactivity may not only affect cerebral blood flow but may also activate brain metabolism.

(ii) REM sleep increases brain metabolism and cerebral blood flow in normal subjects. Migraine on waking often occurs after arousal from a REM sleep period.

(iii) Stress is accompanied by a rise in cerebral oxygen consumption. This correlates with increased activity in cerebral catecholaminergic pathways.

(iv) Psychological factors and precipitants. Migraineurs have been described as having a continuous undercurrent of emotional activity and as being stress-prone, perhaps because they tend to be rather perfectionistic and success-orientated. Psychological preludes to the migraine attack include changes in mood and behaviour which may originate from psychological conflict.

(v) Use of drugs and exogenous substances. Reserpine can trigger migraine in susceptible individuals. The mechanism is suspected to be release of 5HT.

(vi) Spreading depression may be a consequence rather than a cause of brain hypoxia.

8.8 The relationship between the migraine attack and hypoxia

Biochemistry

(i) According to some studies 5HT is released during migraine attacks. It is also released into cerebral venous blood by hypoxia.

(ii) Catecholamines are also released during migraine but this has not been demonstrated in hypoxia.

(iii) Histamine, if involved at all, has only a local role. It is induced and/or released at the site of pain producing discomfort, venous engorgement and oedema.

(iv) Kinins - these act as vasodilators and increase permeability. They are algesics, release prostaglandins and cause vasodilatation and increased peripheral blood flow.

(v) ATP and adenosine. Hypoxia causes a decrease in cortical ATP.

(vi) Prostaglandins - these affect CBF but whether or not they are released in migraine and hypoxia is uncertain.

(vii) Substance P - this appears to have a nociceptive function, may increase CBF and is a potent histamine liberator.

(viii) Ions - cerebral hypoxia causes increased acidity and brain ischaemia releases potassium ions into the extracellular space. Both

hydrogen and potassium ions increase cerebral blood flow.

(ix) Free fatty acid concentrations increase in plasma during migraine.

Haemodynamic Changes

(1) The increased cerebral blood flow seen during the headache phase may be explained by biochemical changes induced by hypoxia.

(2) There may or may not be opening of arterio-venous anastomoses in migraine. This could be indirectly related to hypoxia via the action of 5HT.

(3) Marked changes in platelet behaviour have been observed during the migraine attack.

(i) Serotonin uptake is reduced although this is not the case in the headache-free interval.

(ii) Platelet adhesiveness and aggregation are increased during the aura but aggregation is reported to decrease subsequently whereas increased adhesiveness is maintained. Some authors have also found increased aggregability in the headache-free interval.

Brain ischaemia induces the aggregation of platelets and in the acute stage of stroke there is a decrease in 5HT and adenosine triphosphate (ATP) content in platelets. All the platelet changes seen in migraine may be due to hypoxia.

In summary, according to this hypothesis brain hypoxia occurs in every attack of migraine. Whether this becomes manifest as neurovisual phenomena depends on the severity of the hypoxia and the site at which it occurs. It is likely that excess sympathetic drive with simultaneous activation of brain metabolism and decreased oxygen supply is the underlying mechanism in the majority of patients. This hypothesis does not explain the unilateral nature of migraine in many patients, although it has been suggested that cerebral asymmetry renders some areas of the brain more liable to hypoxia than others. (63)

8.9 Migraine, cerebral ischaemia and infarction

Approximately two thirds of the patients with benign headache referred to a neurologist are afraid that they may have some serious intracranial disease such as a brain tumour or impending cerebral haemorrhage. Those most likely to be worried are women who have more than two headaches per week and have had them for less than two years. Patients with tension headaches are slightly more concerned about this than patients with migraine. The majority of these patients do not have psychiatric symptoms although both anxiety and depression, where present, do predispose to worries about serious illness. (64)

Feré (1881) cited Charcot as saying that any of the transient neurological disturbances seen in migraine could become permanent. He also suggested (1883) that vasospasm in migraine could cause vascular occlusion.

Galezowski (1882) reported four patients with permanent visual defects associated with migraine. In the next 70 years only another 13 cases were described. (65)

The rarity of descriptions of persistent neurological dysfunction after migraine episodes has contributed to the view generally held by physicians that migraine is a benign condition. However there is evidence that for a small proportion of patients, this is not the case.

A comparison has been drawn between classical migraine and reversible focal cerebral ischaemic events (TIAs) and between complicated migraine and stroke. Headache is frequently reported in the history of transient ischaemic attack (TIA) and stroke patients. However the visual, sensory and motor disturbances are much shorter in TIA (1-5 mins) than in classical migraine (15-60min) and the latter also show an orderly build up and 'march'. This pattern, and the rCBF data from studies of patients with classical migraine, both suggest that the neurological symptoms in migraine are not caused by cerebral ischaemia. It seems likely therefore that TIA and classical migraine are pathophysiologically different. (66)

However persistent neurological defects do occur although their incidence is uncertain.

In the first 2 years of the Oxfordshire Community Stroke Project 323 cases of first-ever stroke were registered. Of these 244 had cerebral infarctions. There was a past history of migraine in 17% of the total group and 18% of the patients with cerebral infarction. This is

approximately equivalent to the incidence of migraine in the general population. There was a trend towards a past history of classical migraine in the cerebral infarction group although this was not statistically significant.

The presence of other risk factors makes it very difficult to decide how much migraine has contributed to the pathogenesis of stroke in an individual. There was a high prevalence of risk factors (e.g. hypertension and artheriosclerotic disease) in patients with and without a history of migraine (75% and 70% respectively). This high prevalence was consistent with the results of other studies. The proportion of cerebral infarction directly attributable to migraine has been reported at between 2% and 20%. It is often not easy to decide what defines 'directly attributable'. Possibly only patients with no risk factors other than migraine should be described as having migrainous cerebral infarctions. In this study 7 patients in total were presumed to have migrainous infarctions (an incidence of 3.36 per 100,000 of the population per year). Only 3 of these 7 had no risk factors other than migraine. (In this case the incidence would be 1.44 per 100,000 of the population per year). However as migraine is a common condition this means a substantial number of new cases per year posing a considerable burden on health service resources (67).

Conner (1962) described 18 patients who attended the neurology department at Cardiff Royal Infirmary between 1953 and 1961. In nine patients a lesion developed during the migraine attack and in nine patients there was preceding temporary loss of function in the parts which were eventually permanently damaged. Five patients had retinal

lesions, ten had lesions of the hemisphere and three had lesions in the brainstem. The age incidence of this series was well below the usual age of onset for cerebrovascular disease. (No patient was aged over 50 when first seen and 12 of the 18 were aged under 40.) (65)

An unexpectedly high incidence of CAT scan abnormalities has been found in patients with severe migraine and some of these appear to be old cerebral infarcts.

Dorfman et al (1979) reported on four patients with classical migraine who all developed cerebral infarctions. In two of the patients this was preceded by a typical attack. The criteria used to diagnose infarction were two or more of the following:
(1) acute onset with previously normal examination in the affected area,
(2) a circumscribed zone of decreased density with or without a defect in the blood brain barrier (as shown by contrast enhancement),
(3) relatively little mass effect or oedema in the acute phase,
(4) resolution of the lesion in weeks or months leaving an area of lucency or a normal examination.

The CAT scan abnormality was not always immediately apparent and these patients needed to have complete examinations with or without contrast enhancement, with a repeat examination after several days (if the first examination was normal) in order to detect all abnormalities. These patients all eventually made good recoveries probably due to their youth and general good health. (68)

All patients in Dorfman's series and 12 of the patients in Connor's

had cerebral angiography to exclude significant vascular malformation.

Featherstone (1986) identified 64 cases of stroke which were related to migraine in a literature review which attempted to define a characteristic syndrome. His definition of stroke was arbitary, the data available was often incomplete and there was no control group. Nevertheless the findings were interesting. In 29 out of 40 cases the stroke was associated with an increase in the frequency or intensity of the migraine. In 4 cases there was no headache prior to the stroke. In 20 out of 31 cases onset was sudden and of these 20 patients more than one third had had recent transient neurological symptoms. Cerebral angiography was abnormal in 23 out of 41 cases. Outcome data was reported for 44 out of the 64 cases. Three patients died. Almost half the remaining patients made complete or almost complete recoveries. An age of more than 40, gradual onset of the stroke, or onset of the stroke on awakening, and occlusion of the posterior cerebral artery decreased the chance of complete recovery. Sudden onset increased the risk of death but improved the prognosis in survivors.

The typical patient was a young adult who had previously had classic or complicated migraine, noted an increase in the severity of headaches prior to the stroke and had a homonymous hemianopia with or without a hemiplegia after it. This was consistent with a thrombo-embolic process. (69)

Several factors may predispose migraine patients to infarction: (i) There is epidemiologic evidence of an association between migraine, hypertension and heart disease. The frequency of hypertension is

estimated to be 1.7 times greater in people with migraine than in those without. The risk of myocardial infarction is also increased for people with migraine and this is most evident below the age of 70 years. For both sexes people with migraine tend to die at younger ages than people without. (70) This study does not show any appreciable increase in the risk of stroke although the Collaborative Group for the Study of Stroke in Young Women has reported that a history of migraine increases the likelihood of both ischaemic and haemorrhagic stroke. (66)

(ii) Prodromal arterial spasm may decrease rCBF below the critical level for tissue viability and this could be compounded during the headache phase by diversion of blood into dilated extracranial vessels.

(iii) Abnormalities of platelet function may increase the susceptibility to vascular occlusion.

8.10 Migraine, mood change and rCBF

There are extensive clinical descriptions of migraine in the literature and textbooks frequently quote a figure of approximately 10% for the occurence of affective concomitants. These are generally:

(1) elated and irritable prodromal states,

(2) prostration, dejection, dread and serious depression accompanying the heachache,

(3) euphoric rebound.

They are usually of short duration, lasting from a few hours to 2-3 days at most. Less commonly severe migraine auras may be accompanied by sudden eruptions of overwhelming 'forced' affect. This rarely occurs during every attack but most patients with severe auras experience it occasionally. The reaction may vary from mild pleasure to rapture or

from strangeness to intense terror. The following features are characteristic: (1) sudden onset, (2) apparent sourcelessness and frequent incongruity of the mood, (3) an overwhelming quality, (4) a sense of passivity and the affect being 'forced' into the mind, (5) brief duration (the feelings rarely last more than a few minutes), (6) a sense of stillness and timelessness and (7) difficulty or impossibility of adequate description.

It is likely that alterations in higher cerebral function occur in the majority of migraine auras but go unnoticed because of their subtlety or strangeness or because the patient was not involved in any intricate intellectual or emotional activity at the time. There are four main categories of disturbance:

(1) complex disorders of visual perception,

(2) apraxic and agnosic symptoms,

(3) states of double or multiple consciousness, often associated with feelings of déjà vu or jamais vu and other disorders of time-perception,

(4) elaborate dreamy, nightmarish, or trance-like states.

In addition patients who have previously suffered from both classical and common migraine may later present with affective 'migrainous equivalents' which resemble truncated manic-depressive cycles, being distinguished from manic depressive illness principally by their brevity. (6,7,71)

Surprisingly there is remarkably little literature on this aspect of migraine other than textbook statements which are based on extensive anecdotal clinical observation. There have only been three studies which

attempted to correlate self-ratings of mood with migraine.

Dalkvist et al (1983) obtained twice daily ratings on five mood dimensions from five patients with migraine and 6 patients with muscle contraction headache for a mean period of just over six weeks. All the migraine patients had the common form of the condition. The patients were given visual analogue scales which covered four bipolar dimensions (calm-nervous, drowsy-alert, sad-happy and unconcentrated-concentrated) and two unipolar dimensions (anger and headache). A time-dependent relationship was found between migraine and alertness. Patients were more alert before attacks and less alert during them. No other mood changes were found - either because the scales were not sensitive enough to pick them up or because alertness was the only emotional state related to the migraine. However, it is unsurprising that patients should feel less alert during a debilitating and unpleasant experience. This may explain why the same finding was encountered in the muscle-contraction headache group although there was also a time-dependent relationship with anger in these patients. No support was obtained for a positive relationship between muscle contraction headache and anxiety. (72)

Harrigan et al (1984) recorded 10 mood indicators three times daily in 17 migraine sufferers over periods from 21 to 75 days. Headaches were correlated with mood states during the headache and for periods ranging from 12-36 hours prior to the headache. The patients were a mixed group of classical and common migraine sufferers. The authors found that some mood states were more strongly correlated with migraine than others and that changes in mood were also correlated with subsequent headaches. Feeling of constraint and fatigue were the best predictors of headache.

The migraine patients had less mood variability than has been found in other studies possibly indicating a narrowed range of perceived personal affect and a high degree of control over emotion. Migraineurs may have a unique mood profile characterised by generally suppressed moods with minimal variability. (73)

Heuser (1986) hypothesised, on the basis of previous work by Tunis and Wolff, that there might be vascular instability in the 3 day period preceeding a migraine attack. He used the Hassles Scale - a retrospective questionnaire - to assess the amount of stress each migraineur perceived him/herself as experiencing over the previous month and a set of rating scales to fill prospectively in over the following month three times daily. These scales covered migraine symptoms, stressful events, emotional states and physical activity. Thirty-three patients were involved - 20 with common migraine, 8 with classical migraine and 5 with equivocal neurological symptoms. Twenty- four patients also had muscle contraction headache in addition to their migraine. The data from the rating scales were then analysed for the first day of an attack and the preceding three days and the results compared with headache-free periods. Migraineurs as a group reported the same level of stress as normals. However they did report more stressful events and less physical activity in the 4 day period leading up to the onset of an attack. This could be explained in two ways - either there is a critical threshold for stress beyond which a migraine attack is precipitated or there is increased sensitivity or reduced tolerance to stress just prior to attacks, possibly as an expression of an underlying pathogenetic mechanism. (74)

From a clinical point of view a highly significant association ($p<0.001$) has been found between an increasing number of definite neurological symptoms (paresis, sensory loss, speech disturbance and loss of consciousness) and increasing depression as measured by the Zung Self Rating Depression Scale. The neurological symptoms are part of the aura and prodrome of classical migraine and as such are linked to the cerebral blood flow changes described above. (75)

Cerebral blood flow abnormalities have also been found in affective disorder, although as this is a condition which is episodic, progresses rapidly and responds to medication it is difficult to identify consistent patterns of metabolic change. (76)

The occurrence of mood changes following brain lesions has suggested regional brain abnormalities in patients with disorders of affect. Results obtained with normal subjects indicates differential hemispheric involvement in emotional processing. Damage to the left hemisphere is associated with dysphoric mood whereas lesions of the right hemisphere are associated with euphoria and indifference. It has been suggested, on the basis of studies of patients following hemispherectomy, that dysphoric mood is associated with right hemispheric activation or left hemispheric inactivation.

Using ^{133}Xe inhalation with 13 patients meeting Research Diagnostic Criteria (RDC) for depression, gray matter flow has been found to be lower in more severely depressed patients. In addition negative correlations have been reported between regional cerebral blood flow and the scores on the Hamilton Rating Scale of depression. The bilateral

hemispheric reduction in blood flow has been compared to that seen in conditions where there is loss of brain tissue such as Alzheimer's disease. Symptoms of cognitive dysfunction, such as attention, concentration and memory defects suggestive of mild diffuse organic dysfunction are frequent accompaniments of depression. As regional cerebral blood flow has been shown to reflect levels of neural activity and areas of increased neural metabolism have been associated with regional cerebral vasodilation, the decreased regional cerebral blood flow found in depression suggests neural hypoactivity. (77)

In another study using the same diagnostic criteria in 16 primary, major depressives dexamethasone suppression test (DST) results were correlated with rCBF changes. Non-suppressors had normal rCBF patterns whereas suppressors showed right posterior hypovascularisation and left frontal hypervascularisation. (78)

Gur et al (1984) found no differences in rCBF between 14 depressed patients (RDC criteria again) and normal subjects at rest although differences were seen during cognitive activation. Depressed men had lower rCBF which increased to normal during cognitive activation. Depressed women had higher resting flows than normal women and their flows remained higher during cognitive activation. When these results were compared with earlier work in schizophrenics the findings were consistent with left hemisphere overactivity in schizophrenia but not with right hemisphere overactivation in depression. (79) The lack of consistency with Mathews work (77) may be due to the fact that the former author did not use rCBF values corrected for pCO_2.

There are, as yet, few studies of affective disorder using positron emission tomography. However Buchsbaum et al (1984) used this technique to investigate the three main regional hypotheses in the major psychoses: frontal, temporal and lateralised cerebral dysfunction. Sixteen patients with schizophrenia and 11 patients with affective disorder (Diagnostic Statistical Manual (III) Criteria) were compared with 20 age- and sex-matched controls. All affective disorder patients were depressed and, with one exception, were unipolar depressives. Both normal subjects and patients showed a significant anteroposterior gradient in glucose use with highest values most anteriorly. This gradient was less in both groups of psychiatric disorder when in controls. It was thought to reflect a greater balance of activity in frontal areas responsible for planning of goal-directed behaviour than in posterior sensory-processing areas. This may also be associated with some diffuse system projecting to the cortex e.g. the noradrenergic projections of the locus caeruleus. (80)

CHAPTER 9

Neurotransmitter involvement in migraine and affective disorder

9.1 Neurogenic control of cerebral circulation

The cerebral vasculature is complex and originates from both the vertebral and carotid systems. There are both intracranial and extracranial vessels: the former are composed of the large vessels of the Circle of Willis and small pial vessels on the surface of the brain as well as a network of intracerebral vessels. The cerebral vascular neuromuscular apparatus consists of a varicose perivascular nerve plexus at the adventitial-medial border and smooth muscle cells in the medial coat. The nerve plexus and the smooth muscle cells are functionally connected. (81)

The initial fall in cerebral blood flow during the migraine prodrome may be triggered by a number of factors e.g.

(a) excessive release of noradrenaline from sympathetic vasomotor nerves,
(b) dietary factors,
(c) serotonin,
(d) histamine,
(e) prostaglandins,
(f) hypoglycaemia,
(g) changes in noradrenaline turnover,
(h) inefficiency or failure of non-adrenergic vasodilator mechanisms,
(i) hyperactivity of circulating vasoconstrictor agents or metabolic products.

Multiple factors are probably involved.

The reactive hyperaemia during the headache is thought to involve purine nucleotides and nucleosides, release of substance P from sensory nerve collaterals and secondary release of local agents such as prostanoids, histamine and bradykinin. (82)

9.2 Classical neurotransmitters

Noradrenaline

The superior cervical ganglia and the locus coeruleus supply the cerebral blood vessels with noradrenergic neurones. The sympathetic supply of vessels in the carotid system is more extensive than that in the vertebral system. The sympathetic nervous system may influence the function of the blood-brain barrier, possibly via direct control of the capillary wall. Noradrenaline constricts the cerebral arteries causing a reduction in local blood flow through α-adrenoceptor stimulation. α-adrenoceptors also mediate vasodilation in isolated brain vessels. In a study of 10 classic and 8 common migraine patients plasma noradrenaline concentrations were lower in both groups than in a control group. Patients with migraine had decreased sympathetic function even during headache-free intervals. Biphasic changes in the diameter of cerebral blood vessels during a migraine attack may depend on an equilibrium between noradrenergic deficiency and denervation hypersensitivity. (83)

Acetylcholine

Acetylcholine-containing fibres supply the extracerebral arteries and the Circle of Willis where they produce vasoconstriction.

Acetylcholine and noradrenaline may reciprocally modulate each other's release.

9.3 Non-adrenergic, non-cholinergic transmitters

Dopamine

Dopamine acts centrally and peripherally on α- and β-adrenoceptors and specific dopamine receptors. It has a hypotensive effect which is due to vasodilation. This vasodilation is caused by a direct effect on smooth muscle and an indirect effect on the sympathetic nervous system.

Domperidone is a dopamine receptor blocker which does not cross the blood-brain barrier. It can prevent most classical migraine attacks if taken at the beginning of the prodromal period. This is only successful if the medication is taken six hours or more before the expected onset of the pain. One possible explanation for this is that the dopaminergic system is over-reactive in migraineurs. (84) Dopamine is a mediator in the nociceptive system. (85,86) Migraine patients are more sensitive than normal subjects to the emetic effects of L-DOPA and apomorphine (both dopamine receptor agonists). The nausea and vomiting which are part of the migraine syndrome may be due to acute

hypersensitivity of peripheral postsynaptic dopamine receptors. Chronic dopamine deficiency would predispose to this.

Infusion of piribedil, which is a direct dopamine agonist, has been used as a diagnostic test for migraine. Piribedil produced more neurovegetative disorder and a greater change in pulse and blood pressure in headache sufferers than normal controls. The test differentiated best between migraine and cluster headache. However the results overlapped and did not clearly distinguish between different types of headache. There was some evidence for dysfunction of the dopaminergic system in migraine. (85)

In idiopathic headache haloperidol, a specific dopamine antagonist, has been reported to decrease venospasm and improve headache. (Unfortunately no definition of idiopathic headache was given in this paper.) However chronic use of haloperidol causes depression in 20% of patients after 2-4 months. This subsides spontaneously 1-2 months after treatment is stopped. This may be related to a pre-existing dopamine deficiency. (86)

Serotonin (5-HT)

5-HT has a variety of effects at all levels of the cerebral circulation:

(1) vasoconstriction of the major cerebral arteries,

(2) arteriolar vasoconstriction and vasodilation,

(3) modification of cerebral capillary transfer leading to changes in the blood-brain barrier,

(4) induction of cerebral oligaemia when in direct contact with neural tissue.

The last of the above is probably secondary to 5-HT induced depression of cerebral metabolism. There is an endogenous 5-HT-containing system which innervates brain vessels. This could be the anatomical basis of a link between brain function and cerebral blood flow. (87)

5-HT uptake, release and storage are all disturbed in classical migraine. (87,88) Total plasma 5-HT levels are raised prior to the migraine attack at the same time as cerebral blood flow is decreased. (87) In the headache phase plasma 5-HT concentrations decrease and there is increased excretion of 5-hydroxy-indolacetic acid (5-HIAA), a major metabolite of 5-HT.

Platelets store all the 5-HT in the blood. Platelets have been used as models of monoaminergic function and as such they have been extensively studied in migraine. Unfortunately the results of these studies have often been conflicting. The contradictions may be due to the following: (1) different types of migraine which differ physiologically, (2) the unpredictable nature of the attack, (3) the effects of treatments, (4) the use of unstandardised methods.

Hanington (1986) has pointed out that there is a considerable amount of circumstantial evidence that abnormal platelet behaviour is the primary cause of migraine. However she does not differentiate between classical and common migraine. (89)

Most of the evidence supports the view that the changes in platelet

5-HT metabolism in common migraine are due to plasmatic factors and not due to a primary platelet defect. (90,91) By contrast, patients with classical migraine have significantly increased platelet aggregation and adhesion. An increased number of platelet aggregates in the circulation could play a primary role in producing the prodromal symptoms of migraine. In addition, although platelet 5-HT concentrations are rapidly restored to pre-headache levels after an attack of classical migraine, in one study the release of 5-HT from the platelets was significantly reduced for at least three days after an attack. This may correspond with the refractory period after an attack during which further attacks do not occur. (92) However other studies have found no differences between the binding characteristics of platelet 5-HT receptors or α_2 adrenoceptors in classical migraine patients compared to controls. Therefore increased platelet aggregation with 5-HT and adrenaline may not be due to a primary platelet receptor change.

There is a significant reduction in tritiated ^{3}H-imipramine binding sites in classical migraineurs between attacks compared with controls. ^{3}H-imipramine binding sites are closely associated with 5-HT uptake sites. The uptake of 5-HT by platelets from patients with migraine is reduced between, during and after attacks of migraine. The reduced platelet 5-HT uptake in migraineurs may thus be partially due to a reduced number of platelet 5-HT uptake sites. The reduction in ^{3}H-imipramine binding capacity is independent of the time interval since the last migraine attack and may reflect a predisposition to attacks rather than being a consequence of them. The female predominance in migraine may be related to the fact that women have lower control values for ^{3}H-imipramine binding capacity than men. Classical migraine may be primarily

a brain disorder with secondary vascular changes.

In depressive illness platelet 5-HT uptake is also reduced and ^{3}H- imipramine binding sites are reduced in both platelets and brain. By analogy the decrease in ^{3}H-imipramine binding sites in the platelets of classical migraineurs may reflect changes in ^{3}H-imipramine binding sites in the brain. (93)

The platelet aggregation and release of endogenous platelet amines which occurs early in migraine could lead to altered permeability and diameter of blood vessels. This would contribute to the pain and neurological deficits. The platelets could, therefore, be the link between the systemic circulation and the central nervous system.

There are several small brain sites without a blood-brain barrier which receive a fenestrated capillary blood supply. This provides a route for the diffusion of substances from the systemic circulation into the brain close to the circumventricular organs. The vegetative symptoms associated with migraine are:-

(1) nausea and vomiting,

(2) mood changes,

(3) thirst,

(4) oliguria,

(5) vasomotor instability.

These symptoms are very similar to the known functions of the circumventricular organs - the median eminence acts as a neuroendocrine transducer in hypothalamic/pituitary regulation, the area postrema is the

most potent CNS vomiting centre and the subfornical organ and the vascular organ of the lamina terminalis are involved in thirst and fluid balance. These organs would be particularly susceptible to changes in 5-HT and catecholamines in the systemic circulation. Changes in 5-HT and catecholamine levels and dietary factors could produce the vegetative symptoms of migraine through their entry into the central nervous system via this fenestrated capillary blood supply and their effect on the circumventricular organs. (94)

5-HT containing neurones are located in the raphe nuclei of the medulla, pons, midbrain and centromedial reticular formation. They have widespread connections with the anterior and posterior horns of the spinal cord, the interomediolateral column, the ventral tegmentum, hypothalamus, amygdaloid nuclei and cingulate gyrus. Projections from the brain stem nuclei on to the neurones of the posterior horns of the spinal cord regulate the transmission of pain impulses at that level. Increased activity of 5- HT fibres leads to decreased pain perception and vice versa. 5-HT D receptors mediate vasoconstriction and are blocked by 5-HT antagonists e.g. methysergide, pizotifen, propranolol and amitriptyline. 5-HT M receptors mediate pain and are blocked by morphine, propranolol and metoclopramide. (94) Sicuteri has proposed that, in migraine, a deficiency of 5-HT leads to abnormal perception of pain in sensitive areas such as the head. Chronic deficiency produces a state of supersensitivity. The basic lesion in migraine is thus a genetically determined defect in the biochemical mechanisms underlying the experience of pain. It is unlikely that this would only affect pain and it would probably also involve other appreciative systems such as those involved in mood and sleep.

Ischaemia associated with the migraine prodrome may alter CNS 5-HT metabolism. This could lead to increased pain sensitivity. In animal studies arterial occlusion of the cerebral hemispheres causes depletion of 5-HT which may be maintained for long periods despite cerebral reperfusion. This has been attributed to early neuronal release and synthesis inhibition. Interestingly, there is also depletion of 5-HT in the contralateral non-occluded hemisphere, possibly due to diaschisis (a neurogenically-mediated influence on cerebral blood flow and metabolism in brain areas remote from the focal lesion.) (96)

Adenosine-5'-triphosphate (ATP)

There is growing evidence that adenosine and/or ATP, perhaps released from purinergic nerves, participates in the regulation of cerebral blood flow. Purine nucleosides have been collected in brain tissue and cerebrospinal fluid during ischaemic hyperaemia and hypoxia. Both ATP and adenosine produce dilatation of cerebral vessels. Adenosine may also play an indirect role in the control of cerebral vessels since it is a potent presynaptic inhibitor of the release of noradrenaline and acetyl-choline from adrenergic and cholinergic nerves respectively. Purines are released when there is reactive hyperaemia during the headache phase of migraine. These purines may be involved in headache production. (63,81)

Substance P

Substance P has been linked to the activity of the trigeminovascular

system in migraine. The trigeminal nerve fibres form part of an elaborate defensive network which protects the brain both against the entry of noxious substances from the circulation and damage from such substances within the CNS. In animals the trigeminal ganglia store substance P and 5-HT together. Substance P dilates pial arteries, increases vascular permeability and activates the cells which take part in the inflammatory response. Noxious substances stimulate the release of substance P which leads to the isolation, dilution and clearance of toxins before they have a chance to spread. The release of substance P and 5-HT together from trigeminal nerve endings may explain both the hemicranial pain and the vasodilation characteristic of the headache phase of migraine. (97,98)

Other neuropeptides such as Vasoactive Intestinal Polypeptide (VIP) and Neuropeptide Y have also been found in cerebral perivascular plexuses but, as yet, their function is unknown. (81)

9.4 Locally released agents

Agents which are released locally often as a secondary consequence of neurotransmitter activity are also involved in regulation of cerebral blood vessels.

Prostaglandins

These play a role in the normal physiological response of the circulation to hypercapnia and in the pathogenesis of cerebral spasm after haemorrhage. They are powerful presynaptic inhibitors of the

release of noradrenaline from sympathetic vasomotor nerves. They can be released from platelets and damaged blood vessels or due to the actions of ATP and bradykinin.

Endothelial derived relaxing factor (EDRF)-mediated responses

Acetyl choline, ATP, 5-HT and substance P can produce potent vasodilation via receptors in the endothelial cells lining the lumen of vessels. These endothelial cells also release EDRF. It has been suggested, but not proven, that the endothelial cells contain acetylcholine and ATP and that the release of these substances following damage to the endothelial cells during ischaemia contributes to a pathophysiological mechanism of vasodilatation which protects that segment of the vessel from further damage as well as protecting the brain cells from hypoxia. (81)

9.5 Neurotransmitter dysfunction in anxiety and depression

Anxiety

Pharmacological models of anxiety are based on drug-induced emotional changes which are reduced by anxiolytics. Although the chemical structures of anxiolytics such as benzodiazepines, barbiturates and ethanol vary considerably, all act at benzodiazepine receptor sites. These sites are made up of high affinity, stereospecific receptors for benzodiazepines coupled to a recognition site for γ-aminobutyric acid (GABA) and a chloride ionosphere. (99)

β-carboline - 3-carboxylic acid ethyl ester (β-CCE) is a high affinity benzodiazepine receptor ligand which has powerful behavioural and physiological actions which can be reversed by diazepam. This may provide a valid model for human anxiety. There are high densities of benzodiazepine receptors in the hippocampus and amygdala and anxiety can be induced by hippocampal stimulation. The dense telencephalic representation of the benzodiazepine system could produce fear and conflict on activation. The benzodiazepine receptor model suggests that there is an endogenous ligand for the benzodiazepine receptor. The level of endogenous ligand would correlate with inter-and intra-individual variations in anxiety and level of arousal or rate of habituation.

Diazepam binding inhibitor (DBI) is a neuropeptide found in the brain which displaces diazepam and β-CCE from their specific binding sites. The distribution of DBI-containing neurones may vary between different brain areas. It may be the precursor for a family of neuropeptides. Hormonal factors may be involved in the synthesis or degradation of DBI and it may, in turn, affect GABA-ergic regulation of pituitary hormone release.

The other main model for anxiety involves the noradrenergic system especially the α_2 adrenergic receptor. α_2 adrenergic receptor antagonists produce alarm and increase levels of MHPG (a metabolite of norepinephrine). The noradrenergic activity originates in the pons and is probably a different phenomenon from the emotion aroused by the benzodiazepine receptor system.

Both the benzodiazepine receptor system and the noradrenergic alarm

system may be activated together in some clinical states. (100)

There is preclinical evidence that alterations in serotonin function may be related to the development of anxiety and the therapeutic benefits of anxiolytic drugs.

Serotonin increases prolactin release and intravenous administration of tryptophan, a serotonin precursor, reliably increases serum prolactin levels. This can be used as a measure of central serotonin function. However the results of tryptophan infusion in 21 patients with agoraphobia with panic attacks and 2 patients with panic disorder (DSM-III criteria) failed to show any difference from the results in normal controls both before and after treatment with alprazolam (an anxiolytic). There was thus no support in this study for an involvement of serotonin in panic and anxiety disorders. Unfortunately interpretation of the results is complicated by the fact that 7 of the patients also concurrently met DSM-III criteria for major depression.

Similarities in phenomenology and response to treatment suggest that there is a link between panic disorder and major depression. The exact nature of this link is unknown. Studies of the mechanism of action of antipanic and antidepressant drugs suggest that antipanic effects may be primarily related to regulatory actions on noradrenergic function and antidepressant effects to an enhancement of serotonin function. Tricyclics and monoamine oxidase inhibitors, which have both antipanic and antidepressant properties, affect both brain serotoninergic and noradrenergic function. (101)

Depression

Both first and second generation antidepressant drugs enhance the availability of 5-HT and noradrenaline at central receptors. Long term administration of antidepressants affects monoaminergic systems both pre- and postsynaptically. This generally involves down regulation. Down-regulation of the postsynaptic receptor is usually associated with decreased function while down-regulation of presynaptic receptors is associated with increased function. At present it is believed that the net effect is β-adrenergic suppression and α-adrenergic and serotoninergic activation.

The traditional monoamine hypothesis of depression is of metabolic and functional deficiency of monoamines. Antidepressants would therefore enhance monoaminergic functions. However down-regulation of receptors suggests a second possibility. There may be monoaminergic hyperfunction and antidepressants could act by down-regulating postsynaptic amine receptors.

Serotonin (5-HT)

Biochemical research has provided evidence which suggests that 5-HT turnover in the CNS is decreased in a subgroup of about 45% of depressives. A subgroup of patients also have a reduced ratio of plasma concentrations of tryptophan to concentrations of competing amino acids. This could decrease the amount of tryptophan entering the CNS and therefore decrease 5-HT synthesis. It is not known whether these two subgroups are in fact one and the same.

The disturbed 5-HT uptake in platelets in depression is thought to correlate with the patient's clinical state. The reduced density of ^{3}H-imipramine receptors may be another index of abnormal cellular 5-HT reuptake. Monoamine receptor changes can persist for a considerable period after psychotropic drugs are discontinued.

5-HT disturbance is more likely to predispose to than to cause depression. It is not entirely specific to depression and is also found in 10% of normals, schizoaffective psychoses and chronic alcoholics who are abstinent. Nonetheless it is much commoner in severe depression and conditions closely related to it. It has been suggested that central 5-HT deficiency may contribute to the depressive states seen in alcoholics. Evidence of decreased CNS 5-HT turnover persists even after resolution of depressive illness. Studies of normal subjects indicate that decreased 5-HT turnover predisposes to depression and studies in depressed patients suggest that decreased 5-HT turnover is associated with an increased incidence of hospital admission and suicide. There is preliminary evidence that administration of 5-HT precursors has a prophylactic effect in depression especially in the group with lowered 5-HT turnover.

Noradrenaline

There is no conclusive evidence of noradrenaline disturbance in studies on the CNS. However peripheral studies of urinary 3-methoxy-4-hydroxyphenylglycol (MHPG) concentrations do indicate that these are decreased in depressions with endogenous features. MHPG is the principal CNS metabolite of noradrenaline. Sixty per cent of urinary MHPG is central

in origin and 24 hour urinary MHPG excretion can be used as a crude measure of noradrenaline degradation in the CNS. Noradrenaline is also thought to play a role in the hormonal disturbances found in depression, e.g. disorders of cortisol and thyrotropin releasing hormone secretion and altered growth hormone responses.

Dopamine

Chronic administration of antidepressants subsensitises presynaptic dopamine receptors and thus probably increases dopamine release. Dopamine metabolism is reduced in depression especially if there is marked motor retardation.

If patients differ in the type of catecholamine disturbance they experience they may respond preferentially to different types of antidepressant medication, e.g. patients with non-suppression in the dexamethasone suppression test (DST) are believed to respond best to noradrenaline-potentiating antidepressants whereas patients with a normal DST respond best to 5-HT-potentiating antidepressants.

Overall there appears to be more evidence in support of the traditional monoamine hypothesis that depression is associated with decreased CNS monoaminergic function rather than the alternative view that there is monoaaminergic hyperactivity. Activators of the monoaminergic system have an antidepressant effect and 5-HT synthesis inhibitors antagonise the effects of antidepressants. Catecholamine receptor blockers, e.g. the neuroleptics, are also inefficient antidepressants. (102)

9.6 Summary

As the common central mediators of CNS processes it is likely that neurotransmitters play a major role in the production of both migraine and affective disorders (e.g. anxiety and depression).

Changes in neuronal metabolism are tied in with changes in cerebral blood flow and this, in turn, is partly controlled by noradrenergic and serotoninergic systems.

Noradrenaline can influence the permeability of the blood-brain-barrier and can certainly constrict and possibly also dilate cerebral arteries. α_2 adrenoceptors also mediate the alarm response and thus participate in the production of anxiety. Plasma noradrenaline concentrations are decreased in both classical and common migraine and binary MHPG (a noradrenaline metabolite) is also decreased in endogenous depression.

It has been suggested that serotoninergic neurones may provide the link between brain function and blood flow. Platelet 5HT function is disturbed in migraine and depression with diminished numbers of ^3H imipramine receptors in both conditions. 5HT is also involved in the regulation of pain and is thus likely to be implicated in the close association between pain and depression.

In the present context it is difficult to do more than describe the similarities noted between some of the neurotransmitter disturbances in

migraine and affective disorders as there is insufficient information available to produce firm conclusions. Hopefully more sophisticated biotechnology will provide more definite date on the biochemical links between these conditions.

CHAPTER 10

Epilepsy as a model for migraine and recurrent affective disorder

10.1 The relationship between migraine and epilepsy

The extent of the relationship between migraine and epilepsy has caused considerable controversy.

Epilepsy affects approximately 0.5% of the general population. Figures given for the incidence of epilepsy in migraine patients have ranged from 1-11%. This is partly a consequence of the overlap between the symptomatology of migraine and epilepsy, e.g. both conditions may be preceded by auras and both may be associated with loss of consciousness. Nonetheless there is a higher incidence of epilepsy in unselected migraine sufferers than in the population as a whole. It is also significantly greater than the incidence in patients with tension headache. (103) There is also a slightly higher incidence of migraine in epileptics than in controls. Of the close relatives of epileptics about one third will be epileptic and one fifth will suffer from migraine. (104)

Slatter has suggested that there are four possible ways of explaining the association between migraine and epilepsy:

(i) the two conditions may occur independently in the same patient,

(ii) migraine can precipitate epilepsy in a predisposed patient,

(iii) a common focal structural lesion may be responsible for both conditions,

(iv) irreversible cerebral damage caused by migraine may rarely cause

local epileptic changes. (105)

10.2 EEG abnormalities in migraine

There is no difference between an undifferentiated group of headache sufferers and a headache-free population in terms of the extent of electroencephalogram (EEG) abnormality. However the incidence of EEG abnormality in migraine sufferers is doubled.

There are two categories of EEG disturbance in the migraine group:-
(a) the EEG in the headache-free periods shows a persistent non-focal abnormality. There is excessive, paroxysmal, diffusely occurring 4-7c.p.s. activity which may be related to epileptic phenomena
(b) focal EEG abnormalities:-
(i) brief alteration of the EEG during migraines with transient focal motor or sensory defects,
(ii) EEG abnormalities which develop when migraine is associated with deficits of motor, sensory or mental function and which disappear within hours or days concurrently with the resolution of the clinical signs,
(iii) EEGs taken during the headache-free period which show persistent focal abnormality and which usually occur in patients who have pronounced focal symptoms during their migraine attacks. (6)

Basser has hypothesised that 'there is a fundamental and intimate relation between migraine and epilepsy based on a process which has the characteristics of the spreading depression (SD) of Leao.'

Leaõ's work was originally done to investigate the

electrocorticogram in 'experimental epilepsy'. Leaõ concluded that S.D. and the 'tonic-clonic' activity of experimental cortical epilepsy were closely related. The spread of tonic-clonic responses was felt to be mediated by the same cortical elements which were involved in the spread of the depression. He considered that both processes were mainly cortical, their development and characteristics depending on the local conditions in the affected regions. In a subsequent paper Leao noted marked dilatation and increased blood flow in the pial vessels which was concomitant with, and secondary to, the electrical activity whether or not convulsive activity developed. He concluded that the increase in blood flow probably influenced the activity of cortical neurones.

The propagation of S.D. depends on the release of potassium ions and a high incidence of migraine has been noted in the families of patients with hypokalaemic periodic paralysis (a disorder of potassium metabolism). (103)

10.3 The relationship between epilepsy and affective disorder

Stress disorders (neurotic disorders) are commoner in people with epilepsy than in the general population. Reactions to the condition itself have to be discriminated from concurrent psychiatric disorder. Endogenous depression is also more common in epilepsy and there is a relationship, although not necessarily a direct one, between seizures and aggressive outbursts as both decrease in parallel.

Brief changes in mood ranging from elation to depression are well known in epilepsy and often described as 'dysphoric states'. Landolt

(1958) described them in association with 'forced normalisation' of the EEG or with a decline in attack frequency. They are similar to the prodromal affective symptoms occasionally seen in epileptic patients 2-3 days before the attack. The patient with prodromal affective symptoms is likely to have more prolonged affective changes if his attack frequency decreases. Likewise endogenous depressive episodes occur when the attack frequency is declining. These differ from ordinary depressive illness only in the rapidity with which they can come and go - occasionally the rapid switching in and out of depression suggests an ictal experience. Successful suicide is also more common in epileptics than in the general population. A significant correlation between dominant temporal lobe lesions and schizophrenia and non-dominant (usually right) temporal lobe lesions and depressive symptoms was found by both Flor-Henry and Lishman although these findings have not always been replicated in other studies. (106)

Reynolds (1861), Jackson (1879) and Gowers (1881) were all aware of ictal affective changes. Reynolds described fear and depression as manifestations of the epileptic process, Jackson wrote of 'the symptom fear' and Gowers of 'emotional auras'. The incidence of affective auras has been estimated at between 5% and 6.7%.

The pre-ictal phase is unusual in that the psychological disorders seen may be partly the cause of the subsequent epileptic attack or partly the result of the physiological disturbance which leads to the fit. Stress is frequently anecdotally implicated in the production of fits and increasing irritability and tension are often noted just prior to seizures in chronic epilepsy. The irritability and tension may be

manifestations of an underlying neurophysiological disturbance. (106)

Jackson has commented on the sequential alteration of affect which can occasionally occur with an initially pleasurable aura being replaced by one of depression after repeated seizures over a period of time.

Changes in affect produced by the epileptic discharge are diffuse and undifferentiated. There is a sudden welling-up of emotion inappropriate to the circumstances which may become integrated into the immediate environment. (107)

Depression is relatively rare as an ictal affect although interictal depression is not uncommon especially in temporal lobe epilepsy (T.L.E.). A transient episode of depression can be associated with the onset of an attack and may persist after it is over - possibly as a manifestation of the epileptic discharge.

By contrast pleasure is relatively common in TLE where it is often linked with visual hallucinations or perceptual changes. There have been several reported instances of ictal laughter. A sensation of pleasure can also occur with olfactory hallucinations. Autonomic upset (nausea, sweating and pallor) is almost universal.

The post-ictal period is the commonest time for episodic psychiatric disturbance. This can occur in both major and minor epilepsy. In the latter it is associated with an irregular, slow, often asymmetrical and low voltage EEG. This is thought to reflect lowered cortical control.

In addition to affective changes fits are frequently accompanied by:-

(i) intestinal motor and sensory phenomena,

(ii) vasomotor disturbances,

(iii) sudomotor phenomena.

The autonomic and visceral phenomena are associated with the fronto-temporal region and the mesial parasagittal region of the frontal lobes. It seems likely that the limbic system is involved and Herrick (1930) has suggested that the olfactory cortex is a non specific activator for all cortical activities. Affective change, vegetative phenomena and olfactory and gustatory sensations often occur together. (107,108)

The thalamus was initially thought to be the main site for the central mechanism of emotion. This view was criticised as being oversimplistic. Although thalamotomy did successfully relieve emotional states, relapses following surgery indicated the existence of additional mechanisms. (109) The importance of the autonomic nervous system in the translation of emotional distress into physical illness was recognised at an early stage. The hypothalamus was involved in the expression, whereas the cerebral cortex provided the experience, of emotion.

Papez implicated the limbic system and postulated that 'the central emotive process of cortical origin may ... be conceived as being built up in the hippocampal formation and as being transferred to the mammillary body and thence through the anterior thalamic nuclei to the cortex of the gyrus cinguli. The cortex of the cingular gyrus may be looked on as the receptive region for the experiencing of emotion .... Radiation of the emotive process from the gyrus cinguli to other regions in the cerebral

cortex would add emotional colouring to psychic processes.' (110)

Epileptic automatisms provide evidence that the hippocampal formation and associated structures are concerned in emotional experience. The automatism is a state of clouding of consciousness which occurs during or immediately after a seizure. Control of posture and muscle tone is retained and simple or complex movements can be performed without awareness. This is accompanied by continuous disturbance on the EEG.

Approximately 80% of automatisms are preceded by an aura consisting of epigastric sensations, confusion, memory difficulty, a feeling of strangeness or unreality, dizziness or mastication and salivation. There is usually total amnesia for the automatism.

The commonest cause is epilepsy involving medial temporal lobe structures. During neurosurgery electrical discharges from the medial and inferior temporal lobes have been recorded while automatisms are in progress. Stimulation of the amygdaloid nucleus and the uncus can provoke an automatism. These can also occur when focal pathology in the frontal region or cingulate cortex produces secondary activation of periamygdaloid hippocampal structures. (71) Patients with automatisms also commonly have severe emotional and psychological disturbances between seizures.

The hippocampal formation integrates olfactory, gustatory and other visceral sensation as well as auditory, visual and somaesthetic experiences. (111) This could provide a cortical control mechanism

for autonomic reflexes.

Alternatively there is close liaison between the prefrontal cortex and the limbic system. The prefrontal cortex is involved in anticipation and planning. The reticular system connects it with the limbic system. The association of the limbic system with emotion implicates the cortex in control of the autonomic nervous system. The hypothalamus - through its control over the sympathetic and parasympathetic parts of the autonomic nervous system - could be involved in the patterns of behaviour produced by emotional states. (112)

The temporal lobe and through it the limbic system are the brain regions most often involved when psychiatric disturbance occurs in epilepsy.

Weil commented on 'paroxysmal negative affects' associated with temporal lobe epilepsy. Depression is particularly related to seizures with olfactory auras. (113)

MacRae noted that 75% of epileptics who experienced anxiety, usually as part of the aura, had a temporal lobe focus. Ten per cent of cases of temporal lobe epilepsy had uncinate fits with déjà vu. The epileptic discharge in TLE may block the function of the limbic system resulting in both affective and autonomic changes (111)

An association has also been found between symptoms of psychomotor epilepsy and manic-depressive illness. In a small series of 12 consecutive patients with bipolar mood disorder (DSM-III criteria),

six had 5-6 symptoms of psychomotor epilepsy and five of these six patients had EEG abnormalities. However all patients responded to lithium carbonate and had a first degree relative with bipolar disorder. Although the selection of patients for this study was open to bias the results are interesting and suggest that further investigation of the association of TLE and manic-depressive illness would be worthwhile. (114)

10.4 Migraine and affective disorder

There is a variety of indirect evidence for an association between migraine and depression. Abnormalities of serotonin metabolism have been implicated in both conditions. Amitriptyline is effective both as an antidepressant and as a prophylactic in migraine. Reserpine precipitates headaches in migraine patients and depression in 20% of patients who use the drug regularly. Platelet monoamine oxidase is both low in migrainous and depressed patients. The symptoms of migraine and depression overlap and prevalence rates of 10-20% have been reported for depression in migraine sufferers. However a recent study by Garvey et al (1984) which examined the problem by looking at the lifetime migraine histories of patients with major depressive disorder found only a trend for depressed men, but not depressed women, to experience a higher prevalence of migraine. (115)

10.5 Limbic System Kindling

Limbic epilepsy is closely associated with personality changes and psychosis. Stimulation of the amygdalar region can trigger episodes of

rage and a chronic stimulatory lesion of the limbic system could be aetiologically related to the periodic dyscontrol syndrome. The proportion of psychotic patients with temporal lobe epilepsy is higher than that of the general population. The onset of the epilepsy precedes the onset of psychosis and the two conditions run parallel courses. The frequency of the seizures is the reciprocal of the psychotic episodes. (116)

The two halves of the limbic system operate together although the right and left sides have different functions. There may be subtle emotional distinctions depending on which side is involved in the epileptic process. Flor-Henry found that in limbic epilepsy with unilateral foci the resultant psychosis was schizophreniform if the dominant side was involved and affective if the focus was in the non dominant hemisphere.

The association between dominant hemisphere temporal lobe epilepsy and schizophrenia is stronger than that between non-dominant temporal lobe epilepsy and manic-depressive psychosis. Depression seems to be related to non-dominant frontotemporal dysfunction. When a neuropsychological test battery is used laterality effects are only apparent in severe dysfunction. These effects are stronger in frontal than in temporal regions. The strongest associations between diagnosis and lateralised disturbance are found in the frontal regions, are still evident in the temporal region but disappear in the parietal regions.

Power spectral analysis of the EEG shows bilateral but predominantly right temporal abnormalities in affective psychoses and predominantly

left temporal dysfunction in schizophrenics. There is also some evidence for a defect of interhemispheric integration. (117)

However although there is considerable evidence that the neural basis of psychiatric syndromes, particularly the functional psychoses, is largely in the limbic system whether this is influenced by cerebral asymmetry is more dubious. The studies published have been contradictory and the statistics used questionable. (118)

Kindling occurs when mild repetitive stimulation to the brain causes a progressive change in response which eventually leads to a major convulsion. The brain does not return to normal after repeated kindling but remains in a state of readiness and in some cases convulsions may start to occur spontaneously. The kindling effect results from neuronal activation. There are regional differences in responsiveness to it. The amygdala is the most receptive area. Kindling causes widespread neuronal changes - if stimulation is applied to a second area the kindling process is more rapid than it was the first time. Evoked potential studies have shown that changes in the brain are not limited to the seizure. Kindling can produce a lasting change in how normal activity is transmitted over specific neuronal pathways. The mechanism for this may be a selective increase in excitatory synapses biasing a particular region or set of synapses to become pathologically hyperexcitable. Specific anatomical pathways control specific behaviours. Activity within them may increase some behaviours and decrease others. If kindling selectively strengthened one set of pathways this could in turn cause behavioural change. (116)

There has been considerable interest in the close association between temporal lobe epilepsy and paranoid schizophrenia since Slater & Beard published a series of papers on it in 1963. They noted that the positive symptoms of schizophrenia and the aura of temporal lobe epilepsy were very similar. They also felt that the duration of the epilepsy played a causative role in the onset of the psychosis. This might be related to organic damage. (119)

Betts & Skarrot (1979) found that paranoid symptoms were common in institutionalised epileptics and that there was a continuum of severity. Only a few patients met strict diagnostic criteria for paranoid schizophrenia. Following a similar study in the USA, Stevens suggested a biological antagonism between epilepsy and schizophrenia. Differing diagnostic criteria may partially account for the different results in earlier and later studies.

There is now doubt about the relationship in time between schizophrenia and epilepsy. In chronic mental hospital populations as many patients develope schizophrenia before epilepsy as the reverse and therefore Slater's original finding that the epilepsy predated the psychosis may have been an artefact of the population which he studied. Whether patients develop epilepsy or schizophrenia first they eventually lose both. The end state is institutionalisation but little evidence of organic impairment. The epilepsy and the psychosis often disappear approximately simultaneously. Kristensen & Sindrup found recently that the fit frequency for complex partial seizures was lower in psychotic patients and that there was an interval with a median of 18 years between the onset of the epilepsy and the psychosis. There was a significantly

greater number of patients with automatisms in the psychotic group.

There are two contrasting hypotheses which could explain the association of temporal lobe-limbic system mechanisms and psychotic experiences:-

(1) schizophrenia-like illnesses are epileptic in origin and should be referred to as epileptic psychoses,

(2) they are a manifestation of organic neurological damage and thus not specific for epilepsy.

The first view has been extensively criticised by Flor-Henry on the basis of the lack of control populations in the older studies, the inverse relationship between the frequency of seizures and the onset of psychosis, and the laterality effect. He has suggested that the characteristics of the seizures rather than structural damage lead to the clinical picture. Symonds has suggested an 'epileptic disorder of function' in which loss of balance between synaptic excitation and inhibition causes not only paroxysmal epilepsy but interictal symptoms, the nature of which are related to the site of focal activity. It is possible that chronic subictal activity leads to a kindling process within dopaminergic pathways which in turn causes the development of abnormal behaviour patterns and psychosis. These behaviour changes are enhanced by dopamine agonists and thus it is probable that the kindling itself is associated with altered post-synaptic function of dopamine receptors. (106)

Interictal changes in behaviour may result from seizure activity in the limbic system. (116)

Kindling may provide a model for the production of

(1) epileptic seizures,

(2) migraine,

(3) manic depressive disorder.

10.6 Psychotropic drugs used in the treatment of migraine

A variety of psychotropic drugs are used in the treatment and prophylaxis of both manic depressive disorder and migraine:

(i) anticonvulsants,

(ii) antidepressants,

(iii) calcium channel blockers,

(iv) lithium.

(i) Anticonvulsants

Carbamazepine is particularly effective as an anticonvulsant in temporal lobe epilepsy. It is also useful in other episodic disorders involving pain, e.g. trigeminal neuralgia, and affect e.g. manic depressive psychosis. Kindling may explain the pathological behaviour which can develop after a time lag in temporal lobe epilepsy. This is very similar to the longitudinal development and changing psychopathology in affective disorder over time. By analogy, a form of affective spontaneity may develop after repeated stress-related episodes of affective disorder

Carbamazepine has beneficial effects on mood and behaviour in 50% of

patients being treated for seizures. This can occur in the absence of adequate seizure control. Carbamazepine's chemical structure resembles that of the tricyclic antidepressants. It blocks reuptake of norepinephrine. Its action in affective illness may be related to mechanisms which stabilise limbic system dysfunction and not directly due to its anticonvulsant effect. Clinical trials on non-epileptic manic depressives have also shown that it has both antimanic and antidepressant effects as well as being a useful prophylactic. (120) It is the treatment of choice in trigeminal neuralgia - a recurrent condition involving pain in the face in the distribution of the trigeminal nerve. As yet it has not been investigated extensively as a treatment for migraine.

(ii) Antidepressants

Both amitriptyline and mianserin have been shown to decrease the frequency, duration and intensity of migraine headaches when used as prophylactics. (121,122) The response to both appears to be to some extent independent of their action on mood. Initial work with amitriptyline in open clinical trials suggested that the response of the migraine population was bimodal, i.e. that 80% of patients responded well or not at all. These results were consistent with the presence of two discrete migraine populations - one susceptible to amitriptyline and the other not. (123) This was later confirmed in double blind studies where non depressed subjects with severe migraine and depressed subjects with less severe migraine responded best to amitriptyline, whilst depressed subjects with severe migraine had little headache relief. (121)

The mechanism of action is uncertain but, as far as amitriptyline is

concerned, may relate to blocking reuptake of serotonin and catecholamines. In addition to being a non-specific calcium channel antagonist it also has anticholinergic, antihistaminic and antiserotoninergic actions and may interfere with the release of norepinephrine at nerve endings. (121) An explanation related to an effect on neurotransmitter control of brain circulation or on the antinociceptive central systems has been suggested. (122)

(iii) Calcium channel blockers

Calcium channel blockers all share the ability to slow the entry of calcium ions into cells through voltage - activated, ion-selective channels. They cause both coronary and peripheral vasodilation. They have specific high and low affinity binding sites in brain and skeletal muscle as well as the cardiovascular system. (124) Given continuously by mouth they can provide significant relief in migraine and cluster headaches and reduce prodromes. Ten to 14 days of calcium antagonist therapy is required before prodromes are reduced and a further 2-6 week delay is necessary before headaches are alleviated. This slow time course is similar to that seen when antidepressant drugs are used for the same purpose. Headache symptoms reappear 1-2 weeks after stopping therapy with either type of compound. Most clinically effective antidepressants block calcium entry and inhibit calmodulin action in isolated blood vessels or cardiac preparations. (125) Some drugs employed in treating depression and migraine share common mechanisms of action. It is possible that the antidepressant and antimigraine actions may involve the contractile apparatus of vascular smooth muscle and thereby be linked with the rCBF changes found in both depression and migraine.

(125) Flunarizine, a calcium entry blocker, has also been shown to reduce cortical spreading depression and hypoxia - both of which have been implicated in the pathogenesis of migraine. (126)

(iv) Lithium

Calcium functions as an intracellular second messenger and activates a wide range of enzymes. Lithium can alter many calcium-dependent processes. These include enzyme systems, regulation of receptor sensitivity, parathyroid hormone release and microtubule structure. All neural mechanisms hypothesised to explain successful pharmacological treatment of bipolar illness involve calcium - dependent processes. Lithium's therapeutic effectiveness could be explained by its effect on calcium function. (127)

Lithium is best known for its role in both the acute treatment and the prophylaxis of manic-depressive disorder. However it has also been used as a prophylactic in cluster headache and migraine. This was based on the analogy between conditions which had periodic attacks with remissions and recurrent affective disorder. Clinical trials of lithium in migraine have been generally discouraging as it has exacerbated symptoms. However it has been more beneficial in a subgroup of patients with cyclic migraine, i.e. daily attacks for two or more weeks with recurrences on average five times a year with headache-free periods in between.

Lithium is also effective in hypomanic mood and behaviour disorders which occur as a consequence of structural damage to the brain. It has

been used to treat acute steroid-induced psychoses and as prophylaxis against recurrence during further courses of steroids. (128) It has been suggested that lithium's ability to increase the threshold for after-discharges in the limbic system may interfere with a kindling mechanism and that this underlies its therapeutic activity. (129)

CHAPTER 11

Temporal lobe epilepsy, depression and olfactory hallucinations - is the same mechanism producing the affective changes in temporal lobe epilepsy and migraine

Olfactory hallucinations are produced by irritation of the uncinate gyrus or the adjacent temporal lobe. They occur most frequently in association with tumour or epilepsy. It is only within the last five years that it has been recognised that they can also occur in migraine, where they are thought to be a consequence of temporal lobe ischaemia. (130,131)

In the 1930s Keschner et al compared two series of patients with temporal lobe and frontal tumours. Mental symptoms were found in 94% of patients with temporal lobe tumours, although this was associated with evidence of intracranial hypertension in 72%. Similar figures were found in frontal lobe tumours. Hallucinations were present in 14% of patients - the right and left lobes were equally likely to be affected. When the tumour involved the uncinate gyrus olfactory and gustatory hallucinations were common and sometimes also 'dreamy states' with or without generalised convulsions. Olfactory and gustatory hallucinations were characteristic of the temporal lobe but not particularly frequent. The triad of complex hallucinations, uncinate phenomena plus dreamy states and expressive aphasia was diagnostic of a lesion in the dominant temporal lobe. Disturbances of affect were found in 57% of patients.

The affective changes were much commoner in tumours of the left

temporal lobe. The incidence for all affective disturbance was approximately the same as for frontal lobe tumours. Disturbances of memory and orientation were found in 50% of patients and disordered intellectual and higher psychic functions in 56%. (132)

Ictal hallucinations are especially likely in temporal lobe epilepsy. These hallucinations are 'paroxysmal, involuntary recollections drawn from direct or vicarious experiential records which interrupt consciousness as a sequential part of the ictus'. Hallucinations derived from the right temporal lobe are usually related to space and form whilst those from the left temporal lobe are mainly ventral in content. Generally, hallucinations originate mainly from the right hemisphere whilst illusions are almost equally distributed across the two sides. (133) Olfactory and gustatory hallucinations are relatively rare and have been estimated to occur in from 2-5.9% of patients with temporal lobe epilepsy. The olfactory hallucination is unchanging in character between attacks (i.e. the odour is the same each time), the majority of patients give it an affective quality of being pleasant or unpleasant and a crude and unrecognisable smell is the most common. Olfactory illusions can also occur when there is an alteration in the character of normal olfactory stimuli during the seizure. There may be an interictal defect in the sense of smell with hallucinations or illusions which are sustained over relatively lengthy periods. (134)

The size of the olfactory cortex and the extent to which surrounding areas receive olfactory bulb fibres varies according to the importance of the sense of smell in different species. There is a close anatomic relationship between the entorhinal area and the hippocampus, between the

amygdaloid body and the hypothalamus and between the olfactory tubercle and the basal ganglia. Olfaction is thus closely connected with areas of the brain involved in memory, food and water intake, reproduction and emotional reactions. (135)

In 1899 Jackson & Stewart drew attention to the association of ictal affective states with uncinate paroxysms. The emotion was usually unpleasant. (136) Affective change is not uncommon in temporal lobe epilepsy - Williams found 165 patients with complex feelings as part of the epileptic attack in a survey of 2,000 epileptics. Of these 100 had emotion as part of the epileptic experience. (137) Similarly Weil found that 28 out of a total of 132 temporal lobe epileptics had ictal emotion. (138) Fear and depression were the two emotions most often encountered by both authors. Fear was usually found as part of the aura. Williams described fear in association with 40% of anterior temporal foci and 46% of middle temporal foci whereas depression could not be related to any one area of the temporal lobe. (137) Weil has suggested that depression is caused by subclinical epilepsy in the whole hippocampal-amygdaloid-temporal lobe complex or by after-discharges following overt seizure activity. (138) Ictal aggression was uncommon (17% in Williams' series) but was associated with lesions in the anterior half of the temporal lobe or the inferior part of the frontal lobe. Fear was experienced either immediately before or after visceral sensations or activity, auditory hallucinations or vertigo in over 70% of Williams' patients. This relationship was dependent on the proximity of the limbic and superior temporal cortex to the anterior part of the temporal lobe. Fifty per cent of patients with ictal fear experienced either visceral sensory or visceral motor changes. In order to explain this Williams suggested that

the integration of visceral activity resulting from sensory change was mediated through the fronto-temporal cortex whilst the anterior temporal cortex was concerned with the sensory and motor aspects of fear. (137) Daly came to very similar conclusions. (134) Both Weil and Daly commented on the association between olfactory hallucinations and ictal depression although Daly stressed that in his own series this was not a fixed relationship. (134,138)

Pryse-Phillips described the olfactory reference syndrome. Its the central feature is an intrinsic hallucination of foul body odour. The patients are generally men with premorbid personality traits of sensitivity, self criticism and obsessionality. The mean age of onset is 25 years. The syndrome is interesting in the present context because of its good response to antidepressants. (139,140) A single case has been described in association with an arterio-venous malformation in the lower medial part of the right frontal lobe. Psychomotor epilepsy can be initiated by foci in the frontal and orbitofrontal areas. In this case it was suggested that the olfactory symptoms could be due to ischaemia caused by local vascular shunting. (141)

There are close parallels between migraine and temporal lobe epilepsy: olfactory hallucinations and affective change are features of both conditions. Both may be unilateral or bilateral and this can vary between attacks: a temporal lobe focus in one hemisphere can cause discharges in its opposite number; the pain in migraine can be felt on either one or both sides of the head. Although this has been ascribed to ischaemia in migraine the underlying mechanism may be closer to the electrical discharge of temporal lobe epilepsy. Both migraine and

temporal lobe epilepsy may be a consequence of the kindling of Leao's spreading depression.

CHAPTER 12

Cocaine abuse as a model for migraine hallucinations

Perceptual disturbance is common with chronic cocaine use, particularly visual hallucinations. Olfactory and auditory hallucinations have also been reported. In a survey of 85 recreational cocaine users 43.5% experienced perceptual phenomena such as increased sensitivity to light, halos round bright lights and difficulty in focussing. All these patients had intermittent attentional dysfunction. 17.6% of subjects had frank hallucinations. The limited range of patterns found in the cocaine-related visual hallucinations was very similar to that found in migraine patients. (142) Several authors have commented on the presence of form constants in visual hallucinations with a tendency to geometrisation. These form constants may be a consequence of entoptic structures such as the choriocapillary circulation and retroretinal features. Alternatively they could reflect the organisation of the visual cortex. This is arranged as a mosaic of detectors of contrast. Excitation of these detectors by a wave of spreading depression could elicit the range of hallucinatory experiences found in both cocaine abuse and migraine. (142-145) Sensory inputs are directly controlled by a subcortical modulating system in the midbrain reticular formation. This operates in conjunction with the regulation of arousal. (144) Cocaine's stimulant effects include seizure-type electrical discharges in the temporal lobe and increased activity in the reticular activating system with increased function of arousal mechanisms. In this context it is interesting that 7% of the series of cocaine abusers described above had olfactory hallucinations similar to uncinate

phenomena. (142)

Cocaine abuse and the resultant psychiatric dysfunction provides a model for the endogenous psychoses. Cocaine has a continuum of effect from initial euphoria through dysphoria to frank psychosis. Increasing doses and/or chronicity and parenteral administration all enhance cognitive and affective disorganisation. The biological changes associated with cocaine mimic those associated with stress i.e. it is sympathomimetic, predominantly catecholaminergic. Acute and chronic cocaine abuse may therefore affect catecholamine levels in a parallel way to acute and chronic stress. Cocaine can also induce seizure activity confined to the limbic system which is associated with profound behavioural change without convulsions. Drugs which alter the cocaine seizure threshold have major psychotropic effects (neuroleptics and thymoleptics), while routine anticonvulsants (diphenylhydantoin and phenobarbital) do not significantly affect cocaine seizures and are not useful antipsychotic agents. Pharmacological or functional disconnection of cortical- subcortical integration due to altered limbic system activity could profoundly affect cognitive and affective integration in the cocaine and functional psychoses. (146)

Cocaine can induce a progressive alteration in behaviour with repetitive administration. This is known as reverse tolerance. This cannot be explained by conditioning alone. Kindling has similar effects and a similar time course. Cocaine may produce a pharmacological kindling mechanism - possibly through increasing receptor sensitivity. This would cause a progressive increase in the duration and spread of discharges. This could result in increasingly pathological behaviour.

Psychological kindling would involve disruption of critical limbic areas involved in emotion and cognition. This could, in turn, be related to the onset and maintenance of pathological affective and schizophrenic states. Kindling may be the means by which environmental stress leads to exacerbation of psychiatric illness.

Temporal lobe epilepsy is also associated with psychosis. The longer the duration of the epilepsy and the longer the interval between seizures the commoner this psychosis is. This could be caused by a kindling mechanism. (129) The similarity between the symptoms of cocaine-induced psychoses, temporal lobe epilepsy and migraine suggests that kindling and increased arousal may underlie all three conditions.

CHAPTER 13

Migraine as a stress-related disorder

13.1 Stress and its association with illness

Migraine is one of several illnesses which are thought to be related to emotional stress.

Stress is an inevitable part of life - obstacles must be overcome, choices made and delays tolerated. When progress towards a desired objective is blocked or delayed there is resulting frustration. However, a mild level of emotional arousal is necessary to produce alertness and interest. Sensory deprivation experiments indicate that the absence of normal stimulation has a detrimental effect on functioning. The autonomic nervous system prepares the organism for action in emergencies - prolonged stress can lead to physical disorders in the organ systems involved, e.g. high blood pressure and heart disease.

Three main factors determine individual physiological responses to stress:-

(1) individual differences in the reactivity of the autonomic nervous system,

(2) vulnerability of a particular body organ or system as a result of heredity or prior illness,

(3) early learning experiences.

A wide range of stressful situations can lead to a given type of disorder and conversely a wide range of disorders can result from a given type of stress.

Life stress is generally measured using rating scales e.g. the Holmes & Rahe Social Readjustment Scale. Both pleasant and unpleasant life events require some readjustment. Unfortunately individual reactions to life events are not easy to predict as they depend upon a number of factors e.g. previous experience. The predictability of the outcome of the event is also an important determinant of the reaction to it. There is no adequate animal model which encompasses this aspect of the human response to stress. Uncertainty can be extremely stressful - it can prevent anticipatory coping processes and cause confusion. The more immediate an event is, the more urgent and intense is its effect. Appraisal becomes more complex as imminency decreases - this can either increase threat or allow time for cognitive processes to reduce anxiety and therefore decrease it. If events go on for long enough they can produce the General Adaptation Syndrome - this includes an alarm reaction, resistance and exhausion. This is not inevitable - emotional habituation can also occur with reduction of the stress response. Not knowing when an event will occur also generates coping activity which decreases stress reactions. Ambiguity allows more individual characteristics to determine reaction to an event. The timing of

stressful events in relation to the life cycle can also affect the way in which they are viewed by the individual affected. Normal life events can become stressful if they occur out of phase with the life cycle - they are usually unexpected and deprive the individual of the support of compatible peers, a complete sense of satisfaction and the opportunity to prepare for them. The timing of events in relation to other events can also alter their personal significance. Situational factors and individual factors always interact to produce the final response.

Studies of personal histories suggest that physical and emotional disorders tend to cluster around periods of major change in a person's life. Parkes found a mortality rate (mostly from cardiovascular disease) 40% high than expected for widowers observed for six months following the death of their wives. Studies using the Holmes and Rahe Scale have found a relationship between the number of stressful events and physical and emotional health. When the summed life-change units are between 200 and 300 points over a period of a year more than 50% of individuals have health problems the following year. If the summed scores exceed 300 this percentage goes up to 79%. The assumption is that the more critical the changes in individual experiences the greater the effort required to

adapt. This effort presumably lowers the body's resistance to disease. However this explanation is over simplistic and does not account for all factors - it is difficult to separate the effects of stress from general health habits and to avoid the bias generated by individual variation in help-seeking behaviour when assessing the results of life-change studies on physical and psychiatric illness. Stress is only one factor amongst many others which interact to produce illnesses such as migraine. (147,148)

Both tension headache and migraine sufferers report an association between life stresses and their illness. Neither group reports an increase in major stressful life events compared to controls. Tension headache sufferers do report an increase in numerous, everyday minor stresses. However this could be a consequence rather than a cause of their condition. (17) In some studies up to two-thirds of migraine patients have cited emotional upset as a cause of their headaches and it has also been suggested that emotional factors become of greater aetiological significance as the frequency of attacks increases. (149)

The temporal relationship between stress and migraine is often less clear than that in tension headache. Stress-induced migraine may occur during the relaxation period after stress rather than during the height of the stress itself. This may partly explain the periodicity of migraine i.e. characteristically sufferers can have several weeks free of headaches and then have a number of headaches close together. However there may be other explanations for this e.g. the headaches may trigger a process which leaves the individual temporarily refractory to further

episodes. (3) In addition migraine frequently reported to occur regularly at weekends rather than during the week whilst the patient is at work.

A link between a physical condition and everyday life stress has already been demonstrated in myocardial infarction. Massing & Angermeyer found that there was an increased mortality from myocardial infarction on Saturdays and Mondays in men aged between 25 and 55 years. This association was also found for non-fatal myocardial infarctions but was not seen in deaths due to cancer. (150)

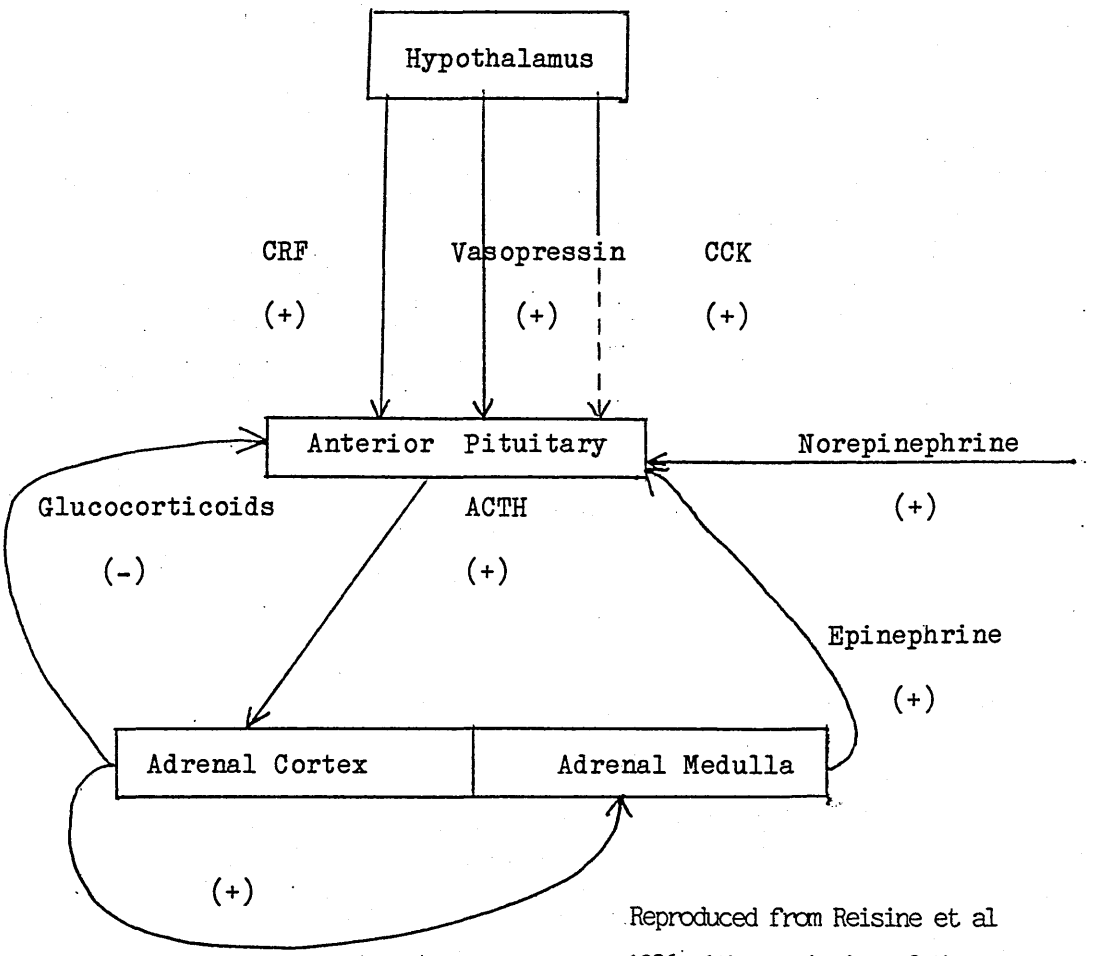
Stress reduction can also decrease the mortality from ischaemic heart disease. In a randomised, controlled trial of a stress monitoring and intervention programme the treated group had a reduction in stress scores and deaths compared to controls although the rate and length of stay in rehospitalisation did not differ. (151)

13.2 External stress and the hypothalamic-pituitary-adrenal axis

The body responds to increased physical or psychological demands by releasing adrenocorticotrophin (ACTH) from the anterior pituitary, glucocorticoids from the adrenal cortex, epinephrine from the adrenal medulla and norepinephrine from sympathetic nerves. These hormones activate the cardiovascular, energy-producing and immune systems and adapt the body to deal with stress. Prolonged stress produces compensatory changes in the activity of the catecholamine biosynthetic enzymes. Catecholamine concentrations in the plasma are generally considered to be a more precise measurement of stress-induced activation of the sympathetic medullary system than urinary measurements. Generally

plasma norepinephrine levels indicate activity in the sympathetic nerves while epinephrine is a measure of secretion from the adrenal medulla. During harassment type A individuals (coronary-prone) have a greater elevation of plasma epinephrine than type B subjects (non coronary-prone). Depressed subjects also show increased basal levels of plasma norepinephrine and epinephrine which correlate with the extent of their anxiety symptoms. (152)

The release of ACTH is controlled by complex regulatory mechanisms. ACTH release is stimulated by the central release of the hypothalamic peptides corticotrophin releasing factor (CRF), cholecystokinin (CCK) and vasopressin which act directly on the anterior pituitary. Peripheral control is mediated by epinephrine and norepinephrine. ACTH stimulates the formation of glucocorticoids in the adrenal cortex. These in turn operate a negative feedback loop to the anterior pituitary, where they inhibit the release and synthesis of ACTH, and to the hypothalamus where they inhibit production of CRF, CCK and vasopressin. They simultaneously stimulate synthesis of catecholamines in the adrenal medulla.



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Multihormonal control of ACTH release

Different neuronal circuits may be affected more by one type of stress than another.

The corticotrophs contain a number of second messenger systems. They provide extracellular factors with a variety of ways to release ACTH. This seems to preserve the corticotroph's ability to produce ACTH even when desensitised to individual releasing factors. Chronic stress also seems to activate the gene for the ACTH precursor pro-opio-melanocortin. This may be a form of cellular memory. This type of cellular memory could be related to the physical ill health associated with prolonged stress. (153)

13.3 Circadian rhythms and the hypothalamic-pituitary-adrenal axis

In addition to being able to respond to external stress the hypothalamic-pituitary-adrenal axis has an internally generated rhythm. There is a circadian variation in plasma 17-hydroxycorticosteroid levels with an early morning peak followed by a downward trend during the day and a nocturnal trough. This is dependent on a circadian pattern in corticotrophin secretion rather than adrenal cortical responsiveness. Pathways from the rostral brain stem reticular activating system and the limbic system together with their hypothalamic projections partly control pituitary ACTH secretion. (154)

The human circadian system is controlled by at least two endogenous, self-sustained, coupled oscillators: a strong one controlling body temperature, REM sleep propensity and cortisol secretion, and a weak one controlling the sleep-wake cycle and sleep-related neuroendocrine activity. (155)

The circadian rhythm of cortisol release can be affected by:

(i) disease of the central nervous system,

(ii) pain,

(iii) affective disorder.

(i) Disease of the central nervous system

Krieger et al compared 48 patients with focal disease in the central nervous system with 47 normal subjects. They divided the former group

into three subgroups:

(A) disease of the temporal lobe,

(B) disease of the pituitary,

(C) disease of other areas.

The circadian cortisol rhythm of groups (A) and (B) differed from (C) and from the normal control group. There was only a significant alteration in circadian 17-OHCS if there was central nervous system disease affecting the pretectum, the temporal lobe or the hypothalamus. Disease in these areas could interfere with the normal function of the regulatory pathways which control ACTH release. This alteration in the circadian rhythm could occur in the absence of overt clinical or laboratory evidence of endocrine dysfunction. Chronic illness, by itself, had no influence on the pattern of circadian variation. It was uncertain whether the organism's ability to respond to stress varied with the phases of the circadian pattern and whether an abnormal circadian rhythm implied an abnormal stress response. (154)

Ziegler et al examined circadian rhythms of cortisol release in 25 migraine patients (type of migraine unspecified) and eight controls. They found little variation in plasma cortisol levels in control subjects but a large disparity within the migraine group. Overall there was a positive association between pain and elevation of the plasma cortisol level. There was also a tendency for the group with abnormal plasma cortisol levels to have higher depression scores. Two abnormalities in circadian rhythms were found to occur in subgroups of the migraineurs: (i) consistently high levels of plasma cortisol (ii) one or more aberrant high values occurring during the day. There was therefore heterogeneity

within the patient group although unfortunately it is impossible to tell from the data presented whether this was related to the type of migraine. The abnormalities seen in migraine could be related either to an interaction between pain and depression or to primary hypothalamic dysfunction. (156)

(ii) Pain

Shenkin examined plasma cortisol levels in 16 healthy, unhospitalised controls and compared them with 66 patients who had objective evidence accompanying a complaint of pain and 45 patients who complained of pain without such evidence. The evaluation of pain and the determination of cortisol levels were performed independently. There were major differences in the patterns of cortisol secretion between the two groups with pain: 9 of the 66 patients (13.6%) with objective evidence of pain had normal mean levels of cortisol and normal diurnal patterns compared to 38 of the 45 patients (84.4%) without such evidence. The average values for the control group were similar to the 'no pain' group. The overall conclusion was that the determination of plasma cortisol diurnal variation could be used to discriminate between organic and non-organic pain with a 15% range of error. It remains uncertain whether systemic and psychic stimuli have different effects on the stress response of the pituitary and adrenal glands. However, there is a good correlation between increasing levels of emotional stress and elevation of cortisol levels. (157)

In a different study Lascelles investigated 25 patients with pain complaints who had been referred for psychiatric assessment. This design

immediately introduced bias into the sample and not surprisingly, when the total group was divided into a principally 'organic' and a principally 'psychogenic' group, emotional problems were seen in both subgroups. All patients were taking some form of medication. Plasma cortisol levels were increased in both groups and this was greater if an organic lesion was present. The differences were most marked in the 9am blood sample. Both a painful organic lesion and psychological illness with pain were associated with a decrease in the diurnal variation of secretion. The patients studied formed a relatively intractable group suffering from pain due to chronic, but not progressive, illness. There were no clear cases of endogenous depression which could have inflated cortisol values. (158)

(iii) Affective disorder

Four clinical features of depression suggest that circadian rhythm disturbances are involved in the disease:

(i) early morning wakening,

(ii) diurnal variation in symptom severity,

(iii) seasonality of the illness,

(iv) cyclicity of the illness.

The shift in the time of awakening suggests an abnormal phase-advance in the sleep-wake circadian rhythm. By contrast there is a delay in the "waking-readiness" rhythm. Together they imply an internal phase-displacement of the two rhythms. Depressive hospital admissions, electroconvulsive treatments and suicides occur most frequently in the spring. There may also be a secondary peak in autumn, although this is

more controversial. Mania too has a seasonal variation in incidence although this is less clear cut.

Seasonal affective disorder is a recently described syndrome in which recurrent depressions begin at the same time each year. Generally they begin in autumn or winter and have remitted by the following spring or summer. Most patients have a bipolar affective disorder and their depressive illnesses are characterised by hypersomnia, overeating and carbohydrate craving. There is some evidence that extending exposure to natural light by using bright artificial light can have an antidepressant effect in this group. (159)

Affective illness tends to be recurrent. Halberg has suggested that long term cycles of relapse and remission could be the result of an abnormal relationship between two circadian rhythms if one of them was free running and slipping slowly in and out of phase with the other. (155)

The circadian pattern of cortisol secretion is phase-advanced in depressives. The degree to which this occurs correlates with the severity of depression. The diurnal rhythmicity also appears to be reduced although this may be due to masking by the effects of sleep. In the dexamethasone suppression test (DST) there is hypersecretion of cortisol and resistance to negative feedback inhibition after administration of the synthetic steroid dexamethasone. Most investigators have found that 35-60% of subjects with endogenous depression fail to suppress cortisol production after dexamethasone administration compared with 5-20% of normal subjects or other

psychiatric patients. (160) It is more sensitive in psychotic affective disorder and mixed manic-depressive states. (161) This may be connected with the phase advance of the circadian rhythm in relation to sleep. DST non-suppression has been linked with endogenous-type depression, increased severity of depression and enhanced treatment response to ECT and antidepressants. The abnormality usually disappears on clinical recovery; if it does not do so the risk of relapse is thought to be increased. (155,162) The use of the DST in the diagnosis of depression is limited by its lack of specifity. No-one knows why half the patients with endogenous depression show hypothalamic-pituitary-adrenal (HPA) axis dysfunction whilst the other half do not. Cortisol is thought to be under stimulatory control by ACTH but ACTH and cortisol concentrations are not directly correlated following dexamethasone administration. Thus changes in ACTH cannot be the only cause of the non- suppression seen in endogenous depression. The pituitary peptides β-EP and β-LPH also show a circadian rhythm, similar to that of ACTH, which is suppressable by dexamethasone. This rhythm can escape suppression in patients with endogenous depression but does not necessarily co-vary with cortisol escape. Using estimation of β-EP and β-LPH together with cortisol could improve the reliability of the DST in major depression. Used together 70% of patients with endogenous depression have evidence of abnormal HPA function. (160,162)

Curtis et al examined the relationship between different levels of emotional arousal and the circadian rhythm of cortisol secretion. They selected two groups of psychiatric inpatients on the basis of the degree of affect they displayed - the high affect group had intense emotion which was sustained virtually all day every day and the low affect group

had no overt emotional arousal and no exaggeration of their emotional responses to everyday situations. They were matched with hospital employees who were felt to be 'well balanced' and without major external stresses. All selections were made subjectively but correlated positively with psychological test results for anxiety and mood. Unfortunately it is uncertain whether or not the psychological ratings were made blind to the affective status of the individual. The inpatients were mainly schizophrenics. There were only two patients with a diagnosis of psychotic depression - one in the high affect and one in the low affect group. Both plasma and urinary corticosteroid levels were highest in the high affect group and lowest in normal subjects. There was a sex difference in both the absolute values and the diurnal trend - both of which were higher in men than women. The high affect group was most variable and the low affect group least variable for plasma and urine steroid values. The overall conclusion was that although adrenal cortical function was slightly increased in states of emotional stress this effect was overshadowed by the sex difference which was stronger and more consistent. (163)

13.4 Summary

Stress is inevitable and a certain amount is essential for normal functioning. The physiological stress response is mediated by the autonomic nervous system. There are considerable problems in assessing the emotional response to a stressful event as this is as much determined by individual variables as the characteristics of the event itself. Both tension headache and migraine sufferers report more minor, everyday stresses than controls. The temporal relationships between these

stresses and the headache is less clear in migraine patients. Reducing the amount of stress can affect the outcome of disease processes.

The anterior pituitary, the adrenal cortex and the sympathetic nerves are all involved in stress responses. This is a complex system which may be involved in the production of stress-related physical and psychiatric illnesses. Central nervous system disease affecting the pretectum, the temporal lobe or the hypothalamus can influence circadian rhythms of 17OHCS excretion. Circadian rhythm disturbances are also found in migraine, pain and depression. A normal level of emotional arousal by itself does not appear to have a major impact on adrenal cortical function.

CHAPTER 14

Endorphins and their relationship with pain and psychiatric disorder

The endorphins are a family of structurally-related peptides which are formed in nerve and endocrine tissues and which have an affinity for opioid receptors. Their complexity, in terms of structure, function and tissue distribution, is such that there is no simple relationship between any one physiological variable and 'endorphinergic' activity. (164) Endorphins mediate their effects through a μ (mu) receptor which can produce analgesia and euphoria. receptor sites predominate in regions which regulate nociception (such as the spinal cord, midbrain or thalamus). The k (kappa) receptor may be involved in the regulation of sedation and sleep, different types of analgesia and dependence whereas the σ (sigma) receptor may be involved in dysphoria and hallucinations. (165) There may be cross-reactivity between naturally occurring opioids and their multiple receptors. This confounds efforts to determine whether any one peptide system is more likely to be involved in pain regulation than another. (166)

The two main approaches to the assessment of endorphinergic activity in humans:-

(1) administration of selective agonists and antagonists e.g. naloxone, which selectively blocks μ, k and σ receptors. This can be used in the investigation of endorphin activity in relation to pain in human subjects.

(2) laboratory techniques e.g. peptide and receptor assays and investigation of endorphin synthesis and degradation.

Lumbar cerebrospinal fluid is the material most often used for assays. Endorphins are also produced by tissues outside of the CNS, e.g. adrenal medulla, and therefore the endorphin content of plasma does not directly reflect CNS activity. The CSF can be viewed as an expansion of the extracellular fluid of the brain. The CSF endorphin content may therefore be more closely related to CNS function. Endorphins are also stable in CSF for reasonably long periods of time. (164)

Anatomical, physiological and clinical studies have shown that the brain has an endogenous pain inhibitory system which operates by activating controls which descend from the brain stem to the spinal cord. The highest concentrations of opiate receptors in the brain have been found in the amygdala and periaqueductal gray area, the medial thalamus and hypothalamus. The substantia gelatinosa of the spinal cord is also rich in opiate receptors. This antinociceptive system is intrinsically activated by terror, rage, sexual excitement and violent pain and can also be extrinsically activated by direct electrical stimulation and the administration of opiate drugs. (167)

14.1 Stimulation-produced analgesia

Stimulation of specific sites in the brain may lead to reduced responsiveness to pain. The fact that this is reversible by naloxone and cross tolerant with morphine suggests that opioid involvement plays a critical part in the phenomenon. Non-opioid systems are also involved to

a lesser extent. Pain relief is accompanied by both an increase in enkephalin-like material and increased β-endorphin immunoreactivity in the CSF. (166)

14.2 Stress-induced analgesia

Analgesia is an adaptive response to acute stress e.g. inescapable footshock in rats. This is partially reversible by naloxone. The effect is an interaction between the duration and the constancy of the shock. (168) Trivial (i.e. acute, localised and mild) stimuli do not activate opioid mechanisms. (169) Repeated daily exposure to stress leads to further adaption. Eventually further stress no longer produces analgesia. This is accompanied by an increase in endogenous opioids. Hypothalamic endorphin content is decreased, possibly due to release of its stores during stress. (167)

Analgesia can also be produced by psychological stress e.g. learned helplessness. This paradigm has also been used as a model for depression. Stimuli indirectly associated with an aversive event, e.g. the smell of shocked rats, can activate the endogenous opiate system in unshocked animals. (168)

Stress-induced analgesia (S.I.A.) activates both opioid and non-opioid systems. Short durations of stress induce non-opioid analgesia whereas longer durations induce opioid analgesia. The type of analgesia can be determined by the part of the body being shocked - it is possible that pain inhibition induced by shock recruits both local circuits, which may not be opioid in nature, as well as more central, partly

endorphinergic, circuits.

Stress appears to activate the hypothalamic-pituitary-adrenal axis of the peripheral sympathetic system leading to the release of endogenous opioid peptides from both the anterior pituitary and the adrenal medulla. β-endorphin and ACTH are secreted together by the anterior pituitary. Administration of dexamethasone inhibits the release of both ACTH and β-endorphin but does not abolish S.I.A. Elevation of the plasma β-endorphin level is not always correlated with analgesia e.g. chronic daily stress leads to the loss of S.I.A. but still produces elevated plasma β-endorphin levels. In acute stress endorphin synthesis is initially increased but then returns to normal. Analgesia diminishes despite high plasma endorphin concentrations. As either no, or total, analgesia would be equally inappropriate opioid and non-opioid pain-relieving systems probably act to set the level of pain perception in situations of potential or actual acute pain. (167)

Psychological factors also influence endogenous opioid production e.g. in placebo analgesia. Approximately one in three people given placebo medication will obtain significant pain relief. The mechanism is similar to narcotic analgesia, at least to the extent that both manifest tolerance, a compulsion to continue with, and increase the dose of medication and an abstinence syndrome when the medication is suddenly withdrawn. A placebo can also partially reverse withdrawal symptoms in narcotic addicts. Patients who respond to placebo gain increased relief from narcotic analgesics post operatively. In a randomised double blind study of dental post operative pain in which patients received morphine, naloxone or placebo, patients on naloxone had more pain than those on

placebo. When naloxone was subsequently given to the placebo group there was no change in the status of placebo non-responders but placebo responders had more pain. The results suggest that endorphin release mediates placebo analgesia. (170) Part of the variation in pain intensity in patients with similar lesions could be due to differences in endorphin activity. This is consistent with results from studies of on-demand post-operative pain relief in which patients themselves control the rate of narcotic infusion. There is an inverse relationship between the steady state level of analgesic in the CSF and the preoperative CSF endorphin level. (171)

14.3 Opioids and control of blood pressure

Morphine and other opiate alkaloids have potent cardiorespiratory effects. Opioid peptides and their receptors are present in brain areas involved in control of the cardiovascular system as well as the heart itself.

There are three main sites where endogenous opioids could influence blood pressure control:-

(i) the vagal-solitary complex in the medulla,

(ii) the anterior lobe of the pituitary,

(iii) the sympathetic nervous system.

The sympathetic nervous system seems to be mainly responsible for the cardiovascular effects of opioid peptides. The vagus may play a subsidiary role but vasopressin does not seem to be important. (172)

There may be an interaction between blood pressure control and nociception. Significant correlations have been found between changes in blood pressure and the response to pain. Stress-induced analgesia has been linked to respiration and stress-induced hyperglycaemia. (166)

14.4 Endogenous opioids in migraine

The endogenous opioid system controls pain, hedonia and neurovegetative systems. The anhedonia, autonomic disturbance and pain in migraine closely resemble the symptoms of morphine abstinence (172, 173). The movement of pain from one side of the head to the other and to different regions within the head, the episodic nature of migraine and physiological and environmental influences on it are all suggestive of a chemical basis which involves neurotransmitter dysfunction. The pain has the characteristics of central pain, i.e. it is poorly localised, it has affective colouration, it outlasts the stimulus, and anaesthesia or paraesthesia are present. (172) Pain which comes from the vascular architecture emerges only when the local pain threshold is decreased. Centrally mediated hypernociception implies dysfunction within the pain-suppressing system. In migraine inhibition of the release of substance P from the trigeminal ganglia by enkephalinergic neurones may be involved in the production of pain. (174)

Morphine is a surprisingly poor analgesic in migraine. This suggests that:

(1) there is under sensitivity of opiate receptors,

(2) there is a failure of serotoninergic function (since serotonin appears necessary for morphine to achieve its analgesic effect),

(3) there may be a deficiency in both systems. (174)

Half of central pain sufferers have a poor or absent response to inhibition of 5HT-mediated venospasm with morphine. This supports a possible reduction in opiate receptor sensitivity in central pain. (174)

Postreceptoral supersensitivity (PRSS) is a condition of exaggerated cellular reaction due to an increase in intrinsic potential. This is mainly because of an elevation in the energy of a second messenger. PRSS is found in both non-organic central pain and morphine abstinence. In non-organic central pain deficiency in the endogenous opiate system may produce neuronal leakage of neurotransmitter into the synaptic cleft of the endorphin-dependent neurones. The neurone is left empty and this leads to an adaptive PRSS. (174)

The results of studies which look at 'morphine-like factors' in migraine conflict although there is general agreement that the concentrations of these factors in the CSF return to normal during headache-free intervals. Interpretation of results is confounded by:
(i) the use of differing diagnostic criteria,
(ii) small numbers of patients in trials,
(iii) differences in the sensitivity, specificity and reproducibility of the techniques employed. (176)

The main endogenous opioid implicated in migraine is β-EP. Both β-EP and ACTH are synthesised from pro-opio-melano-cortin (POMC). One study found no difference between EP and ACTH levels during and between migraine attacks in patients with either classical or common migraine.

However, there was a trend towards increased β-EP levels during attacks and a positive correlation between β-EP and ACTH during attacks but not in headache-free periods. On the basis of this study alone it is uncertain whether the increase in β-EP release was involved in antinociception or simply part of a general stress response. There were methodological problems in the study which should be taken into account when assessing the results - the criteria for common migraine were fairly wide and could have led to the inclusion of some patients with tension headache, there was a higher frequency of headache in the common migraine group and the duration of the headache free interval was a minimum of only three days. (173)

Other researchers with larger groups of patients and looking at only headache-free periods have found that plasma concentrations of β-EP in chronic daily headache and common migraine were similar to those of controls. By contrast the plasma concentrations of β-EP in classical migraine were significantly reduced. (177,178) These results could not be replicated in later studies e.g. Genazzani et al found that there was a progressive reduction in CSF β-EP levels from healthy controls through common migraine sufferers to patients with continuous migraine with interparoxysmal headache who had the lowest levels of all. These changes were independent of ACTH levels. (16)

The evolution of migraine throughout life and its improvement in pregnancy and impairment at the menopause correlates with changes in β-EP which increases in pregnancy and decreases at the menopause. This has led to the hypothesis that the non-organic central pain of migraine is due to decreased activity in the neurones responsible for the CSF

content of β-EP. (16)

Idiopathic headache sufferers are particularly sensitive to hallucinogenic drugs which are chemically related to 5HT. Frank hallucinations can be provoked in migraineurs by doses which are not hallucinogenic in controls. Pentazocine is especially poorly tolerated and patients complain of disagreeable dysphoria, depersonalisation and frank hallucinations more often than non-headache controls. Pentazocine acts mainly on the opiate receptors. By implication both the antinociceptive system and opiate receptors are involved in the production of hallucinatory experiences. Migraine may be a genetic disorder of the central peptidergic (enkephalinergic and endorphinergic) neurones and of serotonergic-dopaminergic neurons. This would result in both pain and functional disorder (nausea, vomiting, oliguria, dysphoria and hallucinations). (172)

Clonidine, an $\alpha 2$ adrenergic stimulant, has been used in the treatment of opiate withdrawal and migraine. It acts principally on the locus coeruleus. Endorphins inhibit the release of norepinephrine and other amines at this site. The link between amines and endorphins in migraine could be a sudden loss of endorphin inhibitory tone due to a sudden decrease in the CSF endorphin concentration. This would lead to an overflow of amines, especially norepinephrine, causing the initial prodromal phase of vasoconstriction. Clonidine could act at this point by counteracting the norepinephrine overflow. The successive vascular phenomena and the pain depend on the release of vascular-activating amines and humoral factors (histamine, prostaglandins, bradykinin) which produce vascular dilation and perivascular oedema, mainly in the

extracranial vessels. (179)

Primary headache disorders border on both ischaemic cerebrovascular disease and affective disorder. Pro-opio-melanocortin (POMC) peptides are involved in pain perception, adaptation to stress and modulation of higher brain functions such as learning, drive and mood. Nappi et al looked at a variety of different groups of headache sufferers, although unfortunately they did not include subjects with uncomplicated classical migraine. Using the Hamilton Rating Scale for Depression (HRSD) an increased incidence of mild depression was found in patients with migraine with interval headache (MIH) and chronic tension headache (CTH) (HRSD scores 14-21). Common migraine (CM), cluster headache (CH) and psychogenic headache (PH) groups all scored as non-depressed. Using the MMPI patients with CM and CH had normal profiles whilst there was a progressive increase in hypochondriasis, depression and hysteria in the MIH, CTH and PH groups. In a study of patients with neurotic and major depression which was carried out at the same time both groups had elevated plasma endorphin levels. ACTH levels were increased only in the patients with major depression and cortisol levels were elevated in both groups. These values were all greater than those in all groups of headache sufferers.

Approximately 50% of patients with acute endogenous depression have a diminished ability to suppress cortisol secretion after the administration of dexamethasone. Patients with daily chronic headache are sometimes considered to have a somatised equivalent of a depressive state. However, the rate of dexamethasone non suppression in these patients is only slightly greater than that in healthy, and much the same

as that found in neurotically depressed, individuals. This suggests that the underlying pathology for this group is different from that underlying acute endogenous depression. The dexamethasone suppression test (DST) is also unable to discriminate between different types of daily chronic headache. Prolonged dexamethasone administration over four days causes suppression of plasma levels of β-EP, β-LPH and cortisol levels in healthy volunteers. Neurotic depression causes diminished β-EP levels. In DCH, β-EP, β-LPH and cortisol are all suppressed.

5HT and acetylcholine (Ach) both enhance pituitary POMC-related peptide secretion. There is also a tonic dopaminergic inhibition of β-EP secretion. Adrenergic pathways could also be involved in the control of resting levels of β-EP and related peptides. β-EP levels are reciprocally related to the frequency of migraine attacks. There is uncertainty as to whether this reflects opioid deficiency or increasing pain. Similar results are found in patients with continuous tension headache. In cluster headache, although plasma concentrations of β-EP, ACTH and cortisol are normal the circadian rhythms of their secretion are disorganised with a delay in acrophase. Chronic pain seems to be accompanied by reduced function of endogenous opioid. There is integrity of the hypothalamic-pituitary-adrenal axis in most headache sufferers. (180) A small additional study by the same author attempted to examine the relationship between pain, affective disorder and CSF β-EP levels. In a comparison of patients with migraine with interparoxysmal headache, major depression, both conditions simultaneously and normal controls, β-EP levels were reduced in migraineurs but not patients with major depression or healthy controls. In patients with both migraine with interparoxysmal headache and major depression there was a significant

further reduction in β-EP levels. This suggests that β-EP is concerned with chronic pain independently of affective state - however the numbers of patients involved were very small and these results cannot be regarded as conclusive. (181)

Sicuteri has grouped the relationships between emotion and headache under four main headings:

(1) headaches may disappear after unexpected strongly-felt emotions,

(2) headaches often occur after psychic tension e.g. 'weekend' headache,

(3) headaches increase concomitantly with increased 'routine' emotion,

(4) the headache history may start after long-lasting stress and repeated episodes of anxiety, especially if there is repressed aggression.

The antinociceptive system is activated mainly by intense emotion. The increase in the pain threshold in emotionally stressed animals supports the hypothesis that pain may be reduced or prevented by psychogenic activation of the antinociceptive system. The 'weekend' headache may be due to stopping daily emotional stimulation of the analgesic-providing system. The immediate increase in headache with increased routine emotion may be due to increased sensitivity to emotionally induced vasomotor reactions. Repetitive life stress should enhance the function of the antinociceptive system and this should result in adaptation to the stressful situation. However, if the system is vulnerable it may fail with hyperalgesia and pain as a consequence. (182)

14.5 Endorphins, Mood and Pain

All pain syndromes have both a somatic and a psychic component. In a study comparing affective disorder (both primary and secondary affective disorder as defined by Research Diagnostic Criteria), organic pain, non organic central pain and a control group there was increased pituitary adrenocortical function and decreased DST suppression in the affective disorder group compared to the others. This was shown by increased cortisol and ACTH levels in primary affective disorder and a gradient of β-EP and β-LPH levels. These were highest in secondary affective disorder, intermediate in primary affective disorder, and least in controls. β-EP and β-LPH levels were decreased in patients with daily chronic headache.

The differing patterns of ACTH and opioid levels in secondary affective disorder patients compared to those with primary affective disorder implies that the increased levels of β-LPH and β-EP are not sustained by the same mechanism in the two conditions.

The normal levels of β-EP and β-LPH in organic pain and the impaired levels in daily chronic headache suggest that impaired β-EP secretion may be linked to headache production. (182)

Almay et al compared 37 patients who had pain of greater than six months duration with 19 healthy volunteers. The pain patients were a series of consecutive admissions to a neurology inpatient unit and were separately evaluated by a neurologist and a psychiatrist. The whole group was then divided into patients with mainly organic pain and

patients with predominantly psychogenic pain. Unsurprisingly the inclusion and exclusion criteria were stronger in the organic than the psychogenic group. Endorphins were estimated in CSF samples using a standard fractionation procedure.

There was no significant relationship between Fraction 1 and the duration of pain for the group as a whole but in the organic group there was a significant negative correlation between the two variables. There was no significant correlation with the severity of the pain. Depressive symptomatology was closely related to Fraction 1 endorphin concentrations - there were significant correlations with:-

(i) the total comprehensive psychopathological rating scale (CPRS) score,
(ii) the total score of reported items,
(iii) the total score of observed items,
(iv) the reported item 'depressed mood',
(v) the observed item 'depressed mood'.

These were seen in both 'organic' and 'psychogenic' pain patients. The depression scores were slightly higher in the psychogenic than in the organic pain group. Patients with organic pain, especially those with clear positive signs of peripheral nerve lesions, show lower levels of Fraction 1 than patients without lesions. (183)

14.6 Endorphins in Affective Disorder and Schizophrenia

There have been several reports of decreased pain sensitivity in psychotic patients. These predate the advent of phenothiazines and antidepressants and are inexplicable on the grounds of a drug effect alone. There has been speculation that either the meaning of pain is

lost in these patients or that there are excessive levels of circulating endogenous opioid peptides. (184)

Opium was extensively used as a cure for agitated depression at the beginning of this century. (185) Exogenous opiates alleviate anxiety and produce euphoria suggesting a link between endogenous opioids and affect. Work on psychiatrically normal populations has suggested that endogenous opiods may be involved in the modulation of mood and feelings of wellbeing. Endorphin deficiency may be involved in the production of endogenous depression. (186) Synthetic β-EP has psychoactive properties when administered to depressed patients and results in transient improvements in overall performance although not in ratings of individual items of behaviour. The response is almost immediate leading to speculation that β-EP may be involved in the 'on-off switch' mechanism of affective disorder. (187,188). Elevated endorphin levels, particularly Fraction 1, have been found in manic-depressive patients. Fraction I levels correlate with measures of depression, especially with depressive hallucinatory episodes. (168) Naloxone has also been reported to reduce manic symptoms. However the numbers of patients in these studies have been very small. (188,189) A decreased sensitivity to somatosensory pain has been noted in a small proportion of depressed patients. These patients may form a subgroup with raised levels of endorphin-like compounds. (188,190) Physostigmine infusion can produce depressive symptoms in patients with a past history of depression. It also has antimanic properties. These depressive mood changes are significantly correlated with increased plasma β-EP levels but not with peak cortisol levels. This suggests a cholinergically-mediated β-EP pathway within which increased activity could cause depressive symptoms. (190)

There is controversy over whether β-EP activity is increased or decreased in schizophrenia. This is likely to be a consequence of

(1) diagnostic variation in the patients in different studies,

(2) concomitant medication,

(3) the use of single blind and open studies as well as double blind designs,

(4) small sample sizes,

(5) different subgroups of patients e.g. both acute and chronic illness included in an apparently homogeneous sample. (188)

Initial reports of increased levels of leucine-5-β-endorphin in schizophrenia have not been replicated. Increased plasma endorphin levels have also not been found consistently. Although some studies of the use of naloxone have reported decreases in psychotic symptoms, especially auditory hallucinations, not all reports agree. Double-blind administration of β-EP worsens schizophrenic symptomatology. (188) Endorphin levels vary markedly in acute and chronic schizophrenia e.g. one study found levels ten times higher than those of controls in acute schizophrenia and 50% less than controls in chronic schizophrenia. (191) Elevated Fraction 1 levels in 'symptom rich' patients (i.e. those with florid illnesses despite several months hospitalisation) returned to normal values or slightly above following treatment with neuroleptics or propranolol. The Fraction 1 levels decreased in parallel with clinical improvement in four out of six patients who responded to medication. (189) There are two possible hypotheses to explain the involvement of brain opioids in schizophrenia:

(i) increased activity of either normally or abnormally functioning

endorphins,

(ii) certain non-opioid, β-endorphin derivatives have neuroleptic properties and these may be defective in schizophrenia.

Somatic treatment methods (e.g. electroconvulsive therapy and insulin coma treatment) result in the mobilsation of endorphins and this may be relevant to their efficacy in both depression and schizophrenia. (186)

14.7 Summary

(1) The endorphins are a group of structurally related peptides with an affinity for opioid receptors.

(2) Stress activates the hypothalmic-pituitary-adrenal axis causing the release of β-EP and ACTH together from the anterior pituitary.

(3) The sympathetic nervous system is mainly responsible for the cardiovascular effects of opioid peptides.

(4) The anhedonia, autonomic nervous system disturbance and pain found in migraine are very similar to the symptoms of morphine abstinence.

(5) The sensitivity of migraineurs to the hallucinogenic effect of drugs which affect both 5HT and δ opiate receptors suggest that both amine and endorphin systems are involved in this condition.

(6) Endogenous opioids are important in the modulation of pain.

(7) There is no clear relationship between endorphins and schizophrenia or major depressive illness.

CHAPTER 15

Pain, depression and migraine

15.1 Psychogenic and somatogenic pain

A dualistic approach to psychogenic and somatogenic pain encounters the major problem that both feel that same. This can be resolved by a description of the pain in either psychological or physical language or both depending upon which option appears most helpful to the individual patient. Psychogenic pain thus implies a pain which is better understood in psychological than in physical language.

There are no significant differences in psychological test scores between psychogenic and somatogenic pain. One study used the MMPI in a medical outpatient department and compared patients who complained of pain with those who had other physical complaints -
(1) depression was less frequent and hypochondriasis more frequent in patients with pain than in those without,
(2) all patients had neurotic patterns in which hypochondriasis and depression were significant features. Patients with pain had a significantly greater degree of hypochondriasis than those without.

These results have been replicated repeatedly. This has led several authors to postulate that pain may be substituted for anxiety and depression. Some people appear to find pain less distressing than these emotions. This group has a greater use of somatisation, denial and repression as defenses.

Merskey examined 100 psychiatric patients with pain complaints of greater than three months duration and compared them with 65 patients without pain. He found a greater percentage of neurotic conditions, especially hysteria, among the pain patients.

Sternbach compared the MMPI profiles of two groups of patients admitted to a low-back pain clinic. One group had physical findings on examination and the other group did not. He found an equal incidence of hypochondriasis and depression in both groups.

The overall conclusion is that people with psychogenic pain tend to be neurotic and in this respect do not differ much from those with chronic pain of organic origin. (46)

15.2 The relationship between pain and depression

Pain is frequently found as a symptom in depression and depression often occurs secondary to chronic pain. Diamond, in a study of 423 patients with various types of depression, described complaints of headache in 84%. Lesse, in a similarly uncontrolled study of 324 depressed patients found that 31% had physical complaints rather than low mood as their main presenting symptoms. (46) This is in agreement with the incidence of 'masked depression ' described by other authors e.g. Kreitman found that only 21 of 120 cases of masked depression were diagnosed as such despite the fact that 25% of them had previous overt psychiatric illness. This is important for two reasons:-

(1) Incorrect diagnosis leads to a delay in psychiatric referral - in one

series 84% of patients had been ill for more than 1 year, 69% for more than 2 years and 30% for more than 5 years. The prognosis worsens with increasing delay in receiving antidepressant treatment.
(2) As two-thirds of patients with masked depression have suicidal ideas the illness may require urgent treatment by the time the psychiatrist is involved. (192)

Cassidy compared 100 severely depressed manic depressive patients with several control groups. A complaint of pain indicated illness but this was as likely to be physical as psychiatric. Merskey & Spear assessed 200 consecutive admissions to a psychiatric clinic and found that pain was a symptom in 53%. Depression was the most common diagnosis (42.5%) and pain occurred in 56% of the depressed patients. In general medical practice Baker & Merskey described pain in 64% of a consecutive sample of patients. Sixty-six per cent of the patients with predominantly physical problems had pain complaints compared with 59% of those with predominantly psychiatric conditions.

The main components of depression which emerge from factor analysis of rating scales for depression are:
(1) subjective misery,
(2) overconcern with physical health,
(3) a general complaining neurotic or irritability factor.

There seems to be an important hypochondriacal element in depression, particularly reactive depression with environmental precipitants. In this context the main symptoms of reactive depression are:

(1) tiredness,

(2) loss of interest,

(3) hypochondriacal complaints,

(4) depression which is accentuated in the evening,

(5) a persistent response to environmental precipitants.

These patients manipulate others by expressions of dependency, but resist outside influences. They are unwilling to please those around them and their behaviour both expresses anger and attempts to get support and concern from others without incurring the responsibility for reciprocating. (46)

In summary a complaint of pain occurs in slightly more than half the general medical and psychiatric populations and in psychiatric populations the presence of a pain complaint is equally likely to predict anxiety, hysteria or reactive depression.

15.3 Antidepressants and pain

In a study of 196 private patients with unipolar depression Lindsay & Wyckoff demonstrated that 59% had chronic benign pain of greater than three months duration. When treated with antidepressant medication 83% obtained significant relief of their pain syndromes. (193)

Bradley studied the response to antidepressant treatment in two groups of patients - 16 whose pain preceded their depression and 19 whose pain and depression occurred together. In the first group only the depression responded to treatment but there was increased tolerance for

the pain. In the second group both the pain and depression were relieved together.

Antidepressants are useful in the treatment of chronic pain. There is some dispute over whether the length of time taken to relieve pain is less than the length of time generally required for antidepressant efficacy. Tricyclic antidepressants may have direct antinociceptive properties. Their analgesic effect is apparent even when there is no evidence of depression. They have been used to treat chronic pain states such as migraine, facial pain, trigeminal neuralgia, arthritis and metastatic carcinoma amongst others. The response rates for these conditions vary between 44-78% (average 62%). The site of the pain has no effect on the likelihood of obtaining a good response to treatment.

The relationship between pain and depression is uncertain. Depression may be:

(1) a psychological consequence of pain,

(2) part of a reverberating circuit between pain and depression,

(3) one aspect of a psychobiologic disorder which underlies both conditions.

There is a monoaminergically-mediated pain - inhibitory mechanism which is located in the mesencephalic ventral central gray area. Increased levels of 5-HT increase analgesia whereas increased levels of norepinephrine decrease it. Dopamine potentiates analgesia to a greater extent than norepinephrine. The relationship between pain and depression may lie in the balance of brain monoamines. The enkephalins are also important as inhibitory neurotransmitters in pain appreciation. They are

found in the periaqueductal gray substance, the nucleus raphe magnus, the locus coeruleus and the substantia gelantinosa of the spinal cord. This distribution closely follows nociceptive pathways. As both the periaqueductal gray substance and the nucleus raphe magnus have high concentrations of 5-HT and the locus coeruleus has a high concentration of norepinephrine it appears that affective and nociceptive pathways overlap. This may explain the coincidence of pain and depression and the response of chronic pain to antidepressant medication. This presupposes that chronic pain and depression are both neurotransmitter deficiency disorders and that antidepressants restore 5-HT, norepinephrine and enkephalin levels to normal. Interaction between the biogenic amines and the enkephalins is thought to take place via mutually interacting feedback loops at midbrain, medullary and spinal cord levels. (46,193)

15.4 Summary

(1) Both psychogenic and somatogenic pain are associated with increased neuroticism.

(2) Anxiety, hysteria and reactive depression are all associated with pain complaints.

(3) Pain may be a symptom of reactive depression and depression may be a reaction to chronic pain.

(4) Depression masked by somatic complaints is underdiagnosed. Early treatment with antidepressant medication improves the prognosis.

(5) The response to antidepressant medication is good - especially if the onset of depression preceded the pain. However even if the reverse is the case treating the depression can still increase the tolerance of the pain.

(6) Some characteristic behaviours in reactive depression can cause difficulty in patient management unless they are understood and attended to.

CHAPTER 16

The influence of ovarian hormones on migraine

16.1 Migraine - its relationship with menstruation, pregnancy and the menopause

Although a variety of hormones have been linked with migraine the marked female preponderance in the condition following puberty has focussed attention on the role of the reproductive hormones.

Various authors have suggested that approximately two-thirds of women associate the periodicity of their migraine with the phases of their menstrual cycle. Most have an increased incidence of migraine just prior to or during menstruation. Ovulatory migraine is much less common. (194-6). However, in a clinical survey of 138 menstruating women with migraine, Epstein and Hockaday found that true menstrual migraine confined to just before or during menstruation was rare, affecting only 14% of the patients. Menstrual migraine was associated with the onset of migraine at the menarche, weight gain and breast discomfort around the time of menstruation and improvement during pregnancy. (197) Although it has been claimed that only common migraine is menstrually-related this does not accord well with clinical experience.

Nattero performed a chi square analysis on data from 720 female migraineurs and defined two populations with menstrual migraine and non-menstrual migraine. These populations differed statistically with regard to family background, history of headache, premenstrual stress,

relationship with menstruation and pregnancy, pattern, frequency and duration of headaches, topography (unilateral, bilateral and radiation of pain), site and accompanying symptoms. (194) However, although Epstein and Hockaday found that plasma levels of oestrogen and progesterone were significantly increased in migraine patients compared with controls there were no significant differences in hormone levels between the menstrually-related and non-related groups. There is, therefore, no evidence that absolute levels of reproductive hormones are responsible for the differences between the two groups of migraine patients. (197)

Nonetheless in a subgroup of migraine patients the reproductive hormones are closely associated with the development of migraine. The fact that the premenstrual and menstrual phases of the cycle are most commonly involved has suggested a relationship with falling levels of oestradiol and progesterone. Normally these hormones decrease synchronously. Somerville manipulated hormone levels by separately administering progesterone and oestradiol to migrainous women and normal controls and prospectively observing the relationship between progesterone and oestradiol levels and the occurrence of migraine. He concluded that withdrawal of oestrogens, rather than progesterone, during the premenstrual phase was more likely to precipitate migraine. (198,199)

In Epstein and Hockaday's survey 66% of women reported improvement during pregnancy. This accords fairly well with the results of two other studies which gave rates of 50% and 77% respectively. (200,201) In the second of these studies Somerville found that the majority of women had relief of their migraine during the second and third trimesters but

could have an exacerbation in early pregnancy. He related this to fluctuating progesterone levels. (201) Migraine can arise for the first time during pregnancy - usually in the first trimester. Callaghan and Somerville differ in their estimates of the frequency with which this occurs - probably because of different diagnostic criteria for migraine and confusion with non-migrainous vascular headaches. (200, 201).

There is little evidence that migraine decreases in frequency after the menopause. (197) Hormone replacement therapy can exacerbate migraine. This can be obviated to a great extent by using a low dose of oestrogen continuously rather than by cyclical administration. (202) Several days exposure to high oestrogen levels appears to be necessary before oestrogen withdrawal precipitates migraine.

16.2 Oestrogen and the sympathetic nervous system

Oestrogen may increase the sensitivity of the blood vessels to other factors. This is likely to be independent of progesterone. Oestrogen could achieve its effects through the sympathetic nervous system. It has been suggested by Welch et al that increasing levels of oestrogen lead to increased noradrenaline receptor production in vascular smooth muscle and also block noradrenaline's action at the neurovascular junction thereby activating 2 adrenoceptors and causing a partial sympathectomy. This is coupled with concurrent inhibition of catechol-ortho-methyl-transferase (COMT) and mono-amine oxidase (MAO) and decreased synaptic release of noradrenaline. The latter has the predominant effect. (195)

16.3 Endogenous opioids, ovarian hormones and migraine

Ovarian steroids are thought to modulate endogenous opioid systems. Opiate μ receptors are found in the arcuate nucleus of the hypothalamus where they are known to exert a tonic inhibition on luteinising hormone releasing hormone (LHRH) secretion. Naloxone, a specific μ antagonist, causes an increase in peripheral concentrations of luteinising hormone (LH). This effect has been used to investigate CNS opiate receptor activity. The major drawback is that pituitary gonadotrophe function inevitably affects the outcome following naloxone administration and a variety of factors can be involved in this. Genazzani et al used this method to examine three groups of patients:

(i) Group A - 7 healthy post menopausal women treated with a combination of sequential oestrogens and progestagens

(ii) Group B - 10 healthy women in the reproductive age group who had had a premature menopause due to hysterectomy and ovariectomy for intrauterine fibrosis. Half of this group had the same treatment as Group A and the other half had progestagen supplementation only

(iii) Group C - 8 post menopausal women suffering from common migraine treated in the same way as Group A.

Group A had no LH rise after naloxone initially but went on to do so after hormone replacement therapy (HRT). The menopause appears to be accompanied by an impairment of opiate receptor function which can be modified by HRT. Group B also lost the LH rise after surgery and

regained it with combined HRT but not with progestagens alone. Oestrogens seem to play a major role in modifying central opiate activity. Group C had no change in LH values after naloxone. An LH rise was again apparent after sequential hormone treatment.

Progesterone seems to enhance the action of oestrogens although it is ineffective alone. The impairment in central opiate receptor function in common migraine can be corrected by HRT suggesting it has a potential role in the treatment of common migraine exacerbated by the menopause. (203)

16.4 Migraine and the oral contraceptive

There is a well recognised relationship between the oral contraceptive and migraine. Headache is the first or second most common symptom described with oral contraceptive use. Patients with established migraine have an 18-49% increase in the frequency and severity of attacks when taking oral contraceptives. This tends to happen during the drug-free interval of the cycle. When migraine begins for the first time after starting on the oral contraceptive this is not the case. A small number of migraine patients seem to improve whilst taking the oral contraceptive but as yet this group has not been systematically investigated. A family history is less likely in patients who develop migraine after, rather than before, starting to take the oral contraceptive. When migraine occurs for the first time after starting on oral contraceptives it is most likely to appear in the early cycles. However it can also occasionally arise after prolonged administration. Stopping the oral contraceptive does not always stop the migraine which

may continue long term. (195)

An exacerbation of migraine following oral contraceptive use may be more likely if:

(i) patients are aged more than 30 years and have menstrual migraine,

(ii) there is an interval of greater than 30 days between menstrual periods,

(iii) patients are multiparous,

(iv) there is postpartum onset. (196)

Phillips, a consultant neurologist, reported on 41 patients attending his outpatient clinic. He himself acknowledged that they were a highly selected group. Half of the patients had pre-existing migraine and half had a new onset of migraine subsequent to starting on the oral contraceptive. Fifteen patients in the total sample were noted to have depressive symptoms. There was no significant difference in the frequency of depression in either group of migraine patients. Unfortunately no rating scale for depression seems to have been used and the assessment of depression was therefore a subjective one. (204)

Mood change and the oral contraceptive

In a small uncontrolled study of 12 volunteers with no previous history of mental illness visual analogue scale ratings of depression increased from day 11 to day 19 of the menstrual cycle. There was no such trend for anxiety scores. (205)

There have also been larger studies of psychological symptoms while

taking the oral contraceptive, both of which included a control group of women who were using physical methods of contraception.

In a study of 168 women taking oral contraceptives and 93 using physical methods of contraception the distribution of scores obtained using the Beck Self-Rating Depression Inventory were very similar except that 6.6% of the oral contraceptive group scored 25 or more compared to none of the control group. The length of time on the oral contraceptive, the type of oral contraceptive taken and age were not significantly related to depression score. Some oral contraceptives appeared more likely to cause depressive symptoms than others but this could have been an artefact of the population studied. This effect was not obviously related to alterations in the balance of oestrogen and progesterone. (206)

In a second study the same author combined a questionnaire survey of menstrual symptoms with administration of the Maudsley Personality Inventory in 152 women about to start on the oral contraceptive and 40 women about to use the cap or the sheath for contraception. Follow-up questionnaires were sent to the oral contraceptive group at 5 weeks, 5 months and 11 months and slightly less regularly to the control group. The oral contraceptive significantly decreased premenstrual depression and irritability and dysmenorrhoea throughout the period of the investigation compared to the retrospective ratings for the period prior to starting oral contraceptive. Six per cent of the oral contraceptive group compared to 2% of the controls had moderate to severe depressive symptoms at follow-up. Both groups had a 5% incidence of irritability. None of the control group complained of headache but 4% of the oral

contraceptive group mentioned this at the 5 week follow-up, 7% at the 5 month review and 2% at 11 months. Neither the subject's age nor the composition of the pill made any difference to the scores for depression or irritability. However complaints of premenstrual moderate or severe depression prior to starting on the oral contraceptive were associated with an increased incidence of depression. Depression on the oral contraceptive was also associated with an increase in dysmenorrhoea. (207)

16.5 The premenstrual syndrome as a model for the association of migraine and affective disorder

In retrospective studies 29-97% of women report cyclical changes of some kind related to menstruation. However, although prospective studies have found increased reporting of pain and water retention premenstrually mood change was randomly distributed throughout the cycle. In retrospective studies women may incorrectly attribute mood change to the premenstrual phase as a result of their expectations.

Premenstrual changes can be positive or negative, e.g. increased energy, sex drive or feelings of affection or the opposite. The most common psychological changes are irritability, depression and lack of energy; the most common somatic symptoms are bloatedness and breast tenderness. There is wide variation in both the types of symptom and their timing. This contributes to the difficulty in obtaining a standard definition of the premenstrual syndrome. Premenstrual changes have been described as a cyclic change in the intensity of the symptom(s) measured from the second week of the menstrual cycle compared to the peak

intensity of the symptom during the late luteal phase (one to seven days prior to the onset of the menses).

Premenstrual depression has been used as a model for affective disorder on the basis of studies which have shown:-

(i) a positive correlation between premenstrual depression and a lifetime diagnosis of affective disorder,

(ii) that premenstrual depression may be severe enough for patients to seek treatment for it,

(iii) that suicide attempts and admissions to psychiatric hospitals for depression are associated with the paramenstrual period,

(iv) that premenstrual exacerbation of depression is seen in patients with depressive disorders.

Typically endogenous depressive symptoms do not occur in premenstrual depression. However endogenous depression is itself only one subgroup of depressive disorder. Using the Premenstrual Assessment Form (PAF) Halbreich et al identified 145 women from a sample of 335 who had what they defined as a Full Depressive Syndrome. This Full Depressive Syndrome has six non-mutually exclusive subtypes. None of the women met the recognised criteria for endogenous depression. However 63% had Atypical Depressive features, 52% characteristics of Hostile Depression, 42% met criteria for the Anxious-Agitated Depressive Syndrome and 42% had features of Withdrawn Depression.

Criteria of the Premenstrual Assessment Form Typological Categories

FULL DEPRESSIVE SYNDROME

A. 1. Depressed or low mood - 1 of the following 5 items must be at least mild (3-6): Feel depressed (233) or Feel "empty" (263) or Feel sad or blue (265) or Feel lonely (271) or Pessimistic outlook (339)

OR 2. Loss of interest or pleasure - all of the following 4 items must be at least mild (3-6): Less sexual interest (323) and Avoid social activities (324) and Want to be alone (328) and Less leisure activities (343)

OR 3. Irritable - 1 of the following 2 items must be rated at least mild (3-6): Outbursts of irritability (264) or Feel "at war" (269)

B. If Depressed - at least 4 of the following 8 items, or item sets, must be rated at least mild (3-6). If Irritable or Loss of interest or pleasure only, at least 5 of the 8 items must be rated at least mild (3-6):

1. Appetite change - Loss of appetite (222) or Weight gain (273) or Increased appetite (331)
2. Sleep change - Hypersomnia (219) or Trouble sleeping (278)
3. Decreased energy (216)
4. Psychomotor change - Physical agitation (228) or Less desire to talk or move (237)

5. Less interest - Less sexual interest (323) or Avoid social activities (324) or Want to be alone (328) or Less leisure activities (343)
6. Self deprecation - Guilt feelings (262) or Decrease in self esteem (316)
7. Concentration difficulties (245)
8. Suicidal ideation (236)

ATYPICAL DEPRESSIVE FEATURES

A. Meets criteria for Full Depressive Syndrome
B. Rapid mood changes (215) or Mood swings (260) (rating of 3 or more)
C. At least 2 of the following 4 items rated 3 or more:
   1. Hypersomnia (219)
   2. Feel sleepy (241)
   3. Crave specific foods (330)
   4. Increased appetite (331)

ANXIOUS-AGITATED DEPRESSIVE FEATURES

A. Meets criteria for Full Depressive Syndrome
B. At least 2 of the following 4 items rated 4 or more:
   1. Feel anxious (218)
   2. Feel jittery or restless (221)
   3. Physical agitation (228)
   4. Pick skin/bite nails (259)

HOSTILE DEPRESSIVE FEATURES

A. Meets criteria for Full Depressive Syndrome

B. At least 3 of the following 6 items rated 3 or more:

1. Violent (240)
2. Outburst of irritability (264)
3. Feel "at war" (269)
4. Act spiteful (270)
5. Intolerant (274)
6. Blames others (317)

IMPAIRED SOCIAL FUNCTIONING

At least 3 of the following 11 items rated 3 or more:

1. Tend to nag (235)
2. Decreased judgment (247)
3. Family notes mood (268)
4. Stay at home (322)
5. Avoid social activities (324)
6. Lowered performance/efficiency (326)
7. Miss time at work (327)
8. Lack of inspiration (329)
9. Less attention to appearance (333)
10. Less housework (342)
11. Less leisure activities (343)

GENERAL DISCOMFORT SYNDROME

At least 1 of the following 3 items rated 3 or more:

1. Headaches or migraines (224)
2. Backaches/joint/muscle pains (267)
3. Abdominal discomfort/pain (276)

WATER RETENTION SYNDROME

At least 3 of the following 6 items rated 3 or more:

1. Breast pain or swelling (223)
2. Urinate less (272)
3. Weight gain (273)
4. Abdominal discomfort/pain (276)
5. Water retention signs (321)
6. Feel bloated (325)

AUTONOMIC PHYSICAL SYNDROME

At least 3 of the following 7 items rated 3 or more:

1. Nausea or vomiting (227)
2. Dizziness, faintness, vertigo (234)
3. Rapid heartbeat (243)
4. Urinate frequently (253)
5. Become constipated (254)
6. Urinate less (272)
7. Feel cold (334)

The authors emphasise the importance of collecting both retrospective and daily prospective data when assessing the association of mood change and menstruation. Day-to-day swings in mood and behaviour are common and are thought to be a reflection of the bipolarity in the changes which are ocurring.

In a study of 194 women which used the Schedule for Affective Disorders and Schizophrenia (SADS) to obtain current and lifetime RDC diagnoses and the PAF assessment 57% of women with a lifetime diagnosis of Major Depressive Disorder also had a Premenstrual Full Depressive Syndrome while only 14% of women who were 'never mentally ill' met the PAF criteria. The PAF Full Depressive Syndrome was particularly closely associated with recurrent unipolar depression. This association of a premenstrual affective syndrome with a lifetime diagnosis of affective disorder is consistently reported in several studies. Two studies have also reported an association between the premenstrual affective syndrome and the later development of affective disorder. However the follow-up period was fairly short and the magnitude of the association was low. They suggest the possibility that dysphoric premenstrual changes may be a predictor for the future development of major depressive disorder. (208).

Oestrogen is thought to produce CNS excitation whereas progesterone produces inhibition. Women with primary generalised petit mal epilepsy have a distribution of attacks which is similar to the pattern of the premenstrual syndrome. In focal epilepsy there are two peaks of seizure frequency - at menstruation and during the pre-ovulatory oestradiol peak.

Improvement in mood typically occurs in the late follicular phase, corelates with the pre-ovulatory oestradiol peak and is consistent with the positive excitatory effect of oestradiol. During the luteal phase however negative changes in mood continue to increase during both the rise and fall of oestradiol and progesterone. The ratio of oestradiol to progesterone may be the crucial variable.

Surveys of oral contraceptive users have tended to find a lower incidence of premenstrual syndrome than those of non pill-users. Although several studies have reported a decrease in premenstrual symptoms while taking the oral contraceptive they have not been placebo-controlled. Early studies on oral contraceptives implicated the progestagenic constituent as a cause of negative psychological symptoms. Pyridoxal phosphate is a co-enzyme which is involved in the decarboxylation of 5-hydroxy-tryptophan to 5-HT and dopa to dopamine. A subgroup of patients who become depressed on the oral contraceptive are pyridoxine deficient and the depression responds to treatment with pyridoxine.

Endogenous opiates have been suggested as the causal agents in the premenstrual syndrome. Opiate receptors have been identified on dopaminergic neurones. Activation of these receptors at presynaptic sites decreases the cell firing rate leading to the gradual development of disuse hypersensitivity in the postsynaptic neurone. This could in turn account for the tolerance associated with chronic opiate administration and withdrawal effects when the opiates are suddenly stopped. A two phase model of opiate effect has been postulated in premenstrual symptoms. This combined inhibition induced by a mid-luteal rise in

opiates, followed by a withdrawal effect accompanying the premenstrual fall in opiates. (209)

16.6 The inter-relationship between prolactin, ovarian steroids and migraine

Prolactin has been closely linked with ovarian steroids in its effect on migraine. Many of the trigger factors and effective treatments for migraine are associated with high prolactin levels. These are, in turn, linked to alterations in free fatty acid concentrations. However Nader et al, in a small study of migrainous patients, was unable to provoke migraine by artificially raising prolactin concentrations. This is in agreement with the finding that migraine is particularly likely to remit in the later stages of pregnancy when there is a 5 to 10 fold increase in prolactin concentrations. Changes in prolactin concentration were also found to be independent of the free fatty acid response to glucose. (210) Nevertheless Polleri et al have shown that there is a disturbance in the regulation of prolactin secretion in migraine. This does not appear to be due to alteration in the rhythm of prolactin secretion, although as this part of the study concerned only 6 male patients and the type of migraine was not specified, the results are not conclusive. Pharmacological studies using drugs which affect monaminergic and serotoninergic systems indicate an altered response to these compounds in migraine - particularly when the drugs used affect dopamine-dependent regulation of prolactin secretion in the pituitary. Prolactin does not appear to be responsible for pain in migraine. (210)

The central regulation of prolactin release is very complex but

involves an interaction of endogenous opioids and neurotransmitters such as dopamine and γ-amino butyric acid (GABA). The pathway through which they achieve their effects is probably serotoninergic. (212) Murialdo et al compared 23 healthy women with 17 women with menstrual and 17 women with non-menstrual migraine. All migraineurs had common migraine. Prolactin secretion was investigated pharmacologically. The overall conclusion was that there was an increased lactotrophe prolactin reserve in migraine. This was likely to be due to increased dopamine receptor sensitivity. There were no statistically significant differences in either prolactin responses or plasma levels of ovarian steroids when the menstrual and non-menstrual migraine groups were compared. However comparing the total group of migrainous women with the healthy controls 17-β-oestradiol levels were higher in both the follicular and luteal phases whilst progesterone levels and the progesterone to oestradiol ratio were lower in the luteal phase. This suggested a change in the oestrogen-dependent modulation of pituitary dopamine receptors. (213)

CHAPTER 17

The relevance of cerebral asymmetry to migraine and affective disorder

One of the most striking features of the migraine headache is that the pain is frequently restricted to one side of the head. There is no satisfactory explanation of how the headache can vary in location in different attacks.

A considerable amount of research has been conducted on cerebral asymmetry and its relationship to both migraine and psychiatric disorder.

It has been apparent since Broca's discovery that the neural basis of language was located primarily on one side of the brain and that there were differences in the capacities of the two hemispheres. (214) There has been controversy over whether this asymmetry is present from birth or whether both hemispheres initially have the capacity for language development. The left hemisphere is usually the dominant hemisphere for speech. (Dominance in this context refers to the predominant lateralisation of any function on one side or the other in the nervous system.) Despite the early predisposition of the left hemisphere to acquire language, damage can result in a partial or complete shift of this function to the opposite hemisphere. There is thus some flexibility in the organisation of asymmetric functions, at least initially. (215) Cerebral dominance develops concurrently with speech and becomes fully established well before maturity. Dominance for language and handedness are linked. In most people both are located in the left hemisphere. However although this is fairly straightforward in the right-handed

members of the population, a proportion of left-handers have bilateral representation of language. (214) Anatomical asymmetries in the auditory regions (temporal planum) and Sylvian fissures have been found in the foetus. They are thought to be related to right-left differences in function. These asymmetries in the temporal planum could be linked with language lateralisation. There are also structural asymmetries in the frontal and occipital lobes and the lateral ventricles which correlate with hand preference. (216)

17.1 Cerebral asymmetry and migraine

Studies of human brains have provided some evidence for developmental malformation in the left posterior superior temporal region in dyslexia. All developmental disorders of language, speech, cognition and emotion which begin before puberty have a strong male predominance and a higher rate of left handedness than that found in the general population. Two studies have found that both migraine and immune diseases (e.g. ulcerative colitis, coeliac disease, regional ileitis, thyroid gland disorders and childhood allergies) have higher frequencies in left- than in right-handers. However a questionnaire method was used and for the first study this was the only evidence on which a diagnosis of immune disease was based. The second part of the investigation, which concerned migraine, used a patient group selected from neurological clinics. No diagnostic criteria were quoted for migraine and the type of migraine was not specified.

The anatomical asymmetries associated with developmental learning disorders appear early in foetal life. Three possible reasons for this

could be:

(i) a fixed developmental pattern,

(ii) intrauterine influences which accelerate development on the right side of the brain,

(iii) intrauterine factors which slow development on the left.

The abnormalities in dyslexic brains suggest a developmental delay in the migration of cells. As these disorders are found mainly in males this delay could be related to testosterone. It has been suggested that testosterone is responsible for the delay in the growth of the left hemisphere, especially the areas related to language and handedness. Testosterone also suppresses the activity of the thymus. The foetal thymus appears to control the development of the lymphocytes which prevent autoimmunity. This theory assume a link between autoimmunity and migraine which is not widely documented elsewhere in the migraine literature. (214, 217)

In addition to structural asymmetries there are also interhemispheric differences in neurotransmitters and cerebral blood flow patterns.

In an analysis of the concentrations of between 3 and 5 neurotransmitters in 9 different structures on the right and left sides of 14 human brains, brains asymmetric for one substance or region were consistently asymmetric for other substances or regions. There was evidence for a diffuse mechanism regulating both the nature and extent of chemical asymmetry in different brain structures. (218)

Both interhemispheric and antero-posterior differences in cerebral blood flow patterns have been demonstrated. The latter are more marked. Complex tasks produce increased activation in multiple areas of the hemispheres. Despite this overall flow patterns are very similar in both hemispheres even during activities such as speech which are mainly located in one hemisphere. (219)

Cerebral asymmetries in migraine have been investigated electrophysiologically by EEG recording of visual evoked potentials (VEPs). VEPs are altered by anatomical changes, abnormalities in neurotransmitters and ischaemic damage to the central nervous system. For the most part changes in VEPs correlate with the severity of the underlying condition. In migraine the hemisphere which is thought to be ischaemic has an altered VEP. In a comparison of 22 normal controls and 16 migraine patients, VEPs were recorded using vertex and temporal lobe placements. All subjects were right handed. The type of migraine was not specified. VEP abnormalities were found in the vertex and temporal recordings in the migraine patients. When the results were analysed according to the side of the headache only the temporal recordings were abnormal in patients with right-sided headache. This group had larger VEP amplitudes at the left temporal site compared to the group with bilateral headache. (More of the patients in the study had left-sided headaches.) There is a difference in the responsiveness of the visual system in migraine patients which could be due to a failure of sensory input modulation or an increased response to such input. The asymmetrical VEP response in patients with right-sided headache could reflect a secondary process in the left hemisphere set in motion by repeated right hemisphere dysfunction. (220)

Unfortunately not all studies on this aspect of migraine agree. In another study of 20 women with classical migraine who were selected from a Neurology Clinic and matched for sex and age with clinic staff there was little difference in pattern-shift VER between migraine and control subjects. There was a slightly longer P100 component latency and slightly smaller P100 amplitude implying that there might be minor abnormalities in visual sensory processing in some migraine patients. When the data were analysed according to the most frequent lateral location of the headaches there were slight differences in P100 amplitudes in left-sided subjects although these did not reach statistical significance. Minor differences were found between the migraine and control populations when spectral analysis of the background EEG was used. However these were not thought to be clinically significant. The authors suggest that the differences between their own and previous work are probably due to the careful matching of migraine and control populations in their study. (221)

Subsequently this work on central regulatory processes in migraine has been extended by investigating the effects of sensory stimuli on autonomic responses. The Pavlovian orienting response and its habituation with repeated stimulation were used to produce autonomic responses which were monitored by measuring skin conductance. Initially 12 normal controls were compared with 11 patients with migraine and 7 patients with bilateral tension headache. All except one of the migraineurs had classical migraine. Anxiety levels were measured using a self-report questionnaire and no differences were found between the 3 groups. Patients with left-sided migraine were less responsive to visual

stimuli than those with right-sided migraine. The left-sided migraine patients were less responsive and the right-sided migraine patients more responsive than the normal controls and the patients with tension headache. Patients with tension headache were no different from normal controls. As some patients were on prophylactic medication a further study was conducted on drug-free patients. On this occasion auditory, rather than visual, stimuli were used. Thirteen patients, 7 with left-sided and 6 with right-sided migraine, participated in the study. A minority of patients in each group had common migraine, the remainder the classical variety. All patients were right-handed. The same pattern of results was demonstrated as in the first study for the migraine group. There appears to be a dysfunction in the mechanism which regulates autonomic responsiveness in migraineurs. This may involve the diffuse thalamic projection system which regulates regional patterns of cerebral activity. (222)

Cerebral asymmetry has been linked to responsiveness and the rate of habituation of electrodermal responses to sensory stimuli. Patients with left hemisphere lesions and dysphasia show higher galvanic skin responses whereas patients with lesions of the right hemisphere and unilateral spatial neglect are under-responsive compared to non brain-damaged patients. (223)

Patients with left hemisphere damage often appear depressed. This is usually described as a reactive depression due to insight into the extent of their loss of function. Patients with left hemispheric lesions are, by contrast, often emotionally indifferent to them. Although patients with right hemisphere damage are unable to understand or convey

emotional expression in speech, this is not enough to explain their lack of reaction. Indifference is usually coupled with unilateral neglect. It has been suggested that this is an attention - arousal defect caused by dysfunction in a cortico-limbic-reticular loop. The cortex is responsible for analysing stimuli and the reticular system mediates arousal. Ablation of the areas of cortex which produce arousal results in neglect and, possibly, hypoarousal. Disruption of this loop has been suggested as the cause of neglect in these right hemisphere damaged patients. The reactive depression seen in left hemisphere damage may be partly a consequence of disinhibition of sympathetic activity coupled with awareness of loss. (223)

In normal subjects fast habituation on electrodermal recordings is associated with left hemisphere influence and slow habituation with predominantly right hemisphere influence. Migraine therefore "would appear to represent a state of extreme hemispheric imbalance and it is this which underpins the laterality of pain." (222,224) Dysregulation of regional activation due to a dynamic process could provide an explanation for the episodic nature of migraine and the inconsistencies in both the laterality of the pain and the laterality of the neurological symptoms which may be associated with the condition. (222)

17.2 Laterality of migraine and cognitive processing

Crisp et al have suggested that migraine may be "a fail-safe reaction to 'information overload' and furthermore that laterality might be determined by the nature of this information i.e. verbal or visuospatial." This overload could result from excessive intellectual or

social effort or from a conflict between current experience and previously held values. Migraine patients show high levels of sociability and dysphoria combined with an absence of excessive neurotic avoidance and ritual mechanisms. In a small study 18 migraine patients were grouped according to the laterality of their symptoms and the type of migraine (i.e. common or classical). Low levels of anxiety and depression were found in the two patients with left-sided classical migraine. Both of these patients were right-handed. This contrasted with generally increased levels of anxiety and depression in the migraine group as a whole when compared to scores obtained in the general population. The low levels of dysphoria observed in left-sided classical migraine and the high levels seen in right-sided classical migraine agree with the hypothesis that euphoria is associated with left hemisphere inactivation and dysphoria with right hemisphere dysfunction. An immediate criticism of this hypothesis is that it applies only to classical and not to common migraine. (225) However there is some indirect support for it in that cerebral blood flow changes are also found in classical, but not in common, migraine.

More recently this work has been extended by an examination of two further hypotheses:

(1) that subjects with exclusively one-sided migraine would have a dysfunction of the same hemisphere. This would leave them susceptible to strain when processing combinations of verbal and non-verbal information,

(2) waking activities would produce migraine in the hemisphere principally involved.

The authors highlight the difficulty of obtaining a sufficiently large sample of patients with exclusively unilateral migraine. Their patients are therefore a highly selected subsample of migraine patients and this must raise doubts about the applicability of the results to the migraine population as a whole. However 9 migraine patients had their verbal and non-verbal abilities measured using the corresponding verbal and non-verbal performance scales of the Wechsler Adult Intelligence Scale (WAIS). The psychologists administering the WAIS were blind to the laterality of the migraine. All patients were right handed. The results obtained were inconsistent with the hypotheses. Verbal-non-verbal discrepancies were small and not always in the expected direction. This could have been because the WAIS was too insensitive to detect interhemispheric differences, or more probably, it suggested that the original hypotheses required revision. (226)

Taken overall, the limited amount of evidence available does not suggest that cognitive processing plays a major role in the laterality of migraine and that it is, at most, only one of many contributory factors.

Evidence for lateral specialisation in the intact brain is found in electroencephalogram and visual evoked potential studies as well as the investigation of left-right visual field differences in perception and reaction time. Typically, right handed people deal primarily with language processes and arithmetic in the left hemisphere and spatial relationships and musical functions in the right hemisphere. Following commissurotomy operations, in which the fibres connecting the right and left hemispheres are cut, the left hemisphere retains the capacity for

speech, writing and calculation but is very limited in its ability to deal with spatial relationships. The right hemisphere can cope with complex spatial and musical patterns but can manage only very simple addition and has few words. Each hemisphere has a different cognitive style: the left has analytical, logical thinking and the right holistic, gestalt processing. It has been suggested that the right hemisphere is the anatomical equivalent of the Freudian unconscious and that repression and denial of material there is neurophysiologically based in inhibition of interhemispheric transfer of information. (227) A breakdown in interhemispheric inhibition has also been suggested by studies of cerebral laterality using dichotic listening tests in acute psychoses e.g. schizophrenia, schizoaffective illness and primary major depressive illness. (228)

Studies of patients with brain lesions show that schizophreniform symptoms are more likely to occur after left sided lesions and affective symptoms arise more often after right sided damage. The thought disorder and auditory hallucinations found in schizophrenia are in keeping with the specialisation of the left hemisphere for language and logic. The mood disorders in affective illness also correspond with the right hemisphere's capacity for non-verbal functions.

The direction of lateral eye movements (LEMs) is thought to reflect differential hemispheric activation. These LEMs are increased to the left following emotionally laden questions and this may reflect right hemisphere involvement in the processing of these questions. When patients with right and left hemispheric damage are compared those with right hemisphere damage have more difficulty in assimilating emotional

cues conveyed in speech. When full face photographs and their mirror reversals are split down the mid-line and composite faces made from two right halves and two left halves, subjects rate left sided composites as expressing more emotion than right sided composites. There is an excess of contralateral projections controlling facial muscles and the results may imply greater involvement of the right hemisphere in the production of emotional expression.

The right hemisphere therefore appears to be more important in the processing of emotional information and the production of emotional expression than the left hemisphere. This is consistent with right hemisphere involvement in affective disorder. (219)

17.3 Summary

The two hemispheres have different capacities. Dominance refers to the predominant lateralisation of any function on one side or the other in the nervous system. Dominance for language and handedness are linked. Hemispheric differences are linked to anatomical asymmetries. Migraine and immune disorders are associated with left-handedness.

There are also lateral asymmetries in the distribution of neurotransmitters and in cerebral blood flow patterns. Electrophysiological investigations in migraine have found lateral differences related to the side of the headache. Although the extent of the differences found has varied there seem to be alterations in visual processing in migraine and possibly also dysfunction in the mechanism which regulates autonomic responsiveness. Abnormalities in

responsiveness and the rate of habituation to sensory stimuli in patients with left and right hemisphere damage have been extrapolated to migraine to provide an explanation for the unilaterality of the headache.

Laterality of migraine might also be linked to hemispheric defects in cognitive processing. However there is little evidence that it makes a major contribution to this.

Cognitive processing does appear to differ hemispherically and this may be related to the different psychological symptoms elicited following right and left hemisphere damage.

CHAPTER 18

Conclusions from the Literature Review

The characteristic prodromal symptoms and the unilateral pain in migraine have been extensively described. The prodromal symptoms are usually assumed to be neurological in origin whereas the headache is assumed to be vascular.

From the 1800s onwards migraine has been described as a multifactorial condition. External factors such as emotional and intellectual stress interact with internal factors such as the phase of the menstrual cycle and emotional disturbance.

Although migraine and muscle contraction headache can occur together in the same patient both conditions are common the association could be coincidental. Clinically there are considerable differences between migraine and muscle contraction headache. Daily chronic headache appears similar to muscle contraction headache in duration but is actually closely related to migraine and antimigraine drugs may be a better choice of treatment for these patients.

As yet, classical and common migraine cannot definitely be said to be different entities, although there are sufficient differences between them to justify studying them separately.

The prevalence of migraine in British women is 24-29% and 15-20% in men. This sex difference may be due to higher reporting of the condition

by women. Half of migraine sufferers do not seek medical help. The typical age of onset is 20 and the probability of developing vascular headaches decreases after age 30. More intelligent migraine sufferers in upper social classes are more likely to consult a doctor about migraine and thus bias studies performed in GPs' surgeries and migraine clinics. There is no evidence that migraine is more common in more intelligent or upper class subjects in the community.

Twin studies, like family studies, suggest that there may be more than one migraine syndrome. In some cases there is a powerful genetic component but in others environmental factors are more important.

Migraine patients do not have a specific personality type nor do they have particular difficulty in expressing anger. There is an increase in obsessionality in migraineurs but this may be an artefact of the clinic population.

Patients with migraine appear to react more to minor life stress. Recurrent headaches are associated with mild depressive illness, somatisation and anxiety. This remains after treatment and seems to be a state rather than a trait. The degree of distress is directly related to the frequency and severity of the pain.

Philosophically, a condition like migraine exemplifies the difficulties in conceptualising the interaction of mind and body. A modern view is a dualist-interactionist model in which the self-conscious mind is viewed as an independent entity which selects from the inputs available and integrates the results to produce conscious

experience.

There is good evidence for a vascular aetiology in the headache phase of migraine. Oligaemia is not closely related in time or in anatomical distribution to these symptoms. A neural origin for migraine attacks could explain the periodicity of migraine, the association of migraine and epilepsy, the relationship between tiredness and the precipitation of attacks and the resolution of attacks with sleep.

Regional cerebral blood flow data indicate that common migraine attacks are not preceded by, or associated with alterations in CBF. However rCBF is focally or possibly even globally reduced during the prodrome of classical migraine. Although older studies described hyperaemia during the headache phase of classical migraine more recent studies have found no change in blood flow. The CBF studies indicate that there is a gradual spread of disturbed function in the cortex. Leaõ's Spreading Depression (S.D.) is likely to be the primary disturbance of neuronal function which initiates cerebral blood flow changes. Stimulation of the visual cortex by light could raise the potassium ion concentration to the threshold required to elicit S.D. The effect of S.D. on pain sensitive fibres at the ventral surface of the brain could also produce the headache in classical migraine.

According to the hypoxic hypothesis cerebral hypoxia occurs in every attack of migraine. Whether or not prodromal symptoms occur is determined by the severity of the hypoxia and the site at which it occurs. It may be caused by excess sympathetic drive.

Migraine can be associated with persistent neurological dysfunction in a small proportion of cases. It is difficult to give an exact figure for the incidence of cerebral infarction in migraine as cerebral infarction is itself a multifactorial condition and it is difficult to separate out the contribution made by migraine from that of other factors.

Textbooks quote a 10% occurence of affective concomitants with migraine. 'Migrainous equivalents' representing brief manic-depressive cycles have been reported subsequently in patients who present initially with migraine. Previous studies of the correlation between self-report of mood changes and migraine have found that subjects with both migraine and muscle contraction headache are less alert during attacks and that feelings of constraint and fatigue are the best predictors of subsequent migraine headaches. It has also been suggested that there is a critical threshold for stress beyond which a migraine attack is produced or that there is increased sensitivity or reduced tolerance to stress just prior to attacks.

Depression has been linked with prodromal neurological symptoms in classical migraine and to the rCBF changes already noted in that condition. A diffuse decrease in rCBF has also been found in depression.

Multiple biochemical factors are probably involved in the CBF changes found in migraine. Noradrenaline and serotonin appear to be the two neurotransmitters which are most concerned. It is likely that they are both involved in the production of anxiety. Serotonin is also

thought to play a major role in depression.

There is a higher incidence of epilepsy in migraine than in the population as a whole. The incidence of EEG abnormality in migraine sufferers is also doubled. Leaõ's Spreading Depression may underlie both conditions. There are similarities between the association of affective symptoms and epilepsy and affective symptoms in migraine. The prefrontal cortex, the limbic system and the hippocampus appear to be the brain regions principally involved in the production of these affective symptoms. Depression is particularly linked to seizures with olfactory auras. Kindling within the limbic system could provide an explanation for the emotional changes seen in limbic epilepsy. Kindling can also occur in spreading depression and could, by analogy, be the underlying mechanism which links affective changes with migraine. This could provide a rationale for investigating the use of carbamazepine in the treatment of migraine.

Calcium channel blockers and antidepressants have some actions in common and a similar time course for their effects. This may involve an action on the contractile apparatus of vascular smooth muscle.

Olfactory hallucinations are produced by irritation of the uncinate gyrus or the adjacent temporal lobe. They are often linked with ictal affective states. There are close parallels between migraine and temporal lobe epilepsy.

Cocaine abuse can be used as a model for migraine hallucinations. Cocaine's stimulant effects include seizure-type discharges in the

temporal lobe and increased activity in the reticular activating system. Olfactory hallucinations have been reported in seven per cent of cocaine abusers.

Cocaine abuse has also been used as a model for the endogenous psychoses. Biological changes assoicated with cocaine mimic the effects of stress. It has been suggested that stress may precipitate psychiatric illness by triggering a kindling process in the limbic system.

Both tension headache and migraine sufferers report more minor life stress than controls. It has been shown that decreasing the effects of stress can affect the outcome of disease processes. The anterior pituitary, adrenal cortex and the sympathetic nerves are all involved in stress responses and possibly in the production of stress-related physical and psychiatric illnesses.

The endorphins affect both the central nervous system and the cardiovascular system. Stress activates the hypothalamic-pituitary-adrenal axis and this releases β-EP and ACTH from the anterior pituitary. The cardiovascular effects are mainly produced by the sympathetic nervous system. Endorphins are more closely implicated in the perception of pain than in psychiatric illness. They do not appear to play a major role in the production of affective changes in migraine.

Pain is associated with increased neuroticism - especially anxiety, hysteria and reactive depression. It can be a symptom of depression and depression can be a reaction to chronic pain.

True menstrual migraine is uncommon (approximately 14% of female migraineurs). It is associated with onset of migraine at menarche, weight gain and breast discomfort around menstruation and improvement in migraine during pregnancy. There is no evidence that absolute levels of reproductive hormones are responsible for this. However the withdrawal of oestrogens appears important. Oestrogens also seem to play a major role in modifying central opiate activity.

Many women incorrectly attribute symptoms to the premenstrual phase of their cycle as a result of their expectations. Premenstrual depression has also been used as a model for affective disorder.

The unilateral pain in migraine suggests that cerebral asymmetry is an important component of the condition. The two hemispheres have different capacities and there are lateral asymmetries in cerebral blood flow patterns and neurotransmitter distribution. There are lateral differences on electrophysiological investigation in migraine which are related to the side of the headache. Visual processing and autonomic responsiveness are also disturbed. Cognitive processing differs between the hemispheres but there is little evidence that this is related to the laterality of migraine.

CHAPTER 19

Research Priorities

19.1 General

This review of the literature has highlighted several important areas for future research. Regional cerebral lood flow studies suggest that the pathophysiology of classical and common migraine differs. It is therefore necessary to examine classical and common migraine separately to avoid obscuring differences between the two conditions. This would also help to identify other divergent factors which might shed further light on the aetiology and pathogenesis of both types of migraine.

The patterns of flow changes found is very reminiscent of Leaõ's spreading depression which has always been linked with migraine. As a consequence there has been a revival of interest in the neural hypothesis of migraine. Migraine has a recognised association with epilepsy. Temporal lobe epilepsy in particular has been linked with affective disorder. There is now evidence which also suggests that some patients with manic depressive illness have symptoms of temporal lobe epilepsy. A better understanding of the kindling phenomenon in temporal lobe epilepsy would be relevant to both affective disorder and migraine. In this context further assessment of the inter-relationship between olfactory hallucinations, temporal lobe epilepsy, depression and migraine would also be of assistance.

The amount of information available on neurotransmitter and

metabolic disturbance in the CNS during migraine is very limited. Hopefully the advent of PET with its increased information access will be useful in this respect. It is obviously extremely difficult to determine and quantify transient biochemical abnormalities but in time the information obtained could be linked with other transient neurotransmitter abnormalities in conditions such as affective disorder and epilepsy as well as acute and chronic pain.

After initial interest in major life events as contributors to the onset of physical and psychiatric illness there is now a growing appreciation of the role played by everyday, minor stresses in precipitating episodic conditions like migraine. Interestingly this does not appear to be linked with any specific personality characteristics. This is another area in which migraine can offer a model for the relationship between social and psychological variables and physical illness and, as such, it has yet to be fully explored.

Another important avenue to explore is the relationship between the hypothalamic-pituitary-adrenal axis, the endogenous opioid system, pain and depression. The HPA axis is involved in the response to stress and is closely affiliated with the endorphin system. How this is linked with pain and depression is yet to be determined.

The hemispheric asymmetry in migraine has always differentiated it from ordinary headache. Advances are now being made in systematically exploring these interhemispheric differences using psychophysiological methods but as better equipment and facilities become available further research opportunities will arise. This type of research could also

benefit from knowledge derived from other fields e.g. the regional cerebral blood flow studies with their implication of pathophysiological differences between common and classical migraine.

19.2 Specific questions to be answered in the present study

(1) What is the incidence of transient mood changes in association with migraine?

(2) What types of affective change are involved?

(3) What is the prevalence of persistent psychiatric disorder within a clinic population of migraine sufferers?

(4) Are there any factors which differentiate patients who experience transient affective change from those who do not?

(5) Do patients with classical and common migraine differ with respect to the incidence of either transient or persistent affective disorder?

(6) Can the affective changes in migraine be linked to regional cerebral blood flow abnormalities?

B. Aims, Design and Hypotheses

Aims

The starting point for this investigation is the clinical observation that some patients with migraine complain of mood changes which they associate with their attacks. An examination of the published literature indicates that, although this is widely recorded anecdotally, there have been few systematic attempts to investigate this symptom.

The first aim of this study is to determine the prevalence of these complaints and the type of mood change involved. The second objective is to define and quantify transient changes in mood and assess their relationship with migraine attacks. The third aim is to identify the factors in the individual which are related to mood changes. The fourth aim is to determine the incidence of psychiatric illness in migraine sufferers and to assess its relationship with acute mood changes associated with migraine attacks. The fifth and final aim is to attempt to determine the relationship between patterns of cerebral blood flow and mood changes in migraine.

Design

The design of this study is in three parts:

(1) the initial psychiatric interview,

(2) a six week prospective period during which data is collected on the occurrence of migraine and fluctuations in mood,

(3) monitoring of regional cerebral blood flow on two occasions - once

while the migraine is absent and once when it is present.

(1) Initial psychiatric interview

The immediate problem of determining the incidence of mood change as part of the migraine syndrome is best resolved by interviewing a group of migraine sufferers. Mood changes associated with migraine can then be identified initially on the basis of self report.

In order to assess the importance of individual factors in the predisposition to these changes information is also collected on:

(a) social and demographic factors,

(b) migraine symptoms,

(c) cerebral dominance,

(d) past history of emotional distress,

(e) family history of migraine and psychiatric illness,

(f) the relationship between migraine and menstruation,

(g) the frequency with which migraine is precipitated by emotional stress.

The next problem is to differentiate acute, transient mood changes from psychiatric illness. This becomes considerably more complex if the two co-exist. It then becomes extremely difficult to assess the contribution of psychiatric illness to acute mood changes related to the migraine attacks.

Concurrent psychiatric illness may influence the reporting of migraine-related mood changes. High levels of emotional distress at the

initial interview might also have the same effect.

A structured clinical interview is administered to obtain current and past psychiatric diagnoses. This is combined with rating the levels of anxiety, depression, euphoria and irritability. These measures provide an opportunity to look at the relationship between self report of mood changes, current and past psychiatric illness and current levels of emotional distress.

(2) Six week prospective rating period

Prospective daily ratings of migraine and mood are used to compare retrospective self-reporting of the association of mood change and migraine with an objective assessment performed at the time.

(3) Regional cerebral blood flow monitoring

Regional cerebral blood flow monitoring using peripheral injection of radioactively labelled technetium provides a safe, reliable and inexpensive method for examining cerebral blood flow changes.

Hypotheses

(1) that the mood changes associated with migraine are due to more than the coincidental expression of two common conditions, i.e. migraine and affective disorder, in the same individual,

(2) that a relationship can be demonstrated between the mood changes and abnormalities in cerebral blood flow - specifically that dysphoria is associated with flow abnormalities in the left hemisphere and euphoria

with flow abnormalities in the right,

(3) that mood changes are more likely to be associated with classical than with common migraine,

(4) that unilateral migraine affecting the dominant hemisphere is associated with depression and unilateral migraine affecting the non-dominant hemisphere is associated with euphoria.

Additional hypothesis based on unexpected findings during the collection of data from the initial interview:

(5) that olfactory hallucinations which are experienced as part of the migraine attack can be related to regional cerebral blood flow changes in the temporal lobes.

(C) Method

A consecutive series of new referrals to a migraine clinic were recruited to the study if they met the criteria of the Ad Hoc Committee on the Classification of Headache for common or classical migraine. All patients were women aged between 18 and 65, who did not have other serious physical illness. All patients who entered the study had to have an average of at least two migraines within a six week period.

All patients had an initial psychiatric interview to obtain social and demographic information, details of their migraine symptoms and migraine history and an account of the personal and family history of psychiatric disorder. The Structured Clinical Interview for DSM-III (SCID)(229) was completed to provide a record of both current and past psychiatric diagnoses and current levels of anxiety, depression and hypomania were evaluated using the Clinical Anxiety Scale (CAS) (230), the Montgomery and Åsberg Depression Rating Scale (MADRS) (231) and the Manic Rating Scale (MRS) (232).

The patients were then asked to complete daily visual analogue scales (VAS) of anxiety, depression and euphoria and daily Irritability, Depression and Anxiety (IDA) (233) questionnaires over the following six week period.

Finally patients who consented had regional cerebral blood flow measures performed on two occasions - once while the migraine was absent and once while it was present. The regional cerebral blood flow examinations were obtained using radioactively labelled technetium given

by peripheral venous injection. The radioactivity was detected using a stationary γ camera and linear slope analysis was performed by computer.

Approval for the study was obtained from the Psychiatry and Clinical Ethics of Medical Research Sub-Committee of Lothian Health Board and the ARSAC prior to initiating the research.

Methodological problems

(i) How to select the population for the survey?

As discussed in Chapter 3 of the literature survey approximately half of migraine subjects do not seek medical help for their condition. These patients can only be included in studies of migraine by using appeals in newspapers or magazines. This involves using questionnaires to screen the, hopefully, large number of respondents and then possibly obtaining specialist advice on the certainty or otherwise of the individual's diagnosis. This is costly and time-consuming and obtains only those individuals sufficiently motivated to reply.

Appeals to local general practitioners (GPs) for patients with migraine would provide a group of patients in whom the diagnosis was more reliable. However, as patients are generally accurate in their replies to questionnaires this is not a great advantage. Contacting a large number of GPs would probably lead to heterogeneity in referrals and, if the GPs were aware of the nature of the study, possibly a bias towards patients who they thought would benefit from psychiatric assessment.

The population selected for this investigation consists of a consecutive series of new referrals to a specialist migraine clinic run by a general physician with a particular interest in migraine.

The disadvantage of using this group is that it is highly selected - firstly because of the patient's own choice over whether to seek medical advice and secondly because of the GP's right to select which patients to refer on for a specialist's opinion. It would therefore be expected that the patients obtained would be at the more severe end of the migraine spectrum with an increased frequency and intensity of headaches. The sample might also be biased towards classical rather than common migraine on the assumption that both patients and GPs would be more concerned about the prodrome to classical attacks.

It is clearly impossible to extrapolate from the results obtained in this population to migraineurs as a whole.

However using patients from a migraine clinic has several advantages. This type of population has been extensively studied and the results of this study can readily be compared with the work of others. This group of patients is relatively easy to obtain if there is close liaison with the physician in charge of the clinic and bias towards a psychiatric type of referral can be avoided by interviewing all new patients. The psychiatric interview can be carried out immediately after the patient's appointment at the migraine clinic provided the patient is agreeable. Most patients find this more convenient than returning for a second appointment. Compliance with the research can also be improved by allowing the patient to meet the investigator before the psychiatric

interview. This often helps to allay the patient's fears that the physician or the GP secretly thinks that she is mad but does not wish to tell her so directly. A migraine clinic population also provides patients who have the high frequency of migraine attacks necessary for a prospective period of daily ratings of mood and migraine.

The marked female predominance in migraine means that it is extremely difficult to obtain a sufficient number of male new referrals within the period of time available for data collection to allow statistical analysis of the results. This study is therefore restricted to women only.

Intercurrent serious physical illness is excluded in order to reduce confounding variables which might obscure the relationship between mood and migraine.

Uncertainty over whether the pathophysiology of migraine and other types of headache, e.g. cluster headache and basilar migraine, is identical makes it preferable, within the limitations of the present study, to restrict the type of headache studied to the classical and common varieties of migraine.

(ii) <u>The selection of appropriate social, demographic and other data</u>

There are no clear guidelines on which questions are most relevant in this type of study. As it is, all information obtained from patients was based on the areas in the literature survey which seemed most appropriate to a psychiatric investigation. General information about

the population studied was also included to allow this investigation to be compared with the work of others.

(iii) Reliability and compliance with self-ratings

Self report is a notoriously unreliable way of collecting information particularly when the subject is asked for a retrospective account. This was one reason for including prospective daily ratings of mood and migraine.

The amount of information patients can be expected to record accurately over a six week period is limited. The methods used for data collection therefore have to be simple and quick and yet provide an objective measure which is reasonably easy for the investigator to score afterwards.

Compliance with this part of the study is difficult to obtain. It is improved if a good relationship is formed with the interviewer at the initial assessment interview and if the patient is given the opportunity to practise completing the scales under the supervision of the investigator. Clear written instructions are necessary on how to complete the scales at home. In an attempt to reduce bias the patients are advised that the interviewer is just as interested in patients without mood changes as in patients who experience them. To improve compliance with, and the reliability of, the ratings it is also suggested to patients that they complete the scale for the preceding 24 hour period just before they go to bed at night. As a 'halo' effect can occur when patients are asked to fill in the same rating scale repeatedly patients

are particularly asked to fill in each scale only for the previous 24 hour period and not to check back with previous ratings.

Patients are sent a follow-up letter at the end of this phase of the study reminding them to return their completed scales to the investigator. If no scales are forthcoming patients are contacted again by telephone. The more direct the contact the more likely the scales are to be returned. (234)

(iv) Choice of rating scales

The aim of the initial interview is to collect a large amount of information over a wide spectrum. To avoid overtaxing the patient, and thereby jeopardising compliance with further phases of the study, this has to be completed within a limited period of time. The overlap between symptoms of medical and psychiatric illnesses can cause considerable difficulty when attempting to classify psychiatric problems in patients who have concurrent physical illness. Where possible scales selected for this investigation are designed for use in a medical outpatient population and chosen to obtain diverse information quickly.

(v) Choice of method for regional blood flow monitoring

As described in the literature survey regional cerebral blood flow can be estimated in several ways. The method used in this survey involves a peripheral bolus injection of a measured dose of radioactively labelled technetium.

This technique has several advantages - it is widely available, inexpensive and safe. The only discomfort for the patient is the venepuncture required for the examination. It is also quick - only flow studies are used in the present investigation and these can be obtained within 15 minutes.

Numerical values can be obtained for hemispheric transit times and fractional flow rates as well as quadratic hemispheric values for areas corresponding approximately to frontal, temporal, parietal and occipital lobes. Unfortunately contamination from radioactivity in neck structures means that the figure for the occipital region is less accurate than the others.

(vi) Difficulty in obtaining patient co-operation for repeat cerebral blood flow studies

Although the majority of patients who complete the six week self-rating period are agreeable to having cerebral blood flow monitoring performed while their migraine is absent it is much more difficult to obtain repeat scans when the migraine is present. This is not unexpected as it is asking a lot for the patient to come up to hospital for an investigation when she is feeling unwell. In an attempt to improve compliance patients always have the first scan when headache-free so that they can meet the staff and become familiar with the radioisotope department when feeling well. They are given a telephone number to ring when they next have a migraine and are promised an immediate appointment so that they do not have to wait in the department while feeling ill. When patients are contacted to ascertain the reasons for noncompliance

with this phase they frequently explain that their headaches arise in the evening or at weekends when the radioisotope department is shut. (The consultant in charge therefore volunteered to come in out-of-hours if patients contacted him and a few more scans were obtained in this way.) Patients are also offered taxi fares to assist them in getting safely to and from the hospital when feeling unwell. However transport does not generally seem to be a problem. Several patients improve considerably following their initial interview at the migraine clinic and as a consequence have far fewer headaches. As migraine is an episodic disorder it is not entirely clear whether this improvement is a result of therapeutic intervention or 'spontaneous' remission. I did consider attempting to induce migraines with red wine or chocolate but few patients had a reliable history of this type of dietary response. It is also unclear whether these induced headaches are identical to spontaneous migraine.

(vii) Problems encountered in interpretation of the results

The first problem is that the self report of mood change at the initial interview frequently disagrees with the data obtained during the six week prospective rating period. As a consequence the data are assessed in two ways - firstly on the basis of the initial interview and then on the basis of the prospective period.

The prospective data are analysed as single cases (using time-series analysis) with cross correlation of migraine and mood. (235) This works well when there are several attacks of migraine during the six week rating period but data are lost if attacks are infrequent. This proved

to be an insoluble problem. It is also difficult to examine the interrelationship of migraine, mood change and menstruation. This has been resolved by using time series plots.

(viii) Difficulty in assessment of personality

Personality is one of the most poorly defined concepts in psychiatry and measures of personality tend, as a consequence, to be unreliable. (236)

Although I initially intended to include an assessment of personality discussion with psychologist colleagues and investigation of the tests and literature available convinced me that it would not be possible to obtain a quick, reliable assessment of personality which would accord with current views on the nature of this concept.

Literature on methods

Questionnaires and scales have three possible uses in psychiatric research:

(i) screening to detect the prevalence of a disorder in a community,

(ii) to establish the pattern of symptoms or characteristics in an individual or a group,

(iii) to measure the severity of disorders.

Scales are employed for all three purposes in the present investigation.

Questionnaires may be completed by the observer or the subject. In

observer-rated scales the investigator's expectations may bias the recording of results e.g. the rating of the severity of illness. The rater's personal experiences will also influence the way he or she views a disorder e.g. a GP and a psychiatrist might well view the level of depression found in a psychiatric in-patient population very differently. The major drawback of self-rating scales is that the patient has only his/her own experience to draw on in rating the severity of a problem. It is particularly important to choose the form of words carefully when visual analogue scales are used so that they are readily understood by a lay population. It has been suggested that the best way of obtaining accurate information is to use a combination of observer and self-rated scales. However discrepancies can arise between the observer's and the subject's views.

There are several general factors which it is important consider when selecting a scale for use in an investigation:

(i) the orientation of the scale. There may be an inherent bias in the items which make up the scale e.g. the Hamilton Rating Scale for Depression (HRSD) emphasises somatic symptoms and psychomotor behaviour whereas the Montgomery and Åsberg Depression Rating Scale concentrates on the patient's report of their mood,

(ii) the scale's ability to distinguish numerically between varying degrees of severity across the whole range of a disorder,

(iii) the amount of information which can be derived from the scale depends on the type of information it has access to e.g. a self report scale cannot assess all somatic symptoms which may or may not be concomitants of anxiety,

(iv) the ease with which it can be used,

(v) how well the scale measures the disorder it was designed to measure - this is a particular problem in psychiatry where the symptoms of different disorders overlap, e.g. anxiety and depression. (237)

The characteristics of the scale and its suitability for a particular study play a major role in determining the validity of the results obtained.

Scales selected for the present investigation

Observer-rated scales used in the initial interview.

Structured Clinical Interview for DSM-III (non-patient version) 1985. (229)

DSM-III diagnoses have particular advantages. The diagnostic criteria are phenomenologically-based and have specific inclusion and exclusion criteria. DSM-III thus offers a high degree of inter-rater reliability. Unfortunately it was developed in psychiatric patients who did not have serious medical conditions.

There are four possible ways of resolving the problem of diagnosing psychiatric illness in patients who have concurrent medical illness: (i) symptoms can be rated irrespective of whether or not they could be attributed to physical disorder. This produces high sensitivity to psychiatric disturbance but low specificity and many cases of physical illness will be falsely diagnosed as also having psychiatric illness, (ii) the criteria for psychiatric illness in medically ill patients can be altered by specifying those symptoms which are most likely to predict

psychiatric illness,

(iii) symptoms which are likely to be confused with physical illness can be eliminated whereas other, more psychiatric symptoms are retained. Which symptoms to include or exclude obviously needs to be clearly specified. This method can result in missing patients who are psychiatrically ill i.e. although it has high specificity the sensitivity is low,

(iv) the investigator can decide, on the basis of clear rules, whether a symptom is caused by physical or psychiatric illness and rate it accordingly. This is the approach used in the SCID. (238)

The most recent revision of the SCID in the non-patient version was obtained for use in the study.

The SCID has two parts - the first takes 5-10 minutes to complete and allows the rater to form a relationship with the subject while obtaining a brief overview of their current health and circumstances and identifying episodes of severe distress in their past history.

The second part of the SCID involves more detailed questioning about current and past emotional distress in order to reach DSM-III diagnoses if these are applicable. This can take anything from 20-40 minutes depending on the amount of psychopathology. The SCID is orientated towards affective disorder and neurotic illness but also includes a brief psychotic screening section. This is appropriate for use in a medical outpatient clinic population. Training in completion of the SCID was carried out in accordance with the Instruction Manual. (229)

A recent study demonstrated that the SCID had high inter-rater reliability and could also distinguish between generalised anxiety disorder and major depression in an outpatient population. (239)

The Montgomery and Åsberg Depression Rating Scale (MADRS). (1979) (231)

This instrument was derived from the Comprehensive Psychopathological Rating Scale (CPRS) (Åsberg et al 1978). (240) The CPRS is made up of 65 scaled items which cover a wide range of psychiatric symptoms. The 17 items which occurred most commonly in depressed patients were used as the basis for the MADRS. The ten items most sensitive to change were then selected to form the final scale. The MADRS has good inter-rater reliability and is valid when compared with a global clinical assessment. The MADRS has fewer items to score than the Hamilton Rating Scale for depression, a standard instrument, but has equally high reliability (241, 242). There is also less emphasis on somatic symptoms than in the HRSD and clear instructions on grading scores of individual items and this makes it particularly useful in a medical outpatient population. The MADRS has high specificity for depression and there is only one item which overlaps with the Clinical Anxiety Scale. This reflects the common association of anxiety symptoms with depression. (241) Nonetheless the two scales appear to measure different dimensions of mood disturbance. Snaith has subsequently established score ranges for the MADRS which allow patients to be grouped into recovered mild, moderate and severe categories. He has recommended that the MADRS be used concurrently with the Clinical Anxiety Scale. (243)

The Clinical Anxiety Scale (1982) (230)

The CAS was obtained by item analysis of the Hamilton Anxiety Scale (HAS). The HAS has 88 symptoms of anxiety included in 15 variables. Each variable is rated on a five point scale. In a two stage procedure correlations of individual items with a severity rating were obtained and then a number of scales made up of items with the highest correlations were compared in a new patient group. The final CAS consists of six items largely confined to psychic anxiety and muscle tension. The HAS and the CAS were both developed in clinical populations suffering from anxiety neurosis. However where the HAS was standardised on a group of 35 patients who were taking part in a drug trial, and therefore presumably all had moderate to severe anxiety requiring medication, the CAS was developed in a group of both out- and in-patients who covered a spectrum from recovery to severe anxiety disorder. The authors of the CAS have suggested that although it is intended for use in a clinical population it may have wider applicability than the HAS and can also be used in patients with anxious personality disorder. The decreased emphasis on somatic anxiety compared to the HAS may make the CAS more valid in the assessment of anxiety in patients with medical rather than psychiatric disorders. (230, 244). Score ranges which allow the severity of anxiety to be graded have subsequently been determined in the same way as for the MADRS described earlier. (243)

Manic Rating Scale (MRS) (232)

Euphoria has been reported as part of the migraine prodrome and subsequent to attacks. It is therefore as important to document

elevation of mood at the initial interview as it is to record depression. There is no totally satisfactory scale is available to measure elation in a non-patient population. All existing scales are for use in psychiatrically ill in-patient populations. The MRS is an eleven item, clinician-administered scale which is based on the core symptoms of the bipolar phase of affective disorder and includes abnormalities which cover the range from mild to severe illness. This scale is reliable, valid and sensitive and appears to function over the entire range of severity of manic illness. It is shorter and more sensitive than other available scales. (232,245,246,247).

Assessment of Handedness and Cerebral Dominance

The assessment of cerebral dominance from handedness is not entirely straightforward as the preferred hand is not necessarily constant when a variety of manual behaviours are sampled. Handedness can be assessed either by presenting the subject with unfamiliar tasks which he is asked to complete with minimal practice or by using inventories of everyday tasks. In the present context, in conjunction with all the other rating scales being used and given that cerebral dominance was not the main focus of the study, I felt that a very simple measure of cerebral dominance was appropriate. This study therefore defines cerebral dominance on the basis of the position of the hand in writing. (248,249)

Self-Rating Scales used in the 6 week prospective rating period

Visual Analogue Scales and recording of migraine and menstruation

The Visual Analogue Scale is a widely used method of obtaining self-ratings of mood rapidly and easily. (250) Three separate 10cm lines are used to record daily estimates of anxiety, depression and auphoria. The anxiety dimension extends from 'completely relaxed' to 'extremely anxious'. Depression is rated on a 10cm line from 'totally miserable' to 'my usual self' and euphoria from 'my usual self' to 'high as a kite'. Care is taken over the language used and the way the lines are printed. Subjects are asked to put across against 'my usual self' if neither elated nor depressed and to use one or other dimension for a 24 hour period taken overall rather than using both lines. Subjects generally found this concept easy to grasp and had little difficulty with the scales. After completing the scales they are asked to check a box for the presence or absence of migraine and, in a subsample of patients, also the presence or absence of menstruation. In retrospect a measure of the intensity of the migraine would have been more useful than a simple record of presence or absence but the initial intention was to look more intensively at the mood changes themselves rather than the characteristics of the migraines. The only measures of migraine severity available are therefore frequency and duration. Subjects are asked to date each scale thus providing a record of the days of the week on which the migraines occurred.

Self-rating scales

The use of self-rating scales depends on the patient's literacy and ability to concentrate and may be biased by the patient's desire to present him/herself in a particular way. However they are economical of time and personnel and can be used repeatedly by the same patient. (257)

Self-assessment scales for depression can be classified into those which measure the symptoms of depressive illness and those that are concerned with measurement of depressed mood. Depressive affect can be assessed by asking patients to check lists of adjectives and mark the ones they feel best apply to them. The Zung Self Rating Scale (ZRS) for Depression is widely used and designed as a simple scale for patients to complete without assistance. The patient indicates the frequency with which he experiences each symptom and the scale includes affective, psychological and somatic features. However by comparison with the observer-rated Hamilton Rating Scale for Depression the ZRS is limited in its access to relevant information for rating depression. The ZRS does not appear to be sensitive over a wide range of clinical depression. (252,253). The Leeds self assessment scales for anxiety and depression might also have been suitable instruments for the present study but are rejected in favour of the Irritability-Depression-Anxiety Scale on the grounds that the IDA gives a measure of irritability in addition to depression and anxiety and the fact that it is easier for patients to complete one scale covering all aspects of mood than a number of scales dealing with each aspect separately. (254)

Irritability-Depression-Anxiety Scale (IDA) (Snaith et al 1978)

Irritability is often described as a concomitant of migraine attacks. Aggression is a difficult concept to define and scales which attempt to measure it often vary in whether they are concerned with enduring personality characteristics (traits) or temporary psychological experiences (states). The concept of irritability used in the IDA is a temporary psychological state characterised by impatience, intolerance and poorly controlled anger. This can be expressed inwardly towards oneself or outwardly towards others. The combination of measurement of irritability with depression and anxiety provides an opportunity to investigate the relationship between the three mood states. The IDA is based on items selected from the Hostility and Direction of Hostility Questionnaire (1967), the Buss-Durkee Inventory (1957) and the Hamilton Rating Scales for anxiety and depression. The IDA consists of 18 items, each with 4 possible responses. There are 5 items each for depression and anxiety and 4 items each for outwardly directed and inwardly directed irritability. The scale has been validated in both inpatient and outpatient populations. (237,243,255). Outwardly expressed irritability appears to be an independent mood disorder but the relationship of irritability to other psychopathological concepts is poorly defined. There are no data on whether irritability differs with gender but there does seem to be an inverse relationship with age. It is also found in association with head injury and temporal lobe and frontal tumours. (255)

Visual Analogue Scales

Three scales were constructed to measure anxiety, depression and euphoria on the basis of information obtained from the pilot study. These are completed daily immediately after the IDA.

Regional cerebral blood flow monitoring by cerebral scintigraphy

Pertechnetate is the most widely used substance for cerebral scintigraphy. The radioactively labelled form is readily avilable and decays giving abundant γ radiation. It has a half-life of 6 hours which allows a large amount of activity to be delivered. The γ radiation emitted is recorded using a γ camera with on-line acquisition facilities. The γ camera uses a stationary detector which views all parts of the field simultaneously. The γ camera consists of a single large area scintillation crystal which absorbs energy from ionising radiation and emits weak flashes of light and an array of photomultipliers which convert the light flashes into electrical pulses. A collimator ensures that each part of the crystal looks at only a small area of the patient. When a scintillation occurs within the crystal the light is divided between the photomultipliers and the relative pulse sizes give the position of the scintillation. Pulses from individual photomultipliers are also summed and passed to a pulse-height analyser to measure the total energy loss in the interaction.

Pertechnetate is bound by the thyroid gland and thyroid blocking agents are therefore routinely administered before cerebral scintigraphy with pertechnetate. The patient is then positioned in front of the

camera and a lead collar not less than 2mm thick is fitted closely round the neck to prevent scattered radiation from the neck and trunk reducing contrast and obscuring abnormalities in the cerebral circulation. A vertex view gives the best visualisation of the greatest part of the cerebral cortex. Data collection starts just before the injection of pertechnetate. As there are few counts in each frame of the study the image quality is correspondingly poor. Visualisation of abnormalities is improved if sets of frames are summed. The optimum timing can be found by plotting the total count rate in each frame against time. The arrival of the bolus at the head can then be identified from the graph. The peak of the curve occurs late in the venous phase when most of the activity is in the superior sagittal sinus. Frames occurring between the arrival of the bolus and this peak can be regrouped into four longer frames with improved count content and image quality. These frames correspond approximately to the angiographic phases referred to as arterial, early capillary, late capillary/early venous and late venous.

An activity of between 600-750 mBq (15-20 mCi) of pertechnetate in up to 2ml of fluid is given as a rapid intravenous bolus into a large vein as centrally as possible. The bolus is flushed into the right atrium with 10-20ml of normal saline or 5% dextrose which is injected as rapidly as possible immediately after the radioactivity.

Data are available on the net cortical transit time, net fractional flow and net large vessel transit time for each hemisphere. In addition values can be provided for each of these variables for each quadrant of the hemisphere. These correspond roughly to the frontal, temporal, parietal and occipital lobes. (256)

Pilot Study

Prior to initiating the main study the physician in charge of the migraine clinic was asked to select, from patients already known to him, those who spontaneously complained of mood changes in association with their migraines. Five patients then had an unstructured interview during which they were asked to describe the mood changes that they and their families were aware of and their pattern with respect to the headaches. They were particularly invited to supply the adjectives which they felt best applied to these mood states. The intention was to obtain an assessment of the kind of mood changes experienced, their intensity and their timing in relation to the migraines themselves. The adjectives suggested by the patients were used as the basis for the wording of the Visual Analogue Scales used later in the study. These patients then took part in the structured clinical interview and the prospective rating period. Their results were not included in the analysis of initial interview data to avoid bias towards an affective change group and to allow assessment of a consecutive series of new referrals to the clinic. However their prospective ratings were included in the total analysis of mood change and migraine.

Modifications

The pilot study highlighted the necessity of allowing subjects to practise completion of the visual analogue scales and the IDA in the presence of the interviewer. This allowed questions and uncertainties about the scales to be dealt with immediately. It also proved necessaary

to give subjects brief written instructions on how to complete the scales at home as they appeared to have difficulty in retaining this information.

(D) Results

The Initial Psychiatric Interview (Table I)

Table I presents the descriptive statistics obtained in the first phase of the study. Data from the pilot study group are not included here to avoid generating a bias towards patients with complaints of affective change.

The sample consists of a consecutive series of new referrals to a specialist migraine clinic. Subjects were collected over the 18 month period between November 1985 and March 1987. All patients were referred to the clinic by their GPs. All new female patients aged between 18 and 65 who had a diagnosis of common or classical migraine and no other serious intercurrent physical illness were invited to participate in the initial interview.

Seven patients did not attend for the research appointment. All had had no personal contact with me when they were seen by the physician at the clinic. Each patient was sent a full written explanation of the purpose of the study and the procedures involved and given the opportunity to decline further contact. They then had two offers of appointment dates and times. Two of these patients found that their migraine improved after they saw the physician and one of them also had a fall which resulted in back pain and temporarily reduced her mobility. Two further patients had addresses outwith the Edinburgh area which could have made travel to the hospital for further appointments more difficult. There is no information available on the reasons for non-participation

amongst the remaining three patients.

Social and Demographic variables

The patients were predominantly middle aged, married ladies in the upper social classes. This age and class distribution is similar to that reported in studies of migraine clinic populations. (11,18)

Migraine variables

Over half the patients had classical migraine, a reversal of the picture seen in the general population where common migraine is more frequent. (28) As expected the majority of patients were having frequent attacks of migraine.

Most patients had unilateral headaches. Unilateral pain is generally accepted as a diagnostic feature of migraine whereas bilaterality is a feature of muscle-contraction headaches.

Migraine symptoms

Symptoms were divided into definite and questionable neurological symptoms and general symptoms on the basis of work by Couch, Hassanein & Ziegler. (75) Amongst definite neurological symptoms paresis, sensory loss and speech disturbance were relatively common whereas loss of consciousness was a rare finding.

Visual disturbance and difficulty in thinking were common questionably, neurological symptoms. Visual disturbance has a well-known

association with migraine attacks. The difficulty in thinking was described by patients in terms of impaired attention and concentration.

The general symptoms of nausea, vomiting and photophobia were all extremely common. In fact, these are often important secondary symptoms which are used in making the diagnosis of migraine.

Hallucinatory experiences were reported by a small percentage of patients on specific questioning. Olfactory hallucinations and distortions of body image in the face, head and neck areas were the most common symptoms.

Most patients had had a long history of migraine prior to referral. The referral was generally made because of a recent increase in the frequency or severity of the migraine attacks. The physician's main therapeutic intervention at the medical consultation was to change the patient's drugs. The results obtained from a comparison of the patient's medication before and after this appointment reflect his objectives. These were:

(1) to decrease the number of different preparations to the minimum required,

(2) to produce effective symptom relief during the acute attack,

(3) to prescribe prophylactic medication if the attack frequency justified regular drug intake.

The main changes were an increase in the use of ergot derivatives and prophylactic medication.

Predisposing factors

Few patients entirely discounted emotional factors as precipitants of their migraine attacks, but only a small number were convinced that this was always the case.

Only a small number of patients were on the oral contraceptive - partly because of their age and partly because a history of migraine is now considered to be a contraindication to its use. Only a third of patients believed that their migraine was always related to menstruation.

Psychiatric history

Just over half the patients had a previous history of psychiatric illness and one third had a current DSM-III diagnosis of affective disorder. This increased to almost two thirds when past diagnoses of affective disorder were also included. However retrospectively-made diagnoses are inevitably less certain than current illnesses as they are so dependent on the patient's recollection of the symptoms which were experienced at that time.

Mood change

The proportion of patients with complaints of mood change in association with their migraines was much higher than that expected from the literature review. Twenty-six per cent felt this was an inevitable part of their attacks. Depression and irritability were the mood changes most often mentioned.

TABLE I

Results (Initial Interview - total group)

(A) Social and demographic variables (46 subjects)

(i) Age

Range	20-61 yrs
Mean	38.8 yrs
Median	40.5 yrs
Standard deviation	11.03

(ii) Marital status

9 (19.6%)	single
27 (58.7%)	married
2 (4.3%)	widowed
6 (13%)	divorced
2 (4.3%)	separated

(iii) Social class 40 subjects (4 subjects were excluded by the Registrar General's classification system and 2 subjects did not provide sufficient information to allow class allocation).

I = 8 (20%) II = 13 (32.5%) III = 16 (40%) IV = 1 (2.5%) V = 2 (5%)

(B) Migraine

(i) Type

classical	= 26 (56.5%)
common	= 20 (43.5%)

(ii) Average number of migraine attacks in a 6 week period
Range 1-42, mean 10.29, median 3, standard deviation 13.22.

(iii) Cerebral dominance

right	= 3 (8.7%)
left	= 42 (91.3%)

(iv) Laterality

unilateral right	17 (37%)
unilateral left	10 (21.7%)
bilateral	7 (15.2%)
unilateral right and left	7 (15.2%)
both bi- and unilateral	5 (10.9%)

(v) Symptoms

Definite neurological symptoms

- paresis	none	35 (76.1%)
	right sided	3 (6.5%)
	left sided	4 (8.7%)
	both	4 (8.7%)
sensory loss	none	36 (78.3%)
	right sided	5 (10.9%)
	left sided	3 (6.5%)
	both	2 (4.3%)
speech disturbance	absent	30 (65.2%)
	present	16 (34.8%)
loss of consciousness	absent	43 (93.5%)
	present	3 (6.5%)

Questionable neurological symptoms	- dizziness	absent	26 (56.5%)
		present	20 (43.5%)
	blurred vision	absent	23 (50%)
		present	23 (50%)
	difficulty thinking	absent	17 (37%)
		present	29 (63%)
General symptoms	nausea	absent	6 (13%)
		present	40 (87%)
	vomiting	absent	19 (41.3%)
		present	27 (58.7%)
	photophobia	absent	7 (15.2%)
		present	39 (84.8%)
	psychotic phenomena	absent	39 (84.8%)
		present	7 (15.2%)

(v) Length of migraine history
Range 1-44 yrs, mean 12.87, median 10, standard deviation 9.97

(vi) Family history of migraine	absent	24 (52.5%)
	present	22 (47.8%)

(vii) Medication at initial presentation	none	6 (13%)
	painkiller	12 (26.1%)
	prophylactic	3 (6.5%)
	antidepressant	1 (2.2%)
	combination with ergot	1 (2.2%)
	combination without ergot	23 (50%)

(viii) Change of medication after interview with physician	no	6 (13%)
	yes	40 (87%)

(ix) New medication	none	6 (13%)
	painkiller	2 (4.3%)
	prophylactic	22 (47.8%)
	antidepressant	3 (6.5%)
	combination with ergot	3 (6.5%)
	combination without ergot	9 (19.6%)
	acupuncture	1 (2.2%)

(C) Predisposing Factors

(i) Emotional trigger to attacks	never	12 (26.1%)
	sometimes	25 (54.3%)
	usually	6 (13%)
	always	3 (6.5%)

(ii) On oral contraceptive	no	39 (84.8%)
	yes	7 (15.2%)

(iii) Migraine associated with menstruation

never	23 (45.7%)
sometimes	6 (13%)
usually	6 (13%)
always	13 (28.3%)

(D) Psychiatric History

(i) Personal psychiatric history

none	21 (45.7%
seen by GP for psychiatric illness	18 (39.1%
seen by psychiatrist for psychiatric illness	6 (13%)
other	1 (2.2%)

(ii) Family history of psychiatric illness

absent	33 (71.7%)
present	13 (28.3%)

(iii) DSM-III diagnosis of affective disorder (current and past)

absent	22 (47.8%)
present	24 (52.2%)

Current only

absent	31 (67.4%)
present	15 (32.6%)

(E) Mood

(i) Frequency of mood change in association with migraine

never	22 (47.8%)
sometimes	7 (15.2%)
usually	5 (10.9%)
always	12 (26.1%)

(ii) Type of mood change

depression	absent	33 (71.7%)
	present	13 (28.3%)
anxiety	absent	42 (91.3%)
	present	4 (8.7%)
irritability	absent	33 (71.7%)
	present	13 (28.3%)
euphoria	absent	40 (87%)
	present	6 (13%)

(iii) Clinical anxiety scales scores

Range = 0-19, mean 4.8, median 3, standard deviation 4.7.

Normal range (<5)	26 patients
Mild anxiety (5-10)	13 patients
Moderate anxiety (11-19)	7 patients

(iv) Montgomery and Asberg depression rating scale scores

Range = 0-31, mean 9.0, median 8, standard deviation 8.

Normal range (>7)	19 patients
Mild depression (7-19)	21 patients
Moderate depression (20-31)	6 patients

(v) Manic rating scale scores

Range = 0-10, mean 2.3, median 1, standard deviation 2.6.

Results from the Initial Interview - Group Comparisons

The initial intention was to define affective and non-affective groups of patients on the basis of the presence or absence of complaints of migraine-related mood changes at the initial interview. However, after these data had been collected it became apparent that a much higher proportion of patients than expected had current and past DSM-III diagnoses of affective disorder using the SCID. It therefore seemed reasonable to reallocate the patients into affective and non-affective groups using this as a criterion and then to re-examine the differences between the groups using the descriptive variables. The diary data also showed that the patients' initial reports of mood change did not correspond well with the mood states which they recorded during the prospective rating period. An arbitrary decision was made to allocate patients into affective and non-affective categories on the basis of the number of significant point biserial correlations found during migraine attacks. This was used as a third way of viewing the affective and non-affective dimension. Finally, as common and classical migraine may have different pathophysiologies and this, in turn, may be related to the production of mood changes patients were also grouped on the basis of the type of migraine they experienced.

The descriptive data was reorganised on the basis of the type of scale used to measure each variable and the appropriate statistical tests were applied. The SPSSX computer package of statistical tests was used throughout. (257)

Interval scales with normally distributed data

Initial interview	Affective 17 patients, Non-affective 29 patients
DSM-III diagnosis	Affective 24 patients, Non-affective 22 patients
Diary data	Affective 12 patients, Non-affective 7 patients
Classical/common	Classical 26 patients, Common 20 patients

(1) t-test Variable = age

Affective Non-Affective		Mean Age	Standard Deviation	Separate Variance Estimate Value	Degrees of Freedom	2 Tailed Probability Value
Initial interview	Aff	40.4	12.9	0.89	27.42	0.38
	N-Aff	37.1	10.04			
DSM-III diagnosis	Aff	38.1	10	-0.14	40.34	0.89
	N-Aff	38.5	12.5			
Diary data	Aff	40.9	10	-0.41	14.51	0.69
	N-Aff	39.1	8.5			
Classical/ common	Cl	37.6	11.1	-0.5	40.57	0.62
	Com	39.25	11.4			

Interval scales where the data were not normally distributed - Mann Whitney U-tests

(1) Clinical Anxiety Scale Scores

Affective/ Non Affective	Mann-Whitney U Value	Two-tailed Probability Corrected for Ties
Initial interview	181	0.13
DSM-III diagnosis	175	0.001
Diary data	28.5	0.25
Classical/common migraine	171	0.05

(2) Montgomery and Åsberg Depression Rating Scale Scores

Affective/ Non Affective	Mann-Whitney U Value	Two-tailed Probability Corrected for Ties
Initial interview	136.5	0.01
DSM-III diagnosis	117	0.001
Diary data	35	0.55
Classical/common migraine	184.5	0.09

(3) Manic Rating Scale Scores

Affective/ Non Affective	Mann-Whitney U Value	Two-tailed Probability Corrected for Ties
Initial interview	107	0.001
DSM-III diagnosis	125	0.002
Diary data	26	0.16
Classical/common migraine	206.5	0.22

(4) Length of Migraine History

Affective/ Non Affective	Mann-Whitney U Value	Two-tailed Probability Corrected for Ties
Initial interview	232	0.87
DSM-III diagnosis	212.5	0.26
Diary data	33.5	0.47
Classical/common migraine	254.5	0.9

Ordinal Scales

(1) Number of attacks of migraine per 6 week period

Affective/ Non Affective	Mann-Whitney U Value	Two-tailed Probability Corrected for Ties
Initial interview	243.5	0.95
DSM-III diagnosis	203	0.17
Diary data	34.0	0.49
Classical/common migraine	21.1	0.27

(2) Frequency of mood change associated with migraines

Affective/ Non Affective	Mann-Whitney U Value	Two-tailed Probability Corrected for Ties
Initial interview	0	0
DSM-III diagnosis	119.5	0.0007
Diary data	25.5	0.12
Classical/common migraine	200	0.15

(3) Emotional trigger to migraine attacks

Affective/ Non Affective	Mann-Whitney U Value	Two-tailed Probability Corrected for Ties
Initial interview	194.5	0.19
DSM-III diagnosis	238.5	0.54
Diary data	30	0.25
Classical/common migraine	250	0.8

(4) Relationship of menstruation to migraine attacks

Affective/ Non Affective	Mann-Whitney U Value	Two-tailed Probability Corrected for Ties
Initial interview	223.5	0.58
DSM-III diagnosis	194.5	0.1
Diary data	30	0.26
Classical/common migraine	256	0.93

Nominal Scales

Chi-squared tests were performed for all other variables unless more than 20% of the cells had an expected frequency of less than 5. In this case the Fisher exact test was used instead. The entries in each cell were independent. The Yates correction was used for all chi-squared tests. These were also always two-tailed.

(1) Type of Migraine

		Initial Interview				DSM-III Diagnosis		
		AFF	NAFF	Row total		AFF	NAFF	Row total
Type of Migraine	Classical	12	14	26 (56.5)	Classical	14	12	26 (56.5)
	Common	5	15	20 (43.5)	Common	10	10	20 (43.5)
Column Total		17 (37)	29 (63)	46 (100)		24 (52.2)	22 (47.8)	46 (100)

Chi square = 1.36, 1 degree of freedom (D.F.) $p < 0.24$, minimum expected frequency (EF) 7.4 no cells with EF < 5.

Chi square = 0, 1 D.F. $p < 1$, min EF 9.6, no cells EF < 5.

Diary data - Fisher's exact test $p < 1$

(2) Cerebral dominance

Initial interview - Fisher's exact test $p < 0.53$
DSM-III diagnosis - Fisher's exact test $p < 0.27$
Diary data - Fisher's exact test $p < 1$
Classical/common - Fisher's exact test $p < 0.41$

(3) Unilateral versus bilateral symptoms

The 5 categories which were initially used to describe the laterality of the migraine headache produced too few patients in each cell to permit either chi square or Fisher exact tests. They were therefore condensed into unilateral and bilateral headache and the appropriate tests applied.

Initial interview - Fisher's exact test $p < 0.77$
Diary data - Fisher's exact test $p < 0.36$

DSM-III Diagnosis

	Aff	NAff	
Unilateral	18 (17.7)	16 (16.3)	34
Bilateral	6 (6.3)	6 (5.7)	12
	24	22	

Chi square = 0.03, 1 DF.
$p > 0.5$, min EF 5.7,
No cells with EF < 5.

Classical/Common

	Class	Common	
Unilateral	19 (19.2)	15 (14.8)	34
Bilateral	7 (6.8)	5 (5.2)	12
	26	22	

Chi square = 0.02, 1 DF.
$p < 0.9$, min EF 5.2,
No cells with EF < 5.

(4) Paresis

The different categories for paresis had to be condensed down to the presence or absence of this symptom to make statistical tests possible.

Initial interview - Fisher exact test $p < 0.15$
Diary data - Fisher exact test $p < 0.24$

DSM-III Diagnosis

	Aff	NAff	
Absent	15 (18.3)	20 (16.7)	35
Present	9 (5.7)	2 (5.3)	11
	24	22	46

Chi square = 5.09, DF = 1
$p < 0.02$, min EF = 5.3,
No of cells with EF < 5 = 0.

Classical/Common

	Class	Common	
Absent	17 (19.8)	18 (15.2)	35
Present	9 (6.2)	2 (4.8)	11
	26	20	46

Chi square = 3.76, DF = 1
$p < 0.06$, min EF 4.8,
1 cell with EF < 5.

(5) Sensory disturbance

The data again had to be condensed down to presence or absence of sensory disturbance to allow statistical analysis.

Initial interview - Fisher exact test p = 0.27
DSM-III diagnosis - Fisher exact test p = 0.05
Diary data - Fisher exact test p = 0.07

Classical/common

	Classical	Common	
Absent	18 (20.3)	18 (15.7)	36
Present	8 (5.7)	2 (4.3)	10
	26	20	46

Chi square = 2.87, DF = 1, $p < 0.08$.
1 cell with EF < 5.

(6) Speech disturbance

Diary data - Fisher's exact test $p < 0.17$

Initial Interview

	Aff	NAff	
Absent	10	20	30 (65.2)
Present	7	9	16 (34.8)
	17 (37)	29 (63)	46 (100)

Chi square = 0.14, DF = 1
$p < 0.7$, min EF = 5.9.

DSM-III Diagnosis

	Aff	NAff	
Absent	15	15	30 (65.2)
Present	9	7	16 (34.8)
	24 (52.2)	22 (47.8)	46 (100)

Chi square = 0.009, DF = 1,
$p < 0.92$, min EF 7.7.

Classical/Common

	Classical	Common	
Absent	14	16	30 (65.2)
Present	12	4	16 (34.8)
	26 (56.5)	20 (43.5)	46 (100)

Chi square = 2.35, DF = 1, $p < 0.13$
Min EF = 6.95

(7) Loss of consciousness

Initial interview - Fisher's exact test $p < 0.7$
DSM-III diagnosis - Fisher's exact test $p < 0.53$
Classical/common - Fisher's exact test $p < 0.6$
Diary data - no patient in either the affective or the non-affective group had this symptom.

(8) Dizziness

Diary data - Fisher's exact test $p < 0.62$

Initial Interview

	Aff	NAff	
Absent	9	17	26 (56.5)
Present	8	12	20 (43.5)
	17 (37)	29 (63)	46 (100)

Chi square = 0.14, DF = 1
$p > 0.5$, min EF = 7.4

DSM-III Diagnosis

	Aff	NAff	
Absent	9	17	26 (56.5)
Present	15	5	20 (43.5)
	24 (52.2)	22 (47.8)	46 (100)

Chi square = 7.39, DF = 1,
$p < 0.01$, min EF=9.6.

Classical/common

	Classical	Common	
Absent	14	12	26 (56.5)
Present	12	8	20 (43.5)
	26 (56.5)	20 (43.5)	46 (100)

Chi square = 0.14, DF = 1, $p < 0.9$
Min.EF = 8.69

(9) Blurred vision

Diary data - Fisher's exact test $p < 0.65$

Initial Interview

	Aff	NAff	
Absent	8	15	23 (50)
Present	9	14	23 (50)
	17 (37)	29 (63)	46 (100)

Chi square = 0, DF = 1
$p < 1$, min EF = 8.5

DSM-III Diagnosis

	Aff	NAff	
Absent	13	10	23 (50)
Present	11	12	23 (50)
	24 (52.2)	22 (47.8)	46 (100)

Chi square = 0.08, DF = 1,
$p < 0.77$, min EF = 11.

Classical/common

	Classical	Common	
Absent	9	14	23 (50)
Present	17	6	23 (50)
	26 (56.5)	20 (43.5)	46 (100)

Chi square = 4.3, DF = 1, $p < 0.04$
Min EF = 10.

(10) Difficulty thinking

Diary data - Fisher's exact test $p < 1$

Initial interview

	Aff	NAff	
Absent	3	13	16 (34.8)
Present	14	16	30 (65.2)
	17 (37)	29 (63)	46 (100)

Chi square = 2.4, DF = 1
$p < 0.12$, min EF = 5.9

DSM-III diagnosis

	Aff	NAff	
Absent	6	11	17 (37)
Present	18	11	29 (63)
	24 (52.2)	22 (47.8)	46 (100)

Chi square = 2.1, DF = 1,
$p < 0.15$, min EF = 8.13

Classical/common

	Classical	Common	
Absent	7	10	17 (37)
Present	19	10	29 (63)
	26 (56.5)	20 (43.5)	46 (100)

Chi square = 1.69, DF = 1, $p < 0.19$
Min EF = 7.4

(11) Nausea

Initial interview - Fisher's exact test $p < 0.61$
Diary data - Fisher's exact test $p < 1$
Classical/common - Fisher's exact test $p < 0.05$
DSM-III diagnosis - Fisher's exact test $p < 0.62$

(12) Vomiting

Diary data - Fisher's exact test $p < 0.66$

DSM-III Diagnosis

	Aff	NAff	
Absent	12	7	19 (41.3)
Present	12	15	27 (58.7)
	24 (52.2)	22 (47.8)	46 (100)

Chi square = 0.9, DF = 1
$p < 0.34$, min EF = 9.1

Initial Interview

	Aff	NAff	
Absent	10	9	19 (41.3)
Present	7	20	27 (58.7)
	17 (37)	29 (63)	46 (100)

Chi square = 2.36, DF = 1,
$p < 0.12$, min EF = 7.

Classical/common

	Classical	Common	
Absent	10	9	19 (41.3)
Present	16	11	27 (58.7)
	26 (56.5)	20 (43.5)	46 (100)

Chi square = 0.02, DF = 1, $p < 0.89$
Min EF = 8.3

(13) Photophobia

Initial interview - Fisher's exact test $p < 0.18$
DSM-III diagnosis - Fisher's exact test $p < 0.55$
Diary data - Fisher's exact test $p < 0.6$
Classical/common - Fisher's exact test $p < 0.65$

(14) Psychotic phenomena

Initial interview	- Fisher's exact test $p < 0.007$
DSM-III diagnosis	- Fisher's exact test $p < 0.28$
Diary data	- Fisher's exact test $p < 0.52$
Classical/common	- Fisher's exact test $p < 0.65$

(15) Family history of migraine

Diary data - Fisher's exact test $p < 0.63$

Initial interview

	Aff	NAff	
Absent	13	11	24 (52.2)
Present	4	18	22 (47.8)
	17 (37)	29 (63)	46 (100)

Chi square = 4.93, DF = 1
$p < 0.03$, min EF = 8.13

DSM-III diagnosis

	Aff	NAff	
Absent	15	9	24 (52.2)
Present	9	13	22 (47.8)
	24 (52.2)	22 (47.8)	46 (100)

Chi square = 1.37, DF = 1,
$p < 0.24$, min EF = 10.5

Classical/common

	Classical	Common	
Absent	13	11	24 (52.2)
Present	13	9	22 (47.8)
	26 (56.5)	20 (43.5)	46 (100)

Chi square = 0.002, DF = 1, $p < 0.97$
Min EF = 9.6

(16) Change of medication

Initial interview - Fisher's exact test $p < 0.88$
Diary data - Fisher's exact test $p < 1$
Classical/common - Fisher's exact test $p < 0.53$
DSM-III diagnosis - Fisher's exact test $p < 1$

(17) Oral contraceptive

Initial interview - Fisher's exact test $p < 0.48$
DSM-III diagnosis - Fisher's exact test $p < 0.45$
Diary data - Fisher's exact test $p < 0.23$
Classical/common - Fisher's exact test $p < 0.098$

(18) Personal psychiatric history

The information available on this variable included data on whether the illness had been treated by the GP or a psychiatrist. In order to obtain sufficient patients for each cell in a chi square test the categories were condensed into (1) absent i.e. no psychiatric illness and (2) present i.e. illness treated by GP, psychiatrist or other specialist in mental illness. (Full details of illnesses are available in the abbreviated case histories in the appendix.)

Diary data - Fisher's exact test $p < 0.08$

Initial interview

	Aff	NAff	
Absent	6 (7.8)	15 (13.2)	21
Present	11 (9.2)	14 (15.8)	25
	17	29	46

Chi square = 1.17, DF = 1
$p < 0.3$, min EF = 7.8

DSM-III diagnosis

	Aff	NAff	
Absent	4 (11)	17 (10)	21
Present	20 (13)	5 (12)	25
	24	22	46

Chi square = 16.99, DF = 1,
$p < 0.001$, min EF = 10

Classical/common

	Classical	Common	
Absent	12 (11.9)	9 (9.1)	21
Present	14 (14.1)	11 (10.9)	25
	26	20	46

Chi square = 0.01, DF = 1, $p < 0.8$
Min EF = 9.1

(19) Family psychiatric history

This was again condensed to the presence of absence of illness. Details of relatives' illnesses and treatment, where available, are contained in the abbreviated case histories in the appendix.

Initial interview - Fisher's exact test $p < 0.87$
Diary data - Fisher's exact test $p < 0.6$

DSM-III Diagnosis

	Aff	NAff	
Absent	16	17	33 (71.7)
Present	8	5	13 (28.3)
	24 (52.2)	22 (47.8)	46 (100)

Chi square = 0.22, DF = 1
$p < 0.6$, min EF = 6.2,

Classical/Common

	Class	Common	
Absent	19	14	33 (71.7)
Present	7	6	13 (28.3)
	26 (56.5)	20 (43.5)	46 (100)

Chi square = 0, DF = 1
$p < 1$, min EF = 5.7

(20) Self report of mood change - Depression

Initial interview - Fisher's exact test $p < 0.006$
Diary data - Fisher's exact test $p < 1$

Classical/Common

	Class	Common	
Absent	16	17	33 (71.7)
Present	10	3	13 (28.3)
	26 (56.5)	20 (43.5)	46 (100)

Chi square = 2.02, DF = 1
$p < 0.16$, min EF = 5.7

DSM-III Diagnosis

	Aff	NAff	
Absent	14	19	33 (71.7)
Present	10	3	13 (28.3)
	24 (52.2)	22 (47.8)	46 (100)

Chi square = 3.17, DF = 1
$p < 0.07$, min EF = 6.2

(21) Self report of mood change - Anxiety

Initial interview - Fisher's exact test $p < 0.14$
DSM-III diagnosis - Fisher's exact test $p < 0.07$
Diary data - Fisher's exact test $p < 1$
Classical/common - Fisher's exact test $p < 0.79$

(22) Self report of mood change - Euphoria

Initial interview - Fisher's exact test $p < 0.12$
DSM-III diagnosis - Fisher's exact test $p < 0.38$
Diary data - Fisher's exact test $p < 0.12$
Classical/common - Fisher's exact test $p < 0.78$

(23) Self report of mood change - Irritability

Initial interview - Fisher's exact test $p < 0.0008$
Diary data - Fisher's exact test $p < 0.12$

DSM-III Diagnosis

	Aff	NAff	
Absent	13	20	33 (71.7)
Present	11	2	13 (28.3)
	24 (52.2)	22 (47.8)	46 (100)

Chi square = 5.9, DF = 1
$p < 0.015$, min EF = 6.2

Classical/Common

	Class	Common	
Absent	17	16	33 (71.7)
Present	9	4	13 (28.3)
	26 (56.5)	20 (43.5)	46 (100)

Chi square = 0.58, DF = 1
$p < 0.45$, min EF = 5.7

(24) DSM-III diagnosis of psychiatric illness - affective disorder

Full details of all DSM-III diagnoses made are contained in Tables III and IV. This concerns only current and past DSM-III diagnoses of affective disorder. (The affective diagnoses available using the SCID are the DSM-III categories of Bipolar Disorder, Cyclothymic Disorder, Major Depression, Dysthymic Disorder and Affective Disorder not otherwise specified.)

Diary data - Fisher's exact test $p < 0.45$

Initial Interview

	NAff (as defined by self report of mood change at the initial interview)	Aff	
SCID Aff Diagnosis Absent	18 (13.2)	3 (7.8)	21
SCID Aff Diagnosis Present	11 (15.8)	14 (9.2)	25
	29	17	46

Chi square = 8.52, DF = 1
$p < 0.01$, min EF = 7.8

Classical/Common

	Classical	Common	
SCID Aff Diagnosis Absent	10 (11)	11 (10)	21
SCID Aff Diagnosis Present	14 (13)	11 (12)	25
	24	22	46

Chi square = 0.32, DF = 1
$p < 0.5$, min EF = 10

Nominal scales with too many categories for chi square or Fisher exact tests

Some variables proved impossible to condense into suitable categories for statistical analysis. The raw data are presented below with the observation that no differences between groups are apparent on visual inspection of the figures.

(1) Marital Status

Initial Interview

	Aff	NAff
Single	3	5
Married	12	15
Widowed	1	2
Divorced	0	6
Separated	1	1
	17	29

DSM-III Diagnosis

	Aff	NAff
Single	4	5
Married	14	13
Widowed	1	1
Divorced	0	6
Separated	2	0
	24	22

Diary Data

	Aff	NAff
Single	1	4
Married	6	7
Divorced	0	1
	7	12

Classical/Common

	Aff	NAff
Single	4	5
Married	18	9
Widowed	1	1
Divorced	1	5
Separated	2	0
	26	20

Marital status was condensed for the classical/common groups and a chi square test was performed on married versus all other groups.

Classical/Common

	Classical	Common	
Married	18 (15.3)	9 (11.7)	27
Others	8 (10.7)	11 (8.3)	19
	26	20	46

Chi square = 2.74, DF = 1, $p < 0.1$
Min EF = 8.3

(2) Current medication (when referred)

Initial Interview	Aff	NAff
None	3	3
Analgesic	4	7
Prophylaxis	1	3
Antiemetic	0	0
Antidepressant	0	1
Combination with Ergot	0	1
Tranquillisers	0	0
Combination without Ergot	9	14
Acupuncture	0	0
Steroids	0	0
	17	29

DSM-III Diagnosis	Aff	NAff
None	3	3
Analgesic	5	7
Prophylaxis	2	1
Antiemetic	0	0
Antidepressant	1	0
Combination with Ergot	1	0
Tranquillisers	0	0
Combination without Ergot	12	11
Acupuncture	0	0
Steroids	0	0
	24	22

Diary Data

	Aff	NAff
None	1	2
Analgesic	1	2
Prophylaxis	0	0
Antiemetic	0	0
Antidepressant	0	1
Combination with Ergot	0	0
Tranquillisers	0	0
Combination without Ergot	5	7
Acupuncture	0	0
Steroids	0	0
	7	12

Classical/Common

	Classical	Common
None	6	0
Analgesic	4	8
Prophylaxis	2	1
Antiemetic	0	0
Antidepressant	1	0
Combination with Ergot	0	1
Tranquillisers	0	0
Combination without Ergot	13	10
Acupuncture	0	0
Steroids	0	0
	26	20

The categories 'no medication' and 'on medication' were compared in the classical versus common groups - the Fisher exact test probability was <0.03.

(3) New medication (after the interview with the physician)

	Initial Interview	Aff	NAff	DSM-III Diagnosis	Aff	NAff
0	None	3	3	None	2	4
1	Analgesic	1	1	Analgesic	2	0
2	Prophylaxis	8	14	Prophylaxis	10	12
3	Antiemetic	0	0	Antiemetic	0	0
4	Antidepressant	2	1	Antidepressant	3	0
5	Combination with Ergot	1	2	Combination with Ergot	2	1
6	Tranquillisers	0	0	Tranquillisers	0	0
7	Combination without Ergot	1	8	Combination without Ergot	4	5
8	Acupuncture	1	0	Acupuncture	1	0
9	Steroids	0	0	Steroids	0	0
		17	29		24	22

Diary Data

		Aff	NAff
0	None	2	2
1	Analgesic	0	0
2	Prophylaxis	3	5
3	Antiemetic	0	0
4	Antidepressant	0	1
5	Combination with Ergot	0	1
6	Tranquillisers	0	0
7	Combination without Ergot	2	3
8	Acupuncture	0	0
9	Steroids	0	0
		7	12

Classical/Common

	Classical	Common
None	5	1
Analgesic	0	2
Prophylaxis	15	7
Antiemetic	0	0
Antidepressant	2	1
Combination with Ergot	1	2
Tranquillisers	0	0
Combination without Ergot	2	7
Acupuncture	1	0
Steroids	0	0
	26	20

For the classical/common group prophylactic medication versus all other categories was compared using a chi square test.

	Classical	Common	
Prophylactic	15 (12.4)	7 (9.6)	22
All others	11 (13.6)	13 (10.4)	24
	26	20	46

Chi square = 2.33, DF = 1, $p < 0.15$
Min EF = 9.6

TABLE II

Summary table of significance levels for all variables

Group 1 Affective/Non affective (Initial Interview)
Group 2 Affective/Non affective (DSM-III diagnosis based on SCID)
Group 3 Affective/Non affective (Diary data)
Group 4 Classical/Common

VARIABLE	(1) Affective/ Non affective Initial interview	(2) Affective/ Non affective (DSM-III)	(3) Affective/ Non affective Diary data	(4) Classical/ Common
Social & Demographic Variables				
Age	0.38 (TT)	0.89 (TT)	0.69 (TT)	0.62 (TT)
Marital status	No difference on visual inspection	No difference on visual inspection	No difference on visual inspection	Married v. others 0.10 (x^2)
Migraine				
Type of migraine	0.24 (x^2)	1 (x^2)	1 (FET)	Not applicable
Frequency of migraine	0.95 (MW)	0.47 (MW)	0.49 (MW)	0.27 (MW)
Cerebral dominance	0.53 (FET)	0.27 (FET)	1 (FET)	0.41 (FET)
Uni/bilat symptoms	0.77 (FET)	NS	0.36 (FET)	0.9 (x^2)
Paresis (A/P)	0.15 (FET)	$p<0.02$* ($x^2=5.09$)	0.24 (FET)	0.06 (x^2)
Sensory disturbance (A/P)	0.27 (FET)	0.05* (FET)	0.07 (FET)	0.08 (x^2)
Speech disturbance	0.7 (x^2)	0.92 (x^2)	0.17 (FET)	0.13 (x^2)
Loss of consciousness	0.7 (FET)	0.53 (FET)	1 (x^2)	0.6 (FET)
Dizziness	0.94 (x^2)	$p<0.02$* ($x^2=5.86$)	0.62 (FET)	0.9 (x^2)
Blurred vision	1 (x^2)	0.77 (x^2)	0.65 (FET)	$p<0.03$* ($x^2=4.3$
Difficulty thinking	0.07 (x^2)	0.15 (x^2)	1.0 (FET)	0.19 (x^2)

Nausea	0.61 (FET)	0.62 (FET)	1 (FET)	0.05* (FET)
Vomiting	0.13 (x^2)	0.34 (x^2)	0.66 (FET)	0.9 (x^2)
Photophobia	0.18 (FET)	0.55 (FET)	0.6 (FET)	0.65 (FET)
Psychotic phenomena	0.007** (FET)	0.52 (FET)	0.52 (FET)	0.65 (FET)
Family history of migraine	$p<0.03$* ($x^2=4.93$)	0.24 (x^2)	0.63 (FET)	0.97 (x^2)
Length of migraine history	0.87 (MW)	0.26 (MW)	0.47 (MW)	0.9 (MW)
Current medication	No difference on visual inspection	No difference on visual inspection	No difference on visual inspection	No med vs others 0.03* (FET)
Change of medication	0.88 (FET)	.1 (FET)	1 (FET)	0.53 (FET)
New medication	No difference on visual inspection	No difference on visual inspection	No difference on visual inspection	Prophylactic vs others 0.15 (x^2)
<u>Predisposing Factors</u>				
Emotional stress	0.19 (MW)	0.54 (MW)	0.25 (MW)	0.8 (MW)
Oral contraceptive	0.48 (FET)	0.45 (FET)	0.23 (FET)	0.098 (FET)
Menstruation	0.58 (MW)	0.1 (MW)	0.26 (MW)	0.92 (MW)
<u>Psychiatric History</u>				
Personal psychiatric history	NS (x^2)	$p<0.001$**($x^2=16.99$)	0.08 (FET)	NS (x^2)
Family psychiatric history	0.87 (FET)	0.64 (x^2)	0.6 (FET)	1 (x^2)
<u>Mood</u>				
Frequency of mood change	$p<0.001$**MW(U=0)	0.0007***MW(U=119.5)	0.12 (MW)	0.15 (MW)
Depression	0.006**(FET)	0.08 (x^2)	1 (FET)	0.16 (x^2)
Anxiety	0.14 (FET)	0.07 (FET)	1 (FET)	0.79 (FET)

Euphoria	0.12 (FET)	0.38 (FET)	0.12 (FET)	0.78 (FET)
Irritability	0.0008***(FET)	p<0.02*(x^2=5.94)	0.12 (FET)	0.5 (x^2)
CAS score	0.13 (MW)	0.05*MW (U=125)	0.25 (MW)	p<0.05 (U=171)(MW)
MADRS score	0.01*MW(U=136)	0.001**MW(U=117)	0.55 (MW)	0.09 (MW)
MRS score	0.001**MW(U=107)	0.002**MW(U=125)	0.16 (MW)	0.22 (MW)
DSM-III diagnosis	p<0.01* x^2=8.52	Not applicable	0.45 (FET)	0.5 (x^2)

TT = t=test
x^2 = chi squared test
FET = Fisher's exact test
MW = Mann-Whitney U test

* = p<0.05
** = p<0.001
*** = p<0.0001

DSM-III diagnosis based on the SCID

Tables III and IV show the DSM-III diagnoses obtained using the SCID for all patients. The patients have been subdivided into an affective and a non-affective group based on whether or not they complained of migraine-related mood change at the initial interview. There are 3 possible categories for each diagnosis, i.e.

(i) DSM-III criteria are not met and the diagnosis is absent,

(ii) DSM-III criteria are not quite fulfilled (1 or 2 criteria are not fulfilled) and the diagnosis is therefore subthreshold,

(iii) DSM-III criteria are satisfied and diagnosis is therefore definitely present.

In the tables the DSM-III current and past diagnoses are specified separately, together with the length of time each has been present for. Past episodes of illness are discrete from present episodes unless otherwise stated. The length of the migraine history is also given to allow comparison of the length of the migraine history and the length of the psychiatric history.

Following the structured clinical interview the dates given for each DSM-III diagnosis were compared with those given on initial questioning as to whether the patient had ever suffered from psychiatric illness and if so whether this had caused them to consult their GP or a psychiatrist. Eleven of the 29 patients in the non-affective (initial

interview) group had a SCID diagnosis of affective disorder. All of this group plus two others, i.e. 13 of the 29, had consulted their GP and/or a psychiatrist because of psychiatric illness. In the affective group (initial interview) 13 out of 17 patients had a SCID diagnosis of affective disorder and all had seen their GP or a psychiatrist because of this. There was complete agreement between the information given on open questioning and information obtained using the SCID with regard to when these illnesses had occurred.

TABLE III

DSM-III Diagnosis based on the SCID

Affective Group (Initial Interview)

D = Definite

ST = Sub threshold

→ = Still present

Patient identification number	Length of migrain history	Current DSM-III diagnosis	Duration of psychiatric illness	Past DSM-III diagnosis	Duration of psychiatric illness
101	10 yrs	D) Panic disorder	2 yrs	D) Major depression	1966-68 (Further episode 1976-8)
102	20 yrs	D) Cyclothymic disorder D) Simple phobia	6 yrs Childhood	None	
103	10 yrs	D) Major depression D) Simple phobia	1981 → 16 yrs	D) Major depression	1981 →
104	15 yrs	D) Cyclothymic disorder	9 yrs	D) Major depression	1979-81
105	17 yrs	ST) Depression during migraine	3 yrs	D) Major depression	1974 (laste three month
106	35 yrs	ST) Mania during migraine	Unknown	None	
107	36 yrs	D) Simple phobia	36 yrs	None	
108	14 yrs	None		D) Bipolar illness D) Alcohol dependence D) Social phobia	1975 → 1977-79 1971-1979
109	25 yrs	D) Dysthymic disorder	Since adolescence	D) Major depression	1963 - last 2 years
110	10 yrs	D) Hypochondriasis ST) Major depression during migraine ST) Simple phobia	6 mths Childhood	D) Major depression	1974 (One episod which laste 1 year)
111	20 yrs	ST) Mania during migraine D) Major depression	1-2 yrs 4 yrs	None	

112	17 yrs	ST) Major depression during migraine	Unknown	None	
113	16 yrs	None		None	
114	6-7 yrs	D) Major depression with migraine	2-3 mths	D) Major depression	1981 (lasted 9 months)
		D) Simple phobia	Childhood		
115	5 yrs	D) Dysthymic disorder	Childhood	None	
		D) Major depression during migraine	2 yrs		
116	1-2 yrs	D) Major depression with melancholia)	Uncertain	D) Major depression	1983 (lasted 4 weeks)
		D) Simple phobia	Childhood		
117	15 yrs	D) Major depression with migraine	12 yrs	None	
		D) Dysthymic syndrome	10 yrs		
		D) Simple phobia	10 yrs		
118	6 mths	D) Major depression	months	None	
119	44 yrs	D) Simple phobia	Childhood	None	
		D) Generalised anxiety disorder	4-5 yrs		
		D) Obsessive - Compulsive disorder	16 yrs		
120	1 yr	D) Generalised anxiety disorder	11 mths	None	
121	2 yrs	ST) Major depression with migraine	18 mths	None	
		D) Dysthymic syndrome	2 yrs		
		D) Simple phobia	15 yrs		

TABLE IV

DSM-III Diagnosis based on the SCID

Non Affective Group (Initial Interview)

D = Definite

ST = Sub threshold

→ = Still present

Patient identification number	Length of migraine history	Current DSM-III diagnosis	Duration of psychiatric illness	Past DSM-III diagnosis	Duration of psychiatric illness
201	7 yrs	D) Simple phobia	7 yrs	None	
202	4 yrs	D) Simple phobia	6 yrs	None	
203	26 yrs	ST) Major depression	Unknown	None	
204	16 yrs	D) Major depression	1976 →	D) Major depression	1975 →
205	12 yrs	D) Cyclothymic disorder) D) Simple phobia)	Since adolescence	None	
206	16 yrs	ST) Generalised anxiety disorder ST) Social phobia	6 mths Unknown	None	
207	10 yrs	D) Generalised anxiety disorder D) Simple phobia ST) Mania with migraine	8 mths Since childhood Unknown	D) Major depression	1977 (one episode only)
208	20 yrs	None		D) Major depression	1978 - 3 episode
209	7-8 yrs	D) Major depression	1979 →	D) Major depression	Since 197
210	30 yrs	None		None	
211	38 yrs	D) Simple phobia	Childhood -	None	
212	17 yrs	D) Anxiety state	Lifelong	D) Anorexia Nervosa)	1973 - 1 year
213	2 yrs	None		D) Major depression	1983-6* (currentl on anti-depressan

214	11 yrs	D) Social phobia	Since childhood	None	
215	26 yrs	None		None	
216	7 mths	D) Simple phobia	5 years	D) Major depression	1985 for 2/12
217	10 yrs	D) Major depression	3 years	None	
218	17 yrs	D) Generalised anxiety disorder	5 years	None	
		D) Simple phobia	Several yrs		
219	25 yrs	None		D) Major depression	One episc 11 yrs ag
220	7-8 yrs	D) Generalised anxiety disorder	4-5 yrs	D) Major depression	1982 -
		ST) Major depression with migraine	3 years		lasted 2-3 month
221	6 yrs	D) Major depression	1984 →	None	
		D) Alcohol dependence	1984 →		
222	2 yrs	D) Obsessional ruminations	3-4 wks	ST) Major depression	1986 lasted 2 weeks x 2
223	9 yrs	None		None	
224	3 yrs	None		None	
225	10 yrs	ST) Hypomania with migraine	1 yr	None	
		ST) Generalised anxiety disorder	1978 →		
226	3 yrs	None		None	
227	27 yrs	None		None	
228	2 yrs	None		None	
229	7 yrs	D) Panic disorder with limited phobic avoidance	1970 →	D) Substance abuse disorder	17 yrs

(2) Six week prospective rating period

The Irritability-Depression-Anxiety questionnaires were scored according to the author's instructions. This produced daily ratings of anxiety, depression, outward irritability and inward irritability. The VAS were scored by simple measurement which provided daily ratings of 1-10 for anxiety, depression and euphoria.

A separate file was made for each patient containing the mood data and the presence or absence of migraine on a daily basis during the study period. The relationship between mood components and the days when migraine was present was examined using point biserial correlation. Mann Whitney U-tests were used to compare:

(i) mood components on the day before a migraine with mood components on the first day of the migraine attack,

(ii) mood components on the day before a migraine with mood components on days when migraine was absent,

(iii) mood components on the day after a migraine with mood components on all days except the first,

(iv) mood components on the day after a migraine with mood components on days when migraine was absent.

(Mann Whitney U tests and point biserial correlations were performed using the Minitab computer programme (258)).

Unfortunately the amount of information available was limited by the frequency and duration of the migraines experienced. If the attacks were infrequent and of short duration there was insufficent data for Mann Whitney tests to be used (a minimum of two migraines, each lasting for more than one day was required for analysis).

Five patients also misunderstood the instructions for completion of the last two VAS scales and there was therefore no data available from them for VAS depression and euphoria.

Data from each individual case was then combined and the affective group and the non-affective group (as defined by the self report of mood change at the initial interview) were compared.

Of the total group of 51 patients (46 new referrals and 5 pilot study patients) 37 patients completed and returned their prospective rating scales. The pilot study group was amalgamated with the affective group for group comparisons. Thus 16 of a possible 22 patients in the affective group returned their scales whereas 21 of a possible 29 in the non-affective group did so.

Seven patients in the affective and 9 patients in the non-affective group had an insufficient number and duration of migraines for examination of mood changes before and after migraines. Thus data on these changes is actually available for 9 patients in the affective group and 12 patients in the non-affective group.

Several attempts were made, both by telephone and by letter, to obtain forms which had not been returned spontaneously. One patient was lost to follow up as she moved to England shortly after her initial interview and a second patient became physically ill and was too unwell to complete the forms. The remaining patients had either forgotten to complete the forms or had done so and then mislaid them.

Few significant associations were found for the 24 hour period immediately prior to, or following, migraine attacks (see Tables V - VIII).

Data was available for point biserial correlations for all except 1 of the 37 patients (this lady had no migraines during the study period). Significant associations were much more frequent between mood and the days when migraine was actually present.

An arbitrary decision was made to reallocate patients into affective and non-affective groups on the basis of the prospective data depending on whether they had a significant ($p<0.05$) association between 4 of the possible 7 mood indices and the migraine days (see Table IX).

TABLE V

Relationship between mood components the day before a migraine with mood components on the first day of the migraine (Mann-Whitney U Test)

Patient Identification Number	IDA Anxiety	IDA Depression	IDA Outward Irrita-bility	IDA Inward Irrita-bility	VAS Anxiety	VAS Depression	VAS Euphoria
Affective (Initial Interview)							
101	NS	NS	NS	NS	p<0.04 (w=27)	NS	NS
102	ID	ID	ID	ID	ID	ID	ID
103	ID	ID	ID	ID	ID	ID	ID
105	NS	NS	NS	NS	NS	NS	NS
106	NS	NS	NS	NS	NS	ND	ND
107	NS	NS	NS	NS	NS	AVI	NS
108	p<0.0009 (w=37)	p<0.0006 (w=36)	p<0.0009 (w=37)	p<0.0061 (w=43)	p<0.0006 (w=36)	ND	ND
109	ID	ID	ID	ID	ID	ND	ND
110	p<0.03 (w=17.5)	p<0.02 (w=16.5)	p<0.04 (w=18.5)	AVI	p<0.008 (w=15)	ND	ND
111	NS	NS	NS	NS	NS	NS	NS
112	AVI	NS	AVI	AVI	AVI	AVI	AVI
113	NS	NS	NS	NS	NS	ND	ND
117	ND	ND	ND	ND	NS	NS	AVI
118	p<0.05 (w=11.5)	NS	NS	NS	NS	NS	AVI
119	ID	ID	ID	ID	ID	ID	ID
121	ID	ID	ID	ID	ID	ID	ID

Non Affective (Initial Interview)

201	NS	NS	AVI	NS	AVI	AVI	AVI
202	NM	NM	NM	NM	NM	NM	NM
203	NS	NS	AVI	AVI	NS	AVI	AVI
204	NS	NS	NS	NS	NS	NS	NS
207	p<0.007 (w=71)	p<0.02 (w=76)	NS	p<0.02 (w=76)	p(0.004) (w=69)	NS	NS
208	NS	NS	AVI	AVI	NS	AVI	AVI
209	ID	ID	ID	ID	ID	ID	ID
210	NS	NS	NS	NS	NS	AVI	AVI
211	ID	ID	ID	ID	ID	ID	ID
212	ID	ID	ID	ID	ID	ID	ID
213	ID	ID	ID	ID	ID	ID	ID
214	NS	NS	NS	AVI	NS	NS	AVI
215	p<0.005 (w=57)	NS	NS	AVI	AVI	NS	AVI
216	AVI	NS	NS	AVI	NS	AVI	AVI
217	p<0.03 (w=16.5)	p<0.02 (w=15.5)	NS	AVI	NS	NS	AVI
218	ID	ID	ID	ID	ID	ID	ID
219	NS	NS	AVI	NS	NS	NS	AVI
222	NS	NS	NS	NS	NS	NS	AVI
224	NS	NS	NS	NS	NS	NS	AVI
225	ID	ID	ID	ID	ID	ID	ID
228	NS	NS	AVI	NS	NS	NS	AVI

NS = Non significant AVI = All values identical

ID = Insufficient data NM = No migraine

ND = No data

TABLE VI

Relationship between mood components the day before a migraine with mood components on the days when a migraine was absent (Mann-Whitney U test)

Patient Identification Number	IDA Anxiety	IDA Depression	IDA Outward Irrita-bility	IDA Inward Irrita-bility	VAS Anxiety	VAS Depression	VAS Euphoria
Affective (Initial Interview)							
101	NS	NS	NS	NS	NS	NS	NS
102	ID	ID	ID	ID	ID	ID	ID
103	ID	ID	ID	ID	ID	ID	ID
105	NS	NS	NS	NS	NS	NS	NS
106	NS	NS	NS	NS	NS	ND	ND
107	$p<0.04$ ($w=134.5$)	NS	NS	NS	NS	AVI	NS
108	NS	NS	NS	NS	NS	ND	ND
109	ID	ID	ID	ID	ID	ND	ND
110	NS	NS	NS	AVI	NS	ND	ND
111	NS	NS	NS	NS	NS	NS	NS
112	AVI	NS	AVI	AVI	AVI	AVI	AVI
113	NS	NS	NS	NS	NS	ND	ND
117	ND	ND	ND	ND	NS	NS	AVI
118	NS	NS	NS	NS	NS	NS	AVI
119	ID	ID	ID	ID	ID	ID	ID
121	ID	ID	ID	ID	ID	ID	ID

Non Affective (Initial Interview)

201	NS	NS	AVI	NS	AVI	AVI	AVI
202	NM	NM	NM	NM	NM	NM	NM
203	NS	NS	AVI	AVI	NS	AVI	AVI
204	NS	NS	$p<0.05$ (w=29)	NS	$p<0.02$ (w=22)	$p<0.05$ (w=28)	NS
207	NS	NS	NS	NS	NS	NS	NS
208	NS	NS	AVI	AVI	NS	AVI	AVI
209	ID	ID	ID	ID	ID	ID	ID
210	NS	$p<0.002$ (w=136)	NS	NS	NS	AVI	NS
211	ID	ID	ID	ID	ID	ID	ID
212	ID	ID	ID	ID	ID	ID	ID
213	ID	ID	ID	ID	ID	ID	ID
214	NS	NS	NS	AVI	NS	NS	NS
215	NS	NS	NS	AVI	NS	NS	AVI
216	AVI	NS	NS	NS	NS	AVI	NS
217	NS	NS	AVI	NS	NS	NS	AVI
218	ID	ID	ID	ID	ID	ID	ID
219	NS	NS	NS	NS	NS	NS	AVI
222	NS	NS	NS	NS	NS	NS	AVI
224	NS	NS	NS	NS	NS	NS	AVI
225	ID	ID	ID	ID	ID	ID	ID
228	NS	NS	AVI	AVI	NS	NS	AVI

NS = Non significant AVI = All values identical

ID = Insufficient data NM = No migraine

TABLE VII

Relationship between mood components on the day after a migraine with mood components on all migraine days except the first (Mann-Whitney U Test)

Patient Identification Number	IDA Anxiety	IDA Depression	IDA Outward Irritability	IDA Inward Irritability	VAS Anxiety	VAS Depression	VAS Euphoria
Affective (Initial Interview)							
101	NS	AVI	NS	NS	$p<0.05$ ($w=50.5$)	NS	AVI
102	ID	ID	ID	ID	ID	ID	ID
103	ID	ID	ID	ID	ID	ID	ID
105	NS	NS	NS	AVI	AVI	NS	AVI
106	NS	AVI	AVI	AVI	NS	ND	ND
107	NS	NS	NS	NS	NS	NS	AVI
108	NS	NS	NS	NS	NS	ND	ND
109	ID	ID	ID	ID	ID	ND	ND
110	$p<0.04$ ($w=27$)	$p<0.05$ ($w=27.5$)	NS	NS	$p<0.01$ ($w=24$)	ND	ND
111	NS	NS	NS	NS	NS	NS	AVI
112	ID	ID	ID	ID	ID	ID	ID
113	ID	ID	ID	ID	ID	ND	ND
117	ND	ND	ND	ND	NS	NS	AVI
118	$p<0.003$ ($w=16.5$)	$p<0.003$ ($w=16.5$)	*$p<0.01$ ($w=20.5$)	*$p<0.003$ ($w=16$)	$p<0.01$ ($w=20$)	$p<0.002$ ($w=15$)	AVI
119	ID	ID	ID	ID	ID	ID	ID
121	ID	ID	ID	ID	ID	ID	ID

Non Affective (Initial Interview)

201	NS	NS	NS	AVI	AVI	AVI	AVI
202	NM	NM	NM	NM	NM	NM	NM
203	AVI	AVI	AVI	AVI	NS	NS	AVI
204	ID	ID	ID	ID	ID	ID	ID
207	p<0.002 (w=93)	p<0.03 (w=111.5)	NS	NS	p<0.0002 (w=80.5)	p<0.006 (w=100.5)	NS
208	AVI	NS	ID	AVI	NS	NS	AVI
209	ID	ID	ID	ID	ID	ID	ID
210	AVI	NS	NS	NS	NS	AVI	AVI
211	ID	ID	ID	ID	ID	ID	ID
212	ID	ID	ID	ID	ID	ID	ID
213	ID	ID	ID	ID	ID	ID	ID
214	NS	NS	NS	AVI	NS	NS	AVI
215	NS	NS	NS	AVI	AVI	NS	AVI
216	ID	ID	ID	ID	ID	ID	ID
217	p<0.05 (w=10)	p<0.05 (w=10)	AVI	AVI	NS	NS	AVI
218	ID	ID	ID	ID	ID	ID	ID
219	AVI	NS	NS	NS	NS	NS	NS
222	NS	NS	NS	AVI	NS	NS	NS
224	NS	NS	NS	NS	NS	NS	NS
225	ID	ID	ID	ID	ID	ID	ID
228	NS	NS	AVI	NS	NS	NS	AVI

NS = Non significant AVI = All values identical

ID = Insufficient data NM = No migraine

ND = No data

TABLE VIII

Relationship between mood components on the day after a migraine with mood components on the days when migraine is absent (Mann-Whitney U Test)

Patient Identification Number	IDA Anxiety	IDA Depression	IDA Outward Irrita-bility	IDA Inward Irrita-bility	VAS Anxiety	VAS Depression	VAS Euphoria
Affective (Initial Interview)							
101	p<0.01 (w=84)	AVI	NS	p<0.03 (w=81)	NS	p<0.007 (w=85.5)	NS
102	ID	ID	ID	ID	ID	ID	ID
103	ID	ID	ID	ID	ID	ID	ID
105	p<0.02 (w=70)	p<0.08 (w=69)	NS	AVI	AVI	NS	AVI
106	NS	AVI	AVI	AVI	NS	ND	ND
107	p<0.07 (w=128)	NS	NS	NS	NS	NS	AVI
108	p<0.0008 (w=40)	p<0.0003 (w=30.5)	p<0.0007 (w=39.5)	p<0.0015 (w=52)	p<0.0005 (w=38.5)	ND	ND
109	ID	ID	ID	ID	ID	ND	ND
110	NS	NS	NS	AVI	NS	ND	ND
111	NS	NS	NS	NS	NS	NS	AVI
112	NS	NS	NS	AVI	AVI	AVI	AVI
113	NS	NS	NS	NS	NS	ND	ND
117	ND	ND	ND	ND	NS	NS	AVI
118	NS	NS	p<0.02 (w=35)	NS	p<0.04 (w=34)	NS	AVI
119	ID	ID	ID	ID	ID	ID	ID
121	ID	ID	ID	ID	ID	ID	ID

Non Affective (Initial Interview)

201	NS	NS	AVI	AVI	AVI	AVI	AVI
202	NM	NM	NM	NM	NM	NM	NM
203	AVI	AVI	AVI	AVI	NS	AVI	AVI
204	NS	NS	NS	NS	NS	NS	NS
207	NS	NS	NS	NS	NS	NS	AVI
208	NS	$p<0.05$ (w=89)	AVI	AVI	NS	NS	AVI
209	ID	ID	ID	ID	ID	ID	ID
210	AVI	NS	NS	NS	NS	AVI	NS
211	ID	ID	ID	ID	ID	ID	ID
212	ID	ID	ID	ID	ID	ID	ID
213	ID	ID	ID	ID	ID	ID	ID
214	NS	NS	NS	AVI	NS	NS	AVI
215	NS	$p<0.006$	NS	AVI	NS	NS	AVI
216	$p<0.04$ (w=69.5)	NS	$p<0.04$ (w=69)	$p<0.05$ (w=67.5)	NS	AVI	NS
217	NS	NS	NS	AVI	NS	NS	AVI
218	ID	ID	ID	ID	ID	ID	ID
219	$p<0.02$ (w=144.5)	NS	AVI	AVI	NS	NS	NS
222	NS	NS	NS	NS	NS	NS	NS
224	NS	NS	NS	NS	NS	NS	NS
225	ID	ID	ID	ID	ID	ID	ID
228	NS	NS	AVI	NS	NS	NS	AVI

NS = Non significant AVI = All values identical

ID = Insufficient data NM = No migraine

ND = No data

TABLE IX

Point biserial correlations of the presence of migraine with mood components together with the patients' initial self report of the type of mood change and the frequency with which it was experienced

Patient Identification Number	Self Report of Mood Change		IDA Anxiety	IDA Depression	IDA Outward Irritability	IDA Inward Irritability	VAS Anxiety	VAS Depression	VAS Euphoria
	Freq.	Type	Affective (Initial Interview)						
101	U	I	p<0.01 (0.412)	p<0.02 (0.41)	NS	NS	p<0.001 (0.57)	p<0.05 (0.328)	NS
102	U	E&I	ND	ND	ND	ND	NS (0.358)	p<0.001 (-0.899)	NS
103	A	I	p<0.001 (-0.723)	NS	NS (-0.36)	NS	NS	p<0.001 (-0.639)	NS
105	A	D&A	NS	NS	NS	NS	p<0.01 (0.46)	p<0.001 (0.696)	NS
106	U	E	NS	NS	NS	NS	p<0.001 (-0.16)	ND	ND
107	U	D	p<0.001 (0.511)	p<0.001 (0.611)	NS	p<0.01 (0.4)	p<0.001 (0.587)	p<0.001 (0.757)	NS
108	A	I	p<0.001 (-0.74)	p<0.001 (0.818)	p<0.001 (-0.693)	p<0.001 (-0.587)	p<0.001 (0.754)	ND	ND
109	A	E	NS	p<0.01 (0.75)	NS	NS	NS	ND	ND
110	A	A&E	p<0.001 (0.629)	p<0.001 (0.611)	p<0.01 (0.476)	p<0.02 (0.39)	p<0.001 (0.652)	ND	ND
111	A	E	NS	NS	NS	NS	NS	NS	NS
112	A	D&I	NS	NS	p<0.02 (0.365)	NS	p<0.02 (0.364)	p<0.001 (0.692)	NS
113	U	I	NS	NS	NS	NS (-0.413)	p<0.02 (-0.511)	ND	ND
117	A	D	ND	ND	ND	ND	p<0.02 (-0.378)	p<0.001 (-0.666)	NS
118	A	D&I	p<0.001 (-0.843)	p<0.001 (-0.801)	p<0.001 (0.752)	p<0.001 (0.789)	p<0.001 (0.797)	p<0.001 (-0.853)	NS

119	U	E	p<0.001 (-0.493)	p<0.001 (0.721)	NS	p<0.001 (-0.585)	p<0.001 (-0.701)	p<0.001 (-0.922)	NS
121	U	D&E	NS	NS	NS	NS	NS	NS	NS
	Non Affective (Initial Interview)								
201	N	-	NS	p<0.01) <-0.501)	NS	p<0.001 <-0.587)	NS	NS	NS
202	N	-	NM	NM	NM	NM	NM	NM	NM
203	S	D	p<0.01 (-0.436)	p<0.02 (-0.379)	NS	NS	ND	p<0.001 (-0.734)	AVI
204	N	-	NS	NS	NS	NS	NS	NS	NS
207	S	E	p<0.001 (0.58)	p<0.01 (0.485)	p<0.05 (0.325)	p<0.01 (0.441)	p<0.001 (0.629)	p<0.001 (0.54)	NS
208	N	-	NS	NS	NS	NS	NS	NS	NS
209	N	-	NS	NS	NS	NS	NS	NS	NS
210	N	-	p<0.05 (-0.33)	p<0.001 (-0.502)	NS	NS	p<0.001 (0.61)	p<0.001 (0.59)	NS
211	N	-	NS	NS	NS	NS	NS	NS	NS
212	N	-	NS	NS	NS	p<0.001 (0.98)	NS	p<0.001 (0.69)	NS
213	N	-	NS	p<0.05 (0.331)	NS	NS	NS	NS	NS
214	N	-	NS	p<0.05 (-0.369)	NS	NS	NS	NS	NS
215	N	-	p<0.05 (-0.3)	p<0.01 (0.48)	p<0.05 (-0.3)	p<0.001 (-0.49)	NS	NS	NS
216	S	I	p<0.001 (-0.505)	p<0.001 (-0.617)	p<0.001 (-0.515)	p<0.01 (-0.418)	p<0.01 (-0.476)	p<0.001 (-0.824)	p<0.1 (0.265)
217	S	D&I	p<0.001 (-0.831)	p<0.001 (-0.861)	p<0.001 (-0.813)	NS	p<0.05 (-0.329)	p<0.01 (-0.47)	NS
218	N	-	p<0.001 (-0.543)	p<0.001 (-0.706)	NS	p<0.001 (-0.488)	p<0.001 (-0.632)	p<0.001 (-0.679)	NS
219	N	-	NS	NS	NS	NS	NS	NS	NS
222	N	-	NS	NS	NS	NS	NS	NS	NS
224	N	-	NS	NS	NS	NS	NS	NS	NS

225	S	E	NS	NS	NS	NS	NS	NS	AVI
228	N	-	NS	p<0.001 (-0.526)	p<0.001 (-0.525)	NS	NS	p<0.05 (-0.365)	AVI

NS = Non significant
ID = Insufficient data
ND = No data

AVI = All values identical
NM = No migraine

N = Never
S = Sometimes
U = Usually
A = Always

A = Anxiety
D = Depression
I = Irritability
E = Euphoria

Twelve out of the 37 patients who completed the prospective rating scales met these criteria for an affective designation. They did not differ materially from the study group as a whole with respect to:

(i) age,

(ii) self report of mood changes at the initial interview,

(iii) type of migraine,

(iv) the presence or absence of past and present DSM-III diagnoses of affective disorder.

The relationship between affective changes and the severity of migraine

The relationship between the frequency and duration of the migraines in the prospective rating period and the presence and absence of affective change was examined for:

(1) initial interview,

(2) SCID DSM-III diagnoses,

(3) diary data,

(4) classical and common migraine.

Chi square tests were used throughout. The median frequency (2) and duration (1.5 days) were used to separate patients into high and low groups for frequency and duration.

Initial Interview (Non-affective 19 patients, Affective 17 patients)

Frequency

	Aff	NAff	
Low Frequency	8 (8.0)	9 (9.0)	17
High Frequency	9 (9.0)	10 (10)	19
	17	19	36

min EF = 8
chi square = 0
DF = 1
p = NS

Duration

	Aff	NAff	
Low Duration	8 (9.0)	11 (10)	19
High Duration	9 (8)	8 (9)	17
	17	19	36

chi square = 0.42
DF = 1
min EF = 8
p > 0.1

DSM-III Diagnosis (Non-affective 18 patients, Affective 18 patients including pilot group)

Frequency

	Aff	NAff	
Low Frequency	10 (9.5)	9 (9.5)	19
High Frequency	8 (8.5)	9 (8.5)	17
	18	18	36

Chi square = 0.11, 1 DF
p<0.5, min EF 8.5

Duration

	Aff	NAff	
Low Duration	11 (9.5)	8 (9.5)	19
High Duration	7 (8.5)	10 (8.5)	17
	18	18	36

Chi square = 1, 1 DF
p<0.5, min EF 8.5

Diary Data (Non-affective 22 patients, Affective 12 patients)

Frequency

	Aff	NAff	
Low Frequency	3 (5.6)	13 (10.4)	16
High Frequency	9 (6.4)	9 (11.6)	18
	12	22	34

Chi square = 3.62, DF = 1
p<0.06, min EF = 5.6

Duration

	Aff	NAff	
Low Duration	4 (6.4)	14 (11.6)	18
High Duration	8 (5.6)	8 (10.4)	16
	12	22	34

Chi square = 2.86, DF = 1
p<0.09, min EF = 5.6

(2 patients were excluded from this analysis because there were insufficient data from the prospective rating scales to allow them to be classified as either affective or non-affective.)

Classical/Common (Classical 16 patients, Common 19 patients)

Frequency

	Classical	Common	
Low Frequency	11 (8.0)	6 (9.0)	17
High Frequency	6 (9.0)	13 (10.0)	19
	17	19	36

Chi square = 3.95, DF = 1,
p<0.05, min EF = 8

Duration

	Classical	Common	
Low Duration	10	9	19
High Duration	7	10	17
	17	19	36

Chi square = 0.47, DF = 1
p<0.5, min EF = 8.

The extent of agreement between the self report measures employed during the prospective rating period.

Comparison were made between the IDA anxiety and depression scores and the VAS anxiety and depression scores where data was available (see Table 10). Both straightforward and differenced correlations were calculated between the raw scores.

Data was available for 14 of the affective group (initial interview) for anxiety and 10 for depression. The corresponding numbers for the non-affective group were 20 for anxiety and 20 for depression.

TABLE X

Correlations and differenced correlations between IDA and VAS Scores for Anxiety and Depression

Patient Identification No.	IDA(A) & VAS Anxiety Correlation	IDA(A) & VAS Anxiety Differenced Correlation	IDA (D) and VAS Depression Correlation	IDA (D) and VAS Depression Differenced Correlation
Affective (Initial Interview)				
101	p<0.01 (0.401)	NS	NS	NS
102	No data	No data	No data	No data
103	NS	NS	p<0.01 (0.482)	NS
105	NS	NS	NS	p<0.02 (-0.391)
106	NS	NS	NS	NS
107	p<0.001 (0.763)	p<0.001 (0.729)	p<0.001 (0.627)	p<0.001 (0.495)
108	p<0.001 (0.687)	p<0.001 (0.737)	No data	No data
109	NS	NS	No data	No data
110	p<0.001 (0.714)	p<0.001 (0.763)	No data	No data
111	p<0.01 (0.504)	p<0.01 (0.528)	p<0.001 (0.707)	p<0.001 (0.619)
112	NS	NS	NS	p<0.01 (0.413)
113	p<0.001 (0.807)	p<0.001 (0.658)	No data	No data
117	No data	No data	No data	No data
118	p<0.001 (0.853)	p<0.001 (0.828)	p<0.001 (0.774)	p<0.001 (0.707)
119	p<0.001 (0.751)	p<0.001 (0.713)	p<0.001 (0.724)	p<0.01 (0.475)
121	p<0.01 (0.461)	NS	p<0.001 (0.642)	p<0.001 (0.565)

Non Affective (Initial Interview)

201	No data	No data	No data	No data
202	p<0.001 (0.69)	p<0.001 (0.628)	NS	p<0.02 (0.384)
203	p<0.01 (0.418)	NS	p<0.001 (0.734)	p<0.001 (0.879)
204	p<0.001 (0.542)	NS	p<0.001 (0.54)	NS
207	p<0.001 (0.52)	p<0.001 (0.592)	p<0.001 (0.529)	p<0.001 (0.588)
208	p<0.02 (0.389)	NS	p<0.001 (0.826)	p<0.001 (0.694)
209	p<0.001 (0.63)	p<0.001 (0.748)	p<0.001 (0.825)	p<0.01 (0.472)
210	p<0.05 (0.323)	NS	p<0.001 (0.579)	NS
211	p<0.001 (0.701)	NS	p<0.001 (0.774)	NS
212	p<0.01 (0.559)	p<0.001 (0.706)	NS	p<0.05 (0.461)
213	p<0.001 (0.639)	p<0.01 (0.476)	p<0.001 (0.736)	p<0.001 (0.6)
214	NS	NS	NS	NS
215	p<0.001 (0.538)	p<0.05 (0.316)	NS	NS
216	p<0.001 (0.79)	p<0.001 (0.704)	p<0.001 (0.81)	p<0.001 (0.807)
217	NS	NS	p<0.001 (0.537)	p<0.05 (0.364)
218	p<0.001 (0.542)	NS	p<0.001 (0.54)	NS
219	p<0.001 (0.686)	p<0.01 (0.488)	NS	NS
222	p<0.05 (-0.373)	NS	p<0.05 (0.387)	NS

224	$p<0.05$ (0.347)	$p<0.05$ (0.357)	$p<0.001$ (0.713)	$p<0.001$ (0.625)
225	NS	$p<0.05$ (-0.364)	$p<0.01$ (0.457)	NS
228	$p<0.05$ (0.388)	$p<0.05$ (0.395)	$p<0.001$ (0.772)	$p<0.01$ (0.477)

'Weekend Headache'

As patients had recorded the date on each daily questionnaire it was possible to examine the frequency of migraine on each day of the week (see Tables XI-XIV).

TABLE XXI

Days of Week vs Affective and Non Affective (Initial Interview) vs Employed and Unemployed

	Mon	Tues	Wed	Thurs	Fri	Sat	Sun	Total No of Patients	Total No of Migraine	Total No of Days	Mean No of days per Patient	Mean No of Migraines per Patient
Total Group (II)												
Affective	7	7	6	9	10	4	7	16	50	561	35.1	3.13
Non Affective	14	6	11	7	12	14	11	20	75	782	39.1	3.75
Total	21	13	17	16	22	18	18	36	125	1343	37.3	3.5
Affective												
Employed	5	6	3	7	5	4	6	11	36	374	34.0	3.3
Unemployed	2	1	3	2	5	0	1	5	14	187	37.4	2.8
Non Affective												
Employed	11	6	9	7	10	13	7	16	63	624	39	3.9
Unemployed	3	0	2	0	2	1	4	4	12	158	39.5	3
Total Group												
Employed	16	12	12	14	15	17	13	27	99	998	36.9	3.5
Unemployed	5	1	5	2	7	1	5	9	26	345	38.3	2.9

TABLE XXII

Days of the Week vs Affective and Non Affective (Initial Interview) vs Classical and Common

	Mon	Tues	Wed	Thurs	Fri	Sat	Sun	Total No of Patients	Total No of Migraine	Total No of Days	Mean No of Days per Patient	Mean No of Migraines per Patient
Affective (II)												
Classical	3	3	3	4	6	0	4	7	23	264	37.7	3.2
Common	4	4	3	5	4	4	3	9	27	297	33	3.
Non Affective (II)												
Classical	5	4	6	1	7	4	6	10	32	384	38.4	3.2
Common	9	2	5	6	5	10	5	10	43	398	39.8	4.3
Total Group												
Classical	8	7	9	5	13	4	10	17	55	648	38.5	3.2
Common	13	6	8	11	9	14	8	19	70	695	36.6	3.7

TABLE XXIII

Days of week vs Affective/Non Affective (Diary Data)
vs Employed/Unemployed

	Mon	Tues	Wed	Thurs	Fri	Sat	Sun	Total No of Patients	Total No of Migraine	Total No of Days	Mean No of Days per Patient	Mean No of Migraines per Patient
Total Group												
Affective (DD)	11	5	6	7	14	6	6	12	55	494	41.2	4.5
Non Affective (DD)	10	8	10	8	7	12	11	22	66	782	35.5	3
Total	21	13	16	15	21	18	17	34	121	1276	37.5	3.6
Affective (DD)												
Employed	10	5	5	7	12	5	5	11	60	449	40.8	5.5
Unemployed	1	0	1	0	1	1	1	1	5	45	45	5
Non Affective (DD)												
Employed	7	8	8	8	4	12	7	16	54	567	33.5	3.4
Unemployed	3	0	2	0	3	0	4	6	12	215	35.8	2
Total Group												
Employed	17	13	15	15	16	17	12	27	114	1016	37.6	4.2
Unemployed	4	0	3	0	4	1	5	7	17	260	37.1	2.4

Days of Week vs Affective/Non Affective (Diary Data)
vs Classical/Common

	Mon	Tues	Wed	Thurs	Fri	Sat	Sun	Total No of Patients	Total No of Migraine	Total No of Days	Mean No of Days per Patient	Mean No of Migraines per Patient
Affective (DD)												
Classical	6	3	4	4	8	3	3	7	31	298	42.6	4.4
Common	5	2	2	3	6	3	3	5	24	196	39.2	4.8
Non Affective (DD)												
Classical	2	4	4	0	5	1	6	10	22	367	36.7	2.2
Common	8	4	6	8	2	11	5	12	44	415	34.6	3.7
Total Group												
Classical	8	7	8	4	13	4	9	17	53	665	39.1	3.2
Common	13	6	8	11	8	14	8	17	68	611	25/9	3/4
Total	21	13	16	15	21	18	17	34	121	1276	37.5	3.6

TABLE XIV

This was then related to employment status and type of migraine. Finally the frequency each day, employment status and type of migraine were examined with respect to affective and non- affective groups as defined by (1) initial complaints of mood change and (2) the diary data. The results were separated into 'mid week', 'weekend' and 'no clear pattern' for each patient. Chi square tests were performed on this data to see whether employment/unemployment or classical/common migraine was associated with weekend headache. There were too few patients in each cell for the statistics to be meaningful and therefore mid-week headaches and no clear pattern groups were amalgamated for chi square testing.

	Midweek	Weekend	No Clear Pattern (NCP)	
Employed	5 (4.5)	15 (15.0)	7 (7.5)	27
Unemployed	1 (1.5)	5 (5.0)	3 (2.5)	9
	6	20	10	36

3 cells with EF < 5.

	Midweek + NCP	Weekend	
Employed	12 (12.0)	15 (15)	27
Unemployed	4 (4)	5 (5)	9
	16	20	36

1 cell EF < 5, chi square = 0

	Midweek	Weekend	NCP	
Classical	5 (2.5)	10 (10)	3 (5.5)	18
Common	0 (2.5)	10 (10)	8 (5.5)	18
	5	20	11	36

2 cells with EF < 5

	Midweek + NCP	Weekend	
Classical	8	10	18
Common	8	10	18
	16	20	36

Obviously here chi square would be zero.

There was no significant association between either the type of migraine or employment status and weekend headaches.

Log linear modelling of the interaction between cerebral dominance, laterality of migraine, the type of migraine and self report of anxiety, depression, euphoria and irritability.

In order to test the hypothesis that unilateral migraine affecting the dominant hemisphere is associated with depression and unilateral migraine affecting the non-dominant hemisphere is associated with euphoria the GLIM computer package (259) was used to fit appropriate models to the data on the variables named above (see appendix). Laterality

and type of migraine were found to be important for depression only. Dominance was not important for any of the mood changes reported.

For complaints of depression the results indicated that this was more commonly associated with classical migraine. The relative risk with respect to common migraine was 6.7. Unilateral migraine affecting the right hemisphere was most closely related to complaints of depression. There was a 20 fold decrease in the relative risk of depression in patients with unilateral symptoms affecting the left hemisphere, a 10 fold decrease for bilateral symptoms, a less than 5 fold decrease for unilateral symptoms intermittently affecting left and right hemispheres and a two fold difference for both bilateral and unilateral symptoms.

Migraine and menstruation

Unfortunately data on this particular aspect of migraine and mood change was not collected for all patients initially. Of the total group of 51 patients 38 were pre-menopausal (i.e. were regularly menstruating), 4 had had hysterectomies, 3 were post-menopausal, 4 were perimenopausal (i.e. had infrequent, irregular periods) and no information was available for the other two patients.

For a subgroup of 6 patients (the last 6 menstruating women to enter the study), the relationship between migraine, mood change and menstruation was examined using time series plots of mood, migraine and menstruation (see graphs in appendix) and Fisher exact tests of the presence or absence of migraine and the presence of absence of

menstruation (see Table XV).

TABLE XV Comparison of subjective estimate of the frequency with which migraine was associated with menstruation with the objective record obtained during the 6 week prospective rating period.

Patient No.	Self report of frequency of migraine vs menstruation	Diary data - Fisher's exact test probability value for the association of migraine and menstruation
121	Never	$p < 1$
219	Always	$p < 0.962$
222	Never	$p < 0.184$
224	Never	$p < 0.45$
225	Usually	$p < 0.044$
228	Never	$p < 0.438$

(3) Regional cerebral blood flow monitoring

Altogether 27 patients had rCBF monitoring performed when their migraine was absent (10 in the affective group (II) and 17 in the non-affective group (II). Descriptive reports on these scans are available for all patients (Tables XVI and XVII). Unfortunately data for two patients were not available for numerical analysis but the numerical data for the remaining 25 patients are summarised in Appendix.

Only 5 patients attended for repeat rCBF monitoring during a migraine (1 in the affective (II) group and 4 in the non-affective (II) group). The descriptive reports on these scans are also available in Tables XVI and XVII. The numerical data is summarised in Appendix, Patient 220 had 2 repeat scans during migraines and data are available for both of these.

TABLE XVI

REGIONAL C.B.F. RESULTS - AFFECTIVE GROUP

Patient's No	Migraine Absent	Migraine Present
102	Slight asymmetry-transit times longer on (R)	
103	Normal	
104	Normal	Little difference in cortical transit times, large vessel transit time substantially increased
105	Normal	
106	Normal	
110	Normal	
113	Asymmetry of perfusion - (L) anterior temporal perfusion better than (R)	
118	Normal	
119	Normal	
120	Normal	

TABLE XVII

REGIONAL C.B.F. RESULTS - NON AFFECTIVE GROUP

Patient's No	Migraine Absent	Migraine Present
201	Normal	
204	Increased perfusion in (R) anterior parietal region	
205	Asymmetry of flow times with prolonged transit in (R) posterior temporal and (L) mid parietal regions	
207	Normal	
208	Normal	Cortical transit times are longer in the base line study than during a migraine
209	Normal	
210	Normal	
211	Normal	Impaired perfusion (L) mid temporal region
212	Normal	
213	Decreased perfusion (R) posterior parietal region	
215	Normal	
218	Normal	
220	Not reported	The large vessel transit time is more asymmetrical, the cortical transit time is unchanged
221	Normal	
222	Normal	
224	Normal	
225	Normal	Transit times shorter but regional flow is less uniform during migraine. The large vessel transit times are asymmetrical.

The numerical data are grouped as follows:

(1) input function - arrival,
transit,

(2) net cortical transit time left hemisphere and quadratic values for frontal, temporal, parietal and occipital regions,

(3) net cortical transit time right hemisphere and quadratic values for frontal, temporal, parietal and occipital regions,

(4) net fractional flow for the left hemisphere and quadratic fractional flow values,

(5) net fractional flow values for the right hemisphere and quadratic fractional flow values,

(6) net large vessel transit time for the left hemisphere and quadratic large vessel transit times,

(7) net large vessel transit times for the right hemisphere and quadratic large vessel transit times.

The cerebral blood flow data were grouped according to:

(i) affective/non-affective initial interview

(ii) affective/non-affective SCID DSM-III diagnoses

(iii) affective/non-affective diary data

(iv) classical/common migraine.

Mann Whitney U tests were performed on each of these four groupings for all baseline data (i.e. for results obtained when migraine was absent). (See Table XVIII). (The input function data were not included in the Mann Whitney tests because this is simply an indication that the

radioactivity was given in a suitable bolus injection and is relevant only in ensuring that correct technique was used.)

The left/right ratios for rCBF are presented for each of the 5 patients for whom results were available for scans performed in both the absence and presence of migraine. (See Tables XIX and XX).

The net values for common and classical migraine in the presence and absence of migraine are compared in Table XXI. The difference between the results is expressed as a percentage increase or decrease from the baseline value (i.e. when migraine was absent).

TABLE XVIII

rCBF - Mann Whitney U tests by group
(2-tailed probability levels corrected for bias are used throughout)

II	Aff = 10	NAff = 15
DSM-III	Aff = 13	NAff = 12
Diary	Aff = 7	NAff = 12
Classical = 15		Common = 10

Variable	Initial Interview		DSM III Diagnosis		Diary Data		Classical/ Common	
	U value	p	U value	p	U value	p	U value	p
Net CTT(L)	56.5	0.3	77.5	0.98	28.5	0.25	56.5	0.3
CTT L(F)	69	0.74	77	0.97	24	0.13	72	0.9
CTT L(T)	75	1.0	66	0.5	21	0.08	69	0.7
CTT L(P)	73	0.91	62.5	0.4	28	0.24	60	0.4
CTT L(O)	66	0.62	70	0.66	34	0.5	61	0.4
Net CTT(R)	67	0.7	72.5	0.76	32.5	0.42	73	0.9
CTT R(F)	69	0.74	77.5	0.97	27	0.2	65	0.58
CTT R(T)	70	0.78	69	0.6	24.5	0.14	63	0.5
CTT R(P)	68	0.70	59	0.3	22	0.09	59	0.4
CTT R(O)	67	0.66	70	0.66	39	0.8	74	0.9
Net FF(L)	69.5	0.76	63.5	0.43	23.5	0.12	54.5	0.3
FF L(F)	70.5	0.8	75	0.9	22.5	0.1	61	0.5
FF L(T)	74	0.96	66	0.5	20	0.06	60.5	0.4
FF L(P)	74	0.96	59	0.3	27.5	0.22	52	0.2
FF L(O)	69	0.74	67.5	0.57	29.5	0.29	50	0.2
Net FF(R)	71.5	0.85	61.5	0.37	28	0.2	64.5	0.6
FF R(F)	71	0.82	76	0.9	26	0.18	66	0.6
FF R(T)	70.5	0.8	69	0.6	23.5	0.12	62	0.5
FF R(P)	70.5	0.8	60.5	0.34	24	0.13	58	0.3
FF R(O)	66.5	0.64	70	0.66	35.5	0.58	74	0.9
Net LVTT(L)	51.5	0.19	46	0.08	25	0.15	48.5	0.1
LVTT L(F)	57	0.32	55	0.2	28	0.24	53	0.2
LVTT L(T)	57	0.32	54	0.19	26	0.18	54	0.2
LVTT L(P)	58	0.35	53	0.17	24	0.13	54	0.2
LVTT L(O)	57	0.32	52	0.16	24	0.13	54	0.2
Net LVTT(R)	50.5	0.17	46	0.08	24.5	0.14	49	0.15
LVTT R(F)	56	0.29	59	0.3	26.5	0.19	55	0.3
LVTT R(T)	56.5	0.31	55	0.2	26	0.18	55.5	0.3
LVTT R(P)	57.6	0.33	53.5	0.18	24	0.13	54	0.2
LVTT R(O)	56	0.29	51	0.14	23	0.1	49	0.15

Table XIX

Left/Right ratios for rCBF in the presence and absence of migraine

Migraine Absent (Classical)

Patient No. 104

	Net CTT	CTT F	CTT T	CTT P	CTT O	Net FF	FF F	FF T	FF P	FF O	Net LVTT	LVTT F	LVTT T	LVTT P	LVT O
Left	5.2	5.23	4.81	5.32	6.04	0.19	0.19	0.21	0.19	0.17	7.6	7.46	7.34	6.62	8.1
Right	5.4	4.96	5.14	5.75	6.44	0.18	0.21	0.20	0.18	0.16	7.5	7.5	7.27	7.59	7.8
Left/ Right Ratio	0.96	1.1	0.94	0.93	0.94	1.1	0.9	1.05	1.06	1.06	1.01	0.99	1.0	1.0	1.0

Migraine Present

Patient No. 104

	Net CTT	CTT F	CTT T	CTT P	CTT O	Net FF	FF F	FF T	FF P	FF O	Net LVTT	LVTT F	LVTT T	LVTT P	LVT O
Left	6.3	5.41	5.78	6.62	8.05	0.16	0.19	0.18	0.16	0.13	4.4	4.55	4.41	4.48	4.4
Right	6.1	4.84	5.23	6.06	7.44	0.17	0.21	0.19	0.17	0.14	4.6	4.72	4.55	4.54	4.6
Left/ Right Ratio	1.03	1.1	1.1	1.1	1.1	0.94	0.9	0.95	0.94	0.93	0.96	0.96	0.97	0.99	0.9

Migraine Absent (Classical)

Patient No. 220

	Net CTT	CTT F	CTT T	CTT P	CTT O	Net FF	FF F	FF T	FF P	FF O	Net LVTT	LVTT F	LVTT T	LVTT P	LVT O
Left	4.2	3.2	3.35	3.75	5.39	0.2	0.2	0.3	0.27	0.2	3.7	1.94	1.68	1.52	1.5
Right	4.1	2.83	2.75	4.01	5.84	0.23	0.35	0.37	0.26	0.19	3.8	1.96	1.78	1.53	1.6
Left/ Right Ratio	1.02	1.13	1.2	0.94	0.92	0.87	0.57	0.81	0.96	1.05	0.97	0.99	0.94	0.99	0.9

Migraine Present

Patient 220

	Net CTT	CTT F	CTT T	CTT P	CTT 0	Net FF	FF F	FF T	FF P	FF 0	Net LVTT	LVTT F	LVTT T	LVTT P	LVT 0
Left	5.0	4.03	4.06	5.33	7.09	0.19	0.25	0.25	0.19	0.16	3.5	3.95	3.77	3.78	3.6
Right	4.7	3.01	3.88	4.84	6.76	0.21	0.29	0.26	0.21	0.15	3.9	4.32	4.02	4.02	4.1
Left/ Right Ratio	1.06	1.15	1.05	1.1	1.05	0.9	0.86	0.96	0.9	1.07	0.9	0.91	0.94	0.94	0.8

Migraine Present

Patient No. 220 (repeat examination)

	Net CTT	CTT F	CTT T	CTT P	CTT 0	Net FF	FF F	FF T	FF P	FF 0	Net LVTT	LVTT F	LVTT T	LVTT P	LVT 0
Left	-	2.28	2.5	3.66	5.53	-	0.44	0.42	0.28	0.19	-	4.83	4.53	4.55	4.4
Right	-	2.14	2.37	3.25	5.67	-	0.48	0.44	0.32	0.17	-	4.88	4.55	4.54	4.3
Left/ Right Ratio	-	1.06	1.05	1.13	0.98	-	0.92	0.95	0.88	1.12	-	0.99	0.99	1.0	1.0

(No net values available)

Migraine Absent (Classical)

Patient No. 211

	Net CTT	CTT F	CTT T	CTT P	CTT 0	Net FF	FF F	FF T	FF P	FF 0	Net LVTT	LVTT F	LVTT T	LVTT P	LVT 0
Left	4.2	4.01	3.75	4.29	4.92	0.24	0.25	0.27	0.24	0.21	3.9	3.71	3.56	3.73	4.4
Right	3.9	3.38	3.17	4.07	4.51	0.27	0.3	0.32	0.25	0.22	4.0	3.74	3.59	3.74	4.8
Left/ Right Ratio	1.08	1.19	1.18	1.05	1.09	0.89	0.83	0.84	0.98	0.95	0.98	0.99	0.99	1.0	0.9

Migraine Present

Patient No. 211

	Net CTT	CTT F	CTT T	CTT P	CTT 0	Net FF	FF F	FF T	FF P	FF 0	Net LVTT	LVTT F	LVTT T	LVTT P	LV 0
Left	6.1	6.3	5.48	6.54	7.23	0.16	0.16	0.18	0.16	0.14	4.9	4.95	4.79	4.76	5.2
Right	6.0	5.69	5.12	5.85	7.22	0.17	0.18	0.2	0.17	0.14	5.0	4.97	4.89	4.87	5.1
Left/ Right Ratio	1.02	1.11	1.1	1.12	1.0	0.94	0.89	0.9	0.94	1.0	0.98	1.0	0.98	0.98	1.0

TABLE XX

Left/right rations for rCBF in the presence and absence of migraine.

Migraine Absent (common)

Patient No. 225

	Net CTT	CTT F	CTT T	CTT P	CTT 0	Net FF	FF F	FF T	FF P	FF 0	Net LVTT	LVTT F	LVTT T	LVTT P	LV 0
Left	4.5	4.35	4.17	4.11	5.42	0.2	0.23	0.24	0.25	0.19	4.8	5.36	4.99	4.85	4.7
Right	4.6	4.47	4.2	4.1	6.36	0.2	0.22	0.24	0.25	0.17	4.8	5.41	5.06	4.89	4.7
Left/ Right Ratio	0.98	0.97	0.99	1.0	0.85	1.0	1.05	1.0	1.0	1.12	1.0	0.99	0.98	0.99	1.0

Migraine Present (Common)

Patient No. 225

	Net CTT	CTT F	CTT T	CTT P	CTT 0	Net FF	FF F	FF T	FF P	FF 0	Net LVTT	LVTT F	LVTT T	LVTT P	LVT 0
Left	3.2	3.48	2.86	2.74	4.02	0.3	0.3	0.35	0.37	0.26	6	6.17	6.1	6.01	5.9
Right	3.4	3.3	2.57	3.15	5.18	0.28	0.31	0.4	0.32	0.21	6	6.17	6.17	6.01	6.0
Left/ Right Ratio	0.94	1.05	1.11	0.87	0.78	1.07	0.97	0.88	1.16	1.24	1.0	1.0	0.99	1.0	0.9

Migraine Absent (Common)

Patient No. 208

	Net CTT	CTT F	CTT T	CTT P	CTT 0	Net FF	FF F	FF T	FF P	FF 0	Net LVTT	LVTT F	LVTT T	LVTT P	LVT 0
Left	5.9	5	4.68	5.61	6.39	0.18	0.21	0.22	0.18	0.16	3.6	3.52	3.48	3.52	3.7
Right	6.2	4.5	4.64	5.94	7.33	0.17	0.22	0.22	0.17	0.14	3.6	3.76	3.57	3.38	3.6
Left/ Right Ratio	0.95	1.1	1.0	0.94	0.87	1.06	0.95	1.0	1.06	1.14	1.0	0.94	0.97	1.04	1.0

Migraine Present

Patient No. 208

	Net CTT	CTT F	CTT T	CTT P	CTT 0	Net FF	FF F	FF T	FF P	FF 0	Net LVTT	LVTT F	LVTT T	LVTT P	LVT 0
Left	4.5	4.21	3.82	4.01	5.86	0.22	0.24	0.27	0.26	0.18	4	4.25	4.11	3.95	4.0
Right	4.6	4.09	3.77	4.46	7.12	0.2	0.25	0.27	0.23	0.15	4	4.37	4.09	3.96	4.1
Left/ Right Ratio	0.98	1.03	1.01	0.9	0.82	1.1	0.96	1.0	1.13	1.2	1.0	0.97	1.0	1.0	1.0

TABLE XXI

Classical vs Common Migraine

Comparison of net rCBF values in the presence and absence of migraine

(The difference between net values in the presence and absence of migraine is expressed as a percentage increase or decrease of the baseline value)

NET VALUES		CLASSICAL		COMMON		
		Patient No. 104	Patient No. 220	Patient No. 211	Patient No. 225	Patient No. 208
CTT	R	↑ 13%	↑ 19%	↑ 45.2%	↓ 28%	↓ 23.7%
P-A	L	↑ 21.2%	↑ 14.6%	↑ 53.8%	↓ 26.1%	↓ 25.8%
FF	R	↓ 15.8%	↓ 5%	↓ 33%	↑ 50%	↑ 22.2%
P-A	L	↓ 5.6%	↓ 8.7%	↓ 37%	↑ 40%	↑ 17.6%
LVTT	R	↑ 42.1%	↓ 5.4%	↑ 25.6%	↑ 25%	↑ 11.1%
P-A	L	↑ 38.7%	↓ 2.6%	↑ 25%	↑ 25%	↑ 11.1%

(E) Discussion

This study aimed to determine the prevalence of migraine-related mood change and investigate the type of mood change involved. The intention was then to identify any factors in the patient's background or migraine history which could be related to the occurrence of these mood changes. This included both current and past psychiatric diagnoses. Finally the study aimed to assess the relationship between cerebral blood flow patterns and mood in migraine.

(i) Reliability and validity of the results

The Initial Interview

The patients were all new referrals to the Migraine Clinic as verified by the GP's referral letter and the hospital case record. Age was obtained from the hospital case record and checked directly with the patient. Marital status was obtained by direct questioning and information about the spouse's employment was obtained when appropriate. Social class was determined using the Registrar General's tables (260). The husband's occupation was used to define social class. The patient's own occupation was used when she was in any other category except married.

The diagnosis of migraine was made by an experienced physician with a special interest in the disorder and was classified into classical or common migraine on the basis of the Ad Hoc Committee on the Classification of Headache guidelines. The average number of migraine attacks was estimated retrospectively for the 6 week period preceding the

interview. This corresponded well with the actual incidence of migraine attacks during the 6 week prospective rating period. Cerebral dominance, as assessed by the simple method selected, was checked at interview by asking the patients to demonstrate how they held a pen for writing and watching them when they signed the consent form. Laterality of the headache was obtained directly from the patient and checked against the history given to the physician by the patient and the GP's letter.

The neurological symptoms were discussed carefully with the patients who were asked to describe their own symptoms in detail before the presence or absence of each category was decided. It was always made clear to the patient that these symptoms were being enquired about only when they were clearly related to migraine attacks. Where unilateral symptoms were complained of patients were asked to demonstrate which side was affected and to indicate whether this was the same as or opposite to the headache. A careful distinction was made between total loss of consciousness and dizziness. Difficulty in thinking was only rated as present if there was poor concentration and attention. Disinterest because of pain was not rated here. Nausea, vomiting and photophobia were familiar concomitants of migraine in the majority of patients. The symptoms described were all in accordance with a diagnosis of migraine and the low incidence of unconsciousness suggested it was unlikely that many patients were misdiagnosed epileptics.

The length of migraine history given was subjective. As it was generally long patients often had difficulty giving exact dates. Patients often spontaneously attempted to resolve this problem by linking the onset of their migraine with major life events e.g. before leaving

school or just after marriage etc. However the figure given was generally an estimate rather than a precise date.

Hallucinatory experiences were elicited during the psychotic screening section of the SCID. Patients were always asked to describe the phenomena in their own words and questioned carefully about the relationship with migraine and medication.

Patients were asked specifically about a family history of migraine. If positive they were asked which relative had been affected. A description of the relative's symptoms was obtained and by whom their diagnosis had been made. However no relative was questioned independently and it is recognised that this generally increases the incidence figure for familial illness. (261)

Medication prior to the initial visit was obtained from the GP's letter, the physician's notes and questioning the patient. Patients were asked particularly about proprietary medications and herbal remedies as well as doctor's prescriptions. Any change of medication made at the clinic and the new prescription given was always verified with the physician.

The information on emotional triggers to attacks and their relationship with menstruation was based entirely on the patient's own report and was therefore inevitably subjective. However if a menstrual relationship was claimed patients were asked to specify whether this was prior to, during or after the menstrual bleeding. (One patient arrived at her appointment with a calendar for the previous year with both

migraine and menstruation marked on it - but this was atypical!)

With regard to personal psychiatric history - patients were questioned on three occasions; during the collection of social and demographic data, in the SCID overview section and in more detail in the relevant portion of the SCID interview. This information was cross checked with dates given for the onset of illnesses and attendance at their GP or psychiatrist for treatment. There were no discrepancies in the dates or descriptions of the illnesses given by the patients.

The same sort of problem is encountered in assessing the prevalence of a family history of psychiatric illness as in a family history of migraine. Where positive patients were asked to describe which relatives had had the illness, their symptoms, diagnosis and treatment. However, as there is an even greater social stigma attached to psychiatric then physical illness it is even more likely that this information is incomplete.

The DSM-III diagnoses were made using the SCID after training according to the SCID manual. The DSM-III handbook (262) was referred to in all cases of doubt. Past diagnoses based on retrospective reports of symptoms are inevitably less objective than current diagnoses. If in doubt the subthreshold rather than the definite category was used. The results, in terms of diagnoses, were in close agreement with the patient's reports of attendance at their GP/psychiatrist both for dates and type of treatment received.

The frequency of mood change was highly subjective although again,

if a positive response was given, patients were asked to describe the change and its relationship in time with the migraine (e.g. before, during or after). A report of mood change was only accepted if the mood change differed in intensity or quality from a general reaction to discomfort and if it was clearly related to the migraine attack. Patients were asked if relatives had also noted the change in mood and, if so, what comments they had made about it.

Rating scale scores were all made by the interviewer at the conclusion of the interview. All scales were scored according to the author's instructions.

Group comparisons

A major difficulty in testing differences between groups on a number of variables simultaneously is that it becomes more probable that significant associations will be found by chance alone unless the multiple hypotheses are compensated for by adjusting the significance level to avoid type I errors. One method of doing this is to apply the Bonferroni inequality. (263) The overall significance level is chosen and then individual significance levels are selected to satisfy the equation: α overall $\leq \sum_{i}^{k} = 1 \alpha i$ where $\sum_{i}^{k} = 1$ denotes the sum of k terms. In other words the α level is adjusted according to the overall number of comparisons made. The tests are then carried out at αi and the risk of a type I error is reduced to α overall.

For the group comparisons of data from the initial interview the variables fell into two subtypes

(i) the social, demographic and migraine variables,

(ii) the predisposing factors, psychiatric history and mood variables.

There were 36 variables in total and as 22 of these were in group (i) and 14 were in group (ii) the α were 0.0023 and 0.0039 respectively and α overall was 0.05. On this basis the only significant result from the group comparisons would have been the frequency of complaints of irritability in the affective and non-affective groups at the initial interview.

However, the Bonferroni method is a very stringent method of assessing significance if the number of tests is large as it was here and even dividing the data into two subgroups does not resolve this problem. Another way to deal with this difficulty would have been to obtain more patients but the constraints on the time available for completion of the study did not permit this. The overall significance level can be increased to avoid an excessive risk of type II errors while accepting that this inevitably implies a greater possibility of a type I error. If the significance level for α overall is set at 0.1 the α_i for group (i) becomes 0.005 and for group (ii) 0.007. In this way an increased number of associations become statistically significant e.g. frequency of mood change in the affective/non-affective initial interview group. However as this is the variable which was used to divide these groups and define them in the first place it is obviously <u>clinically</u> highly significant regardless of the level of <u>statistical</u> significance assigned to it.

When testing a large number of associations in this way the degree to which a relationship is clinically relevant may be more meaningful

than an absolute level of statistical significance. Thus, from a clinical viewpoint, the association of psychotic phenomena with the affective complaint group may be an indication of temporal lobe dysfunction. This may well be linked with complaints of depression and irritability which are known to be closely related to limbic system function. The increase in MADRS and MRS scores in the affective group would reflect this as would the increased incidence of DSM-III affective diagnoses. The only association which would remain uncertain clinically would be the family history of migraine.

Likewise, in the DSM-III diagnostic groupings personal psychiatric history could be expected to correlate with past and present psychiatric diagnoses. Complaints of irritability could be linked to current and past illness as could elevated CAS, MADRS and MRS scores.

It is interesting that no associations approached statistical significance using the diary data to define affective and non-affective populations as it implies that the actual presence of mood change during migraine is independent of psychiatric history and current levels of symptoms.

In the classical/common group it is not unexpected that blurred vision should be more common in the classical group as it is a well recognised part of the migraine aura. In fact it is slightly surprising that it is not more common in this group. The significance of the observation that fewer patients with common migraine are on no medication probably reflects higher patient and physician concern about the classical group as they have both an unpleasant and debilitating

condition together with an, often frightening, prodrome. This concern may make it more likely that the classical group will receive medication. The elevated CAS scores in the classical group may be related to frightening prodromal symptoms or be a secondary consequence of the physiological disturbance engendered by the illness process.

However clinical interpretation can be biased by an investigator's own clinical experience and interests and the best test of the significance of the associations found in this study would be replication of the results in a further sample.

DSM-III diagnoses based on the SCID

Current information is generally more reliable than information about past events. (261) The retrospective diagnoses and their dates are therefore likely to be less reliable than current diagnoses. Likewise the length of migraine history can only be regarded as an approximation.

For both generalised anxiety disorder and affective disorder considered together, migraine appears to precede psychiatric illness in 21 patients, psychiatric illness appears to precede migraine in 6 patients and in 5 patients the order in which the two conditions arose is uncertain because the two problems were almost simultaneous in onset.

However migraine generally has an earlier age of onset than generalised anxiety disorder and major depression. It is also difficult to assess sequencing of illnesses retrospectively e.g. Slater's work on the association of TLE and paranoid schizophrenia could not be replicated

by Betts and Skarrot and may have been an artefact of the population originally studied (see Chapter 10 of literature survey). Migraine, anxiety and depression are all common disorders and they are therefore likely to occur occasionally in the same individual by chance alone.

The significance of the observation that migraine generally preceded affective disorder in this sample is therefore questionable.

(2) Six week prospective rating period

The results of the 6 week prospective rating period were analysed separately for each individual patient. Mann Whitney U tests were performed on the data to examine the association of mood components with the migraine prodrome and the recovery period after an attack. Seven Mann Whitney U tests were performed (one for each mood index). There were few significant associations for either period using an arbitrary α of 0.05. When the Bonferroni inequality was used to obtain an α overall of 0.05 the actual α level became 0.007.

Using either the original α level of 0.05 or the Bonferroni-obtained 0.007 to assess significance, no patient had four or more significant differences between mood components the day before a migraine and days when migraine was absent. Three patients had four or more significant differences (i.e. above $p<0.05$) for mood the day before a migraine with mood on the first day of the migraine. Using an α level of 0.007 this fell to only one patient. This lady (patient No.108) complained of irritability which she usually experienced as a concomitant of a migraine attack. The other two patients were No.110 who complained

of always experiencing anxiety and euphoria and No.207 who sometimes experienced euphoria.

Setting an α of 0.05 or 0.007 only one patient (No.108) had significant differences between 4 mood indices when the day after a migraine was compared with days when migraine was absent. Using an α of 0.05 two patients had more than four significant differences between mood components on the day after a migraine and mood components on all migraine days except the first (patients Nos.118 and 207). Using an α of 0.007 only patient 118 meets these criteria. This patient complained of always experiencing anxiety, depression and irritability. Patient No.207 has already been described.

Of these patients only No.207 was able to estimate when her mood changes occurred and she felt that they were prior to the migraine.

The data available suggest that only a small number of patients have convincing evidence of mood changes in the period prior to and subsequent to migraine attacks. Three of these four patients had current diagnoses of generalised anxiety disorder or affective disorder.

By contrast 12 of 37 patients had at least four significant (at $p<0.05$) point biserial correlations between mood indices and migraine. This was reduced to 8 of 37 if a significance level of 0.007 was used. This did not correspond well with the patient's subjective estimates of the frequency and type of mood change they experienced prior to the prospective rating period.

This lack of correspondence may be genuine but it is also possible that the rating scales used were not sensitive enough to register the transient disturbances in mood which the patients described. However the patients' mood changes were often quite severe, as assessed by the descriptions given during the SCID. Eleven patients were subthreshold for affective disorder during migraine episodes, generally only because these were shorter than ordinary affective illnesses, and it seems unlikely that patients would have failed to record this degree of distress on either the IDA or the VAS.

Chi square tests of the association of affective and non-affective groups (as defined by self report, DSM-III diagnoses and diary data) with frequency and duration of headaches were not significant. It is therefore unlikely that the severity of the migraine, as assessed using these indices, played any significant role in the affective/non-affective distinction in any of these groups. The only significant association (at the 0.05 level) was between a high frequency of migraine and the common variety of the condition.

Agreement between the IDA and VAS Scales

There was agreement between the scales measuring anxiety and depression in approximately half of the patients. This may reflect the different construction of the VAS and the IDA, i.e. the two scales may be tapping different areas of experience.

Migraine and the day of the week

The day of the week was shown on each questionnaire and VAS scale. Employment status and migraine diagnosis were recorded at the initial interview as described above. There was no evidence of a relationship between either employment status or migraine diagnosis and weekend versus mid-week headaches.

Log linear analysis of cerebral dominance, laterality, type of migraine and self-report of mood change

The type of migraine, laterality of migraine symptoms and cerebral dominance were all assessed with regard to their association with self report of mood change at the initial interview. Laterality and type of migraine were important for depression only. Dominance was not related independently or in combination with type and laterality for any mood change.

Given that no association was found between classical migraine and DSM-III diagnoses of affective disorder or Montgomery and Asberg depression scale scores the significance of this finding is uncertain. The self reports of depression were also associated with right hemisphere dysfunction which was the opposite of the anticipated association. These results require replication and further investigation.

Migraine and menstruation

Unfortunately data on the relationship of mood change, migraine and menstruation was not collected routinely from all patients throughout the

study. However, for five of the six patients there was no significant association (i.e. $p<0.05$) between migraine and menstruation. The sixth patient menstruated during 50% of migraine episodes in the study period. This could be a chance finding but a longer period of observation would be required to determine this more definitely. Graphs of the relationship of mood components, migraine and menstruation also failed to show a relationship between these three parameters for the other five patients. It was thus impossible to demonstrate menstrual mood change and menstrual migraine in five of these six patients but it has to be remembered that four of the six said that their migraine was never associated with menstruation. However this type of self report is often unreliable.

(3) Regional CBF monitoring

Unfortunately it was not possible to obtain rCBF scans on all patients during the absence of migraine. Patients gave a variety of reasons for their refusal to consent to this - a fear of injections, difficulty in obtaining time off work (especially as they often had frequent absences because of migraine and medical appointments), residence outwith the city or, in only 2-3 cases, a fear of the radiation involved in the procedure. Of the 27 patients who attended, 10 had complained of affective changes at the initial interview and 17 had not. Fourteen of the patients had classical migraine and 13 common migraine. The age range was from 20-62 years with a mean of 40.1 years, a median of 43 years and a standard deviation of 11.4. The population of patients who had rCBF scans performed was thus comparable with the total population of patients within the study.

Regional cerebral blood flow values do not differ significantly with age. In patients who do not have neurological signs there is no significant difference in the median values for the left and right hemispheres and no evidence of systematic differences between the hemispheres. For frontal, temporal and parietal regions there is no trend towards lateralisation. The values obtained in the occipital region are too heavily influenced by radiation from structures in the neck to be valid for analysis (personal communication, Dr M. Merrick, 1988 - see appendix).

The net values represent the following:

(1) cortical transit time - the time such that, at equilibrium, the volume of tracer entering or leaving the cortex is equal to the volume of blood within the cortex,

(2) fractional flow - at equilibrium the volume of blood entering the organ is equal to the fraction already there. Autoregulation causes vasodilatation which, in turn, increases the volume of blood within the tissue. Measurement of fractional flow therefore corrects for this,

(3) the large vessel transit time is the time take for the leading edge of the bolus of radioactivity to travel from the aorta to the head. It demonstrates asymmetry of flow - particularly in the neck vessels and to a lesser extent in the larger cranial vessels. In the majority of subjects there is little difference between large vessel transit time values on the right and left sides.

Repeatability of rCBF measures

As there is a high background count rate if rCBF measurements are repeated within a short period the quality of statistical analysis is decreased on the occasion of the repeat measurement. It is thus difficult to estimate the stability of regional CBF measurements. However the normal range of rCBF values is narrow and symmetry between the hemispheres is less affected than individual values in repeat examinations.

Analysis of the baseline rCBF data in terms of the differentiation of affective and non-affective groups using Mann-Whitney U tests failed to show any significant differences between any of the categorisations of affective/non-affective which were used. Presumably either no differences in rCBF were present in the baseline condition or the technique employed to measure rCBF was insufficiently sensitive to demonstrate it. It is unfortunate that the number of patients who had scans during a migraine attack was so small that no statistical comparison of the rCBF results was possible.

Undoubtedly, the interpretation of the rCBF results would have been much easier if results could also have been obtained from a control population (e.g. of patients with muscle-contraction headache). However rCBF measurement, whilst a very safe technique, does involve exposure to a small dose of radiation, a venepuncture and the inconvenience of attending for the examination. The Nuclear Medicine department was also extremely busy and would have been overloaded by scanning both groups of patients. An attempt was made to obtain a control population of patients without headache who were attending for scans of other body organs. They could have had a cerebral blood flow scan at the same time, with their

consent, without any additional radiation or inconvenience. Again, however, this proved too time-consuming for the staff of the department.

The reporting of the rCBF scans for the migraine patients in the presence and also in the absence of migraine suggested that migraineurs generally have a more reactive vasculature than non-migraineurs.

The left/right ratios did not demonstrate any convincing asymmetry of flow in either the baseline condition or when migraine was present. However as the number of patients who had scans performed while a migraine was present was so small this was inconclusive and not generalisable to migraineurs as a whole. This was equally applicable to the comparison of the results for classical and common migraineurs obtained during the course of a migraine attack. The differences between the results for classical and common migraine were interesting nonetheless, and in accordance with the differences found between the two conditions using other techniques of rCBF measurement.

(ii) Review of original aims and hypotheses

Aims

(1) To determine the prevalence of complaints of mood change in conjunction with migraine and to identify the type of mood change involved.

37% of this sample of new referrals to a migraine clinic complained of experiencing mood changes in more than 50% of their attacks. In order

of frequency these mood changes were depression (28.3%), irritability (28.3%), euphoria (13%) and anxiety (8.7%).

(2) To define and quantify transient changes in mood components and assess their relationship with migraine attacks.

The self reports of mood changes did not correspond well with the alterations in mood components which the patients documented during the six week prospective rating period. No evidence was found for a prodromal change in mood components or for a change in mood components immediately following the migraine attack. However in 12 out of the 37 patients who completed the prospective rating period there was a statistically significant increase in depression, anxiety and irritability scores on days when a migraine was present. These changes in mood components were not related to the frequency or duration of the migraines.

(3) To identify the factors in the individual which are related to changes in mood components.

The factors most associated with complaints of mood changes were current or past DSM-III diagnoses of affective disorder and increased MADRS and MRS scores. The latter presumably reflect increased levels of current distress. A subgroup of the patients who complained of mood changes had olfactory hallucinations which implied temporal lobe disturbance.

(4) To determine the prevalence of psychiatric illness in migraine sufferers and to assess its relationship with the acute mood changes associated with migraine attacks.

52.5% of migraine patients in this study had current and past DSM-III diagnoses of affective disorder. 32.6% of patients had current DSM-III diagnoses of affective disorder. This was closely related to complaints of changes in mood components in conjunction with migraine.

(5) To determine the relationship between patterns of cerebral blood flow and mood changes in migraine.

The number of patients who had scans during both the presence and absence of migraine was insufficient to investigate this fully.

No significant associations between rCBF and affective and non-affective groups of patients no matter how these were defined, were found in the baseline data.

The scan results from the baseline data and the small number of scans from occasions when migraine was present suggested that migraineurs generally had a more reactive vasculature.

The differences found between classical and common migraine in the presence and absence of migraine were too small for statistical analysis. Nevertheless they were interesting, particularly as they were in accordance with the results found using other forms of rCBF monitoring.

The hypotheses in the light of the results

(1) That the mood changes associated with migraine are due to more than the coincidental expression of two common conditions, i.e. migraine and affective disorder in the same individual.

This could not be confirmed in the present study. The factors most related to the complaints of changes in mood components in conjunction with migraine attacks were current and past DSM-III diagnoses of affective disorder and increased MADRS and MRS scores.

There were no obvious differences between 12 patients who had changes in mood components during migraine days in the prospective rating period and the total sample.

(2) That a relationship can be demonstrated between the mood changes and abnormalities in cerebral blood flow - specifically that dysphoria is associated with flow abnormalities in the left hemisphere and euphoria with flow abnormalities in the right.

No such pattern could be identified in the baseline data and too few patients had scans performed in the presence of migraine to allow any conclusion to be reached.

(3) That mood changes are more likely to be associated with classical than with common migraine.

The affective/non-affective designation based on the diary data and the presence or absence of past and present DSM-III diagnoses of

affective disorder were both unrelated to the type of migraine.

(4) That unilateral migraine affecting the dominant hemisphere is associated with depression and unilateral migraine affecting the non-dominant hemisphere is associated with euphoria.

Cerebral dominance could not be shown to be important in the self-reporting of the changes in mood components examined in this study. However right hemisphere dysfunction was 20 times more commonly associated with complaints of depression than left hemisphere dysfunction.

(5) That olfactory hallucinations which are experienced as part of the migraine attack can be related to regional cerebral blood flow changes in the temporal lobes.

Unfortunately these changes were present in only seven patients and it was impossible to obtain a sufficient number of scans in either the baseline condition or during the presence of migraine to investigate this possibility.

(iii) A critical appraisal of the study

(i) The lack of a control population

The initial intention of this study was to investigate the hypothesis that mood changes were part of migraine attacks. Patients who complained of mood changes were to be compared with those who did not.

The need for a control group outwith the migraine clinic population was therefore not obvious when the study began. However the initial hypothesis that migraine-related mood changes could be separated from concurrent psychiatric illness could not be proven and the prevalence of affective disorder was much higher than anticipated. This makes it necessary to compare the results found for the prevalence of psychiatric disorder in this study with the rates found in community surveys and studies of other medically ill populations.

Community surveys

It is generally recognised that the rates for the occurrence of depression based on hospital admissions do not reflect the community picture.

However studies of hospital admissions by their nature focus on depressive illness. Community surveys include, in addition, depression as a symptom and as a syndrome. (264)

One large community survey in the USA, which covered both city and semi-rural populations, found a consistent trend for a decrease in depression scores (on the Centre for Epidemiologic Studies Scale) with age. (30% of 18-25 year olds had high depression scores compared with 3-10% of those over 65 years old.)

Unemployment and lower household income increased depression scores whereas increased education decreased them.

This particular survey (265) also found that although women had higher rates for clinical depression and hospital admissions for depression than men depressive symptoms were only slightly increased in population surveys of women. These differences were reduced by adjusting for socio-economic variables.

There was no age trend for the frequency of psychoneuroses in women but this definitely increased with age in men.

Despite the effect of socioeconomic status on perceived sex differences in depression there is a wide variety of evidence from other sources that there is a real female preponderance in depression.

A 2:1, female:male ratio for all depression is found consistently in studies within psychiatric clinics in the USA. (This ratio is lower in manic-depressive psychosis and higher in neurotic depression.)

This sex ratio has also been found in community surveys of non-patients.

As the sex difference is found in both 'patient' and 'non-patient' populations it cannot be accounted for by different patterns of health-care seeking behaviour in men and women. (264)

A slightly more recent survey, again in the USA, compared both the lifetime and the six month prevalences of specific psychiatric disorders in three communities.

The lifetime prevalence of a disorder is the proportion of people in a representative sample who have ever experienced the disorder up to the date of assessment. The six month prevalence refers to the occurrence of the condition in the six months prior to the interview.

Data was collected from 9,000 adults and DSM-III diagnoses were based on the Diagnostic Interview Schedule. The most predominant disorders for women in all three communities were depressive episodes and phobias. The lifetime prevalence of major depression for women in the three centres was 8.7% (New Haven), 4.9% (Baltimore) and 8.1% (St Louis). The corresponding percentages for dysthymia were 3.7%, 2.9% and 5.4%.

The six month prevalence rates also found that the commonest diagnoses for women were phobias and major depression and that the rates of psychiatric disorder dropped sharply after age 45 years. (266,267)

In summary - community surveys show a female preponderance in depression. The second survey quoted is closer in design to the present one in that it quotes prevalence rates for DSM-III diagnoses. The lifetime prevalence rate for major depressive disorder is approximately 5-8%. Both studies found that younger adults had higher prevalence rates of disorder than older subjects. Higher figures in the first study are probably related to a different definition of depressive diosrder inherent in the use of the Centre for Epidemiologic Studies' depression scale which is based on ratings of items from self report inventories whereas the Diagnostic Interview Schedule is observer-rated.

General medical patient populations

A study of 143 medical in-patients in the late 1960s used a combination of the Beck Depression Inventory and the Hamilton Rating Scale for Depression to establish a diagnosis of depression. The overall occurrence of depression was 21%; 26% in women and 16% in men. There was no age difference between depressed and non-depressed patients. Depressed women were much more commonly detected in middle or upper social classes. Medical staff under-diagnosed depression in lower social class patients.

Anxiety, irritability, inability to work, retardation and somatic preoccupation were non-specific symptoms which were found in more than 50% of non-depressed patients and in 75% of the total sample. (268,269)

It has been recognised for many years that there is a considerable overlap between medical and psychiatric illness. The incidences quoted for psychiatric illness in medical patients have ranged from 25-83% (270, 271). However this is often overlooked in quiet and uncomplaining patients.

Psychiatric illness in medical outpatients may occur in the absence of evidence of organic disease (this has been quoted at the rate of 38%. (272)) or psychiatric and medical illness may be concurrent. Depression and anxiety are recognised as the commonest psychiatric disorders occurring in hospital outpatient populations. (270,272) This is not always transient - particularly in patients with a previous psychiatric history. (267)

It has been pointed out that psychiatric classifications and concepts are based on research conducted with psychiatric inpatients. It can be difficult to differentiate appropriate distress from affective disorders in medically ill patients. It has been estimated that 51% of medical outpatients and 14.6-61% of medical inpatients suffer from affective disorder. The inpatient study used a psychiatric interview and the Cornell Medical Index, the outpatient studies used the GHQ 30. Most of these inpatients had improved four months after discharge. A previous psychiatry history tended to predict a chronic course. Disorders of moderate severity were the most common - particularly in younger women. (273)

Overall it is clear that the incidence of affective disorder is high in general medical populations although it is often impossible to distinguish whether the rates quoted are for psychiatric illness in the presence or absence of medical (organic) disorder.

Relevance to the present study

The patients with affective disorder in this study also have a definite diagnosis of a medical condition. The studies quoted above do not usually supply sufficent information to indicate which are most closely related to this patient group. However Robins study suggests that the community prevalence of DSM-III diagnosis of affective disorder is much lower than that found in the migraine group.

(ii) Limitations of measures used

The overlap between medically and psychiatrically ill populations and the fact that the rating scales available to measure emotional change have mainly been standardised with psychiatrically ill populations means that the scales are not specific enough to reliably differentiate between psychiatric and physical illness.

In this study a structured clinical interview was used to make the psychiatric diagnosis and rating scales were only present to make an assessment of the current severity of distress. This assisted in making the discrimination betwen medical illness alone with appropriate distress and medical and psychiatric illness occurring together but was still, to some extent, subjective and did not totally resolve the problem.

In the prospective rating period the IDA was used to measure fluctuations in mood components. In many ways it was surprising that only one third of the patients who completed the scales had changes in these mood components which were significantly associated with migraine attacks and that no such changes could be demonstrated before or after attacks. Possibly the IDA was not sensitive enough to pick up transient changes in mood or patients were more aware of their physical migraine symptoms than their affective state. Anecdotally, on the basis of information supplied by the patients at the initial interview, it is possible that close relatives are more aware of mood changes than the patients themselves - particularly irritability!

There is a particular lack of rating scales suitable for estimating euphoria and irritability in general population samples. It may be

partly because of this deficiency that no patient could be shown to have euphoria during the prospective period using the VAS. Fluctuations in irritability were demonstrable using the IDA which has four items for inward and four items for outward irritability.

(iii) Difficulties in separating contributory factors inherent in multifactorial conditions

The literature review dealt with the problems in trying to define the roles of different contributory factors in migraine. The situation is very similar with regard to trying to differentiate the factors important in mood change. This is even more complex as the number of factors is so great and so much is determined by the individual's personality.

This makes it difficult to convincingly demonstrate an association between an alteration in mood components and events such as migraine attacks and menstrual periods. Complex statistical techniques are required to evaluate the relationships between continuous and dichotomous variables.

(iv) Bias

The initial self-reports of the frequency of change in mood in association with migraine attacks were very different from the results obtained in the prospective rating period. If it is accepted that the IDA data is more objective and therefore more reliable there is then the problem of explaining why patients attribute changes in mood to migraine attacks when this is not, in fact, the case. Attribution theory offers

one possible model for this. The presence of initial self reports of mood change was significantly associated with a DSM-III diagnosis of past and/or present affective disorder. Perhaps women with a persistent mood disorder become habituated to aconstant level of distress and are aware of its only when the physical stress of a migraine is superimposed and their ability to cope is temporarily overwhelmed. They therefore falsely attribute changes in mood which are really chronic to the acute event of the migraine episode. (274)

(v) Lack of an independent witness

As mentioned earlier in the section on the reliability of results, the opportunity to interview a close member of the family can significantly improve the quality of the information avilable on both the personal and the familial history of physical and psychiatric illness.

It has been shown that 10% of people under-report hospital admissions for medical illness and 30% of women under-report hospitalisation and major illness in their children even when this has taken place within the last year. (261)

It would have been helpful in this study to interview a relative with regard to the frequency and type of the patient's mood changes and their reltionship to migraine episodes as well as to verify the historical details. However relatives did not generally attend the medical clinic with the patient and constraints on time and resources made it very difficult to arrange to see relatives separately.

Robins has indicated that interview schedules which apply a lifetime strategy, such as the SCID, provide lifetime diagnoses which are acceptably close to 'best-estimate' diagnoses based on all sources of data available for most disorders. (266)

(vi) Data on the relationship of migraine and menstruation are not available for the entire sample

Unfortunately data on mood change, migraine and menstruation were not obtained from all patients but only from the last six menstruating women. Of these only one patient had a significant association between the three variables. In retrospect more could have been said about the relationship between migraine and menstruation if more data had been available. This is an area which deserves further study in its own right.

(vii) Limitations of regional cerebral blood flow monitoring

No significant differences in rCBF were found between affective and non-affective groups, however these were defined, in the baseline condition. This may indicate that no differences in rCBF were present or that the technique was insufficiently sensitive to show them up in this type of psychiatric disorder (i.e. in affective disorder as specified by DSM-III criteria).

The technique seemed to be more effective in discriminating between common and classical migraine during migraine episodes and this was in

line with data already in the literature. However there were to few patients to investigate this thoroughly in the present study.

(4) Future research priorities

General areas of interest suggested by the literature review have already been covered in Chapter 19. A number of specific research topics were suggested by the study itself.

There is a great need to develop scales for rating emotional distress in physically ill patients which are also standardised in medically rather than psychiatrically ill populations. This involves tackling the difficult problem of defining what is an appropriate level of distress in the setting of physical ill health and what constitutes psychiatric illness.

Similarly more information is required on the fluctuations in mood components over time within the general population and the relationship between minor life stresses and migraine. Studies of subgroups of migraine patients are likely to be more useful than studies of migraineurs as a whole. Migraine patients with olfactory hallucinations during attacks are a particularly interesting group because of the association of the symptom with both temporal lobe disturbance and affective changes. Although relatively uncommon (15% of this sample) with patience a large enough group could be collected for study. EEG and more specialised assessments using rCBF measurement and possibly positron emission tomography in this group would be relevant to understanding the pathophysiology of the hallucinations and the

interrelationship between this and depression.

Similarly the relationship between migraine, menstruation and mood change needs further exploration, particularly the links between migraine and the premenstrual syndrome noted in the literature survey.

Finally there is considerable evidence from regional cerebral blood flow studies that common and classical migraine differ. In the present study classical migraine was significantly associated with complaints of depression and there was a suggestion of possible differences between classical and common migraine in rCBF studies performed in the presence of migraine. More studies of these types of migraine, particularly differences between them observed during migraine attacks are necessary before any definite statements can be made about their underlying pathophysiology.

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Migraine and Mood Change Information Sheet

Migraine patients attending Dr. Price's out-patient clinic are being asked to help in a study of the association of mood change and migraine. Taking part in the study involves an interview with the researcher, a qualified psychiatrist, lasting 45 minutes and completing simple rating scales daily for the next 6 weeks. The latter take approximately 5 to 10 minutes to fill in. The interview will involve providing the researcher with information about the symptoms suffered as part of your migraine and about your past and present mood. The rating scales provide a record of how your mood varies over a short period of time. It is possible that some patients may be found to have mild psychological problems in addition to their migraine. They would be informed of this at the end of the 6 week period and could then decide whether they wished their G.P. to be informed. Any information which would be helpful to Dr. Price with regard to treatment of the migraine would be shared with him.

The treatment Dr. Price prescribes for migraine will not be influenced by whether or not a patient takes part in the study. Each patient is also free to withdraw from the study at any time without this affecting further medical treatment. All information obtained will be confidential.

Consent

I have read and understood the above information which has also been explained to me by Dr. Morrison. I agree to participating in the study and understand that I may withdraw at any time without this affecting future medical treatment. I agree to information being passed to my G.P. if necessary.

Signed

Date

Supplementary information and consent for regional blood flow studies.

Patients who are taking part in the above study are being offered the opportunity to also have brain blood flow measurements performed. This is a very simple and straightforward procedure which is performed in the X-ray Department at the Western General Hospital by the Radiology Staff. The whol procedure takes approximately 5 minutes and the only discomfort involved is one injection into a vein in the patient's arm. A very small amount of a radioactive isotope is used to measure the blood flow on a special monitor - the radioactivity involved is approximately the same as that used in an ordinary skull X-ray investigation. Patients are being asked to have this test on two occasions - once when they have a migraine and once without one. The information obtained from the test should be very helpful in understanding the type of changes in blood flow which occur during migraine and their association with mood changes.

Patients are free to refuse to take part in this study or withdraw at any time without this interfering in their medical treatment in anyway. Information obtained from the investigations will be passed onto Dr. Price routinely.

Consent

I agree to participating in the blood flow studies outlined above which I have had explained to me and discussed with me by Dr. Morrison.

Signature

Date

Signature of Medical Practitioner

Date

NAME	D.O.B.
HOSPITAL NO.	
MIGRAINE TYPE (RING APPROPRIATE CLASSIFICATION)	CLASSICAL COMMON
FREQUENCY OF MIGRAINE (N.B.) FREQUENCY MUST BE AT LEAST ONE ATTACK EVERY 6 WEEKS	
FREQUENCY OF ASSOCIATED MOOD CHANGE	NEVER SOMETIMES USUALLY ALWAYS
CURRENT MEDICATION	
CHANGE OF MEDICATION RECOMMENDED	YES/NO IF YES SPECIFY NEW TREATMENT

MARITAL STATUS	S M W D SEP.		
CURRENT EMPLOYMENT / HUSBAND'S EMPLOYMENT		CEREBRAL DOMINANCE	R L MIXED
MIGRAINE SYMPTOMS	BILATERAL	UNILATERAL	R or L
DEFINITE NEUROLOGICAL	PARESIS R/L	SENSORY LOSS R/L	SPEECH DISTURBANCE / LOSS OF CONSCIOUSNESS
QUESTIONABLE NEUROLOGICAL	DIZZINESS	BLURRED VISION	DIFFICULTY THINKING
GENERAL	NAUSEA	VOMITING	PHOTOPHOBIA
TYPE OF MOOD CHANGE	DEPRESSION	ANXIETY / EUPHORIA	IRRITABILITY
LENGTH OF MIGRAINE HISTORY		FAMILY HISTORY OF MIGRAINE	YES/NO SPECIFY
PERSONAL HISTORY PSYCHIATRIC ILLNESS	YES/NO	IF YES SPECIFY TYPE	GP/PSYCH OP/IP
FAMILY HISTORY OF PSYCHIATRIC ILLNESS	YES/NO	IF YES SPECIFY	
EMOTIONAL STRESS TRIGGER	NEVER	SOMETIMES / USUALLY	ALWAYS
ORAL CONTRACEPTIVE	YES/NO	IF YES TYPE	
MIGRAINE RELATED TO MENSTRUATION	NEVER	SOMETIMES / USUALLY	ALWAYS
	SPECIFY IF PRESENT	PRE / DURING	POST
DSM-III DIAGNOSIS			
CLINICAL ANXIETY SCALE SCORE			
MONTGOMERY & ASBERG SCORE			
MANIC RATING SCALE SCORE			
IDA SCORE			

APPENDIX II

THE CLINICAL ANXIETY SCALE

Instructions for the use of the Clinical Anxiety Scale

The Scale is an instrument for the assessment of the present state of anxiety; therefore the emphasis on eliciting information for the ratings should be on how the patient feels at the present time. However, the interview itself may raise, or lower, the severity of anxiety and the interviewer should inform the patient that he should describe how he has felt during the period of the past two days.

Psychic tension (care should be taken to distinguish tension from muscular tension - see next item).

Score 4: Very marked and distressing feeling of being 'on edge', 'keyed up', 'wound up' or 'nervous' which persists with little change throughout the waking hours.
Score 3: As above, but with some fluctuation of severity during the course of the day.
Score 2: A definite experience of being tense which is sufficient to cause distress.
Score 0: No feeling of being tense apart from the normal degree of tension experienced in response to stress and which is acceptable as normal for the population.

Ability to relax (muscular tension)

Score 4: The experience of severe tension throughout much of the bodily musculature which may be accompanied by such symptoms as pain, stiffness, spasmodic contractions, and lack of control over movements. The experience is present throughout most of the waking day and there is no ability to produce relaxation at will.
Score 3: As above, but the muscular tension may only be experienced in certain groups of muscles and may fluctuate in severity throughout the day.
Score 2: A definite experience of muscular tension in some part of the musculature sufficient to cause some, but not severe, distress.
Score 1: Slight recurrent muscular tension of which the patient is aware but which does not cause distress. Very mild degrees of tension headache or pain in other groups of muscles should be scored here.
Score 0: No subjective muscular tension or of such degree which, when it occurs, can easily be controlled at will.

Startle response (hyperarousability)

Score 4: Unexpected noise causes severe distress so that the patient may complain in some such phrase as "I jump out of my skin". Distress is experienced in psychic and somatic modalities so that, in addition to the experience of fright, there is muscular activity and autonomic symptoms such as sweating or palpitation.
Score 3: Unexpected noise causes severe distress in psychic or somatic, but not in both modalities.
Score 2: Unexpected noise causes definite but not severe distress.
Score 1: The patient agrees that he is slightly "jumpy" but is not distressed by this.
Score 0: The degree of startle response is entirely acceptable as normal for the population.

Worrying (The assessment must take into account the degree to which worry is out of proportion to actual stress.)

Score 4: The patient experiences almost continuous preoccupation with painful thoughts which cannot be stopped voluntarily and the distress is quite out of proportion to the subject matter of the thoughts.
Score 3: As above, but there is some fluctuation in intensity throughout the waking hours and the distressing thoughts may cease for an hour or two, especially if the patient is distracted by activity requiring his attention.
Score 2: Painful thoughts out of proportion to the patient's situation keep intruding into consciousness but he is able to dispel or dismiss them.
Score 1: The patient agrees that he tends to worry a little more than necessary about minor matters but this does not cause much distress.
Score 0: The tendency to worry is accepted as being normal for the population; for instance even marked worrying over a severe financial crisis or unexpected illness in a relative should be scored as 0 if it is judged to be entirely in keeping with the degree of stress.

Apprehension

Score 4: The experience is that of being on the brink of some disaster which cannot be explained. The experience need not be continuous and may occur in short bursts several times a day.
Score 3: As above, but the experience does not occur more than once a day.
Score 2: A sensation of groundless apprehension of disaster which is not severe although it causes definite distress. The patient may not use strong terms such as "disaster" or "catastrophe" but may express his experience in some such phrase as "I feel as if something bad is about to happen".
Score 1: A slight degree of apprehensiveness of which the patient is aware but which does not cause distress.
Score 0: No experience of groundless anticipation of disaster.

Restlessness

Score 4: The patient is unable to keep still for more than a few minutes and engages in restless pacing or other purposeless activity.
Score 3: As above, but he is able to keep still for an hour or so at a time.
Score 2: There is a feeling of "needing to be on the move" which causes some, but not severe, distress.
Score 1: Slight experience of restlessness which causes no distress.
Score 0: Absence of restlessness.

APPENDIX III

MONTGOMERY AND ÅSBERG (MADRS) DEPRESSION RATING SCALE

The rating should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0,2,4,6) or between them (1,3,5).

It is important to remember that it is only on rare occasions that a depressed patient is encountered who cannot be rated on the items in the scale. If definite answers cannot be elicited from the patient all relevant clues as well as information from other sources should be used as a basis for the rating in line with customary clinical practice.

The scale may be used for any time interval between ratings, be it weekly or otherwise but this must be recorded.

Item List

1. Apparent sadness
2. Reported sadness
3. Inner tension
4. Reduced sleep
5. Reduced appetite
6. Concentration difficulties
7. Lassitude
8. Inability to feel
9. Pessimistic thoughts
10. Suicidal thoughts

1. Apparent Sadness

Representing despondency, gloom and despair, (more than just ordinary transient low spirits) reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

0. No sadness.
1.
2. Looks dispirited but does brighten up without difficulty.
3.
4. Appears sad and unhappy most of the time.
5.
6. Looks miserable all the time. Extremely despondent.

2. Reported sadness

Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency or the feeling of being beyond help and without hope.

Rate according to intensity, duration and the extent to which the mood is reported to be influenced by events.

0. Occasional sadness in keeping with the circumstances.
1.
2. Sad or low but brightens up without difficulty.
3.
4. Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
5.
6. Continuous or unvarying sadness, misery or despondency.

3. Inner tension

Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread or anguish.

Rate according to intensity, frequency duration and the extent of reassurance called for.

0. Placid. Only fleeting inner tension.
1.
2. Occasional feelings of edginess and ill-defined discomfort.
3.
4. Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
5.
6. Unrelenting dread or anguish. Overwhelming panic.

4. Reduced sleep

Representing the experience of reduced duration or depth of sleep compared to the subject's own normal pattern when well.

0. Sleeps as usual.
1.
2. Slight difficulty dropping of to sleep or slightly reduced, light or fitful sleep.
3.
4. Sleep reduced or broken by at least two hours.
5.
6. Less than two or three hours sleep.

5. Reduced appetite

Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

0. Normal or increased appetite.
1.
2. Slightly reduced appetite.
3.
4. No appetite. Food is tasteless.
5.
6. Needs persuasion to eat at all.

6. Concentration difficulties

Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration.

Rate according to intensity, frequency, and degree of incapacity produced.

0. No difficulties in concentrating.
1.
2. Occasional difficulties in collecting one's thoughts.
3.
4. Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
5.
6. Unable to read or converse without great difficulty.

7. Lassitude

Representing a difficulty getting started or slowness initiating and performing everyday activities.

0. Hardly any difficulty in getting started. No sluggishness.
1.
2. Difficulties in starting activities.
3.
4. Difficulties in starting simple routine activities which are carried outwith effort.
5.
6. Complete lassitude. Unable to do anything without help.

8. Inability to feel

Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

0. Normal interest in the surroundings and in other people.
1.
2. Reduced ability to enjoy usual interests.
3.
4. Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
5.
6. The experience of being emotionally paralysed, inability to feel anger, grief or pleasure and a complete or even painful failure to feel for close relatives and friends.

9. Pessimistic thoughts

Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse and ruin.

0. No pessimistic thoughts.
1.
2. Fluctuating ideas of failure, self-reproach or self depreciation.
3.
4. Persistent self-accusations, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future.
5.
6. Delusions of ruin, remorse or unredeemable sin. Self-accusations which are absurd and unshakable.

10. Suicidal thoughts

Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide.

Suicidal attempts should not in themselves influence the rating.

0. Enjoys life or takes it as it comes.
1.
2. Weary of life. Only fleeting suicidal thoughts.
3.
4. Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
5.
6. Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

APPENDIX IV

MANIA RATING SCALE

Guide for Scoring Items - The purpose of each item is to rate the severity of that abnormality in the patient. When several keys are given for a particular grade of severity, the presence of only one is required to qualify for that rating.

The keys provided are guides. One can ignore the keys if that is necessary to indicate severity, although this should be the exception rather than the rule.

Scoring between the points given (whole or half points) is possible and encouraged after experience with the scale is acquired. This is particularly useful when severity of a particular item in a patient does not follow the progression indicated by the keys.

1. Elated Mood

0. Absent
1. Mildly or possibly increased on questioning
2. Definite subjective elevation; optimistic, self-confident; cheerful; appropriate to content
3. Elevated, inappropriate to content; humorous
4. Euphoric; inappropriate laughter; singing

2. Increased Motor Activity-Energy

0. Absent
1. Subjectively increased
2. Animated; gestures increased
3. Excessive energy; hyperactive at times; restless (can be calmed)
4. Motor excitement; continuous hyperactivity (cannot be calmed)

3. Sexual Interest

0. Normal; not increased
1. Mildly or possibly increased
2. Definite subjective increase on questioning
3. Spontaneous sexual content; elaborates on sexual matters; hypersexual by self-report
4. Overt sexual acts (towards patients, staff, or interviewer)

4. Sleep

0. Reports no decrease in sleep
1. Sleeping less than normal amount by up to one hour
2. Sleeping less than normal by more than one hour
3. Reports decreased need for sleep
4. Denies need for sleep

5. Irritability

0. Absent
2. Subjectively increased
4. Irritable at times during interview; recent episodes of anger or annoyance on ward
6. Frequently irritable during interview; short, curt throughout
8. Hostile, unco-operative; interview impossible

6. Speech (Rate and Amount)

0. No increase
2. Feels talkative
4. Increased rate or amount at times, verbose at times
6. Push; consistently increased rate and amount; difficult to interrupt
8. Pressured; uninterruptible, continuous speech

7. Language-Thought Disorder

0. Absent
1. Circumstantial; mild distractibility; quick thoughts
2. Distractible; loses goal of thought; changes topics frequently; racing thoughts
3. Flight of ideas; tangentiality; difficult to follow; rhyming, echolalia
4. Incoherent; communication impossible

8. Content

0. Normal
2. Questionable plans, new interests
4. Special project(s); hyperreligious
6. Grandiose or paranoid ideas; ideas of reference
8. Delusions; hallucinations

9. Disruptive-Aggressive Behaviour

0. Absent, co-operative
2. Sarcastic; loud at times, guarded
4. Demanding; threats on ward
6. Threatens interviewer; shouting; interview difficult
8. Assaultive; destructive; interview impossible

10. Appearance

0. Appropriate dress and grooming
1. Minimally unkempt
2. Poorly groomed; moderately dishevelled; overdressed
3. Dishevelled; partly clothed; garish make-up
4. Completely unkempt; decorated; bizarre garb

11. Insight

0. Present; admits illness; agrees with the need for treatment
1. Possibly ill
2. Admits behaviour change, but denies illness
3. Admits possible change in behaviour, but denies illness
4. Denies any behaviour change

APPENDIX V

Latest Revision: 7/1/85

STRUCTURED CLINICAL INTERVIEW FOR DSM-III-R - NON-PATIENT VERSION

S C I D - NP

Robert L. Spitzer, M.D. and Janet B. W. Williams, D.S.W.

Study: _____ Study No.: _ _ _ _ xx xx

Subject: _____ I.D. No.: _ _ _ _ _ _ _ xx xx

Rater: _____ Rater No.: _ _ _ xx xx

Rater is: Interviewer 1 xx
Observer 2

Date of interview: _ _ _ _ _ _ xx xx
Mo. Day Year

The SCID is being developed in collaboration with Miriam Gibbon, M.S.W.
See Instruction Manual for other acknowledgments.

The development of the SCID has been supported in part by
NIMH Contract #278-83-0007(DB) and NIMH Grant #1 R01 MH40511-01.

For citation: Spitzer, Robert L. and Williams, Janet B. W.
"Structured Clinical Interview for DSM-III-R - Non-patient Version (SCID-NP 7/1/85)"
Biometrics Research Department
New York State Psychiatric Institute
722 West 168th Street
New York, New York 10032

SCID-NP SUMMARY SCORE SHEET

Overall quality and completeness of information: 1 = poor, 2 = fair, 3 = good, 4 = excellent

Duration of interview (minutes): ___ ___ ___

Diagnosis

	Lifetime Prevalence Diagnostic Index					Sx Present Past Month		Meets Symptomatic Dx. Past Month	
						(see chronology modules)			
	Inadequate info.	Absent	Subthreshold	Threshold		Absent	Present	Absent	Present
AFFECTIVE DISORDERS (A and C)									
Bipolar	?	1	2	| 3 |------->		1	| 3 |------>	1	3
___ current episode manic									
___ current episode depressed									
___ current episode mixed									
___ current episode with psychotic features									
Cyclothymic Disorder (current only)	?	1	2	3					
Major Depression	?	1	2	| 3 |------->		1	| 3 |------>	1	3
___ current episode without melancholia or psychotic features									
___ current episode with melancholia									
___ current episode with psychotic features									
Dysthymic Disorder (current only)	?	1	2	3					
Affective Disorder NOS	?	1	2	| 3 |------->		1	| 3 |------>	1	3

Diagnosis	Lifetime Prevalence Diagnostic Index				Sx Present Past Month		Meets Symptomatic Dx Cr Past Mont	
					(see chronology modules)			
	Inadequate info.	Absent	Subthreshold	Threshold	Absent	Present	Absent	Present
SUBSTANCE DEPENDENCE DISORDERS (D)								
Alcohol Dependence	?	1	2	3	1	3	1	3
Barb-Sed. Dependence	?	1	2	3	1	3	1	3
Cannabis Dependence	?	1	2	3	1	3	1	3
Stimulant Dependence	?	1	2	3	1	3	1	3
Opioids Dependence	?	1	2	3	1	3	1	3
Cocaine Dependence	?	1	2	3	1	3	1	3
Hall. PCP Dependence	?	1	2	3	1	3	1	3
Other Dependence	?	1	2	3	1	3	1	3

Diagnosis	Lifetime Prevalence Diagnostic Index					Sx Present Past Month		Meets Symptomatic Dx Crit Past Month	
						(see chronology modules)			
	Inadequate info.	Absent	Subthreshold	Threshold		Absent	Present	Absent	Present
ANXIETY DISORDERS (E)									
Panic Disorder	?	1	2	| 3 |------->		1	| 3 |------>	1	3
___ current episode without phobic avoidance									
___ current episode with limited phobic avoidance									
___ current episode with extensive phobic avoidance									
Limited Symptom Attacks with Phobic Avoidance	?	1	2	| 3 |------->		1	| 3 |------>	1	3
Social Phobia	?	1	2	| 3 |------->		1	| 3 |------>	1	3
Simple Phobia	?	1	2	| 3 |------->		1	| 3 |------>	1	3
Obsessive Compulsive	?	1	2	| 3 |------->		1	| 3 |------>	1	3
Generalized Anxiety (current only)	?	1	2	3					
Anxiety Disorder NOS	?	1	2	| 3 |------->		1	| 3 |------>	1	3
POST-TRAUMATIC STRESS DISORDER (F)	?	1	2	| 3 |------->		1	| 3 |------>	1	3
SOMATOFORM DISORDERS (G)									
Somatization Disorder	?	1	2	| 3 |------->		1	3		
Hypochondriasis (current only)	?	1	2	| 3 |------->		1	| 3 |------>	1	3

SCID-NP 7/1/05 Summary Score Sheet

Diagnosis	Lifetime Prevalence Diagnostic Index					Sx Present Past Month		Meets Symptatic Dx Cri Past Month	
						(see chronology modules)			
	Inadequate info.	Absent	Subthreshold	Threshold		Absent	Present	Absent	Present
EATING DISORDERS (H)									
Anorexia Nervosa	?	1	2	| 3 |	------->	1	| 3 | ------>	1	3
Bulimia Nervosa	?	1	2	| 3 |	------->	1	| 3 | ------>	1	3
Eating Disorder NOS	?	1	2	| 3 |	------->	1	| 3 | ------>	1	3
ADJUSTMENT DISORDER (CURRENT ONLY) (I)	?	1	2	3					
___ with depressed mood									
___ with anxious mood									
___ with mixed emotional features									
___ with disturbance of conduct									
OTHER DSM-III-R DISORDER:	?	1	2	| 3 |	------->	1	| 3 | ------>	1	3

_____

INTRODUCTION OF INTERVIEW (INCLUDING EXPLANATION OF PURPOSE OF INTERVIEW AND OBTAINING WRITTEN INFORMED CONSENT IF NECESSARY)

DEMOGRAPHIC DATA

SEX
1 male
2 female

How old are you?

AGE ___ ___

Are you married?

IF NO: Were you ever?

(Children?)

MARITAL STATUS (most recent)
1 married
2 separated
3 divorced/annulled
4 widowed
5 never married

Where do you live?
(Who do you live with?)

NOTES:

What kind of work do you do?
(Do you work outside of the home?)

[illegible]UPATION

Are you working now?

IF NOT WORKING NOW: Why is that? What kind of work have you done?

How long have you worked there?

IF LESS THAN 6 MONTHS: Why did you leave your last job?

Have you always done that kind of work?

Has there ever been a period of time that you were unable to work?

IF YES: When? Why was that?

IF NOT OBVIOUS FROM WORK HISTORY: How far did you get in school?

EDUCATIONAL LEVEL

IF FAILED TO COMPLETE A PROGRAM IN WHICH THEY WERE ENROLLED: Why didn't you finish?

PAST PERIODS OF PSYCHOPATHOLOGY

Have you ever, seen anybody for emotional or psychiatric problems?

IF YES: What was that for?

IF NO: Was there ever a time when you, or someone else, thought you should see someone because of the way you were feeling or acting?

Have you ever been a patient in a psychiatric hospital?

IF YES: What was that for?

IF GIVES AN INADEQUATE ANSWER, CHALLENGE GENTLY:
e.g., "Wasn't there something else? People usually don't go to psychiatric hospitals just because they are tired or nervous."

IF NO EVIDENCE OF PAST PSYCHOPATHOLOGY: Thinking back over your whole life, when were you the most upset?

(Why? What was that like? How were you feeling?)

When were you feeling the best you have ever felt?

(Were you feeling so good that other people were worried about you?)

PSYCHOPATHOLOGY DURING PAST YEAR

Now I would like to ask you about the past year - since last (MONTH)?

How have things been going for you?

Has anything happened that has been especially hard for you?

What about difficulties at work or with your family?

How has your mood been?

What have your drinking habits been like?

Have you taken any drugs?
(What about marijuana, cocaine, other street drugs?)

What about your physical health?
(Do you take any medications now?)

APPENDIX VI

Latest Revision: 7/1/85

STRUCTURED CLINICAL INTERVIEW FOR DSM-III - OUTPATIENT VERSION

S C I D - OP

Robert L. Spitzer, M.D. and Janet B. W. Williams, D.S.W.

Study: _____ Study No.: _ _ _ _ xx xx

Subject: _____ I.D. No.: _ _ _ _ _ _ _ xx xx

Rater: _____ Rater No.: _ _ _ xx xx

Rater is: Interviewer 1 xx
Observer 2

Date of interview: _ _ _ _ _ _ xx xx
Mo. Day Year

Sources of information (check all that apply): xx
__ Subject xx
__ Family/friends/associates xx
__ Health professional/chart/ referral note

The SCID is being developed in collaboration with Miriam Gibbon., M.S.W.
See Instruction Manual for other acknowledgments.

For citation: Spitzer, Robert L. and Williams, Janet B. W.
"Structured Clinical Interview for DSM-III-Outpatient Version (SCID-OP, 6/1/85)"
Biometrics Research Department
New York State Psychiatric Institute
722 West 168th Street
New York, New York 10032

AFFECTIVE SYNDROMES

IN THIS SECTION, MAJOR DEPRESSIVE, MANIC, CYCLOTHYMIC AND DYSTHYMIC SYNDROMES ARE EVALUATED. THE DIAGNOSES ARE MADE IN C. AFFECTIVE DISORDERS, FOLLOWING B. PSYCHOTIC SCREENING.

CURRENT MAJOR DEPRESSIVE SYNDROME	MDS CRITERIA					
Now I am going to ask you some questions about your mood.	A. At least 5 of the following symptoms have been present during the same two-week period; at least one of the symptoms was either (1) depressed mood, or (2) loss of interest or pleasure. NOTE: DO NOT INCLUDE SXS THAT ARE CLEARLY DUE TO A PHYSICAL DISORDER, DELUSIONS, HALLUCINATIONS, INCOHERENCE OR MARKED LOOSENING OF ASSOCIATIONS.					
IF CURRENTLY ILL: Since this began... IF NOT CURRENTLY ILL: In the last month... ...has there been a period of time when you were feeling depressed or down nearly every day?	(1) prominent depressed mood most of the day, nearly every day (either by subjective account, e.g., feels "down," "low," "hopeless," or observed by others to look sad or depressed) DESCRIBE:	?	1	2	3	
What about not being interested in things or unable to enjoy the things you used to? IF YES: What was that like? Was it nearly every day? How long did it last?	(2) loss of interest or pleasure in all or almost all activities nearly every day DESCRIBE:	?	1	2	3	x> GO TO PAST MDS, A. 7
When was this the worst?						

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or true

During this time...

..did your weight change? (How much?) ..how was your appetite? (What about compared to your usual appetite? Did you have to force yourself to eat? Eat [less/more] than usual? Was that nearly every day?)	(3) significant weight loss (when not dieting) or weight gain; or decrease or increase in appetite nearly every day DESCRIBE:	?	1	2	3	
..how were you sleeping? (Trouble falling asleep, waking frequently, trouble staying asleep, waking too early, sleeping too much? How many hours a night compared to usual? Was that nearly every night?)	(4) insomnia or hypersomnia nearly every day DESCRIBE:	?	1	2	3	›
..were you so fidgety or restless that you were unable to sit still? (If I had seen you, would I have noticed it? Was that nearly every day?) IF NO: What about the opposite -- talking or moving more slowly than is normal for you? (If I had seen you, would I have noticed it? Was that nearly every day?)	(5) psychomotor agitation or retardation nearly every day (observable by others and not merely subjective feelings of restlessness or being slowed down) DESCRIBE:	?	1	2	3	×
..what was your energy like? (Tired all the time? Nearly every day?)	(6) fatigue or loss of energy nearly every day DESCRIBE:	?	1	2	3	››
..did you feel worthless or guilty about things you had done or not done? (Nearly every day?)	(7) feelings of worthlessness or excessive or inappropriate guilt nearly every day (not merely self-reproach or guilt for being sick) DESCRIBE:	?	1	2	3	×›

During this time...

..did you have trouble thinking or concentrating?

(Was it hard to make decisions about everyday things?)

(Nearly every day?)

(8) diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or observed by others)

DESCRIBE:

? 1 2 3 x

..were you thinking a lot about death or about hurting yourself? (Nearly every day?)

(Did you do anything to hurt yourself?)

(9) recurrent thoughts of death of self or others, suicidal ideation, or wishes to be dead, nearly every day; suicide attempt

DESCRIBE:

? 1 2 3 x

AT LEAST FIVE OF THE ABOVE CRITERIA [A (1-9)] ARE CODED "3"

1 3 x

GO TO PAST MDS, A. 7

ETIOLOGIC ROLE OF AN ORGANIC FACTOR IN FULL DEPRESSIVE SYNDROME

Just before this began, were you taking any drugs or medicines?

Drinking a lot?

Were you physically ill? (What did the doctor say?)

IF YES TO ANY OF THESE QUESTIONS, DETERMINE IF ANY DEPRESSIVE EPISODE WAS NOT DUE TO AN ORGANIC MENTAL DISORDER. IF SO, CODE "3".

B.(1) Not sustained by a specific organic factor or substance (although there may be an organic precipitant).

? 1 3 x

R/O ORG AFF SYN — GO TO PAST MDS, A. 7

NO ORG ETIOLOGY — CONTINUE

IF DURATION OF DEPRESSION HAS BEEN RELATIVELY BRIEF: Did this begin soon after someone close to you died?

IF YES, DETERMINE IF ANY DEPRESSIVE EPISODE WAS NOT DUE TO UNCOMPLICATED BEREAVEMENT. IF SO, CODE "3".

B.(2) Not a normal reaction to the loss of a loved one (Uncomplicated Bereavement). (NOTE: Morbid preoccupation with worthlessness, suicidal ideation, marked functional impairment or psychomotor retardation, or prolonged duration, suggest bereavement complicated by Major Depression.)

?	1	3	×
	R/O UNCOMP. BEREAVEMENT. GO TO PAST MDS, A. 7	CURRENT EPISODE NOT DUE TO UNCOMP BEREAVEMENT	

MAJOR DEPRESSIVE SYNDROME CRITERIA A AND B ARE CODED "3"

	1	3	×
	GO TO PAST MDS, A. 7	CURRENT MDS	

How old were you when you first had a lot of these symptoms for at least two weeks?

Age at onset of Major Depressive Syndrome

		×
___	___	×

How many separate times were you (depressed/OWN EQUIVALENT) nearly every day for at least two weeks and had several of the symptoms that you described, like (SXS OF WORST EPISODE)?

Number of episodes of Major Depressive Syndrome (CODE 97 IF TOO NUMEROUS TO COUNT)

		×
___	___	×

MELANCHOLIA DURING CURRENT EPISODE

SEE A(2) OF CURRENT MAJOR DEPRESSIVE SYNDROME

MELANCHOLIA CRITERIA

A. Loss of pleasure in all or almost all activities. ? 1 2 3 xx

Have there been things that can make you feel better, like talking to a friend or hearing good news?

B. Lack of reactivity to all or almost all usually pleasurable stimuli. ? 1 2 3 xx

CODE "3" IF NOT REACTIVE TO ENVIRONMENTAL EVENTS OR SAYS NOTHING GOOD HAS HAPPENED

WITHOUT MELANCHOLIA

C. At least three of the following:

Is your feeling of (OWN EQUIVALENT FOR DEPRESSION) different from the kind of feeling you would get if someone close to you died? (Or something else really bad happened to you?)

IF YES: How is it different?

(1) Distinct quality of depressed mood ? 1 2 3 xx

CODE "3" ONLY IF QUALITATIVELY DIFFERENT FROM BEREAVEMENT (NOT MERELY MORE SEVERE OR ASSOCIATED WITH FUNCTIONAL IMPAIRMENT)

Do you feel worse in the morning, or in the evening, or doesn't it make any difference?

(2) the depression is regularly worse in the morning ? 1 2 3 xx

Do you wake up as early as two hours before your usual time, without being able to get back to sleep?

(3) early morning awakening (at least two hours before usual time of awakening) ? 1 2 3 xx

Have you been pacing up and down?

Have you been so slowed down that you could hardly have a conversation or move at all?

(4) marked psychomotor agitation or retardation ? 1 2 3 xx

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or true

Have you had no appetite or lost a lot of weight?	(5) marked anorexia or weight loss	?	1	2	3	x
Do you feel guilty about anything?	(6) excessive or inappropriate guilt (other than for being sick)	?	1	2	3	x
	AT LEAST THREE "C" SXS ARE CODED "3"		1		3	x
	MELANCHOLIA CRITERIA A, B, AND C ARE CODED "3"		1		3	x

MELAN-CHOLIA

PAST MAJOR DEPRESSIVE SYNDROME

(In the past...)

MDS CRITERIA

A. At least 5 of the following symptoms have been present during the same two-week period; at least one of the symptoms was either (1) depressed mood, or (2) loss of interest or pleasure.

NOTE: DO NOT INCLUDE SXS THAT ARE CLEARLY DUE TO A PHYSICAL DISORDER, DELUSIONS, HALLUCINATIONS, INCOHERENCE OR MARKED LOOSENING OF ASSOCIATIONS.

Have you ever had a period when you were feeling depressed or down nearly every day?

IF YES: What was that like? How long did it last?

(1) prominent depressed mood most of the day, nearly every day (either by subjective account, e.g., feels "down," "low," "hopeless," or observed by others to look sad or depressed)

DESCRIBE:

? 1 2 3 x>

What about a time when you were uninterested in things or unable to enjoy the things you used to?

IF YES: What was that like? Was it nearly every day? How long did it last?

Have you had more than one time like that?

IF MORE THAN ONE: Which time was the worst?

(2) loss of interest or pleasure in all or almost all activities nearly every day

DESCRIBE:

? 1 2 3 x>

GO TO CURRENT MANIC SYND. A. 11

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or true

FOCUS ON THE WORST EPISODE
THAT THE SUBJECT CAN REMEMBER

During that time...

..did your weight change? (How much?) ..how was your appetite? (What about compared to your usual appetite? Did you have to force yourself to eat? Eat [less/more] than usual? Was that nearly every day?)	(3) significant weight loss (when not dieting) or weight gain; or decrease or increase in appetite nearly every day DESCRIBE:	?	1	2	3	»
..how were you sleeping? (Trouble falling asleep, waking frequently, trouble staying asleep, waking too early, sleeping too much? How many hours a night compared to usual? Was that nearly every night?)	(4) insomnia or hypersomnia nearly every day DESCRIBE:	?	1	2	3	»
..were you so fidgety or restless that you were unable to sit still? (If I had seen you, would I have noticed it? Was that nearly every day?) IF NO: What about the opposite -- talking or moving more slowly than is normal for you? (If I had seen you, would I have noticed it? Was that nearly every day?)	(5) psychomotor agitation or retardation nearly every day (observable by others and not merely subjective feelings of restlessness or being slowed down) DESCRIBE:	?	1	2	3	»
..what was your energy like? (Tired all the time? Nearly every day?)	(6) fatigue or loss of energy nearly every day DESCRIBE:	?	1	2	3	»
..did you feel worthless or guilty about things you had done or not done? (Nearly every day?)	(7) feelings of worthlessness or excessive or inappropriate guilt nearly every day (not merely self-reproach or guilt for being sick) DESCRIBE:	?	1	2	3	»

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or true

During that time...

..did you have trouble thinking or concentrating?

(Was it hard to make decisions about everyday things?)

(Nearly every day?)

(8) diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or observed by others)

DESCRIBE:

? 1 2 3 xx

..were you thinking a lot about death or about hurting yourself? (Nearly every day?)

(Did you do anything to hurt yourself?)

(9) recurrent thoughts of death of self or others, suicidal ideation, or wishes to be dead, nearly every day; suicide attempt

DESCRIBE:

? 1 2 3 xx

AT LEAST FIVE OF THE ABOVE CRITERIA ARE CODED "3"

1 3 xx

GO TO CURRENT MANIC SYND. A. 11

ETIOLOGIC ROLE OF AN ORGANIC FACTOR IN FULL DEPRESSIVE SYNDROME

Just before this began, were you taking any drugs or medicines?

Drinking a lot?

Were you physically ill? (What did the doctor say?)

IF YES TO ANY OF THESE QUESTIONS, DETERMINE IF ANY DEPRESSIVE EPISODE WAS NOT DUE TO AN ORGANIC MENTAL DISORDER. IF SO, CODE "3".

B.(1) Not sustained by a specific organic factor or substance (although there may be an organic precipitant).

? 1 3 xx

R/O ORG AFF SYN — GO TO CURRENT MANIC SYND., A. 11

NO ORG ETIOL — CONTINUE

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or true

IF DURATION OF DEPRESSION HAS BEEN RELATIVELY BRIEF: Did this begin soon after someone close to you died?

IF YES, DETERMINE IF ANY DEPRESSIVE EPISODE WAS NOT DUE TO UNCOMPLICATED BEREAVEMENT. IF SO, CODE "3".

B.(2) Not a normal reaction to the loss of a loved one (Uncomplicated Bereavement). (NOTE: Morbid preoccupation with worthlessness, suicidal ideation, marked functional impairment or psychomotor retardation, or prolonged duration, suggest bereavement complicated by Major Depression.)

NOTE: CODE "3" IF AT LEAST ONE EPISODE IS NOT UNCOMPLICATED BEREAVEMENT

? 1 3 x

R/O UNCOMP. BEREAVEMENT	AT LEAST ONE EPISODE NOT DUE TO UNCOMP BEREAVEMENT
GO TO CURRENT MANIC SYND., A. 11	

MAJOR DEPRESSIVE SYNDROME CRITERIA A AND B ARE CODED "3"

1 3 x

GO TO CURRENT MANIC SYND., A. 11	PAST MDS

How old were you when you first had a lot of these symptoms for at least two weeks?

Age at onset of Major Depressive Syndrome

__ __

How many separate times were you (depressed/OWN EQUIVALENT) nearly every day for at least two weeks and had several of the symptoms that you described, like (SXS OF WORST EPISODE)?

Number of episodes of Major Depressive Syndrome (CODE 97 IF TOO NUMEROUS TO COUNT)

__ __

CURRENT MANIC SYNDROME

IF THOROUGH OVERVIEW OF PRESENT ILLNESS PROVIDES NO BASIS FOR SUSPECTING A CURRENT MANIC SYNDROME, GO TO PAST MS, A. 15.

IF CURRENTLY ILL: Since this began...

IF NOT CURRENTLY ILL: In the last month...

...has there been a period of time when you were feeling so good or high that other people thought you were not your normal self or you were so high that you got into trouble? (Did anyone say you were manic?)

IF UNCLEAR: Was that more than just feeling good?

IF NO: What about being unusually irritable or getting into fights or arguments?

What was that like?

How long did that last?

When were you the most (OWN EQUIVALENT FOR EUPHORIA OR IRRITABILITY)?

FOR THE WORST PERIOD OF CURRENT EPISODE, ASK ABOUT ASSOCIATED SXS

(During this time...)

..how did you feel about yourself?

(More self-confident than usual?)

(Any special powers or abilities?)

MANIC SYNDROME CRITERIA

A. One or more distinct periods lasting at least one week (or any duration if marked impairment in social or occupational role functioning) when mood was abnormally and persistently elevated, expansive, or irritable. ? 1 2 3 X

GO TO PAST MANIC SYND., A. 15

DATE:

DESCRIBE:

IF IRRITABLE MOOD ONLY, CHECK HERE AFTER CODING ABOVE ___

B. During the period of mood disturbance, at least three of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:

(1) inflated self-esteem (grandiosity, which may be delusional) ? 1 2 3 X

DESCRIBE:

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or true

During this time...

..did you need less sleep than usual? IF YES: Did you still feel rested?	(2) decreased need for sleep, e.g., feels rested after only three hours of sleep DESCRIBE:	?	1	2	3	x
..were you more talkative than usual? (People had trouble stopping you or understanding you? People had trouble getting a word in edgewise?)	(3) more talkative than usual or pressure to keep talking DESCRIBE:	?	1	2	3	x
..were your thoughts racing through your head?	(4) flight of ideas or subjective experience that thoughts are racing DESCRIBE:	?	1	2	3	x
..did you have trouble concentrating because any little thing going on around you could get you off the track?	(5) distractibility, i.e., attention too easily drawn to unimportant or irrelevant external stimuli DESCRIBE:	?	1	2	3	x
..how did you spend your time? (Work, friends, hobbies?) Were you so active that your friends or family were concerned about you? IF NO: Were you physically restless? How bad was it?	(6) increase in activity (either socially, at work, or sexually) or physical restlessness DESCRIBE:	?	1	2	3	x
..did you do anything that could have caused trouble for you or your family? (Buying things you didn't need?) (Anything sexual that was unusual for you?) (Reckless driving?)	(7) excessive involvement in activities that have a high potential for painful consequences which is not recognized, e.g., buying sprees, sexual indiscretions, foolish business investments, reckless driving DESCRIBE:	?	1	2	3	x

AT LEAST THREE "B" SXS ARE CODED "3" (FOUR IF MOOD ONLY IRRITABLE)

1 | 3

GO TO PAST MANIC SYND., A. 15

IF NOT KNOWN: At that time, did you have serious problems at home or at work (school) because you were (SYMPTOMS) or did you have to be admitted to the hospital?

C. The episode of mood disturbance was sufficiently severe to cause marked impairment in social or occupational functioning, or hospitalization was necessary.

1 | 3

HYPO-MANIC | MANIC

DESCRIBE:

ETIOLOGIC ROLE OF AN ORGANIC FACTOR IN FULL MANIC SYNDROME

Just before this began, were you taking any drugs or medicines? Drinking a lot?

D. Not sustained by a specific organic factor or substance (although there may be an organic precipitant)

? | 1 | 3

R/O ORG AFF SYN | NO ORG ETIOL CON-TINUE

MANIC SYNDROME CRITERIA A, B, C AND D ARE CODED "3"

1 | 3

CURRENT MANIC SYND.

GO TO CYCLOTHYMIC SYNDROME, A. 18

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or tr

How old were you when you first had serious problems or had to go to the hospital because you were (OWN EQUIVALENT/MANIC)?	Age at onset of Manic Syndrome.	__ __	x x
How many separate times were you (HIGH/OWN EQUIVALENT) and had several of these problems for a week or more (or were hospitalized)?	Number of episodes of Manic Syndrome (CODE 97 IF TOO INDISTINCT OR NUMEROUS TO COUNT)	__ __	x x

PAST MANIC SYNDROME

Have you ever had a time when you were feeling so good or high that other people thought you were not your normal self or you were so high that you got into trouble? (Did anyone say you were manic?)

IF UNCLEAR: Was that more than just feeling good?

IF NO: What about being unusually irritable or getting into fights or arguments?

When was that?

What was it like?

Have you had more than one time like that?

IF YES: Which time were you the most (HIGH/OWN EQUIVALENT)?

(During that time...)

..how did you feel about yourself?

(More self-confident than usual?)

(Any special powers or abilities?)

..did you need less sleep than usual?

IF YES: Did you still feel rested?

MANIC SYNDROME CRITERIA

A. One or more distinct periods lasting at least one week (or any duration if marked impairment in social or occupational role functioning) when mood was abnormally and persistently elevated, expansive, or irritable. ? 1 2 3 X

GO TO CYCLOTHYMIC SYND., A. 18

DATE:

DESCRIBE:

IF IRRITABLE MOOD ONLY, CHECK HERE AFTER CODING ABOVE ___

B. During the period of mood disturbance, at least three of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:

(1) inflated self-esteem (grandiosity, which may be delusional) ? 1 2 3 X

DESCRIBE:

(2) decreased need for sleep, e.g., feels rested after only three hours of sleep ? 1 2 3 X

DESCRIBE:

During that time...

..were you more talkative than usual? (People had trouble stopping you or understanding you? People had trouble getting a word in edgewise?)	(3) more talkative than usual or pressure to keep talking DESCRIBE:	?	1	2	3	›
..were your thoughts racing through your head?	(4) flight of ideas or subjective experience that thoughts are racing DESCRIBE:	?	1	2	3	›
..did you have trouble concentrating because any little thing going on around you could get you off the track?	(5) distractibility, i.e., attention too easily drawn to unimportant or irrelevant external stimuli DESCRIBE:	?	1	2	3	›
..how did you spend your time? (Work, friends, hobbies?) Were you so active that your friends or family were concerned about you? IF NO: Were you physically restless? How bad was it?	(6) increase in activity (either socially, at work, or sexually) or physical restlessness DESCRIBE:	?	1	2	3	›
..did you do anything that could have caused trouble for you or your family? (Buying things you didn't need?) (Anything sexual that was unusual for you?) (Reckless driving?)	(7) excessive involvement in activities that have a high potential for painful consequences which is not recognized, e.g., buying sprees, sexual indiscretions, foolish business investments, reckless driving DESCRIBE:	?	1	2	3	›

AT LEAST THREE "B" SXS ARE CODED "3" (FOUR IF MOOD ONLY IRRITABLE)

1 3

GO TO CYCLOTHYMIC SYND. A.18

IF NOT KNOWN: At that time, did you have serious problems at home or at work (school) because you were (SYMPTOMS) or did you have to be admitted to the hospital?

C. The episode of mood disturbance was sufficiently severe to cause marked impairment in social or occupational functioning, or hospitalization was necessary.

DESCRIBE: -

1 3

HYPO-MANIC MANIC

ETIOLOGIC ROLE OF AN ORGANIC FACTOR IN FULL MANIC SYNDROME

Just before this began, were you taking any drugs or medicines? Drinking a lot?

D. Not sustained by a specific organic factor or substance (although there may be an organic precipitant)

? 1 3 x

R/O ORG AFF SYN

NO ORG ETIOL

CONTINUE

MANIC SYNDROME CRITERIA A, B, C AND D ARE CODED "3"

1 3 x

PAST MS

How old were you when you first had serious problems or had to go to the hospital because you were (OWN EQUIVALENT/MANIC)?

Age at onset of Manic Syndrome.

___ ___ x x

How many separate times were you (HIGH/OWN EQUIVALENT) and had several of these problems for a week or more (or were hospitalized)?

Number of episodes of Manic Syndrome (CODE 97 IF TOO INDISTINCT OR NUMEROUS TO COUNT)

___ ___ x x

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or tru

CYCLOTHYMIC SYNDROME (CURRENT ONLY)

CYCLOTHYMIC SYNDROME CRITERIA

SKIP TO B. PSYCHOTIC SCREENING, IF THE OVERVIEW INDICATES THAT A CHRONIC PSYCHOTIC DISORDER IS LIKELY.

[Other than the times we've talked about when you were (OWN EQUIVALENT FOR MDS OR MS)] During the past couple of years, have you had lots of ups and downs, that is, some days you feel too good or even a little high, and other days you feel down or depressed?

IF YES: Are the good days really too good, or are they just better than the bad days?

IF YES: What are you like at those times? How often do you have these (OWN EQUIVALENT OF UPS AND DOWNS)? Describe the typical pattern. How long do they usually last?

A. During the past two years, there have been numerous periods with abnormally elevated, expansive or irritable mood that did not meet the criteria for a Manic Syndrome, and numerous periods with depressed mood or loss of interest or pleasure that did not meet the criteria for a Major Depressive Syndrome.

DESCRIBE:

? 1 2 3 >

GO TO DYSTHYMIC SYND., A. 21

What is the longest period of time in the last two years that you felt okay without being either high or low (OR OWN EQUIVALENT)? (How long do you feel normal in between these ups and downs?)

B. For the past two years, never without hypomanic or depressive symptoms for more than three months.

? 1 2 3 >

GO TO DYSTHYMIC SYND., A. 21

During the times that you are a little high (OR OWN EQUIVALENT), do you usually...

C. During hypomanic periods there are at least three of the following:

...need less sleep than usual?

(1) decreased need for sleep

? 1 2 3 >

...feel particularly full of energy?

(2) more energy than usual

? 1 2 3 >

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or tr

During the times that you are a little high (OR OWN EQUIVALENT), do you usually...

...feel especially self-confident? (especially good about yourself?)	(3) inflated self-esteem	?	1	2	3	
...get a lot more done?	(4) increased productivity, often associated with unusual and self-imposed working hours	?	1	2	3	
...have unusually good ideas and think especially clearly?	(5) sharpened and unusually creative thinking	?	1	2	3	x
...go out of your way to be with or talk with people?	(6) uninhibited people-seeking (extreme gregariousness)	?	1	2	3	x
...do anything sexual that is unusual for you?	(7) hypersexuality without recognition of possibility of painful consequences	?	1	2	3	x
...do things that cause or could cause trouble for you or your family? (Buying things you don't need? Reckless driving?)	(8) excessive involvement in pleasurable activities with lack of concern for the high potential for painful consequences, e.g., buying sprees, foolish business investments, reckless driving	?	1	2	3	x
...feel physically restless? (Have trouble sitting still?)	(9) physical restlessness	?	1	2	3	x
...talk more than usual?	(10) more talkative than usual	?	1	2	3	x
...feel overly optimistic about the future?	(11) overoptimism	?	1	2	3	x

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or tru

During the times that you are a little high (OR OWN EQUIVALENT), do you usually...

...laugh and joke about things that other people don't find funny (or think are in poor taste)?

(12) inappropriate laughing, joking, punning ? 1 2 3 x

AT LEAST THREE "C" HYPOMANIC SXS ARE CODED "3" 1 3 x

GO TO DYSTHYMIC SYND. A.21

Now tell me what you are like during the times that you are feeling down.

D. During the depressive periods, there are at least three of the symptoms listed in criterion C of Dysthymic Syndrome (A. 21). 1 3 x

GO TO DYSTHYMIC SYND. A.21

EXPLORE POSSIBLE ETIOLOGIC ROLE OF SUBSTANCE USE

Were you taking any drugs or medicines when you were (OWN EQUIVALENT FOR HYPOMANIC AND DEPRESSIVE PERIODS)?

Were you drinking a lot?

E. Not sustained by a specific organic factor or substance, e.g., repeated intoxication from drugs or alcohol. ? 1 3 x

R/O ORG AFF SYN

NO ORG ETIOL

CONTINUE

CYCLOTHYMIC SYNDROME CRITERIA A, B, C, D, AND E ARE CODED "3" 1 3 x

GO TO DYSTHYMIC SYND. A.21

CYCLOTHYMIC SYND.

When was the last time you felt OK (NO DYSTHYMIC SXS) for more than three months?

Age at onset of current Dysthymic Syndrome ___ ___ x x

GO TO NEXT MODULE

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or tru

DYSTHYMIC SYNDROME (CURRENT ONLY)

IF EVER HAD A MAJOR DEPRESSIVE SYNDROME: Other than the time(s) that we have already talked about when you were (OWN EQUIVALENT FOR MDS)...

During the past couple of years, have you been bothered by depressed mood or not being interested in things you ordinarily enjoyed, more days than not?

IF YES: What was it like?

IF EVER HAD A MAJOR DEPRESSIVE SYNDROME: Did this (PERIOD OF MILD DEPRESSION) first begin right after the time you had a (OWN EQUIVALENT FOR MDS)?

DYSTHYMIC SYNDROME CRITERIA

A. During the past two years there has been depressed mood or loss of interest or pleasure in all or almost all activities more days than not that did not meet the criteria for a Major Depressive Syndrome, and did not develop immediately after one (i.e., was not a partial remission of a Major Depressive Syndrome).

DESCRIBE:

? 1 2 3 x

GO TO NEXT MODULE

What is the longest period of time in the last two years, when you have not felt depressed (OR OWN EQUIVALENT)?

B. For the past two years, never without depressive symptoms for more than three months at a time (may have had a superimposed MDS at some time during period, e.g., currently).

CODE "1" IF NORMAL MOOD FOR MORE THAN THREE MONTHS AT A TIME

? 1 3 x

GO TO NEXT MODULE

During these periods of (OWN EQUIVALENT FOR MILD DEPRESSION), do you often...

C. When depressed, at least three of the following symptoms are present:

...have trouble sleeping or sleep too much?

(1) insomnia or hypersomnia

? 1 2 3 x

...have little energy to do things or feel tired all of the time?

(2) low energy level or chronic tiredness

? 1 2 3 x

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or tr

During these periods of (OWN EQUIVALENT FOR MILD DEPRESSION), do you often...

...feel down on yourself? (feel worthless, or a failure?)	(3) feelings of inadequacy	?	1	2	3	x
...have trouble getting things done or doing things well?	(4) decreased effectiveness or productivity at school, work, or home	?	1	2	3	x
...have trouble concentrating or thinking clearly?	(5) decreased attention, concentration, or ability to think clearly	?	1	2	3	x
...avoid being with people?	(6) social withdrawal	?	1	2	3	x
...have little or no interest in doing things that you ordinarily enjoy?	(7) loss of interest in or enjoyment of pleasurable activities, including sex	?	1	2	3	x
...feel irritable or get angry easily?	(8) irritability or excessive anger	?	1	2	3	x
...find yourself less active or talkative than usual?	(9) less active or talkative than usual	?	1	2	3	x
...feel restless?	(10) feel restless	?	1	2	3	x
...feel pessimistic about the future, or brood about the past or feel sorry for yourself?	(11) pessimistic attitude toward the future, brooding about past events, or feeling sorry for self	?	1	2	3	x
...get tearful or cry?	(12) tearfulness or crying	?	1	2	3	x
...think about death or wish you were dead?	(13) thoughts of death or suicide	?	1	2	3	x

AT LEAST THREE DEPRESSIVE SXS ARE CODED "3"

1 3 x

GO TO NEXT MODULE

EXPLORE POSSIBLE ETIOLOGIC ROLE OF SUBSTANCE USE

Have you been taking any drugs or medicines during this time?

D. Not sustained by a specific organic factor or substance

? 1 3 x

R/O ORG AFF SYN

NO ORG ETIOL CON-TINUE

DYSTHYMIC SYNDROME CRITERIA A, B, C, AND D ARE CODED "3"

1 3 x

GO TO NEXT MODULE

DYS-THY-MIC SYN-DROME

When was the last time you felt OK (NO DYSTHYMIC SXS) for more than three months?

Age at onset of current Dysthymic Syndrome.

___ ___ xx

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or true

PSYCHOTIC SCREENING

THIS MODULE IS FOR DETERMINING WHETHER NON-ORGANIC PSYCHOTIC SYMPTOMS HAVE BEEN PRESENT AT ANY TIME DURING THE SUBJECT'S LIFE. (IN SOME CLINICAL AND RESEARCH SETTINGS SUBJECTS WITH A HISTORY OF NON-ORGANIC PSYCHOTIC SYMPTOMS WILL BE EXCLUDED.)

FOR PSYCHOTIC SYMPTOMS CODED "3", DETERMINE WHETHER THE SYMPTOM IS "NOT ORGANIC" OR WHETHER THERE IS A POSSIBLE OR DEFINITE ORGANIC CAUSE. THE FOLLOWING QUESTIONS MAY BE USEFUL IF THE OVERVIEW HAS NOT ALREADY PROVIDED THE INFORMATION:
When you were (PSYCHOTIC SXS), were you taking any drugs or medicines? Drinking a lot? Physically ill?

IF HAS NOT ACKNOWLEDGED PSYCHOTIC SXS: Now I am going to ask you about unusual experiences that people sometimes have.

IF HAS ACKNOWLEDGED PSYCHOTIC SXS: You have told me about (PSYCHOTIC EXPERIENCES). Now I am going to ask you more about those kinds of things.

DELUSIONS
A false personal belief based on incorrect inference about external reality and firmly sustained in spite of what almost everyone else believes and in spite of what constitutes incontrovertible and obvious proof or evidence to the contrary. Code overvalued ideas (an unreasonable and sustained belief that is maintained with less than delusional intensity) as "2."

Did it ever seem that people were talking about you or taking special notice of you?

What about receiving special messages from people or from the way things were arranged around you, or from the newspaper, radio or TV?

Delusions of reference, i.e., personal significance is falsely attributed to objects or events in environment

DATES:

DESCRIBE:

?	1	2	3	
				x>

1	3	
POSS/DEF ORG	NOT ORG	x>

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or true

What about anyone going out of the way to give you a hard time, or trying to hurt you?

IF YES: Do you know why this happened to you?

Persecutory delusions, i.e., the individual (or his or her group) is being attacked, harassed, cheated, persecuted, or conspired against.

DATES:

DESCRIBE:

? 1 2 3

1 3

POSS/DEF ORG | NOT ORG

Did you ever feel that you were especially important in some way, or that you had powers to do things that other people couldn't do?

Grandiose delusions, i.e., content involves exaggerated power, knowledge or importance

DATES:

DESCRIBE:

? 1 2 3

1 3

POSS/DEF ORG | NOT ORG

Did you ever feel that parts of your body had changed or stopped working (when your doctor said there was nothing wrong with you)? (What did your doctor say?)

Somatic delusions, i.e., content involves change or disturbance in body functioning

DATES:

DESCRIBE:

? 1 2 3

1 3

POSS/DEF ORG | NOT ORG

Other delusions, e.g., delusions of guilt, jealousy, nihilism, poverty

DATES:

DESCRIBE:

? 1 2 3

1 3

POSS/DEF ORG | NOT ORG

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or tru

HALLUCINATIONS
A sensory perception without external stimulation of the relevant sensory organ.

Did you ever hear things that other people couldn't hear, such as noises, or the voices of people whispering or talking?

What did you hear?

Auditory hallucinations when fully awake and heard either inside or outside of head.

DATES:

DESCRIBE:

? 1 2 3 xx

1 3

POSS/DEF ORG | NOT ORG

Did you ever have visions or see things that other people couldn't see?

Visual hallucinations

DATES:

DESCRIBE:

? 1 2 3

1 3 xx

POSS/DEF ORG | NOT ORG

Other hallucinations, e.g., gustatory, olfactory

DATES:

DESCRIBE:

? 1 2 3 xx

1 3 xx

POSS/DEF ORG | NOT ORG

A psychotic symptom has been present at some time

? 1 2 3

GO TO NEXT MODULE

EXPLORE DETAILS AND DESCRIBE DIAGNOSTIC SIGNIFICANCE (E.G., SUBSTANCE-INDUCED PSYCHOTIC DISORDER, SCHIZOPHRENIA, PSYCHOTIC AFFECTIVE DISORDER, OR A TRANSIENT SX OF A NONPSYCHOTIC DISORDER, SUCH AS BORDERLINE PERSONALITY DISORDER OR POST-TRAUMATIC STRESS DISORDER)

DESCRIBE:

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or true

AFFECTIVE DISORDERS

GO TO NEXT MODULE IF THERE HAS NEVER BEEN AN AFFECTIVE SYNDROME (MAJOR DEPRESSIVE, MANIC, CYCLOTHYMIC, OR DYSTHYMIC), OR IF AN AFFECTIVE SYNDROME OCCURRED ONLY AS PART OF SCHIZOAFFECTIVE DISORDER.

THIS SECTION IS FOR MAKING AFFECTIVE DISORDER DIAGNOSES AFTER THE PRESENCE OF AN AFFECTIVE SYNDROME HAS BEEN ESTABLISHED AND PSYCHOTIC FEATURES HAVE BEEN RULED IN OR OUT.

CHECK THE APPROPRIATE DIAGNOSES AND SUBTYPES BELOW. (IF YOU ARE HERE, YOU HAVE ALREADY COLLECTED ALL THE INFORMATION NECESSARY TO MAKE THESE DETERMINATIONS.)

BIPOLAR DISORDER (one or more manic episodes, with or without major depressive episodes)		?	1	3	x>
INDICATE SUBTYPES:	Currently manic	?	1	3	x>
	Currently depressed	?	1	3	x>
	Currently mixed	?	1	3	x>
	Currently with mood-congruent psychotic features, i.e., all delusions involved the theme(s) of either guilt, disease, death, nihilism or deserved punishment	?	1	3	x>
	Currently with mood-incongruent psychotic features	?	1	3	x>
CYCLOTHYMIC DISORDER (past two years)		?	1	3	x>
BIPOLAR DISORDER NOS	DESCRIBE:	?	1	3	x>

Examples:

(1) Bipolar II: An individual has had at least one hypomanic episode and at least one major depressive episode but never had either a manic episode or cyclothymia.

(2) An individual has had one or more hypomanic episodes but does not have cyclothymia and has never had either a manic or a major depressive episode.

MAJOR DEPRESSION (no history of manic or hypomanic episodes) ? 1 3 x

CHECK SUBTYPE (ONE ONLY):

_____ currently without melancholia or psychotic features x

_____ currently with melancholia x

_____ currently with mood-congruent psychotic features, i.e., all delusions involved the theme(s) of either guilt, disease, death, nihilism or deserved punishment x

_____ currently with mood-incongruent psychotic features x

DYSTHYMIC DISORDER (past two years; no history of manic or hypomanic episodes) ? 1 3 x

DEPRESSIVE DISORDER NOS DESCRIBE: ? 1 3 x

Examples:

(1) Major depressive episode superimposed on residual Schizophrenia

(2) Intermittent dysthymic episodes

(3) Non-stress-related minor depression

CHRONOLOGY FOR MANIC EPISODES

IF NO MANIC EPISODE EVER, CHECK HERE AND SKIP TO CHRONOLOGY FOR MAJOR DEPRESSIVE EPISODES ___.

IF UNCLEAR: During the past month, have you been (OWN EQUIVALENT FOR EUPHORIC OR IRRITABLE MOOD)?	Has had euphoric or irritable mood during past month	?	1	3	
When were you last (OWN EQUIVALENT FOR EUPHORIC OR IRRITABLE MOOD)?	Number of months prior to interview when last had euphoric or irritable mood	___			
IF UNCLEAR: During the past month, have you had (LIST OF MANIC SXS CODED "3")?	Has met symptomatic criteria for manic syndrome during the past month (criteria A and B)	?	1	3	
During the past five years, how much of the time have you been bothered by (ANY SXS OF MANIC SYNDROME)?	Duration in months during past five years that any manic symptoms were present	___			

CHRONOLOGY FOR MAJOR DEPRESSIVE EPISODES

IF NO MAJOR DEPRESSIVE EPISODE EVER, CHECK HERE AND SKIP TO NEXT MODULE ___.

IF UNCLEAR: During the past month, have you been (OWN EQUIVALENT FOR DEPRESSED MOOD OR LOSS OF INTEREST OR PLEASURE)?	Has had depressed mood or loss of interest or pleasure during past month	?	1	3	
When did you last have (OWN EQUIVALENT FOR DEPRESSED MOOD OR LOSS OF INTEREST OR PLEASURE)?	Number of months prior to interview when last had depressed mood or loss of interest or pleasure	___			
IF UNCLEAR: During the past month, have you had (LIST OF DEPRESSIVE SXS CODED "3")?	Has met symptomatic criteria for depressive syndrome during the past month (criterion A)	?	1	3	
During the past five years, how much of the time have you been bothered by (ANY SXS OF DEPRESSIVE SYNDROME)?	Duration in months during past five years that any depressive symptoms were present	___			

SUBSTANCE DEPENDENCE DISORDERS

ALCOHOL DEPENDENCE (LIFETIME) **CRITERIA**

What are your drinking habits like?

How much do you drink?

Was there ever a period in your life when you drank too much?

Has anyone ever objected to your drinking?

IF YES: Why?

IF NEVER OR ONLY RARELY DRINKS ALCOHOL, CHECK HERE AND SKIP TO NEXT SECTION _____

When in your life were you drinking the most?

(How long did it last?)

Now I am going to ask you several questions about that time.

IF CAN'T IDENTIFY A PARTICULAR PERIOD, REPHRASE EACH QUESTION TO BEGIN WITH "Have you ever..."

At least three of the following:

Did you often spend a lot of time thinking about drinking or making sure that you had alcohol available?	(1) Frequent preoccupation with seeking or taking alcohol	?	1	2	3	xx
Did you often find that when you started drinking you ended up drinking much more than you thought you would? What about drinking for a much longer period of time than you thought you would?	(2) Often takes alcohol in larger amounts or over a longer period than he or she intended:	?	1	2	3	xx

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or true

Did you find that you needed to drink a lot more in order to get high than you did when you first started drinking? What about finding that when you drank the same amount, it had much less effect than before?	(3) Tolerance: need for increased amounts of alcohol in order to achieve intoxication or desired effect, or diminished effect with continued use of the same amount	?	1	2	3	xx
Did you ever have the shakes when you cut down or stopped drinking (that is, your hands shook so much that other people would have been able to notice it)?	(4) Withdrawal symptoms, such as coarse tremor ("shakes"), seizures, DTs. (Do not include simple "hangover.")	?	1	2	3	xx
After not drinking for a few hours or more, did you often drink to keep yourself from getting the shakes or becoming sick? What about drinking when you were having the shakes or feeling sick so that you would feel better?	(5) Relief drinking: often drinks to relieve or avoid withdrawal symptoms	?	1	2	3	xx
Did you try to cut down or stop drinking alcohol? IF YES: Did you ever actually stop drinking altogether? (How many times did you try to cut down or stop altogether?) IF NO: Did you want to stop or cut down? IF YES: Is this something you kept worrying about or was it just a passing concern?	(6) Persistent desire or repeated efforts to cut down or control alcohol use	?	1	2	3	xx

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or true

Did you have a time when you were intoxicated or high or very hungover, when you were doing something important, like being at school or work, or taking care of children? What about missing something important, like staying away from school or work or missing an appointment because you were intoxicated, high or very hungover? Did you ever drink while doing something where it was dangerous to drink at all?	(7) Often intoxicated or impaired by alcohol use when expected to fulfill social or occupational obligations, or when substance use is hazardous (e.g., doesn't go to work because hungover or high, goes to work high, drives when drunk)	?	1	2	3	xx
Did you drink so often that you started to drink instead of working or spending time at hobbies or with your family or friends?	(8) Has given up some important social, occupational or recreational activity in order to seek or take the substance	?	1	2	3	xx
Did you keep drinking even though you knew that you had a physical problem or illness that was made worse by alcohol? What about continuing to drink when you knew that it was increasing problems you were having with other people, such as with family members or people at work?	(9) Continuation of alcohol use despite a physical disorder or a significant social or legal problem that the individual knows is exacerbated by the use of alcohol	?	1	2	3	xx
	AT LEAST 3 ITEMS ARE CODED "3"		1		3	xx

NOTE: IN A SUBJECT WHO DENIES BEHAVIORAL EVIDENCE OF THE DISORDER, A PROVISIONAL DIAGNOSIS IS WARRANTED IF THERE IS EVIDENCE OF A MENTAL OR PHYSICAL DISORDER OR CONDITION THAT IS USUALLY A COMPLICATION OF PROLONGED ALCOHOL USE, E.G., DT'S, CIRRHOSIS, ALCOHOLIC NEUROPATHY, ESOPHAGEAL VARICES.

ALCOHOL DEPENDENCE

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or true

CHRONOLOGY

IF UNCLEAR: During the past month, have you had problems with alcohol?	Has had some symptom(s) of Alcohol Dependence during past month	?	1	3	xx
When did you last have problems with alcohol?	Number of months prior to interview when last had symptoms of Alcohol Dependence	—	—	—	xx xx xx
IF UNCLEAR: During the past month, have you had (LIST OF ALCOHOL DEPENDENCE SXS CODED "3")?	Has met criteria for Alcohol Dependence during past month	?	1	3	xx
During the past five years, how much of the time have you had problems with alcohol?	Duration in months during past five years that any symptoms of Alcohol Dependence were present	—	—		xx xx
How old were you when you first had (LIST OF ALCOHOL DEPENDENCE SXS CODED "3")?	Age at onset of Alcohol Dependence	—	—		xx xx

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or true

NON-ALCOHOLIC SUBSTANCE DEPENDENCE (LIFETIME)

Now I would like to ask you about your use of certain drugs or medicines that affect how you think or feel. I am talking about things like sleeping pills or tranquilizers that a doctor might prescribe, and also about drugs that you would probably get on the street, like narcotics, stimulants, marijuana, cocaine and psychedelics. Have you ever taken any drugs like these to get high, to sleep better or to change your mood?

IF A DRUG THAT IS SOMETIMES PRESCRIBED: Was that prescribed or did you take it on your own?

IF PRESCRIBED: Did you take more than was prescribed?

IF EVER HAS TAKEN ANY OF THESE DRUGS ON OWN OR MORE THAN WAS PRESCRIBED: Have you taken any of these drugs more than twenty times (on your own)? (Have you ever used any of these drugs nearly every day for a week or longer?)

Has taken non-alcoholic drug on his or her own more than twenty times to sleep or to alter mood or thinking, or nearly every day for more than one week

? 1 2 3 xx

IF YES, ASK ABOUT EACH DRUG CLASS MENTIONING THE SPECIFIC DRUGS NOTED BELOW. CHECK DRUG CLASS USED 20+ TIMES OR EVERY DAY FOR ONE WEEK AND NOTE SPECIFIC DRUGS USED.

	DRUG CLASS USED 20+ TIMES ON OWN	SPECIFIC DRUG USED ("MULTIPLE" IF A VARIETY OF DRUGS WITHIN A CLASS)
____	Barbiturates-sedatives-hypnotics (e.g., quaalude, seconal, valium librium, "downers")	_____
____	Cannabis (e.g., marijuana, THC, "grass," "weed," "reefer," "pot")	

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or true

DRUG CLASS USED 20+ TIMES ON OWN	SPECIFIC DRUG USED ("MULTIPLE" IF A VARIETY OF DRUGS WITHIN A CLASS)
____ Stimulants (e.g., amphetamine, "speed," "uppers")	_____
____ Opioids (e.g., heroin, morphine, methadone, darvon, opium, codeine, demerol, percodan)	_____
____ Cocaine ("coke")	
____ Hallucinogens-PCP (e.g., LSD, "acid," mescaline, peyote, psilocybin, STP, "angel dust," "peace pill")	_____
____ Other (e.g., steroids, "glue")	_____

WRITE "1," "2," OR "3" FOR EACH ITEM OR EACH DRUG CATEGORY THAT THE SUBJECT HAS USED 20+ TIMES OR EVERY DAY FOR ONE WEEK. QUESTIONS SHOULD BE FOCUSED ON THE TIME PERIOD WHEN THE SUBJECT WAS TAKING THE LARGEST AMOUNTS OF THE DRUG.	BARB-SED.	CANN ABIS	STIMU LANTS	OPI OIDS	COCA INE	HALL-PCP	OTH
At least three of the following:							
Did you often spend a lot of time thinking about taking (DRUG) or making sure that you had (DRUG) available?							
(1) Frequent preoccupation with seeking or taking drug	— (xx)	— (xx)	— (xx)	— (xx)	— (xx)	— (xx)	— (xx)
Did you often find that when you started taking (DRUG) you ended up taking much more of it than you thought you would?							
What about taking it over a much longer period of time than you thought you would?							
(2) Often takes drug in larger amounts or over a longer period than he or she intended	— (xx)	— (xx)	— (xx)	— (xx)	— (xx)	— (xx)	— (xx)

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or true

	BARB-SED.	CANN ABIS	STIMU LANTS	OPI OIDS	COCA INE	HALL-PCP	OTH
Did you find that you needed to take a lot more (DRUG) in order to get high than you did when you first started taking it? What about finding that when you took the same amount, it had much less effect than before? (3) Tolerance: need for increased amounts of drug in order to achieve intoxication or desired effect, or diminished effect with continued use of the same amount	—	—	—	—	—	—	—
	(xx)	(xx)	(xx)	(xx)	(xx)	(xx)	(xx
Have you ever had withdrawal symptoms, that is, felt sick when you cut down or stopped taking (DRUG)? IF YES: What symptoms did you have? IF UNCLEAR WHETHER SYMPTOMS REPRESENT WITHDRAWAL, CONSULT DSM-III CRITERIA FOR WITHDRAWAL SYNDROMES (SEE PG.) (4) Characteristic withdrawal symptoms	—	—	—	—	—	—	—
	(xx)	(xx)	(xx)	(xx)	(xx)	(xx)	(x>
After not taking (DRUG) for a few hours or more, did you often take it to keep yourself from getting sick (WITHDRAWAL SXS)? What about taking (DRUG) when you were feeling sick (WITHDRAWAL SXS) so that you would feel better? (5) Relief drug use: often takes drug to relieve or avoid withdrawal symptoms	—	—	—	—	—	—	—
	(xx)	(xx)	(xx)	(xx)	(xx)	(xx)	(x:

—

xx)

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or true

	BARB-SED.	CANN ABIS	STIMU LANTS	OPI OIDS	COCA INE	HALL+ PCP	OTHER
Did you try to cut down or stop taking (DRUG)? IF YES: Did you ever actually stop taking [DRUG] altogether? (How many times did you try to cut down or stop altogether? IF NO: Did you want to stop or cut down? IF YES: Is this something you kept worrying about or was it just a passing concern? (6) Persistent desire or repeated efforts to cut down or control drug use	— (xx)	— (xx)	— (xx)	— (xx)	— (xx)	— (xx)	— (xx)
Did you have a time when you were intoxicated or high from (DRUG) when you were doing something important, like being at school or work, or taking care of children? What about missing something important, like staying away from school or work or missing an appointment because you were intoxicated or high? Did you ever take (DRUG) while doing something where it was dangerous to take (DRUG) at all? (7) Often intoxicated or impaired by drug use when expected to fulfill social or occupational obligations, or when substance use is hazardous (e.g., doesn't go to work because high, goes to work high, drives when intoxicated)	— (xx)	— (xx)	— (xx)	— (xx)	— (xx)	— (xx)	— (xx)

=inadequate information 1=absent or false 2=subthreshold 3=threshold or true

	BARB-SED.	CANN ABIS	STIMU LANTS	OPI OIDS	COCA INE	HALL-PCP	OTHI
Did you take (DRUG) so often that you started to take (DRUG) instead of working or spending time at hobbies or with your family or friends?							
(8) Has given up some important social, occupational or recreational activity in order to seek or take the substance	— (xx)	— (xx)	— (xx)	— (xx)	— (xx)	— (xx)	— (xx
Did you keep taking (DRUG) even though you knew that you had a physical problem or illness that was made worse by (DRUG)? What about continuing to take (DRUG) when you knew that it was increasing problems you were having with other people, such as with family members or people at work?							
(9) Continuation of drug use despite a physical disorder or a significant social or legal problem that the individual knows is exacerbated by the use of the drug	— (xx)	— (xx)	— (xx)	— (xx)	— (xx)	— (xx)	— (xx
AT LEAST THREE ITEMS CODED "3"	— (xx)	— (xx)	— (xx)	— (xx)	— (xx)	— (xx)	— (xx)
AT LEAST THREE ITEMS FOR ONE OF THE DRUG CLASSES CODED "3"					1	3	x>

SUB-STANCE DEPEN-DENCE

NOTE: IN A SUBJECT WHO DENIES BEHAVIORAL EVIDENCE OF THE DISORDER, A PROVISIONAL DIAGNOSIS IS WARRANTED IF THERE IS EVIDENCE OF A PHYSICAL DISORDER OR CONDITION THAT IS USUALLY A COMPLICATION OF DRUG USE, E.G., NEEDLE MARKS OR ABSCESSES ON THE ARMS.

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or true

CHRONOLOGY

IF UNCLEAR: During the past month, have you had problems with (DRUG)?	Has had some symptom(s) of Non-alcohol Substance Dependence during past month	?	1	3	xx
When did you last have problems with (DRUG)?	Number of months prior to interview when last had symptoms of Non-alcohol Substance Dependence	__	__	__	xx xx xx
IF UNCLEAR: During the past month, have you had (LIST OF NON-ALCOHOL SUBSTANCE DEPENDENCE SXS CODED "3")?	Has met criteria for Non-alcohol Substance Dependence during past month	?	1	3	xx
During the past five years, how much of the time have you had problems with (DRUG)?	Duration in months during past five years that any symptoms of Non-alcohol Substance Dependence were present	__	__		xx xx
How old were you when you first had (LIST OF NON-ALCOHOL SUBSTANCE DEPENDENCE CODED "3")?	Age at onset of Non-alcohol Substance Dependence	__	__		xx xx

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or true

ANXIETY DISORDERS

PANIC DISORDER

PANIC DISORDER CRITERIA

Have you ever had an attack when you suddenly felt frightened or extremely uncomfortable in a situation in which you didn't expect to feel uncomfortable?

IF YES: Tell me about it. How many times did that happen? In what situations?

A. At some time during the illness at least three panic attacks (discrete periods of intense discomfort or fear) that were (1) unexpected (i.e., did not occur immediately before or upon exposure to a situation that almost always caused anxiety), and (2) not triggered by situations in which the individual was the focus of others' attention.

? 1 2 3 >

GO TO LIMITED SYMPTOM ATTACKS E. 6

Have you ever had three attacks like that in a three-week period?

IF NO: Did you worry a lot about having another one? (How long did you worry?)

B. Either the three attacks of criterion A occurred within a three-week period, or one or more attacks were followed by a period of at least a month of persistent fear of having another attack.

? 1 2 3 >

GO TO LIMITED SYMPTOM ATTACKS E. 6

When was the last bad one?

Now I am going to ask you about that attack. What was the first thing you noticed? Then what?

During that attack...

C. At least four of the following symptoms developed during at least one of the attacks:

..were you short of breath? (Have trouble catching your breath?)

(1) shortness of breath (dyspnea) or smothering sensations

? 1 2 3 x

..did you feel as if you were choking?

(2) choking

? 1 2 3 x

..did your heart race, pound or skip?

(3) palpitations or accelerated heart rate (tachycardia)

? 1 2 3 x

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or tru

During that attack...

..did you have chest pain or pressure?	(4) chest pain or discomfort	?	1	2	3	xx
..did you sweat?	(5) sweating	?	1	2	3	xx
..did you feel like you might faint (pass out)?	(6) faintness	?	1	2	3	xx
..were you dizzy or lightheaded, or did you feel unsteady, like you might fall?	(7) dizziness, lightheadedness or unsteady feelings	?	1	2	3	xx
..did you have nausea or upset stomach or the feeling that you were going to have diarrhea?	(8) nausea or abdominal distress	?	1	2	3	xx
..did things around you seem unreal or did you feel detached from things around you or detached from part of your body?	(9) depersonalization or derealization	?	1	2	3	xx
..did you have tingling or numbness in parts of your body?	(10) numbness or tingling sensations (paresthesias)	?	1	2	3	xx
..did you have flushes (hot flashes) or chills?	(11) flushes (hot flashes) or chills	?	1	2	3	xx
..did you tremble or shake?	(12) trembling or shaking	?	1	2	3	xx
..were you afraid that you might die?	(13) fear of dying	?	1	2	3	xx
..were you afraid you were going crazy or might lose control?	(14) fear of going crazy or doing something uncontrolled	?	1	2	3	xx

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or true

AT LEAST FOUR "C" SXS ARE CODED "3"

1 3 x

GO TO LIMITED SYMPTOM ATTACKS E. 6

When you have bad attacks, how long does it take from when it begins to when you have most of the symptoms? (Is it often less than ten minutes?)

D. During at least some of the attacks, at least four of the "C" symptoms occurred within ten minutes of the beginning of the first "C" symptom noticed in the attack.

? 1 2 3 x

GO TO LIMITED SYMPTOM ATTACKS E. 6

Just before you began having panic attacks, were you taking any drugs, stimulants or medicines?

IF YES: Did you keep having the attacks after you stopped?

Were you physically ill? (What did the doctor say?)

IF YES: Did you ever have these attacks when you weren't (taking any drugs or medicines, physically ill?)

E. Not sustained by a known organic factor (e.g., Amphetamine Intoxication, Caffeine Intoxication, Hyperthyroidism).

NOTE: Mitral valve prolapse may be an associated condition but does not rule out a diagnosis of Panic Disorder.

NOTE: CODE "3" IF DRUG OR ALCOHOL USE OR PHYSICAL ILLNESS WAS NOT ETIOLOGIC TO PANIC ATTACKS

? 1 3 x

GO TO LIMITED SYMPTOM ATTACKS E. 6

PANIC DISORDER CRITERIA A, B, C, D AND E ARE CODED "3"

1 3 x

GO TO LIMITED SYMPTOM ATTACKS E. 6

PANIC DIS- ORDER

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or true

PANIC DISORDER SUBTYPES-
PAST MONTH

		Past month (xx)
IF NOT OBVIOUS FROM OVERVIEW: Are there situations or places that you avoid because you are afraid you might have an attack?	1. Panic Disorder without Phobic Avoidance	1
(Tell me all the things you avoid, or can only do by forcing yourself?) (What about going out of the house alone, being in crowds or certain public places like tunnels, bridges, buses or trains?) (How often do you go outside of your house alone?) (Do you often need a companion?)	2. Panic Disorder with Limited Phobic Avoidance (significant phobic avoidance or endurance despite intense anxiety)	2
	3. Panic Disorder with Agoraphobia (generalized travel restrictions, often needs a companion away from home, or markedly altered life style)	3
(What effect does avoiding these situations or places have on your life?)	If no panic attacks during last 6 months specify: (No current panic attacks) (CODED IN CHRONOLOGY SECTION BELOW)	

CHRONOLOGY

IF UNCLEAR: During the past month, have you had any panic attacks (even little ones), or worried a lot that you might have one, or have you avoided situations or places because you were afraid you might have one?	Has had some symptom(s) of Panic Disorder during past month	?	1	3	xx
When did you last have (ANY SX OF PANIC DISORDER)?	Number of months prior to interview when last had a symptom of Panic Disorder	__	__	__	xx xx xx
IF UNCLEAR: During the past month, how many panic attacks have you had?	Has met symptomatic criteria for Panic Disorder during past month, i.e., at least 3 panic attacks	?	1	3	xx

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or true

During the past five years, how much of the time have you been bothered by (PANIC ATTACKS, PERSISTENT FEAR OF HAVING AN ATTACK, OR PHOBIC AVOIDANCE)?	Duration in months during past five years that any symptoms of Panic Disorder were present	___	___	x x
How old were you when you first started having a lot of panic attacks (or worried all the time that you might have one)?	Age at onset of Panic Disorder (at least three attacks over a three week period or one or more attacks followed by persistent fear of having another attack)	___	___	x x

LIMITED SYMPTOM ATTACKS WITH PHOBIC AVOIDANCE (AGORAPHOBIA WITHOUT PANIC ATTACKS)

SKIP IF EVER HAD PANIC ATTACKS

Were you ever afraid of going out of the house alone, being in crowds or certain public places like tunnels, bridges, buses or trains?

What were you afraid could happen?

(CODE FROM PREVIOUS INFORMATION)

Tell me all the things you avoided (or could only do by forcing yourself?)

(How often did you go outside of your house alone?)

(Did you often need a companion?)

(What effect did avoiding these situations or places have on your life?)

LIMITED SYMPTOM ATTACKS WITH PHOBIC AVOIDANCE (AGORAPHOBIA WITHOUT PANIC ATTACKS)

A. Fear of being outside the home alone or in public places because of the possibility of developing a symptom that is incapacitating, such as dizziness, loss of bladder or bowel control or cardiac distress.

? 1 2 3 x

GO TO SOCIAL PHOBIA, E. 8

PRIMARY FEAR Check:

___ becoming dizzy or falling x

___ loss of bladder or bowel control x

___ fear of cardiac distress x

___ other (Specify:_____) x

B. Never had an unexpected panic attack, as defined in criteria A, C, D and E of Panic Disorder.

? 1 2 3 xx

GO TO SOCIAL PHOBIA, E. 8

C. As a result of A. there are either travel restrictions, need for a companion when away from home, or altered life style, or there is endurance of phobic situations despite intense anxiety.

? 1 2 3 xx

GO TO SOCIAL PHOBIA, E. 8

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or true

LIMITED SYMPTOM ATTACKS WITH PHOBIC AVOIDANCE (AGORAPHOBIA WITHOUT PANIC ATTACKS) CRITERIA A, B, AND C ARE CODED "3"

1 3 X>

GO TO SOCIAL PHOBIA E. 8	LIMITED SYMPTOM ATTACKS WITH PHOBIC AVOIDANCE (AGORAPHOBIA WITHOUT PANIC ATTACKS)

CHRONOLOGY

IF UNCLEAR: During the past month, have you avoided (PHOBIC SITUATIONS)?	Has had some symptom(s) of Limited Symptom Attacks with Phobic Avoidance	?	1	3	X>
When did you last avoid (PHOBIC SITUATIONS)?	Number of months prior to interview when last had a symptom of Limited Symptom Attacks with Phobic Avoidance	__	__	__	X> X> X>
During the past five years, how much of the time have you avoided these situations because you were afraid?	Duration in months during past five years that any symptoms of Limited Symptom Attacks with Phobic Avoidance were present	___	___		X> X>
How old were you when you first had this problem?	Age at onset of Limited Symptom Attacks with Phobic Avoidance	___	___		X> X>

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or true

SOCIAL PHOBIA

Is there anything that you were ever afraid to do or felt uncomfortable doing in front of other people, like speaking, eating or writing?

Anything else?

What were you afraid would happen when _____ ?

SOCIAL PHOBIA CRITERIA

A. A persistent and compelling desire to avoid one or more situations in which the individual is the focus of others' attention and fears that he or she may behave in a way that will be humiliating or embarrassing.

? 1 2 3 xx

GO TO SIMPLE PHOBIA, E. 11

PHOBIC SITUATION(S) Check:

___ public speaking xx
___ eating in front of others xx
___ writing in front of others xx
___ generalized (most social situations) xx
___ other (Specify:_____) xx

IF NOT OBVIOUS: Have you ever been afraid that (WHAT INDIVIDUAL FEARED WOULD HAPPEN) would happen when you were alone?

B. What the individual fears will happen occurs only when he or she is the focus of others' attention; or if it occurs while alone, causes little or no distress (i.e., upset by hand trembling only when observed).

? 1 2 3 xx

GO TO SIMPLE PHOBIA, E. 11

NOTE: SOCIAL PHOBIC SYMPTOMS THAT HAVE DEVELOPED CLEARLY SECONDARY TO PANIC DISORDER DO NOT MEET THIS CRITERION.

Did you always feel anxious when you (CONFRONTED PHOBIC STIMULUS)?

C. During some phase of the illness, exposure to the specific phobic stimulus (or stimuli) almost invariably provokes an immediate anxiety response.

? 1 2 3 xx

GO TO SIMPLE PHOBIA, E. 11

IF NOT OBVIOUS: Did you go out of your way to avoid _____ ?

IF NO: How hard is it for you to _____?

D. The situation(s) is avoided or endured with intense anxiety.

? 1 2 3 x:

GO TO SIMPLE PHOBIA, E. 11

IF NOT OBVIOUS: How important was it to you to be able to _____ ?

(How bothered were you that you were afraid of _____ ?)

E. The fear or the avoidant behavior causes marked distress or interferes with social or occupational functioning.

? 1 2 3 x:

GO TO SIMPLE PHOBIA, E. 11

Did you think that you were more afraid of (PHOBIC ACTIVITY) than you should have been (or than made sense)?

F. Recognition by the individual that his or her fear is excessive or unreasonable.

? 1 2 3 x:

GO TO SIMPLE PHOBIA, E. 11

IF NOT ALREADY CLEAR: RETURN TO THIS ITEM AFTER COMPLETING SECTION ON OBSESSIVE COMPULSIVE DISORDER.

G. The phobic stimulus (or stimuli) is unrelated to the content of the obsessions of Obsessive Compulsive Disorder or to a Psychosexual Dysfunction.

? 1 3 x:

GO TO SIMPLE PHOBIA, E. 11

SOCIAL PHOBIA CRITERIA A, B, C, D, E, F, AND G ARE CODED "3"

1 3 x:

GO TO SIMPLE PHOBIA, E. 11

SOCIAL PHOBIA

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or tru

CHRONOLOGY

IF UNCLEAR: During the past month, have you been bothered by (SOCIAL PHOBIA ACTIVITY)?	Has had some symptom(s) of Social Phobia during past month	?	1	3	x
When were you last bothered by (SOCIAL PHOBIA ACTIVITY)?	Number of months prior to interview when last had a symptom of Social Phobia	— — —			x x x
During the past five years, how much of the time have you been bothered by (SOCIAL PHOBIA ACTIVITY)?	Duration in months during past five years that any symptoms of Social Phobia were present	— —			x x
How old were you when you first were bothered by (SOCIAL PHOBIA ACTIVITY)?	Age at onset of Social Phobia	— —			x

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or true

SIMPLE PHOBIA

Are there any other things that you have been especially afraid of, like heights, seeing blood, closed places, or certain kinds of animals?

What are you afraid could happen when _____?

SIMPLE PHOBIA CRITERIA

A. A persistent fear of a circumscribed stimulus (object or situation), other than of having a panic attack (Panic Disorder) or of humiliation or embarrassment in certain social situations (Social Phobia).

? 1 2 3 xx

GO TO OBSESSIVE COMPULSIVE DIS., E. 13

PHOBIC OBJECT(S) OR SITUATIONS(S). Check:

___ animals xx
___ heights xx
___ closed spaces xx
___ blood/injury xx
___ other: _____ xx

Did you always feel anxious when you (CONFRONTED PHOBIC STIMULUS)?

B. During some phase of the illness, exposure to the specific phobic stimulus (or stimuli) almost invariably provokes an immediate anxiety response.

? 1 2 3 xx

GO TO OBS-COMP. E. 13

Did you go out of your way to avoid _____?

IF NO: How hard was it for you to _____ ?

C. The object or situation is avoided or endured with intense anxiety.

? 1 2 3 xx

GO TO OBS-COMP. E. 13

IF NOT OBVIOUS: How important was it to you to be able to _____ ?

(How bothered were you that you were afraid of _____ ?)

D. The fear or the avoidant behavior causes marked distress or interferes with social or occupational functioning.

? 1 2 3 xx

GO TO OBS-COMP. E. 13

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or true

Did you think that you were more afraid of _____ than you should have been (or than made sense)?	E. Recognition by the individual that his or her fear is excessive or unreasonable.	? 1 2 3	x
		GO TO OBS-COMP. E. 13	
IF NOT ALREADY CLEAR: RETURN TO THIS ITEM AFTER COMPLETING SECTION ON OBSESSIVE COMPULSIVE DISORDER.	F. The phobic stimulus is unrelated to the content of the obsessions of Obsessive Compulsive Disorder.	? 1 2 3	x
		GO TO OBS-COMP. E. 13	
	SIMPLE PHOBIA CRITERIA A, B, C, D, E, AND F ARE CODED "3"	? 1 3	xx
		GO TO OBS-COMP. E. 13 / SIMPLE PHOBIA	

CHRONOLOGY

IF UNCLEAR: During the past month, have you been bothered by (SIMPLE PHOBIA)?	Has had some symptom(s) of Simple Phobia during past month	? 1 3	xx
When were you last bothered by (SIMPLE PHOBIA)?	Number of months prior to interview when last had a symptom of Simple Phobia	__ __ __	xx xx xx
During the past five years, how much of the time have you been bothered by (SIMPLE PHOBIA)?	Duration in months during past five years that any symptoms of Simple Phobia were present	__ __	xx xx
How old were you when you first were bothered by (SIMPLE PHOBIA)?	Age at onset of Simple Phobia	__ __	xx

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or true

OBSESSIVE COMPULSIVE DISORDER

Now I would like to ask you if you have ever been bothered by thoughts that kept coming back to you even when you tried not to have them?

IF YES: DISTINGUISH FROM BROODING ABOUT PROBLEMS (SUCH AS HAVING A PANIC ATTACK) OR ANXIOUS RUMINATION ABOUT REALISTIC DANGERS: What were they? (What about awful thoughts, or thoughts that didn't make any sense to you--like actually hurting someone even though you didn't want to, or being contaminated by germs or dirt?

Was there anything that you had to do over and over again and couldn't resist doing, like washing your hands again and again, or checking something several times to make sure you'd done it right?

IF YES: What did you have to do? (What were you afraid would happen if you didn't do it?) (How many times did you have to _____? How much time did you spend each day _____?)

OBSESSIVE COMPULSIVE DISORDER CRITERIA

A. Either obsessions or compulsions:

Obsessions: (1), (2) and (3):

(1) Recurrent, persistent ideas, thoughts, impulses, or images that are experienced as intrusive, unwanted, and senseless or repugnant (at least initially). ? 1 2 3 x

(2) The individual attempts to ignore or suppress them or to neutralize them with some other thought or action. ? 1 2 3 x

(3) The individual recognizes that they are the product of his or her own mind and not imposed from without (as in thought insertion). ? 1 2 3 x

OBSESSIONS

DESCRIBE:

Compulsions: (1), (2) and (3):

(1) Repetitive, purposeful and intentional behavior that is performed according to certain rules or in a stereotyped fashion. ? 1 2 3 x

GO TO GADE. 16

(2) The behavior is not an end in itself, but is designed to neutralize or prevent extreme discomfort or some dreaded event or situation. However, either the activity is not connected in a realistic way with what it is designed to neutralize or prevent or it is clearly excessive. ? 1 2 3 x

GO TO GADE. 16

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or true

IF UNCLEAR: Do you think that you (DO COMPULSIVE BEHAVIOR) more than you should? (Do you think [COMPULSION] makes sense?)

(3) Recognition by the individual that the behavior is excessive or unreasonable.

? 1 2 3

GO TO GAD E. 16

COMPULSIONS

DESCRIBE:

What effect did this (OBSESSION OR COMPULSION) have on your life? (Did _____ bother you a lot?)

Did anyone in your family, or your friends, have to go out of their way because of your (OBSESSION OR COMPULSION)?

B. The obsessions or compulsions cause marked distress or interfere with the individual's social or occupational functioning.

? 1 2 3 X

GO TO GAD E. 16

DESCRIBE:

OBSESSIVE COMPULSIVE DISORDER CRITERIA A AND B ARE CODED "3"

1 3 X

Specify: without phobic avoidance, with limited phobic avoidance, with extensive phobic avoidance

GO TO GAD, E. 16

OBSESSIVE COMPULSIVE DISORDER

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or true

CHRONOLOGY

IF UNCLEAR: During the past month, have you had any (OBSESSIONS OR COMPULSIONS)?	Has had some symptom(s) of Obsessive Compulsive Disorder during past month	?	1	3	
When did you last have (ANY OBSESSIONS OR COMPULSIONS)?	Number of months prior to interview when last had a symptom of Obsessive Compulsive Disorder	__	__	__	x x x
IF UNCLEAR: During the past month, did the (OBSESSIONS OR COMPULSIONS) have any effect on your life or bother you a lot?	Has met criteria for Obsessive Compulsive Disorder during past month (criteria A and B)	?	1	3	x
During the past five years, how much of the time have you been bothered by (OBSESSIONS OR COMPULSIONS)?	Duration in months during past five years that any symptoms of Obsessive Compulsive Disorder were present	__	__		x x
How old were you when the (OBSESSIONS OR COMPULSIONS) first had any effect on your life or bothered you a lot?	Age at onset of Obsessive Compulsive Disorder (criteria A and B)	__	__		x x

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or true

GENERALIZED ANXIETY DISORDER (CURRENT ONLY)

For most of the time during the last six months...

...have you been anxious or nervous?

...have you worried a lot?

CODE BASED ON PREVIOUS INFORMATION. REVISE AT END OF INTERVIEW IF NECESSARY.

When you feel that way, what is it like?

At these times...

...do you tremble, twitch or feel shaky?

...do your muscles often feel tense, sore or achy?

...do you often feel physically restless--can't sit still?

...do you tire easily?

...do you feel short of breath? (have trouble getting your breath?)

GENERALIZED ANXIETY DISORDER CRITERIA

A. During the last six months, the individual has been bothered more days than not by anxious mood (nervousness), or worry about possible misfortune to self or others.	?	1	2	3	
DESCRIBE:	GO TO NEXT MODULE				
B. Not occurring only during the course of another Axis I disorder, such as a psychotic disorder, an Affective Disorder, a Substance Dependence Disorder or another Anxiety Disorder.	?	1	2	3	
	GO TO NEXT MODULE				
C. At least six of the following eighteen symptoms are present some of the time when anxious:					
Motor tension					
(1) trembling, twitching or feeling shaky	?	1	2	3	
(2) muscle tension, aches or soreness	?	1	2	3	
(3) restlessness	?	1	2	3	
(4) easy fatigability	?	1	2	3	
Autonomic hyperactivity					
(5) shortness of breath or smothering sensation	?	1	2	3	

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or true

At these times...

...does your heart often pound or race?	(6) palpitations or accelerated heart rate (tachycardia)	?	1	2	3	xx
...do you often sweat a lot? Are your hands often cold or clammy?	(7) sweating, or cold, clammy hands	?	1	2	3	xx
...does your mouth often feel dry?	(8) dry mouth	?	1	2	3	xx
...do you often feel dizzy or lightheaded?	(9) dizziness or lightheadedness	?	1	2	3	xx
...is your stomach often upset, or do you have nausea or diarrhea?	(10) nausea, diarrhea or other abdominal distress	?	1	2	3	xx
...do you have flushes (hot flashes) or chills?	(11) flushes (hot flashes) or chills	?	1	2	3	xx
...do you urinate more often than usual?	(12) frequent urination	?	1	2	3	xx
...do you have trouble swallowing, or get a lump in your throat?	(13) trouble swallowing or lump in throat	?	1	2	3	xx
	<u>Vigilance and scanning</u>					
...do you feel keyed up or on edge?	(14) feeling keyed up or on edge	?	1	2	3	xx
...do sudden noises startle you?	(15) exaggerated startle response	?	1	2	3	xx
...are you often so nervous you have trouble concentrating?	(16) difficulty concentrating or mind going blank because of anxiety	?	1	2	3	xx
...do you often have trouble falling or staying asleep?	(17) trouble falling or staying asleep	?	1	2	3	xx

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or true

At these times...

...are you often irritable or especially impatient?

(18) irritability ? 1 2 3 x

AT LEAST SIX "C" SXS ARE CODED "3" 1 3 x

GO TO NEXT MODULE

Have you been taking any drugs? Have you been physically ill?

IF YES: EXPLORE POSSIBLE RELATIONSHIP BETWEEN ORGANIC FACTOR AND ANXIETY

D. Not sustained by a specific organic factor (e.g., Hyperthyroidism, Caffein Intoxication). ? 1 3 x

GO TO NEXT MODULE

GENERALIZED ANXIETY CRITERIA A, B, C, AND D ARE CODED "3" 1 3 x

GO TO NEXT MODULE

GENERALIZED ANXIETY DISORDER

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or true

CHRONOLOGY

IF UNCLEAR: During the past month, have you had (ANY SX OF GAD)	Has had some symptom(s) of Generalized Anxiety Disorder during past month	?	1	3	x□
When did you last have (ANY SX OF GAD)?	Number of months prior to interview when last had a symptom of Generalized Anxiety Disorder	__	__	__	x□ x□ x□
IF UNCLEAR: During the past month, have you had (LIST OF GAD SXS CODED "3")?	Has met symptomatic criteria for Generalized Anxiety Disorder during past month (criteria A, B and C)	?	1	3	x□
During the past five years, how much of the time have you been bothered by (ANY SX OF GAD)?	Duration in months during past five years that any symptoms of Generalized Anxiety Disorder were present	__	__		x□ x□
How old were you when you first were bothered a lot by anxiety or worry and had a lot of (SXS OF GAD)?	Age at onset of Generalized Anxiety Disorder (criteria A, B, and C)	__	__		x□ x□

Have you ever...						
..had a period of amnesia, that is, a period of several hours or days when you couldn't remember anything afterwards about what happened during that time?	(24) amnesia	?	1	2	3	›
..had a seizure or convulsion?	(25) seizure or convulsion	?	1	2	3	›
..had trouble walking?	(26) trouble walking	?	1	2	3	×
..been paralyzed or had periods of weakness when you couldn't lift or move things that you could normally?	(27) paralysis or muscle weakness	?	1	2	3	×
..been completely unable to urinate for a whole day (other than after childbirth or surgery)?	(28) urinary retention or difficulty urinating	?	1	2	3	×
	Psychosexual symptoms for the major part of individual's life after opportunities for sexual activity					
Now I'm going to ask you some questions about sex.						
Would you say that your sex life has been important to you or could you have gotten along as well without it?	(29) sexual indifference	?	1	2	3	××
Has having sex often been physically painful for you?	(30) pain during intercourse	?	1	2	3	××
FOR MEN: Have you often had any other sexual problem, like having an erection?	(31) impotence	?	1	2	3	××
	Female reproductive symptoms judged by the individual as occurring more frequently or severely than in most women					
Other than during your first year of menstruation (or during menopause), have you had irregular periods? IF YES: More than most women?	(32) irregular periods	?	1	2	3	××

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or true

Have you ever had...

..pain in your genitals (other than during intercourse)?	(10) pain in genitals other than during intercourse	?	1	2	3	xx
..pain when you urinate?	(11) pain during urination	?	1	2	3	xx
..pain anywhere else (other than headaches)?	(12) other pain (other than headaches)	?	1	2	3	xx

Cardiopulmonary (other than during panic attacks)

Have you ever been bothered by...

..shortness of breath	(13) shortness of breath when not exerting self	?	1	2	3	xx
..your heart race, pound or skip?	(14) palpitations	?	1	2	3	xx
..chest pain?	(15) chest pain	?	1	2	3	xx
..dizziness?	(16) dizziness	?	1	2	3	xx

Conversion or pseudoneurological (other than during panic attacks)

Have you ever...

..had trouble swallowing?	(17) difficulty swallowing	?	1	2	3	xx
..lost your voice for more than a few minutes?	(18) loss of voice	?	1	2	3	xx
..been completely deaf for a period of time?	(19) deafness	?	1	2	3	xx
..had double vision for a period of time?	(20) double vision	?	1	2	3	xx
..had blurred vision (when you didn't need glasses)?	(21) blurred vision	?	1	2	3	xx
..been completely blind for more than a few seconds?	(22) blindness	?	1	2	3	xx
..had fainting spells or been Cunconscious?	(23) fainting or loss of consciousness	?	1	2	3	xx

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or true

When you had (SYMPTOM) were you taking any medicine, drugs or alcohol?

IF HAS HAD PANIC ATTACKS: Was that only when you were having a panic attack?

Did you take any medicine for it?

Did it interfere with your life a lot?

4. caused the individual to take medicine (other than aspirin), see a doctor or alter life style

SYMPTOM LIST

Now I am going to ask about specific physical symptoms you may have had.

Gastrointestinal

Have you ever had a lot of trouble with...

..abdominal or belly pain (not counting times when you were menstruating)?	(1) abdominal pain (other than when menstruating)	?	1	2	3	x
..nausea--feeling sick to your stomach but not actually vomiting?	(2) nausea (other than motion sickness)	?	1	2	3	x
..vomiting (when you weren't pregnant)?	(3) vomiting (other than during pregnancy)	?	1	2	3	x
..excessive gas or bloating of your stomach or abdomen?	(4) bloating (gassy)	?	1	2	3	x
..loose bowels or diarrhea	(5) diarrhea	?	1	2	3	x
Have there been any foods that you couldn't eat because they made you sick? What are they?	(6) intolerance (gets sick) of several different foods	?	1	2	3	x

Pain

Have you ever had...

..a lot of trouble with back pain?	(7) back pain	?	1	2	3	x
..pain in your joints?	(8) joint pain	?	1	2	3	x
..pain in your arms or legs other than in the joints?	(9) pain in extremities	?	1	2	3	x

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or tru

SOMATOFORM DISORDERS

SCREENING QUESTIONS

Over the last several years, what has your physical health been like?

Do you have any serious physical problems? (What?)

In the last few years, how often have you had to go to a doctor because you weren't feeling well? (What for?)

Do you worry much about your physical health?

IF NOTHING SUGGESTS THE POSSIBILITY OF A SOMATIZATION DISORDER, CHECK HERE ___ AND GO TO EATING DISORDERS.

NOTES

SOMATIZATION DISORDER

How old were you when you first started to have a lot of physical problems or illnesses?

SOMATIZATION CRITERIA

A. A belief that he or she has been sickly or had many physical problems for several years beginning before the age of 30.

? 1 2 3

GO TO HYPOCHONDRIASIS, G. 6

FOR EACH SYMPTOM REPORTED, DETERMINE THAT THE FOUR CRITERIA FOR SIGNIFICANCE ARE MET BY SUCH QUESTIONS AS:

Did you tell a doctor about (SYMPTOM)?

What was his diagnosis? (What did he say was causing it?)

Did he find anything abnormal when he took tests or x-rays?

B. At least 12 symptoms for women and 10 for men from the list of symptoms below. To count a symptom as significant (a code of "3") the following criteria must be met:

1. not adequately explained by physical disorder or injury
2. not due to medication, drugs or alcohol
3. not occurring only during a panic attack

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or true

What about very painful periods? IF YES: More than most women?	(33) painful menstruation	?	1	2	3	xx
What about too much bleeding during your periods? IF YES: More than most women?	(34) excessive menstrual bleeding	?	1	2	3	xx
IF HAS GIVEN BIRTH: Did you vomit throughout any pregnancy?	(35) vomiting throughout pregnancy	?	1	2	3	xx
	AT LEAST 12 "B" SXS FOR WOMEN OR 10 "B" SXS FOR MEN ARE CODED "3"		1		3	xx
	SOMATIZATION DISORDER CRITERIA A AND B ARE CODED "3"		1		3	xx

SOMATIZATION DISORDER

CHRONOLOGY

IF UNCLEAR: During the past month, have you had (ANY SXS OF SOMATIZATION DISORDER CODED "3")?	Has had some symptom(s) of Somatization Disorder during past month	?	1		3	xx
When did you last have (ANY SX OF SOMATIZATION DISORDER CODED "3")?	Number of months prior to interview when last had a symptom of Somatization Disorder	__	__	__		xx xx xx
During the past five years, how much of the time have you been bothered by (ANY SX OF SOMATIZATION DISORDER)?	Duration in months during past five years that any symptoms of Somatization Disorder were present	___	___			xx xx
How old were you when you first started having a lot of (SXS OF SOMATIZATION DISORDER)?	Age at onset of Somatization Disorder	___	___			xx xx

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or true

HYPOCHONDRIASIS (CURRENT ONLY)

HYPOCHONDRIASIS CRITERIA

What part(s) of your body bother you?

When did you first have this trouble?

What do you think is wrong? (Do you think that these could be due to a serious physical disease?)

A. Preoccupation with the fear of having, or the belief that one has, a serious disease, based on the individual's interpretation of physical signs or sensations as evidence of physical illness.

DESCRIBE:

? 1 2 3 xx

GO TO NEXT MODULE

Have you been to a doctor for these symptoms?

What tests were done?

What did the doctor say was wrong?

B. Thorough physical evaluation does not support the diagnosis of any physical disorder that can account for the physical signs or sensations or the individual's unwarranted interpretation of them.

? 1 2 3 xx

GO TO NEXT MODULE

Were you reassured by what the doctor said? (Did you feel better when he told you that ...?)

What did the doctor say was wrong?

C. The fear of having or belief that one has a disease persists despite medical reassurance.

? 1 2 3 xx

GO TO NEXT MODULE

D. Duration of the disturbance at least six months.

? 1 2 3 xx

GO TO NEXT MODULE

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or true

	E. Not occurring only during the course of Schizophrenia, Schizoaffective Disorder, Paranoid Disorder, or an episode of Major Depression with Melancholia or psychotic features.	?	1 GO TO NEXT MODULE	3 xx
	HYPOCHONDRIASIS CRITERIA A, B, C, D, E, AND F ARE CODED "3"		1 GO TO NEXT MODULE	3 HYPOCHONDRIASIS xx

CHRONOLOGY

IF UNCLEAR: During the past month, have you had (HYPOCHONDRIACAL FEAR OR BELIEF)?	Has had some symptom(s) of Hypochondriasis during past month	?	1	3 xx
When did you last have (HYPOCHONDRIACAL FEAR OR BELIEF)?	Number of months prior to interview when last had a symptom of Hypochondriasis		__ __ __	xx xx xx
IF UNCLEAR: During the past month, have you had (SXS OF HYPOCHONDRIASIS)?	Has met symptomatic criteria for Hypochondriasis during past month (criteria A, B and C)	?	1	3 xx
During the past five years, how much of the time have you been bothered by (HYPOCHONDRIACAL FEAR OR BELIEF)?	Duration in months during past five years that any symptoms of Hypochondriasis were present		__ __	xx xx
How old were you when you first had (HYPOCHONDRIACAL FEAR OR BELIEF)?	Age at onset of Hypochondriasis (criteria A, B and C)		__ __	xx xx

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or true

EATING DISORDERS

ANOREXIA NERVOSA

ANOREXIA NERVOSA CRITERIA

Now I would like to ask you some questions about your eating habits and your weight.

Have you ever had a time when you weighed much less than other people thought you ought to weigh?

IF YES: How old were you then? How much did you weigh? How tall were you?

A. Refusal to maintain body weight over a minimal normal weight for age and height, e.g., weight loss leading to maintenance of body weight 15% below expected; failure to make expected weight gain during period of growth, leading to body weight 15% below expected.

? 1 2 3 xx

GO TO BULIMIA NERVOSA, H. 2

At that time, were you very afraid that you could become fat?

B. Intense fear of becoming obese, even when underweight.

? 1 2 3 xx

GO TO BULIMIA NERVOSA, H. 2

At your lowest weight, how did you think you looked? (Did you still feel too fat or that part of your body was too fat?)

C. Disturbance in the way in which one's body weight, size or shape is experienced, e.g., claiming to "feel fat" even when emaciated; belief that one area of the body is "too fat" even when obviously underweight.

? 1 2 3 xx

GO TO BULIMIA NERVOSA, H. 2

FOR FEMALES: Before this time, were you having your periods? Did they stop? (For how long?)

D. In females, absence of at least three consecutive menstrual cycles when otherwise expected to occur (primary or secondary amenorrhea).

? 1 2 3 xx

GO TO BULIMIA NERVOSA, H. 2

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or true

ANOREXIA NERVOSA CRITERIA
A, B, C, AND D ARE CODED "3"

1 3 x

GO TO BULIMIA NERVOSA BELOW	ANOREXIA NERVOSA

BULIMIA NERVOSA

BULIMIA NERVOSA CRITERIA

Have you ever had eating binges during which you ate a lot of food in a short period of time--less than two hours?	A. Recurrent episodes of binge-eating (rapid consumption of a large amount of food in a discrete period of time, usually less than two hours).	?	1	2	3	xo
		GO TO NEXT MODULE				
During these binges, did you feel that your eating was out of control?	B. During the eating binges there is a feeling of lack of control over the eating behavior.	?	1	2	3	xo
		GO TO NEXT MODULE				
Did you do anything to counteract the effects of the binges? (Like making yourself vomit, taking laxatives, strict dieting, fasting?)	C. The individual regularly engages in either self-induced vomiting, use of laxatives, or rigorous dieting or fasting in order to counteract the effects of the binge eating.	?	1	2	3	xx
		GO TO NEXT MODULE				

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or true

During this time, did you have eating binges as often as twice a week for three months?

D. A minimum average of two binge-eating episodes per week for at least three months.

? 1 2 3 xx

GO TO NEXT MODULE

BULIMIA NERVOSA CRITERIA
A, B, C, AND D ARE CODED "3"

1 3 xx

BULIMIA NERVOSA

?=inadequate information 1=absent or false 2=subthreshold 3=threshold or true

APPENDIX VII

Social Class by occupation

Affective (Initial Interview)

Patient's No.	Patient's Occupation	Husband's Occupation	Social Class
102	Cashier	Supervising engineer	I
103	Owns dress shop	Stockmarket	II
104	Housewife	Soldier	Excluded
105	-	Physiologist	I
108	Housewife	Engineer	I
109	University lecturer	Architect	I
110	Computer operator	-	IIIN
112	Housewife	Nautical surveyor	II
113	Cleaner	Factory worker	V
114	Housewife	Unknown	Unknown
115	Teacher	-	II
116	Housewife	Heavy goods driver	IIIM
117	Records officer	-	IIIN
118	Teacher	-	II
119	Retired teacher	Unknown	II
120	Student	-	Excluded
121	Part-time secretary	Painter & decorator	IIIM

APPENDIX VII

Social Class by occupation

Non-Affective (Initial Interview)

Patient's No.	Patient's Occupation	Husband's Occupation	Social Class
201	Auxiliary nurse	-	II
202	Student	-	Excluded
203	-	Chartered engineer	I
204	Teacher	-	II
205	Secretary	Unknown	IIIN
206	Bookkeeper/cashier	-	IIIN
207	Part-time cleaner	Postman	IIIM
208	Office worker	-	IIIN
209	Clerical worker	Customs & Excise officer	II
210	Nurse	Press photographer	IIIN
211	Retired teacher	Retired	II
212	Lecturer	Director of Observatory	I
213	Restaurant assistant	Unknown	IV
214	Secretary	-	IIIN
215	Telephonist	Unknown	IIIN
216	Teacher	Merchant Navy	IIIM
217	Housewife	-	Unknown
218	Sales assistant	Clerical	IIIN
219	Psychology lecturer	-	I
220	Asst. bank manager	-	II
221	Shop assistant	-	IIIN
222	Secretary	-	IIIN
223	Housewife	Electronics engineer	I
224	Factory worker	-	V
225	Market research	-	II
226	Housing manager	Local councillor	II
227	Research worker	Unknown	Unknown
228	Housewife	Executive	II
229	Telephonist	-	IIIN

APPENDIX VIII

Log linear modelling of the interaction between cerebral dominance, laterality of migraine, the type of migraine and self report of anxiety, depression, euphoria and irritability.

Depression

	Scaled Deviance	df	Deviance Change	df
Null Fit	59.3	49		
Type + Laterality + Deviance	44.7	43	14.6	6
Type + Laterality	44.8	44	0.1	1

Thus dominance is not significantly associated with depression, but type and laterality are.

APPENDIX IX

27th January 1988

Dr. Diana Morris,
Astra Alab AB,
S-151 85 Sodertalje,
Sweden.

Dear Diana,

Thank you for your letter. Going through all your data again I think it is clear that the values all come within our normal range both in the basal state and during migraine, and that there are no significant asymmetries or abnormalities of the distribution pattern which I can identify as being associated with migraine. Indeed the only significant difference is the fact that all three patients with classical migraine showed a small increase in transit times during migraine, whereas both patients with common migraine showed a decrease. Although the numbers are small, this is obviously very suggestive and will probably justify a larger scale study.

The big unknown is the delay between the onset of migraine and performing the examination. I do not have a note of this and I think it may have varied from one patient to another. There is one reference (which unfortunately I cannot now lay my hands on) which suggests that the blood flow changes alter during the course of the migraine.

With kindest regards.

Yours sincerely,

M.V. Merrick.

c.c. Prof. Kendall's Secretary, Royal Edinburgh Hospital. ✓

APPENDIX X

Regional CBF Results - Baseline-Non Affective Group (Initial Interview)

Patient ID No	IP Arrival	IP Transit	NET CTT (L)	CTT (L)F	CTT (L)T	CTT (L)P	CTT (L)O	NET CTT (R)	CTT (R)F	CTT (R)T	CTT (R)P	CTT (R)O	NET FF (L)	FF (L)F
Classical														
220	5.0	6.4	4.2	3.2	3.35	3.75	5.39	4.1	2.83	2.75	4.01	5.84	0.22	0.20
211	8.0	8.4	4.2	4.01	3.75	4.29	4.92	3.9	3.38	3.17	4.07	4.51	0.24	0.25
215	3.0	6.0	5.2	3.94	2.34	3.75	7.58	4.7	3.76	2.33	3.56	7.05	0.25	0.3
218	6.2	6.2	5.5	5.64	4.76	5.17	6.56	5.3	5.59	4.47	4.88	6.15	0.18	0.18
207	5.6	5.6	2.8	1.98	2.08	3.15	3.7	2.6	2.24	1.84	2.48	3.99	0.39	0.52
212	5.1	5.4	3.5	2.68	2.99	3.25	4.7	3.6	2.58	2.85	3.74	5.38	0.3	0.38
210	3.6	4.3	3.8	4.1	3.08	3.5	4.5	3.8	3.62	3.39	3.66	4.43	0.28	0.25
213	6.9	5.3	5.8	4.68	4.79	5.79	7.12	5.0	4.2	4.12	4.71	6.1	0.17	0.21
209	4.2	4.0	4.4	3.71	3.66	4.57	5.61	3.8	3.38	3.31	3.73	4.62	0.24	0.27
Common														
225	4.2	4.4	4.5	4.35	4.17	4.11	5.42	4.6	4.47	4.20	4.10	6.36	0.20	0.23
208	5.0	5.3	5.9	5.0	4.68	5.61	6.39	6.2	4.5	4.64	5.94	7.33	0.18	0.21
205	4.5	4.5	6	5.36	5.4	5.93	7.35	5.7	4.53	4.49	5.92	7.54	0.16	0.19
204	4.7	4.7	2.5	2.33	2.11	2.33	3.02	2.4	2.42	1.83	2.42	3.14	0.4	0.44
201	4.2	5.7	4.2	4.55	3.72	4.11	4.59	4.1	3.93	3.67	3.96	4.24	0.25	0.23
224	4.8	3.9	3.6	3.02	2.55	3.01	4.65	3.7	3.11	2.55	3.33	4.83	0.31	0.33

IP = Input Function
CTT = Cortical Transit Time
FF = Fractional Flow
CVTT = Large Vessel Transit Time

L = Left hemisphere
R = Right hemisphere
F = Frontal region
T = Temporal region
P = Parietal region
O = Occipital region.

IP = Input Function
FF = Fractional Flow
CTT = Cortical Transit Time
LVTT = Large Vessel Transit Time

FF (L)T	FF (L)P	FF (L)O	NET FF (R)	FF (R)F	FF (R)T	FF (R)P	FF (R)O	NET LVTT (L)	LVTT (L)F	LVTT (L)T	LVTT (L)P	LVTT (L)O	NET LVTT (R)	LVTT (R)F	LVTT (R)T	LVTT (R)P	LVT (R)
0.30	0.27	0.20	0.23	0.35	0.37	0.26	0.19	3.7	1.94	1.68	1.52	1.56	3.8	1.96	1.78	1.53	1.6
0.27	0.24	0.21	0.27	0.30	0.32	0.25	0.22	3.9	3.71	3.56	3.73	4.4	4.0	3.74	3.59	3.74	4.8
0.44	0.28	0.16	0.26	0.30	0.44	0.28	0.17	6.2	6.47	6.37	6.24	6.08	6.3	6.51	6.35	6.4	6.1
0.22	0.2	0.15	0.19	0.18	0.23	0.21	0.17	3.6	3.75	3.65	3.67	3.58	3.6	3.74	3.63	3.63	3.7
0.5	0.33	0.28	0.42	0.46	0.56	0.42	0.27	2.6	2.72	2.5	2.63	2.89	2.6	2.70	2.55	2.67	2.7
0.35	0.32	0.22	0.29	0.39	0.36	0.28	0.18	5.5	5.74	5.35	5.36	5.54	5.7	5.86	5.47	5.68	5.8
0.33	0.29	0.23	0.27	0.29	0.3	0.27	0.23	4.5	4.54	4.29	4.38	4.67	4.4	4.23	4.424.6		
0.21	0.17	0.14	0.20	0.24	0.25	0.22	0.17	5.4	5.4	5.26	5.35	5.66	5.3	5.47	5.34	5.25	5.4
0.28	0.22	0.19	0.27	0.3	0.31	0.27	0.22	4.0	4.06	3.93	3.98	4.17	4.1	4.23	4.05	4.07	4.1
0.24	0.25	0.19	0.20	0.22	0.24	0.25	0.17	4.8	5.36	4.99	4.85	4.75	4.8	5.41	5.06	4.89	4.7
0.22	0.18	0.16	0.17	0.22	0.22	0.17	0.14	3.6	3.52	3.48	3.52	3.77	3.6	3.76	3.57	3.38	3.6
0.19	0.17	0.13	0.18	0.22	0.23	0.17	0.14	3.4	3.63	3.45	3.42	3.36	3.5	3.64	3.49	3.42	3.43
0.48	0.43	0.34	0.4	0.43	0.56	0.43	0.29	2.2	2.28	2.11	2.21	2.22	2.2	2.28	2.21	2.24	2.17
0.27	0.24	0.22	0.25	0.26	0.27	0.25	0.21	5.3	5.26	5.18	5.33	5.55	5.3	5.38	5.23	5.37	5.35
0.4	0.34	0.22	0.29	0.33	0.4	0.31	0.21	4.0	4.18	4.1	4.06	3.97	4.1	4.16	4.09	4.03	4.07

APPENDIX X

Regional CBF Results - Baseline - Affective Group (Initial Interview)

Patient ID No	IP Arrival	IP Transit	NET CTT (L)	CTT (L)F	CTT (L)T	CTT (L)P	CTT (L)O	NET CTT (R)	CTT (R)F	CTT (R)T	CTT (R)P	CTT (R)O	NET FF (L)	FF (L)F
Classical														
104	5.1	8.7	5.2	5.23	4.81	5.32	6.04	5.4	4.96	5.14	5.75	6.44	0.19	0.19
118	5.9	5.9	2.2	1.47	1.74	2.41	3.16	2.0	1.44	1.45	2.13	2.87	0.48	0.71
102	3.6	3.6	3.8	3.5	3.58	3.67	4.47	4.1	3.83	3.27	4.34	4.9	0.26	0.29
120	8.3	5.7	6.0	4.96	5.05	6.02	7.42	5.5	4.6	4.66	5.57	7.35	0.17	0.2
105	4.8	7.1	4.7	4.42	4.1	4.99	5.31	4.8	4.45	4.14	5.05	5.23	0.22	0.23
119	6.0	9.3	9.0	7.74	9.02	8.58	9.87	8.4	8.64	8.11	6.93	9.74	0.12	0.14
Common														
103	7.5	7.5	3.6	2.92	2.61	3.32	5.16	4.2	3.01	2.88	3.71	6.59	0.31	0.35
110	5.7	5.7	2.9	3.23	2.27	2.91	3.24	2.9	3.08	2.2	2.68	3.88	0.37	0.34
113	6.1	6.1	3.0	2.3	2.44	3.10	4.22	3.1	2.64	2.2	3.37	5.09	0.35	0.45
106	4.2	3.8	3.9	3.6	3.17	3.86	4.98	4.0	3.4	3.21	3.86	5.58	0.26	0.28

FF (L)T	FF (L)P	FF (L)O	NET FF (R)	FF (R)F	FF (R)T	FF (R)P	FF (R)O	NET LVTT (L)	LVTT (L)F	LVTT (L)T	LVTT (L)P	LVTT (L)O	NET LVTT (R)	LVTT (R)F	LVTT (R)T	LVTT (R)P	LVT (R)
0.21	0.19	0.17	0.18	0.21	0.20	0.18	0.16	7.6	7.46	7.34	7.62	8.13	7.5	7.50	7.27	7.59	7.8
0.61	0.42	0.31	0.52	0.70	0.73	0.48	0.33	1.3	1.62	1.37	1.39	1.11	1.4	1.61	1.50	1.58	1.2
0.28	0.27	0.21	0.24	0.27	0.31	0.23	0.19	3.8	3.86	3.76	3.79	3.7	3.8	3.84	3.80	3.74	3.7
0.2	0.17	0.13	0.19	0.22	0.22	0.18	0.14	3.6	3.65	3.5	3.55	3.78	3.6	3.72	3.53	3.56	3.8
0.25	0.2	0.19	0.21	0.23	0.24	0.2	0.2	7.1	7.14	6.84	6.86	7.48	7.1	7.3	7.02	6.76	7.5
0.13	0.12	0.11	0.13	0.13	0.14	0.15	0.12	3.1	3.23	2.95	3.07	3.07	3.0	3.17	3.01	3.04	3.0
0.4	0.3	0.23	0.27	0.34	0.36	0.28	0.17	1.9	1.98	1.81	1.96	1.83	1.8	1.93	1.8	1.86	1.6
0.45	0.35	0.32	0.38	0.36	0.47	0.38	0.27	2.1	1.91	1.85	2.25	2.52	2.0	1.91	1.82	2.08	2.3
0.42	0.33	0.25	0.34	0.41	0.47	0.31	0.21	2.2	2.37	1.9	2.09	2.48	2.1	2.3	1.96	1.94	2.0
0.33	0.27	0.2	0.26	0.29	0.32	0.27	0.18	4.3	4.46	4.26	4.27	4.38	4.3	4.66	4.23	4.26	4.3

APPENDIX X

Regional CBF Results - During Migraine

Patient ID No.	IP Arrival	IP Transit	NET CTT (L)	CTT (L)F	CTT (L)T	CTT (L)P	CTT (L)O	NET CTT(R)	CTT (R)F	CTT (R)T	CTT (R)P	CTT (R)O	NET FF (L)	FF (L)F
Classical														
104	8.5	6.9	6.3	5.41	5.78	6.62	8.05	6.1	4.84	5.23	6.06	7.44	0.16	0.19
220	7.9	5.8	5.0	4.03	4.06	5.33	7.09	4.7	3.51	3.88	4.84	6.76	0.19	0.25
220 (repeat examination)				2.28	2.5	3.66	5.53		2.14	2.37	3.25	5.67		0.44
211	6.0	6.4	6.1	6.3	5.48	6.54	7.23	6.0	5.69	5.12	5.85	7.22	0.16	0.16
Common														
225	4.8	5.9	3.2	3.48	2.86	2.74	4.02	3.4	3.3	2.57	3.15	5.18	0.3	0.3
208	4	4	4.5	4.21	3.82	4.01	5.86	4.6	4.09	3.77	4.46	7.12	0.22	0.24

FF (L)T	FF (L)P	FF (L)O	NET FF (R)	FF (R)F	FF (R)T	FF (R)P	FF (R)O	NET LVTT (L)	LVTT (L)F	LVTT (L)T	LVTT (L)P	LVTT (L)O	NET LVTT (R)	LVTT (R)F	LVTT (R)T	LVTT (R)P	LVTT (R)O
0.18	0.16	0.13	0.17	0.21	0.19	0.17	0.14	4.4	4.55	4.41	4.48	4.46	4.6	4.72	4.55	4.54	4.6
0.25	0.19	0.16	0.21	0.29	0.26	0.21	0.15	3.5	3.95	3.77	3.78	3.65	3.9	4.32	4.02	4.02	4.1
0.42	0.28	0.19		0.48	0.44	0.32	0.17		4.83	4.53	4.55	4.44		4.88	4.55	4.54	4.3
0.18	0.16	0.14	0.17	0.18	0.2	0.17	0.14	4.9	4.95	4.79	4.76	5.24	5.0	4.97	4.89	4.87	5.1
0.35	0.37	0.26	0.28	0.31	0.4	0.32	0.21	6.0	6.17	6.1	6.01	5.91	6.0	6.17	6.17	6.01	6.0
0.27	0.26	0.18	0.2	0.25	0.27	0.23	0.15	4	4.25	4.11	3.95	4.08	4	4.37	4.09	3.96	4.1

CORTICAL TRANSIT TIME

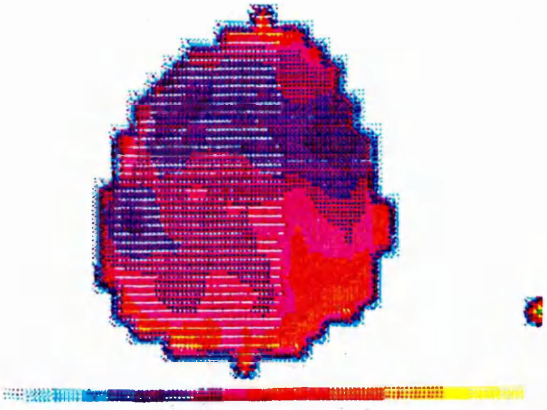
29	3.50	+- .52	18	3.83	+- .64
40	3.58	+- .42	34	3.27	+- .36
43	3.67	+- .37	40	4.34	+- .41
24	4.47	+- .54	25	4.90	+- .73

FRACTIONAL FLOW

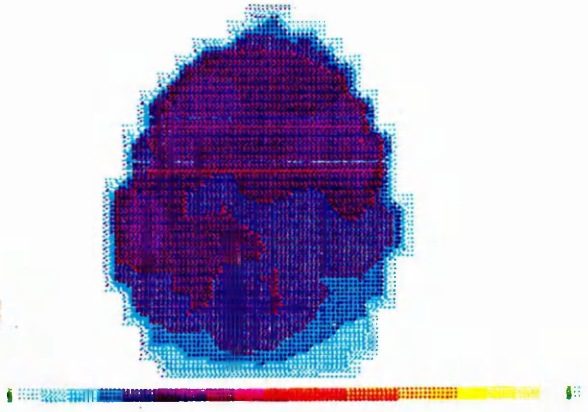
29	.29	+- .04	18	.27	+- .04
40	.28	+- .03	34	.31	+- .03
43	.27	+- .03	40	.23	+- .02
31	.21	+- .04	35	.19	+- .04

LARGE VESSEL TRANSIT TIME

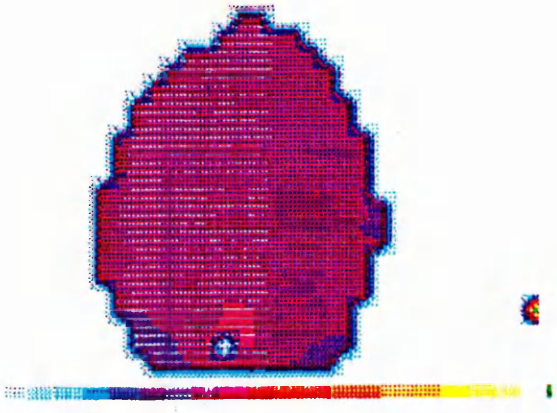
29	3.86	+- .08	18	3.84	+- .06
40	3.76	+- .09	34	3.80	+- .10
43	3.79	+- .10	40	3.74	+- .11
30	3.70	+- .23	35	3.77	+- .19



L METT TRANSIT TIME R
L 3.8 +-.6 N=137
R 4.1 +-.8 N=117



L FRACTIONAL FLOW R
L .26 +-.05 N=145
R .24 +-.06 N=127



L LARGE VESSEL TT R
L 3.8 +-.1 N=144
R 3.8 +-.1 N=127

INPUT FUNCTION
ARRIVAL TIME 3.6 SEC.
TRANSIT TIME 3.6 SEC.

I.D. No 103

CORTICAL TRANSIT TIME

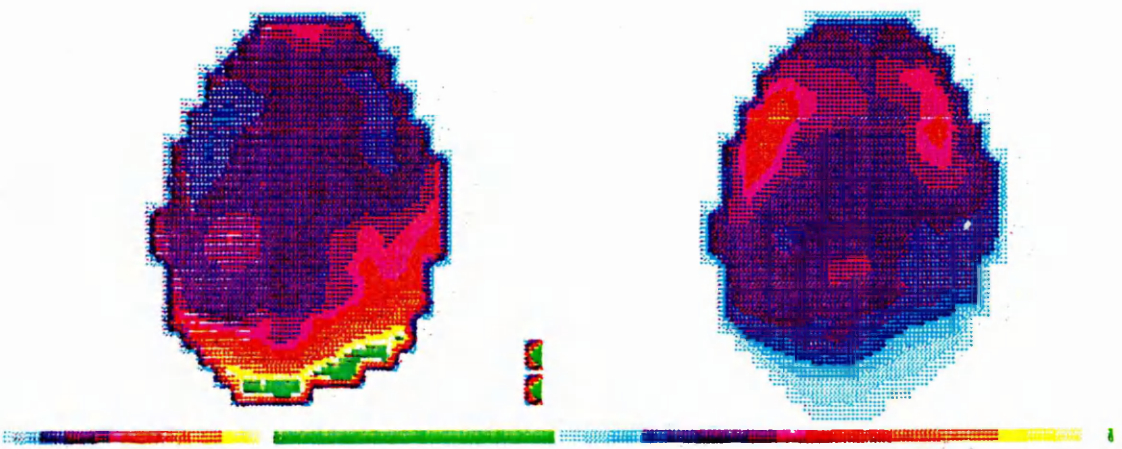
24	2.92 +- .59	23	3.01 +- .57
36	2.61 +- .48	38	2.88 +- .45
38	3.32 +- .41	44	3.71 +- .66
39	5.16 +- 2.82	41	6.59 +- 3.26

FRACTIONAL FLOW

24	.35 +- .06	23	.34 +- .06
36	.40 +- .08	38	.36 +- .06
38	.31 +- .04	44	.28 +- .05
39	.23 +- .08	45	.17 +- .08

LARGE VESSEL TRANSIT TIME

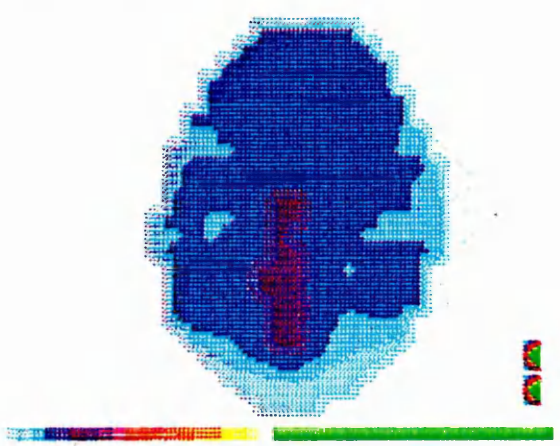
24	1.98 +- .07	23	1.93 +- .08
36	1.81 +- .14	38	1.80 +- .13
38	1.96 +- .38	44	1.86 +- .31
39	1.83 +- .56	45	1.62 +- .55



L NETT TRANSIT TIME R L FRACTIONAL FLOW R

L 3.6 +-1.9 N=137 L .31 +-.10 N=139

R 4.2 +-2.4 N=146 R .27 +-.10 N=152



L LARGE VESSEL TT R

L 1.9 +-.4 N=139

R 1.8 +-.4 N=152

INPUT FUNCTION

ARRIVAL TIME 7.5 SEC.

TRANSIT TIME 7.5 SEC.

I.D. No. 104

BASELINE

CORTICAL TRANSIT TIME

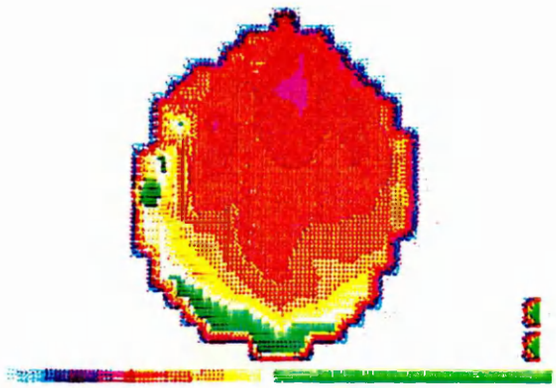
20	5.41 +- .75	14	4.84 +- .46
33	5.78 +- 1.60	26	5.23 +- .89
39	6.62 +- 2.45	25	6.06 +- .87
38	8.05 +- 1.96	26	7.44 +- 1.09

FRACTIONAL FLOW

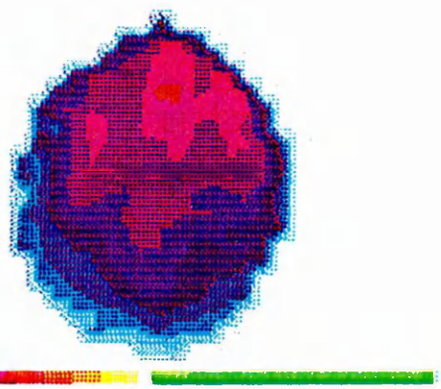
20	.19 +- .03	14	.21 +- .02
33	.18 +- .04	26	.19 +- .03
39	.16 +- .04	25	.17 +- .02
38	.13 +- .03	26	.14 +- .02

LARGE VESSEL TRANSIT TIME

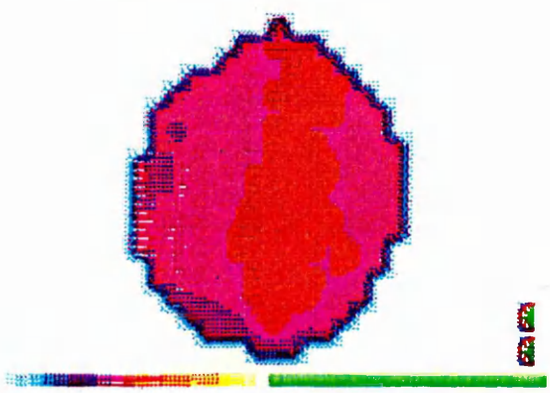
20	4.55 +- .11	14	4.72 +- .07
33	4.41 +- .23	26	4.55 +- .21
39	4.48 +- .36	25	4.54 +- .22
38	4.46 +- .38	26	4.60 +- .20



L MEAN TRANSIT TIME R
L 6.3 +-1.6 N=125
R 6.1 +-1.4 N=92



L FRACTIONAL FLOW R
L .16 +-.04 N=138
R .17 +-.04 N=95



L LARGE VESSEL TT R
L 4.4 +-.3 N=138
R 4.6 +-.2 N=95

INPUT FUNCTION
ARRIVAL TIME 8.5 SEC.
TRANSIT TIME 6.9 SEC.

I.D. No 104

DURING MIGRAINE

CORTICAL TRANSIT TIME

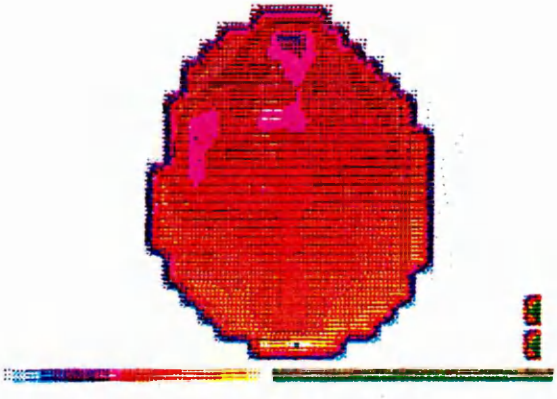
23	5.23 +- .72	20	4.96 +- .72
36	4.81 +- .48	38	5.14 +- .66
39	5.32 +- .50	40	5.75 +- .69
28	6.04 +- 1.33	24	6.44 +- 1.05

FRACTIONAL FLOW

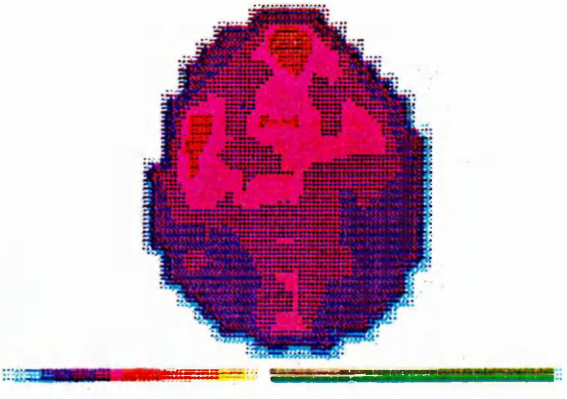
23	.19 +- .03	20	.21 +- .03
36	.21 +- .02	38	.20 +- .02
39	.19 +- .02	40	.18 +- .02
28	.17 +- .03	24	.16 +- .03

LARGE VESSEL TRANSIT TIME

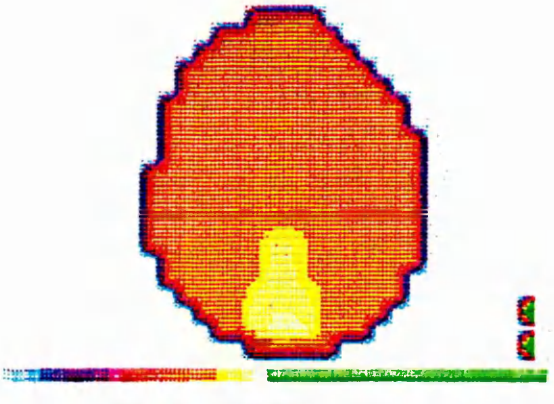
23	7.46 +- .15	20	7.50 +- .20
36	7.34 +- .14	38	7.27 +- .16
39	7.62 +- .32	40	7.59 +- .34
28	8.13 +- .61	24	7.84 +- .47



L NETT TRANSIT TIME R
L 5.2 +-.7 N=123
R 5.4 +-.7 N=114



L FRACTIONAL FLOW R
L .19 +-.03 N=125
R .18 +-.03 N=121



L LARGE VESSEL TT R
L 7.6 +-.5 N=126
R 7.5 +-.4 N=122

INPUT FUNCTION
ARRIVAL TIME 5.1 SEC.
TRANSIT TIME 8.7 SEC.

I.D. No. 105

CORTICAL TRANSIT TIME

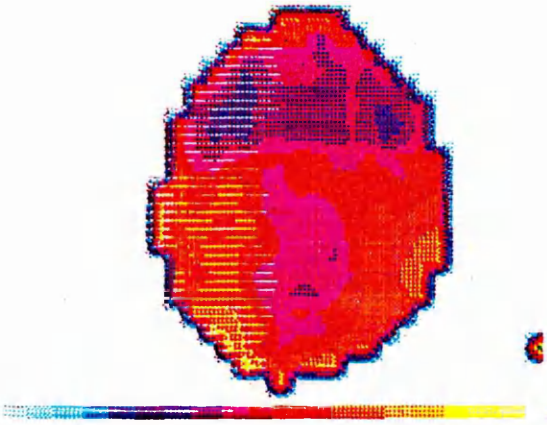
28	4.42 +- .85	16	4.45 +- .73
43	4.10 +- .57	33	4.14 +- .47
45	4.99 +- .55	39	5.05 +- .71
35	5.31 +- 1.09	34	5.23 +- .86

FRACTIONAL FLOW

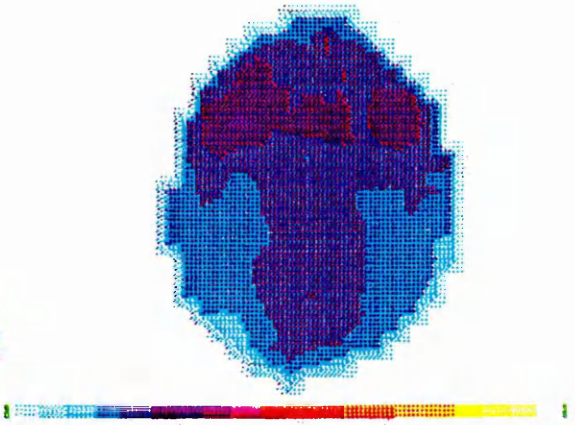
28	.23 +- .04	16	.23 +- .03
43	.25 +- .03	33	.24 +- .03
45	.20 +- .02	39	.20 +- .03
35	.19 +- .04	34	.20 +- .03

LARGE VESSEL TRANSIT TIME

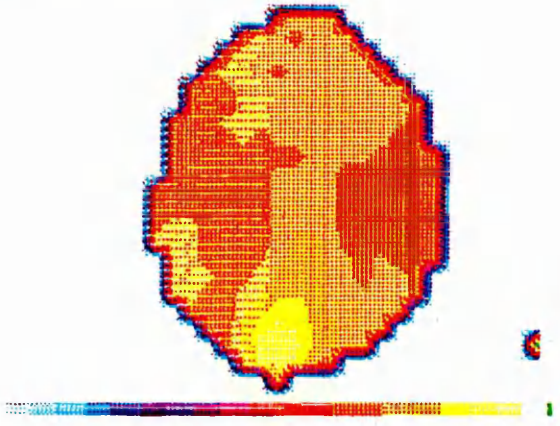
28	7.14 +- .35	16	7.30 +- .24
43	6.84 +- .41	33	7.02 +- .42
45	6.86 +- .47	39	6.76 +- .45
35	7.48 +- .77	34	7.51 +- .46



L NETT TRANSIT TIME R
L 4.7 +-.9 N=152
R 4.8 +-.8 N=122



L FRACTIONAL FLOW R
L .22 +-.04 N=152
R .21 +-.04 N=122



L LARGE VESSEL TT R
L 7.1 +-.6 N=152
R 7.1 +-.5 N=122

INPUT FUNCTION
ARRIVAL TIME 4.8 SEC.
TRANSIT TIME 7.1 SEC.

I.D. No 106

CORTICAL TRANSIT TIME

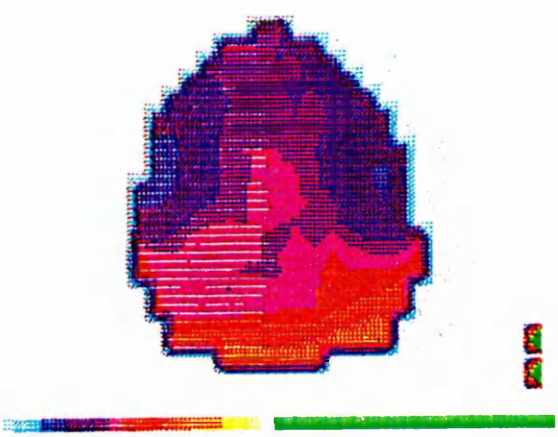
23	3.60	+- .30	15	3.40	+- .15
37	3.17	+- .62	37	3.21	+- .54
43	3.86	+- .57	40	3.86	+- .62
34	4.98	+- .99	28	5.58	+- .97

FRACTIONAL FLOW

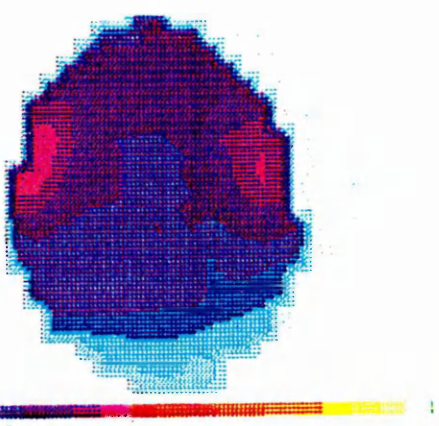
23	.28	+- .02	15	.29	+- .01
37	.33	+- .07	37	.32	+- .05
43	.27	+- .05	40	.27	+- .05
35	.20	+- .04	31	.18	+- .03

LARGE VESSEL TRANSIT TIME

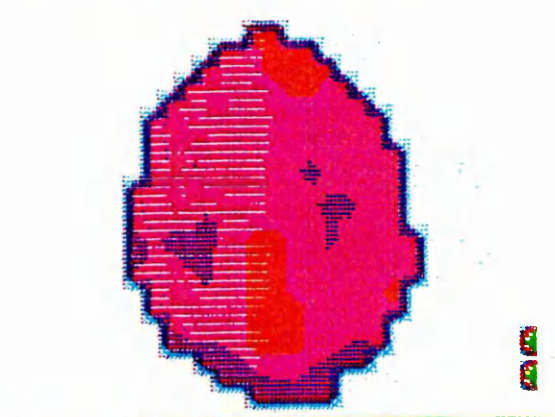
23	4.46	+- .25	15	4.66	+- .28
37	4.26	+- .06	37	4.23	+- .07
43	4.27	+- .25	40	4.26	+- .14
35	4.38	+- .37	31	4.35	+- .28



L NETT TRANSIT TIME R
L 3.9 +-1.0 N=137
R 4.0 +-1.1 N=120



L FRACTIONAL FLOW R
L .26 +-.07 N=144
R .26 +-.08 N=129



L LARGE VESSEL TT R
L 4.3 +-.3 N=144
R 4.3 +-.2 N=129

INPUT FUNCTION
ARRIVAL TIME 4.2 SEC.
TRANSIT TIME 3.8 SEC.

I.D. No 110

CORTICAL TRANSIT TIME

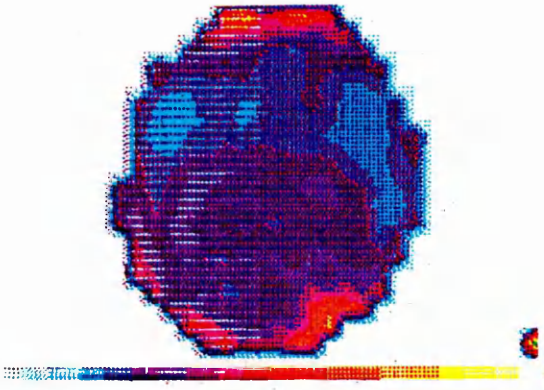
30	3.23 +- 1.10	25	3.08 +- 1.16
43	2.27 +- .41	40	2.20 +- .43
43	2.91 +- .31	43	2.68 +- .43
30	3.24 +- .76	27	3.88 +- 1.07

FRACTIONAL FLOW

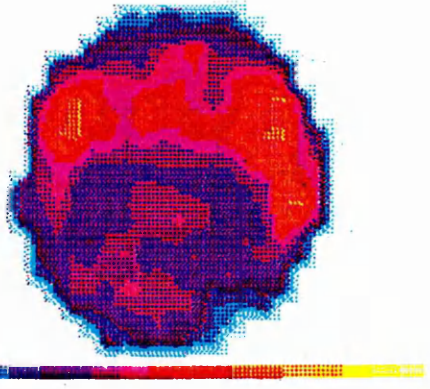
30	.34 +- .09	25	.36 +- .10
43	.45 +- .09	40	.47 +- .09
43	.35 +- .04	43	.38 +- .08
30	.32 +- .07	27	.27 +- .07

LARGE VESSEL TRANSIT TIME

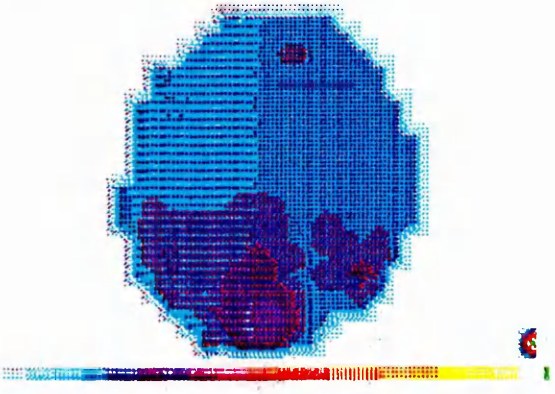
30	1.91 +- .10	25	1.91 +- .15
43	1.85 +- .08	40	1.82 +- .08
43	2.25 +- .30	43	2.08 +- .29
30	2.52 +- .46	27	2.32 +- .53



L NETT TRANSIT TIME R
L 2.9 +-.8 N=146
R 2.9 +-1.0 N=135



L FRACTIONAL FLOW R
L .37 +-.09 N=146
R .38 +-.11 N=135



L LARGE VESSEL TT R
L 2.1 +-.4 N=146
R 2.0 +-.3 N=135

INPUT FUNCTION
ARRIVAL TIME 5.7 SEC.
TRANSIT TIME 5.7 SEC.

I.A. No 113

CORTICAL TRANSIT TIME

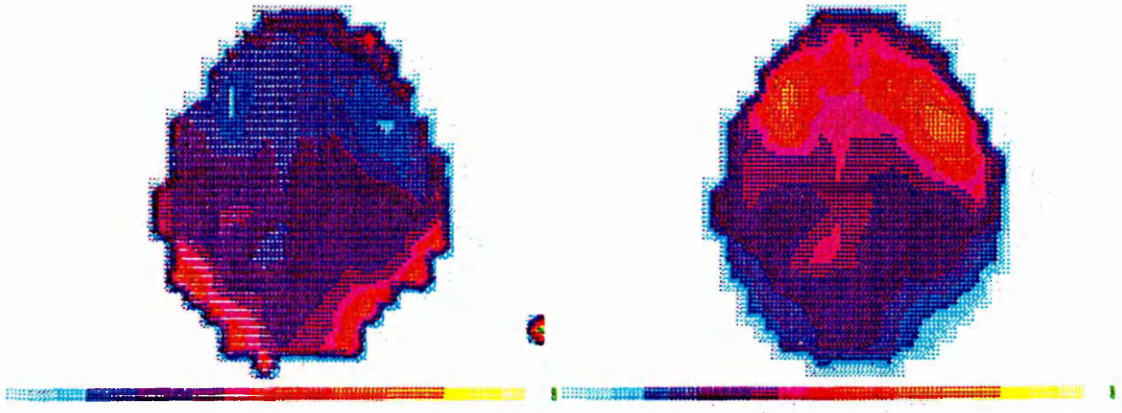
24	2.30 +- .40	22	2.64 +- .78
39	2.44 +- .44	36	2.20 +- .45
43	3.10 +- .58	40	3.37 +- .74
36	4.22 +- 1.20	31	5.09 +- 1.50

FRACTIONAL FLOW

24	.45 +- .09	22	.41 +- .10
39	.42 +- .08	36	.47 +- .10
43	.33 +- .06	40	.31 +- .05
36	.25 +- .06	31	.21 +- .06

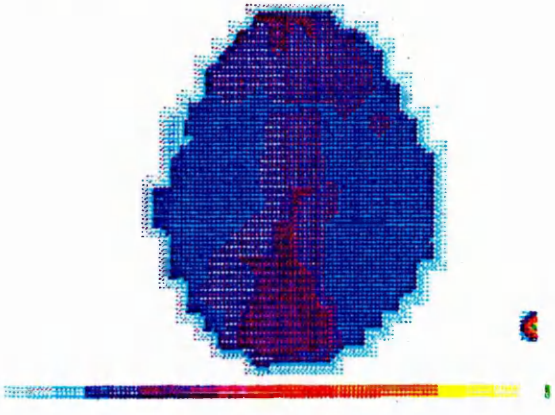
LARGE VESSEL TRANSIT TIME

24	2.37 +- .25	22	2.30 +- .29
39	1.90 +- .30	36	1.96 +- .22
43	2.09 +- .35	40	1.94 +- .26
36	2.48 +- .56	31	2.04 +- .42



L NETT TRANSIT TIME R
L 3.0 +-.8 N=138
R 3.1 +-1.0 N=119

L FRACTIONAL FLOW R
L .35 +-.10 N=142
R .34 +-.13 N=129



L LARGE VESSEL TT R
L 2.2 +-.5 N=142
R 2.1 +-.3 N=129

INPUT FUNCTION
ARRIVAL TIME 6.1 SEC.
TRANSIT TIME 6.1 SEC.

I.D. No. 118

CORTICAL TRANSIT TIME

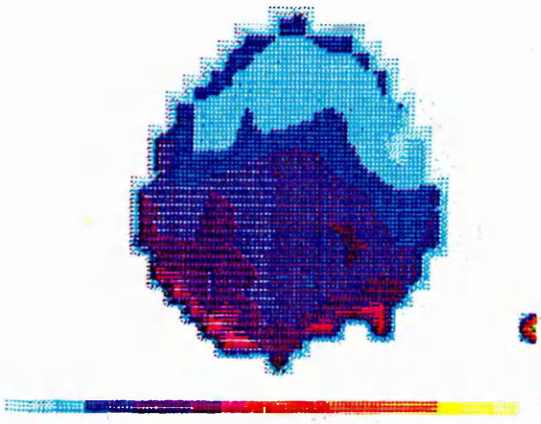
24	1.47	+- .30	17	1.44	+- .20
43	1.74	+- .40	33	1.45	+- .35
48	2.41	+- .31	40	2.13	+- .30
30	3.16	+- .79	26	2.87	+- .84

FRACTIONAL FLOW

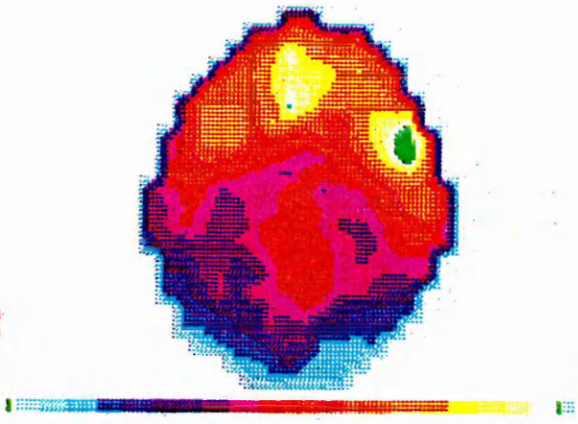
24	.71	+- .15	17	.70	+- .09
43	.61	+- .15	33	.73	+- .18
48	.42	+- .05	40	.48	+- .08
36	.31	+- .10	33	.33	+- .12

LARGE VESSEL TRANSIT TIME

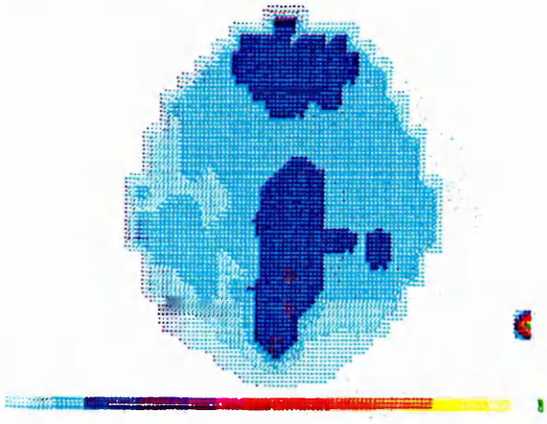
24	1.62	+- .07	17	1.61	+- .06
43	1.37	+- .25	33	1.50	+- .06
48	1.39	+- .29	40	1.58	+- .09
36	1.11	+- .54	33	1.29	+- .54



L NETT TRANSIT TIME R
L 2.2 +-.8 N=146
R 2.0 +-.7 N=116



L FRACTIONAL FLOW R
L .48 +-.19 N=158
R .52 +-.22 N=130



L LARGE VESSEL TT R
L 1.3 +-.4 N=158
R 1.4 +-.4 N=130

INPUT FUNCTION
ARRIVAL TIME 5.9 SEC.
TRANSIT TIME 5.9 SEC.

I.D. No 119

CORTICAL TRANSIT TIME

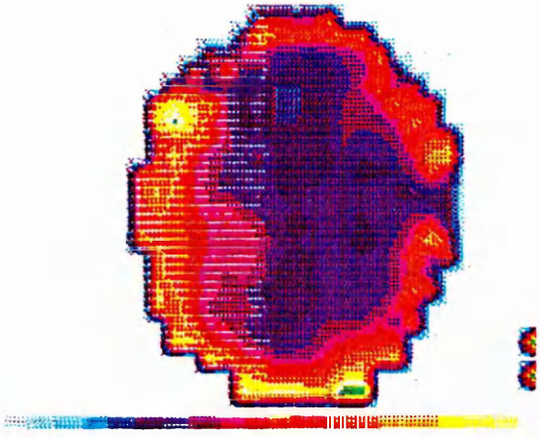
28	7.74 +- 2.24	24	8.64 +- 2.78
46	9.02 +- 4.01	43	8.11 +- 2.80
53	8.58 +- 2.32	41	6.93 +- 1.88
57	9.87 +- 3.95	50	9.74 +- 4.25

FRACTIONAL FLOW

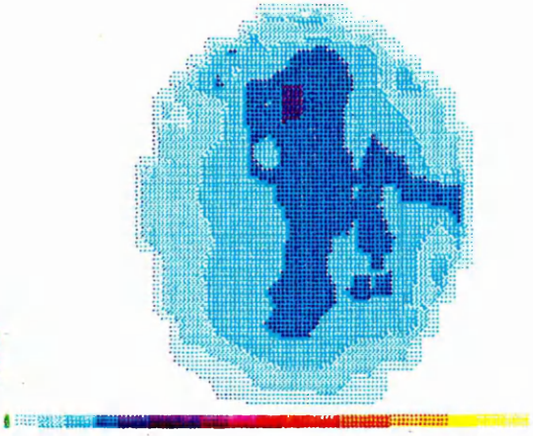
28	.14 +- .04	24	.13 +- .04
46	.13 +- .05	43	.14 +- .04
53	.12 +- .03	41	.15 +- .03
64	.11 +- .05	50	.12 +- .04

LARGE VESSEL TRANSIT TIME

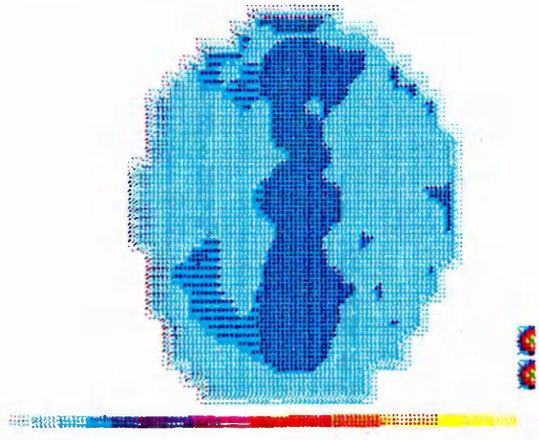
28	3.23 +- .18	24	3.17 +- .24
46	2.95 +- .22	43	3.01 +- .15
53	3.07 +- .20	41	3.04 +- .18
64	3.07 +- .45	50	3.03 +- .31



L NETT TRANSIT TIME R
L 9.0 +-3.4 N=184
R 8.1 +-3.3 N=158



L FRACTIONAL FLOW R
L .12 +-.04 N=191
R .13 +-.04 N=158



L LARGE VESSEL TT R
L 3.1 +-.3 N=191
R 3.0 +-.2 N=158

INPUT FUNCTION
ARRIVAL TIME 6.0 SEC.
TRANSIT TIME 9.3 SEC.

I.D. NO 120

CORTICAL TRANSIT TIME

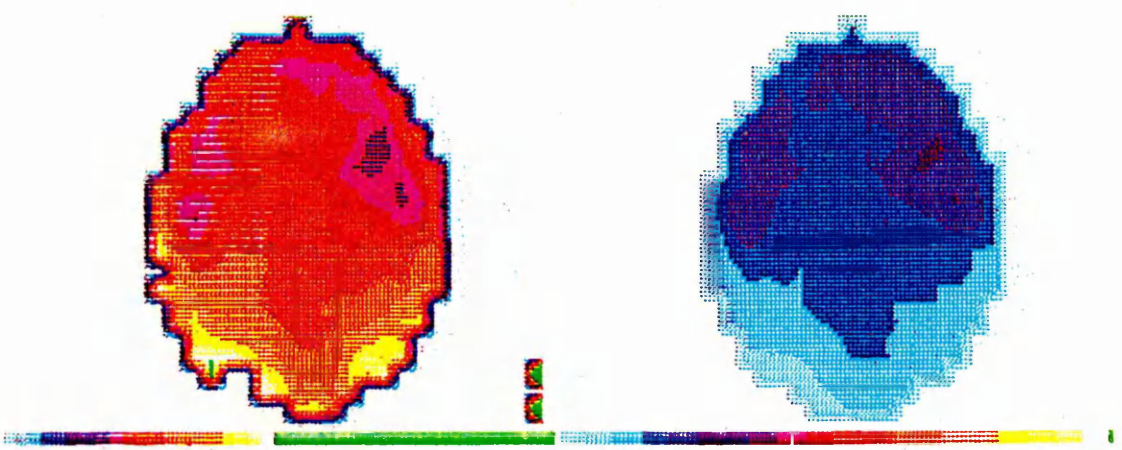
28	4.96 +- .47	24	4.60 +- .31
40	5.05 +- .71	40	4.66 +- .61
44	6.02 +- 1.09	40	5.57 +- .72
43	7.42 +- 1.29	31	7.35 +- .99

FRACTIONAL FLOW

28	.20 +- .02	24	.22 +- .01
40	.20 +- .02	40	.22 +- .03
45	.17 +- .03	40	.18 +- .02
48	.13 +- .03	31	.14 +- .02

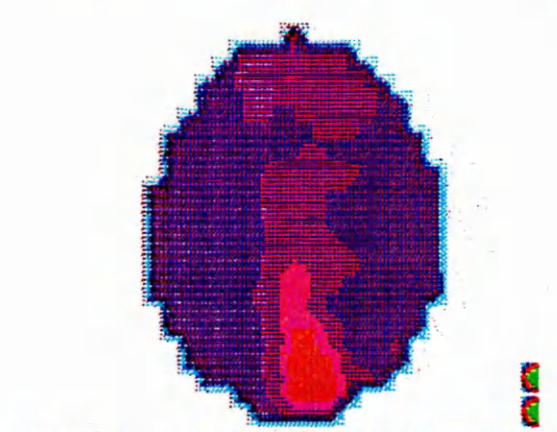
LARGE VESSEL TRANSIT TIME

28	3.65 +- .13	24	3.72 +- .11
40	3.50 +- .15	40	3.53 +- .18
45	3.55 +- .34	40	3.56 +- .20
48	3.78 +- .59	31	3.81 +- .42



L NETT TRANSIT TIME R
L 6.0 +-1.4 N=156
R 5.5 +-1.3 N=135

L FRACTIONAL FLOW R
L .17 +-.04 N=162
R .13 +-.04 N=135



L LARGE VESSEL TT R
L 3.6 +-.4 N=162
R 3.6 +-.3 N=135

INPUT FUNCTION
ARRIVAL TIME 8.3 SEC.
TRANSIT TIME 5.7 SEC.

I.D. No. 201

CORTICAL TRANSIT TIME

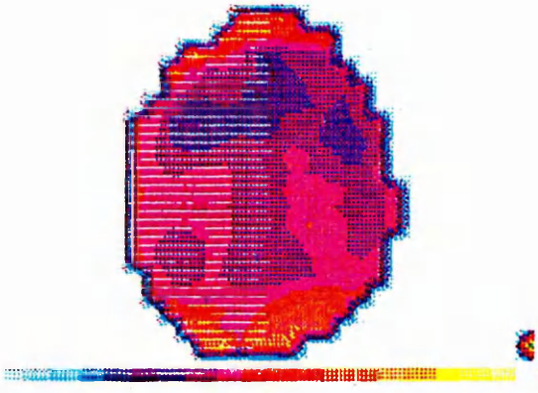
24	4.55 +- .97	19	3.93 +- .68
38	3.72 +- .46	35	3.67 +- .30
35	4.11 +- .28	43	3.96 +- .26
24	4.59 +- .84	29	4.84 +- .81

FRACTIONAL FLOW

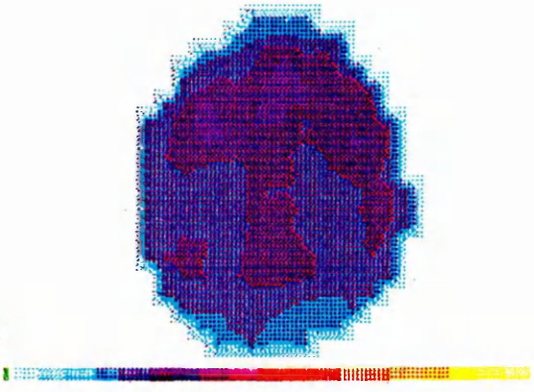
24	.23 +- .05	19	.26 +- .04
38	.27 +- .03	35	.27 +- .02
35	.24 +- .02	43	.25 +- .02
24	.22 +- .03	29	.21 +- .03

LARGE VESSEL TRANSIT TIME

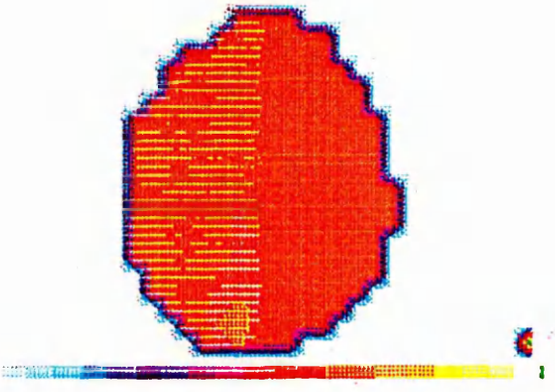
24	5.26 +- .14	19	5.38 +- .07
38	5.18 +- .08	35	5.23 +- .08
35	5.33 +- .15	43	5.37 +- .09
24	5.55 +- .43	29	5.35 +- .15



L NETT TRANSIT TIME R
L 4.2 +-.7 N=121
R 4.1 +-.7 N=126



L FRACTIONAL FLOW R
L .25 +-.04 N=121
R .25 +-.04 N=126



L LARGE VESSEL TT R
L 5.3 +-.3 N=121
R 5.3 +-.1 N=126

INPUT FUNCTION
ARRIVAL TIME 4.2 SEC.
TRANSIT TIME 5.7 SEC.

I.D. NO 204

CORTICAL TRANSIT TIME

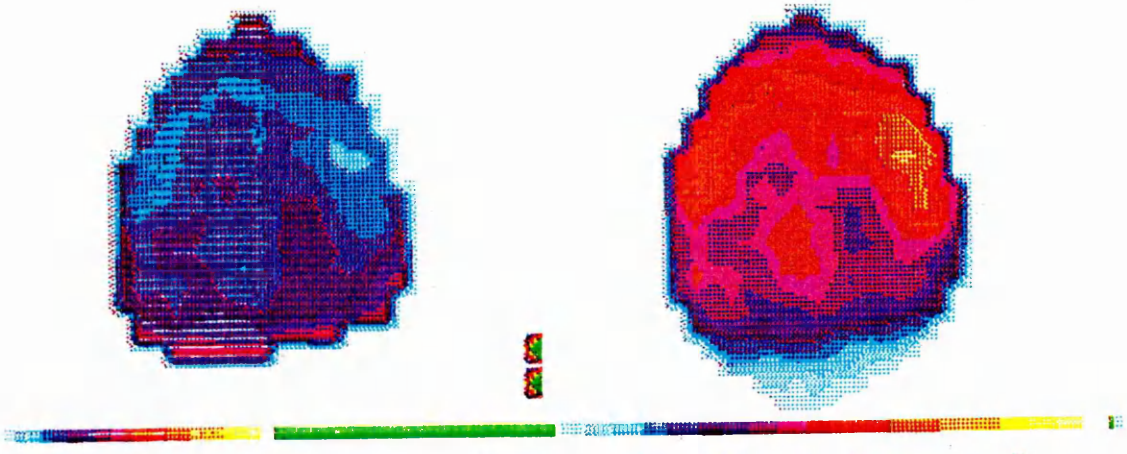
24	2.33	+- .48	15	2.42	+- .48
41	2.11	+- .19	33	1.83	+- .26
45	2.33	+- .27	40	2.42	+- .43
40	3.02	+- .67	26	3.14	+- .50

FRACTIONAL FLOW

24	.44	+- .08	15	.43	+- .07
41	.48	+- .04	33	.56	+- .08
45	.43	+- .05	40	.43	+- .08
41	.34	+- .08	33	.29	+- .08

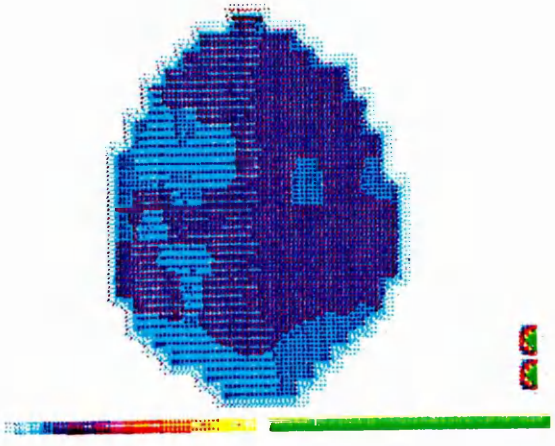
LARGE VESSEL TRANSIT TIME

24	2.28	+- .06	15	2.28	+- .05
41	2.11	+- .07	33	2.21	+- .07
45	2.21	+- .11	40	2.24	+- .09
41	2.22	+- .17	33	2.17	+- .19



L NETT TRANSIT TIME R
L 2.5 +-.6 N=150
R 2.4 +-.6 N=114

L FRACTIONAL FLOW R
L .40 +-.12 N=164
R .40 +-.15 N=129



L LARGE VESSEL TT R
L 2.2 +-.2 N=164
R 2.2 +-.2 N=130

INPUT FUNCTION
ARRIVAL TIME 4.7 SEC.
TRANSIT TIME 4.7 SEC.

I.D. No. 205

CORTICAL TRANSIT TIME

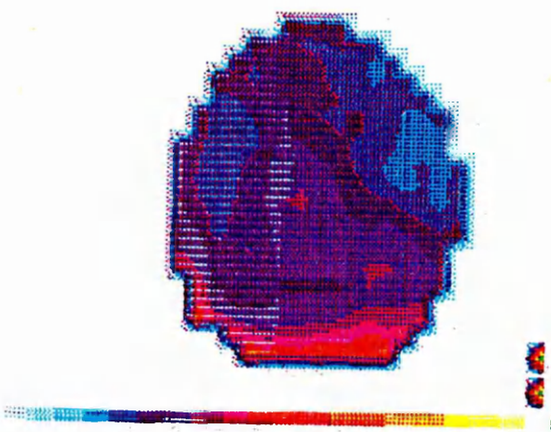
27	5.36 +- .36	20	4.53 +- .44
39	5.40 +- .82	41	4.49 +- .80
40	5.93 +- .81	43	5.92 +- .87
32	7.35 +- 1.56	31	7.54 +- 1.36

FRACTIONAL FLOW

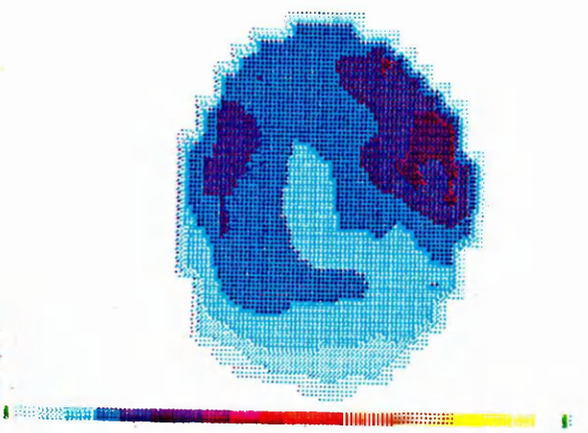
27	.19 +- .01	20	.22 +- .02
39	.19 +- .03	41	.23 +- .04
40	.17 +- .02	43	.17 +- .03
36	.13 +- .04	31	.14 +- .02

LARGE VESSEL TRANSIT TIME

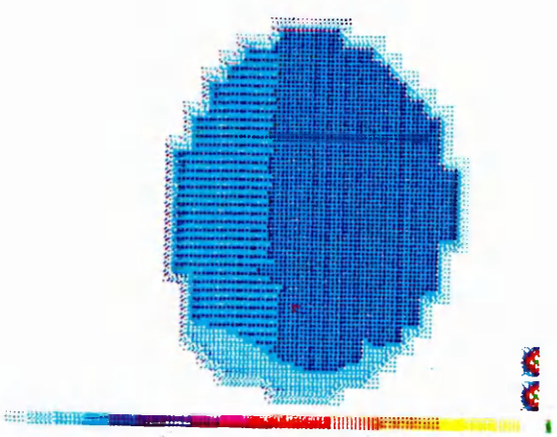
27	3.63 +- .10	20	3.64 +- .07
39	3.45 +- .12	41	3.49 +- .08
40	3.42 +- .12	43	3.42 +- .12
36	3.36 +- .31	31	3.43 +- .20



L NETT TRANSIT TIME R
L 6.0 +-1.2 N=138
R 5.7 +-1.5 N=135



L FRACTIONAL FLOW R
L .16 +-.04 N=149
R .18 +-.05 N=140



L LARGE VESSEL TT R
L 3.4 +-.2 N=150
R 3.5 +-.2 N=140

INPUT FUNCTION
ARRIVAL TIME 4.5 SEC.
TRANSIT TIME 4.5 SEC.

I.D. No 207

CORTICAL TRANSIT TIME

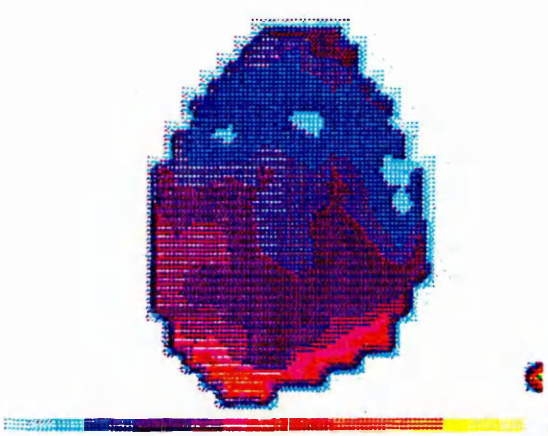
25	1.98 +- .30	17	2.24 +- .40
38	2.08 +- .47	34	1.84 +- .37
40	3.15 +- .56	40	2.48 +- .48
41	3.70 +- .77	40	3.99 +- 1.10

FRACTIONAL FLOW

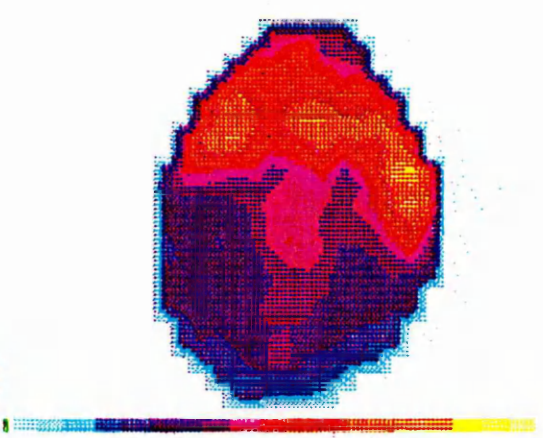
25	.52 +- .07	17	.46 +- .08
38	.50 +- .11	34	.56 +- .11
40	.33 +- .07	40	.42 +- .10
41	.28 +- .06	40	.27 +- .07

LARGE VESSEL TRANSIT TIME

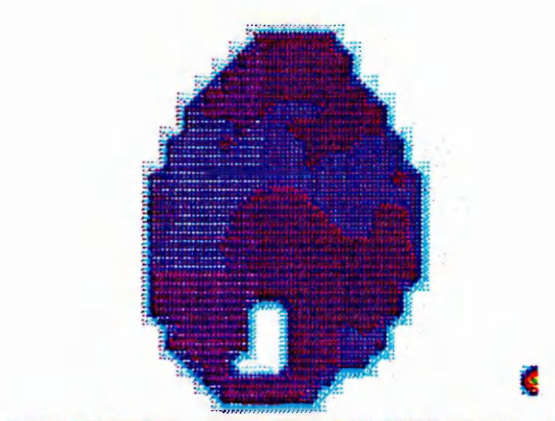
25	2.72 +- .13	17	2.70 +- .10
38	2.50 +- .07	34	2.55 +- .06
40	2.63 +- .19	40	2.67 +- .11
41	2.89 +- .35	40	2.72 +- .28



L NETT TRANSIT TIME R
L 2.8 +-.9 N=144
R 2.6 +-.9 N=126



L FRACTIONAL FLOW R
L .39 +-.13 N=144
R .42 +-.14 N=131



L LARGE VESSEL TT R
L 2.6 +-.2 N=137
R 2.6 +-.1 N=129

INPUT FUNCTION
ARRIVAL TIME 5.6 SEC.
TRANSIT TIME 5.6 SEC.

I.D. No 208

BASELINE

CORTICAL TRANSIT TIME

18	5.00 +- .98	16	4.50 +- .57
32	4.68 +- .84	28	4.64 +- .52
36	5.61 +- .86	34	5.94 +- 1.12
59	6.39 +- .93	54	7.33 +- 1.11

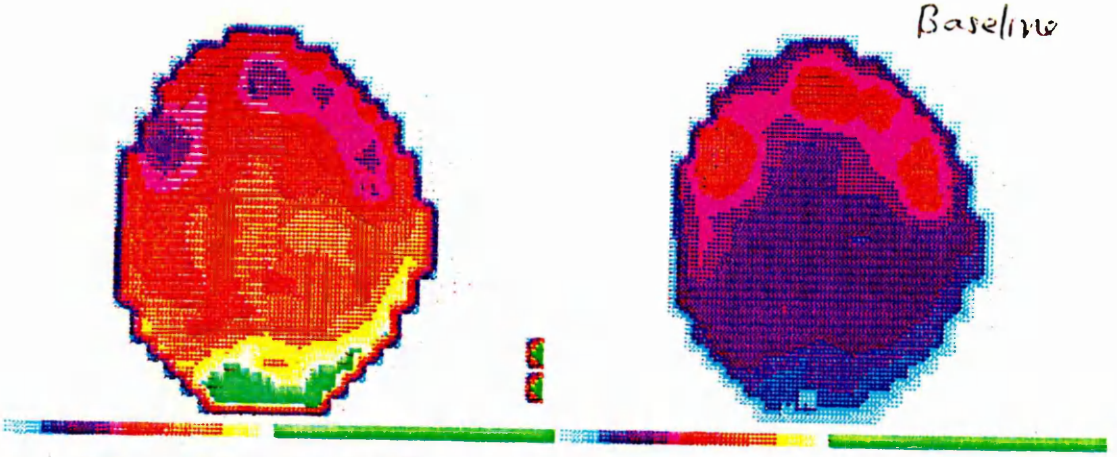
FRACTIONAL FLOW

18	.21 +- .04	16	.22 +- .03
32	.22 +- .04	28	.22 +- .02
36	.18 +- .03	34	.17 +- .04
59	.16 +- .02	54	.14 +- .02

LARGE VESSEL TRANSIT TIME

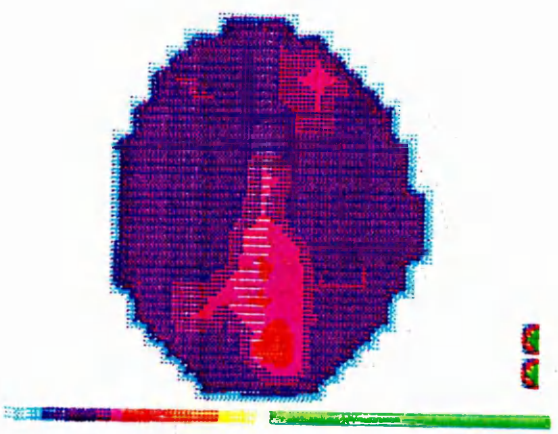
18	3.52 +- .07	16	3.76 +- .28
32	3.48 +- .08	28	3.57 +- .21
36	3.52 +- .26	34	3.38 +- .22
59	3.77 +- .45	54	3.68 +- .48

Baseline



L NETT TRANSIT TIME R
L 5.9 +-1.4 N=155
R 6.2 +-1.6 N=137

L FRACTIONAL FLOW R
L .18 +-.05 N=162
R .17 +-.05 N=142



L LARGE VESSEL TT R
L 3.6 +-.3 N=161
R 3.6 +-.4 N=141

INPUT FUNCTION
ARRIVAL TIME 5.0 SEC.
TRANSIT TIME 5.3 SEC.

I.D. NO. 208

DURING MIGRAINE

CORTICAL TRANSIT TIME

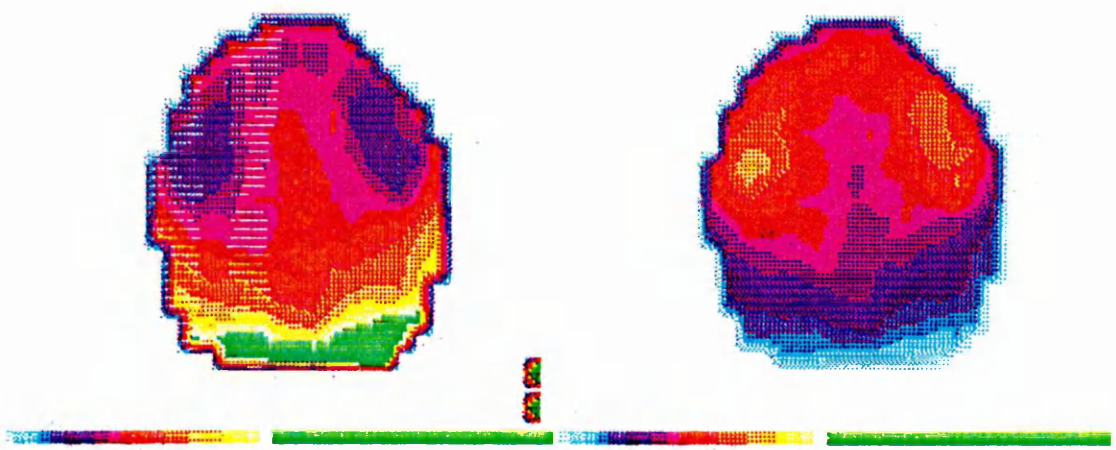
19	4.21 +- .45	16	4.09 +- .34
30	3.82 +- .61	29	3.77 +- .61
36	4.01 +- .68	32	4.46 +- .82
52	5.86 +- 1.17	41	7.12 +- 1.70

FRACTIONAL FLOW

19	.24 +- .03	16	.25 +- .02
30	.27 +- .04	29	.27 +- .04
36	.26 +- .05	32	.23 +- .04
52	.18 +- .03	41	.15 +- .03

LARGE VESSEL TRANSIT TIME

19	4.25 +- .15	16	4.37 +- .27
30	4.11 +- .17	29	4.09 +- .20
36	3.95 +- .17	32	3.96 +- .15
52	4.08 +- .30	41	4.10 +- .18



L MEAN TRANSIT TIME R

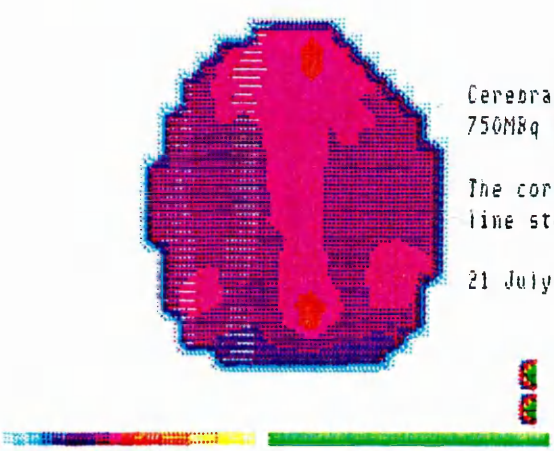
L 4.5 +-1.1 N=131

R 4.6 +-1.1 N=101

L FRACTIONAL FLOW R

L .22 +-.06 N=144

R .20 +-.07 N=134



L LARGE VESSEL TT R

L 4.0 +-.2 N=142

R 4.0 +-.3 N=132

Cerebral Scintigraphy
750MBq 99mTc Pertechnetate

The cortical transit times are longer in the base line study than during a migraine.

21 July 1987 M.V. MERRICK

INPUT FUNCTION
ARRIVAL TIME 7.9 SEC.
TRANSIT TIME 6.4 SEC.

I.D. No. 209

CORTICAL TRANSIT TIME

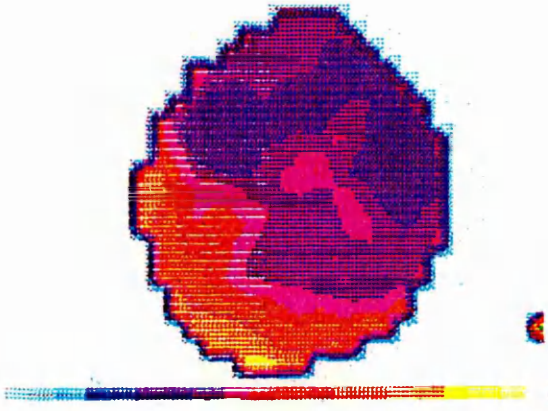
25	3.71 +- .30	20	3.38 +- .28
46	3.66 +- .80	37	3.31 +- .46
48	4.57 +- .78	39	3.73 +- .30
39	5.61 +- 1.38	30	4.62 +- .94

FRACTIONAL FLOW

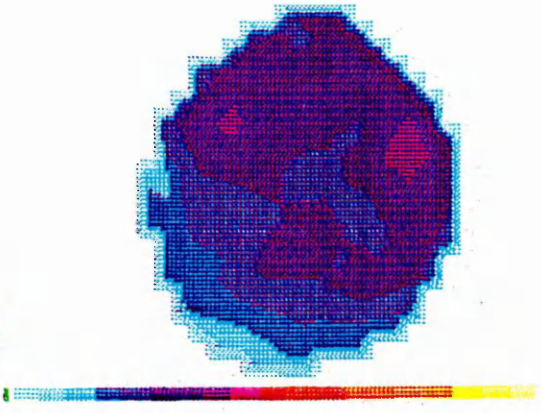
25	.27 +- .02	20	.30 +- .02
46	.28 +- .05	37	.31 +- .04
48	.22 +- .03	39	.27 +- .02
39	.19 +- .04	30	.22 +- .04

LARGE VESSEL TRANSIT TIME

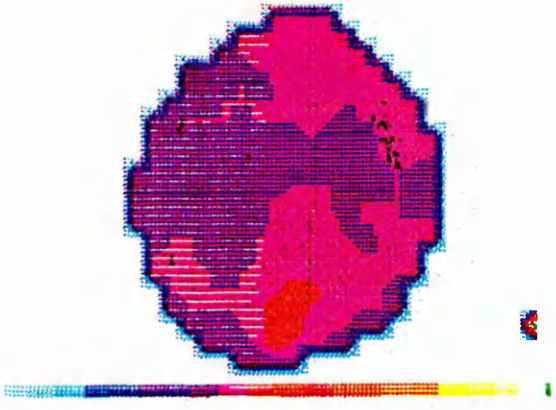
25	4.06 +- .10	20	4.23 +- .07
46	3.93 +- .11	37	4.05 +- .08
48	3.98 +- .15	39	4.07 +- .10
39	4.17 +- .36	30	4.18 +- .26



L NETT TRANSIT TIME R
L 4.1 +-1.2 N=158
R 3.8 +-.8 N=126



L FRACTIONAL FLOW R
L .24 +-.06 N=158
R .27 +-.05 N=126



L LARGE VESSEL TT R
L 4.0 +-.2 N=158
R 4.1 +-.2 N=126

INPUT FUNCTION
ARRIVAL TIME 4.2 SEC.
TRANSIT TIME 4.0 SEC.

I.D. No 210

CORTICAL TRANSIT TIME

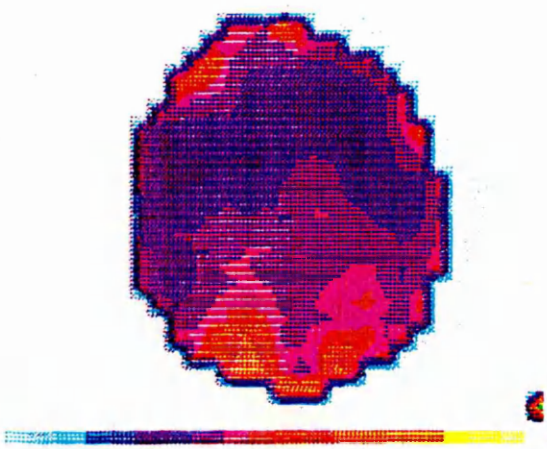
24	4.10	+- .70	27	3.62	+- .85
44	3.08	+- .35	40	3.39	+- .54
45	3.50	+- .32	45	3.66	+- .30
48	4.50	+- .96	37	4.43	+- .72

FRACTIONAL FLOW

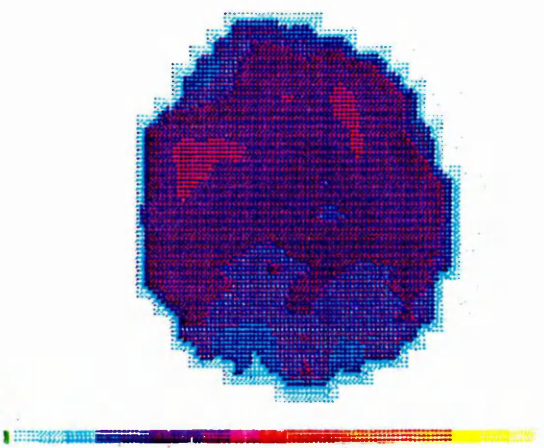
24	.25	+- .04	27	.29	+- .06
44	.33	+- .04	40	.30	+- .04
45	.29	+- .03	45	.27	+- .02
48	.23	+- .04	37	.23	+- .03

LARGE VESSEL TRANSIT TIME

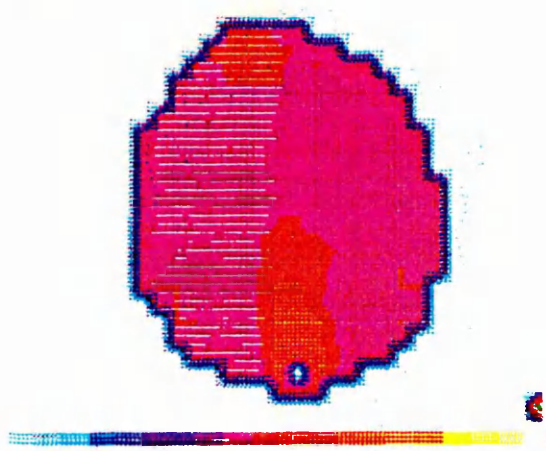
24	4.54	+- .16	27	4.43	+- .09
44	4.29	+- .06	40	4.23	+- .09
45	4.38	+- .14	45	4.42	+- .14
47	4.67	+- .42	37	4.60	+- .36



L METT TRANSIT TIME R
L 3.8 +-.9 N=161
R 3.8 +-.7 N=149



L FRACTIONAL FLOW R
L .28 +-.05 N=161
R .27 +-.05 N=149



L LARGE VESSEL TT R
L 4.5 +-.3 N=160
R 4.4 +-.2 N=149

INPUT FUNCTION
ARRIVAL TIME 3.6 SEC.
TRANSIT TIME 4.3 SEC.

I.D. No. 211

BASELINE

CORTICAL TRANSIT TIME

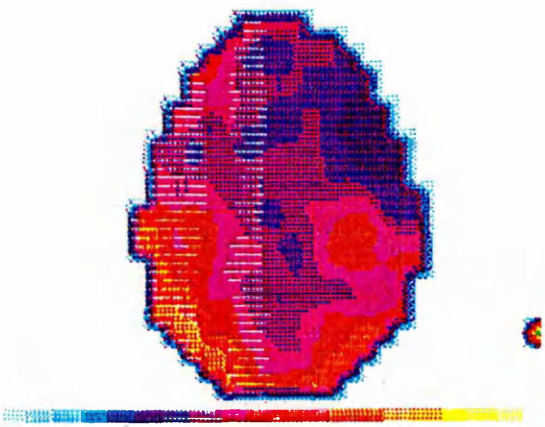
21	4.01 +- .51	21	3.38 +- .28
35	3.75 +- .28	36	3.17 +- .37
42	4.29 +- .56	41	4.07 +- .53
46	4.92 +- 1.01	39	4.51 +- .60

FRACTIONAL FLOW

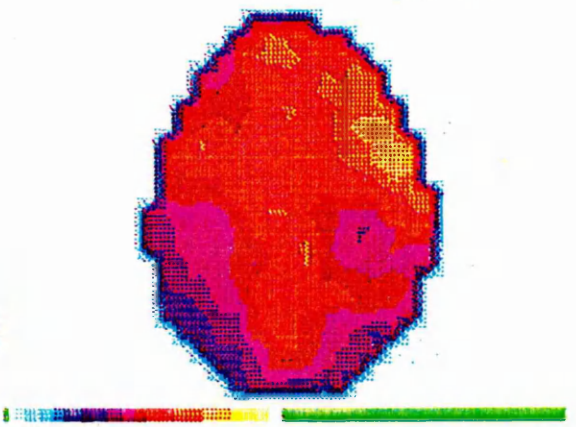
21	.25 +- .04	21	.30 +- .02
35	.27 +- .02	36	.32 +- .04
42	.24 +- .03	41	.25 +- .03
46	.21 +- .04	39	.22 +- .03

LARGE VESSEL TRANSIT TIME

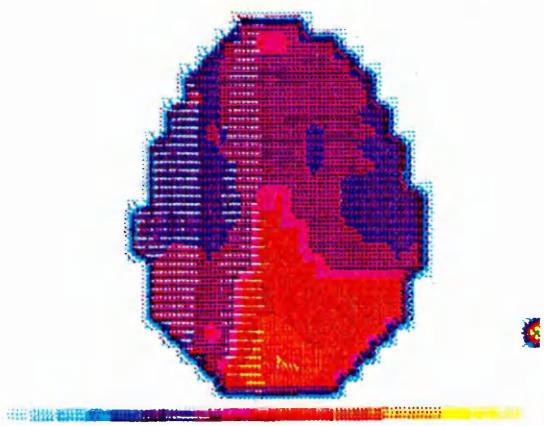
21	3.71 +- .23	21	3.74 +- .18
35	3.56 +- .17	36	3.59 +- .10
42	3.73 +- .52	41	3.74 +- .37
46	4.40 +- .74	39	4.87 +- .28



L NETT TRANSIT TIME R
L 4.2 +-.7 N=137
R 3.9 +-.7 N=137



L FRACTIONAL FLOW R
L .24 +-.04 N=144
R .27 +-.05 N=137



L LARGE VESSEL TT R
L 3.3 +-.6 N=142
R 4.0 +-.6 N=136

INPUT FUNCTION
ARRIVAL TIME 8.0 SEC.
TRANSIT TIME 8.4 SEC.

I. D. No 211

DURING MIGRAINE

CORTICAL TRANSIT TIME

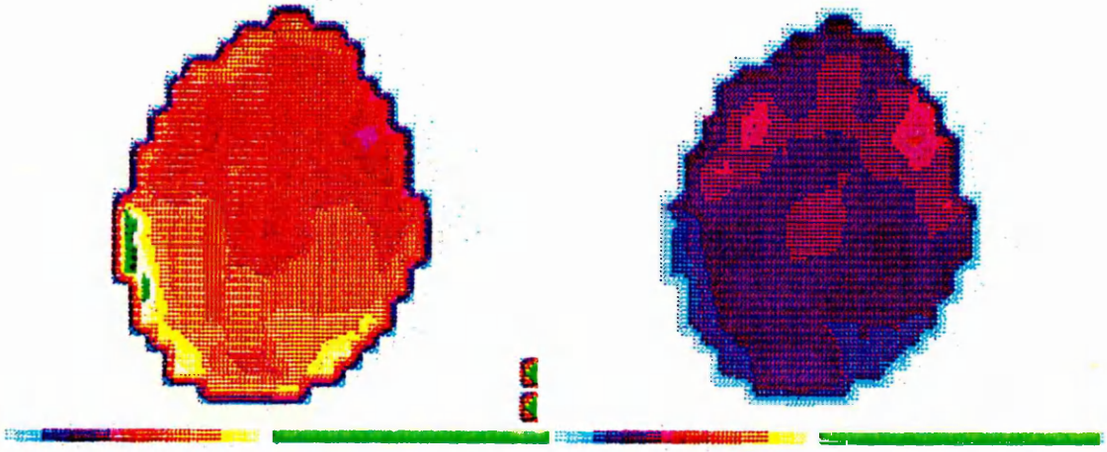
23	6.30 +- .78	15	5.69 +- .58
41	5.48 +- .56	33	5.12 +- .41
46	6.54 +- 1.69	42	5.85 +- .53
56	7.23 +- 1.33	47	7.22 +- .82

FRACTIONAL FLOW

23	.16 +- .02	15	.18 +- .02
41	.18 +- .02	33	.20 +- .02
46	.16 +- .03	42	.17 +- .02
56	.14 +- .02	47	.14 +- .02

LARGE VESSEL TRANSIT TIME

23	4.95 +- .12	15	4.97 +- .08
41	4.79 +- .14	33	4.89 +- .09
46	4.76 +- .28	42	4.87 +- .18
56	5.24 +- .61	47	5.15 +- .27



L METT TRANSIT TIME R

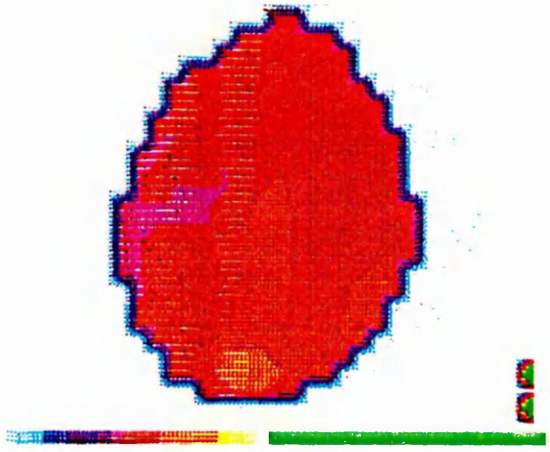
L 6.1 +-.8 N=149

R 6.0 +-.9 N=132

L FRACTIONAL FLOW R

L .16 +-.03 N=166

R .17 +-.03 N=137



L LARGE VESSEL TT R

L 4.9 +-.3 N=158

R 5.0 +-.2 N=136

INPUT FUNCTION

ARRIVAL TIME 6.0 SEC.

TRANSIT TIME 6.4 SEC.

I.D. No. 212

CORTICAL TRANSIT TIME

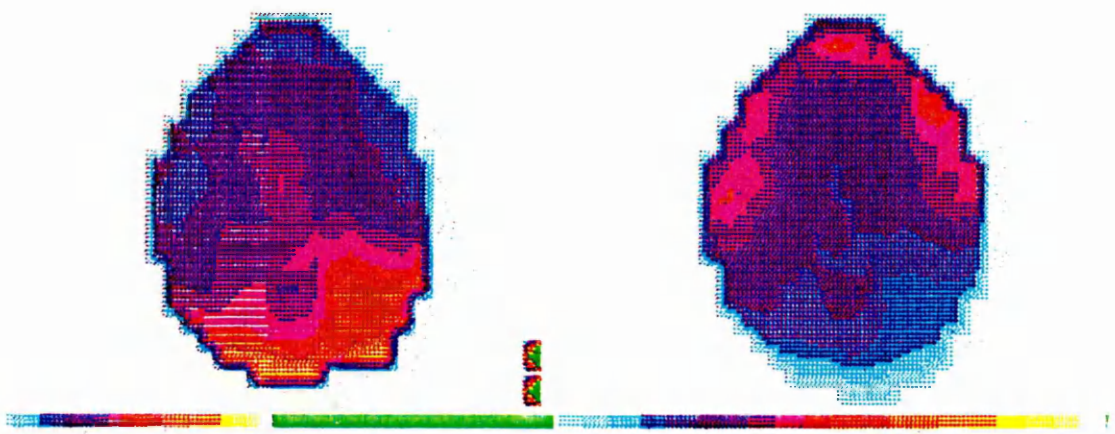
20	2.68 +- .26	20	2.58 +- .30
36	2.99 +- .54	37	2.85 +- .47
39	3.25 +- .55	40	3.74 +- .63
40	4.70 +- 1.31	27	5.38 +- .89

FRACTIONAL FLOW

20	.38 +- .04	20	.39 +- .05
36	.35 +- .06	37	.36 +- .06
39	.32 +- .06	40	.28 +- .05
41	.22 +- .05	30	.18 +- .04

LARGE VESSEL TRANSIT TIME

20	5.74 +- .22	20	5.86 +- .14
36	5.35 +- .23	37	5.47 +- .27
39	5.36 +- .36	40	5.68 +- .31
41	5.54 +- .60	30	5.84 +- .44



L NETT TRANSIT TIME R

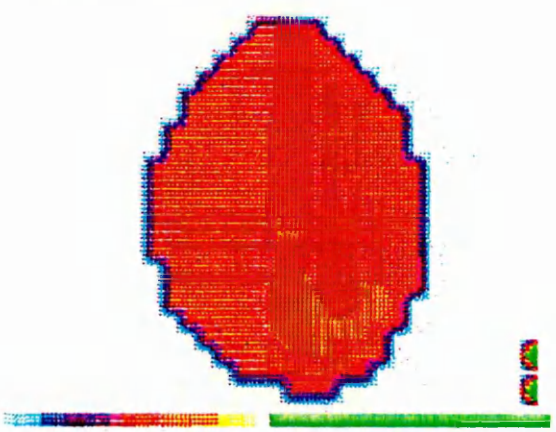
L 3.5 +-1.1 N=135

R 3.6 +-1.2 N=124

L FRACTIONAL FLOW R

L .30 +-.08 N=138

R .29 +-.09 N=128



L LARGE VESSEL TT R

L 5.5 +-.4 N=138

R 5.7 +-.4 N=128

INPUT FUNCTION

ARRIVAL TIME 5.1 SEC.

TRANSIT TIME 5.4 SEC.

I.D. NO. 213

CORTICAL TRANSIT TIME

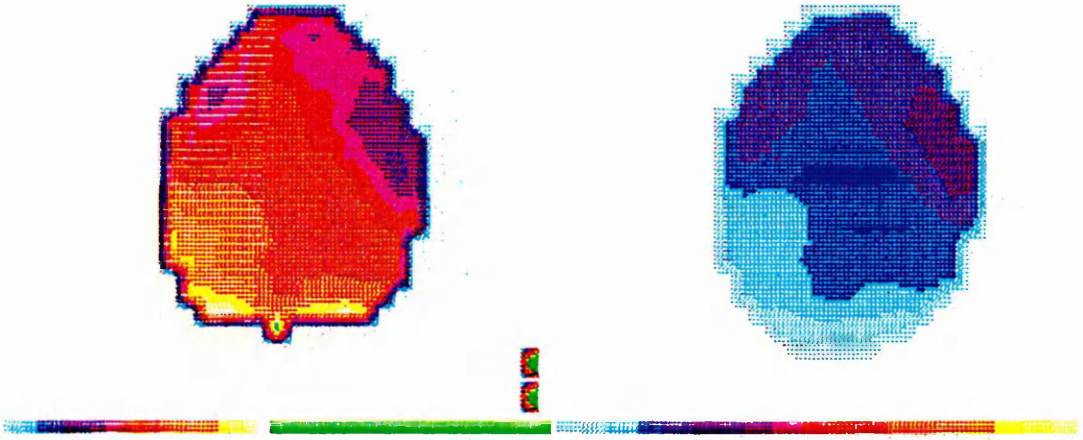
18	4.68 +- .28	14	4.20 +- .18
30	4.79 +- .45	24	4.12 +- .47
28	5.79 +- .70	32	4.71 +- .76
38	7.12 +- 1.01	40	6.10 +- 1.09

FRACTIONAL FLOW

18	.21 +- .01	14	.24 +- .01
30	.21 +- .02	24	.25 +- .03
28	.17 +- .02	32	.22 +- .04
38	.14 +- .02	40	.17 +- .02

LARGE VESSEL TRANSIT TIME

18	5.40 +- .09	14	5.47 +- .06
30	5.26 +- .09	24	5.34 +- .09
28	5.35 +- .14	32	5.25 +- .13
38	5.66 +- .33	40	5.42 +- .37



L NETT TRANSIT TIME R

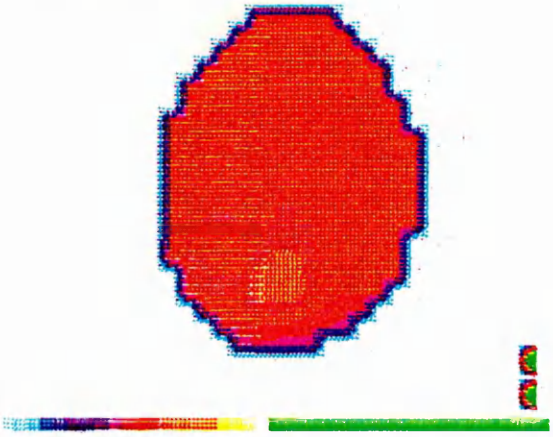
L 5.8 +-1.3 N=115

R 5.8 +-1.2 N=110

L FRACTIONAL FLOW R

L .17 +-.04 N=121

R .20 +-.05 N=116



L LARGE VESSEL TT R

L 5.4 +-.3 N=121

R 5.3 +-.3 N=116

INPUT FUNCTION

ARRIVAL TIME 6.9 SEC.

TRANSIT TIME 5.3 SEC.

I.D.No 215

CORTICAL TRANSIT TIME

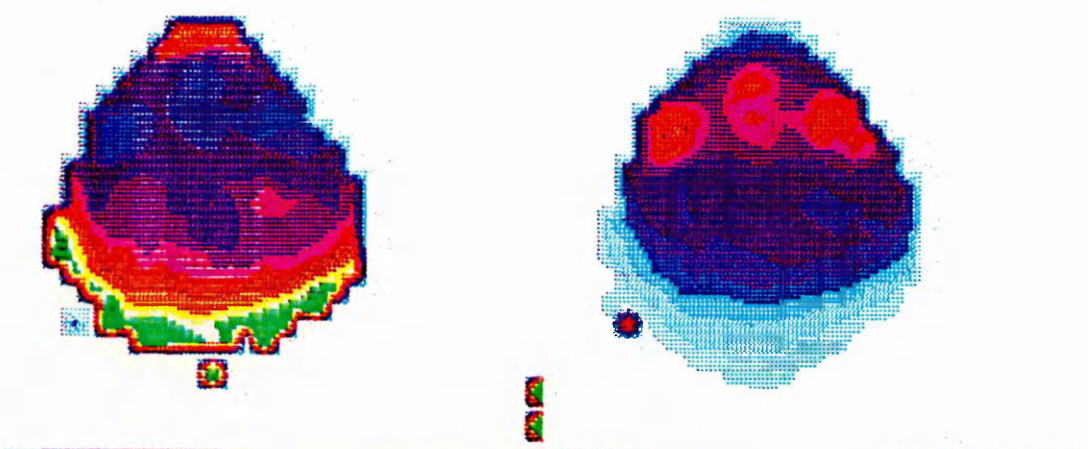
14	3.94 +- 1.67	14	3.76 +- 1.49
27	2.34 +- .38	27	2.33 +- .33
33	3.75 +- 1.12	35	3.56 +- .42
52	7.58 +- 3.78	48	7.05 +- 4.26

FRACTIONAL FLOW

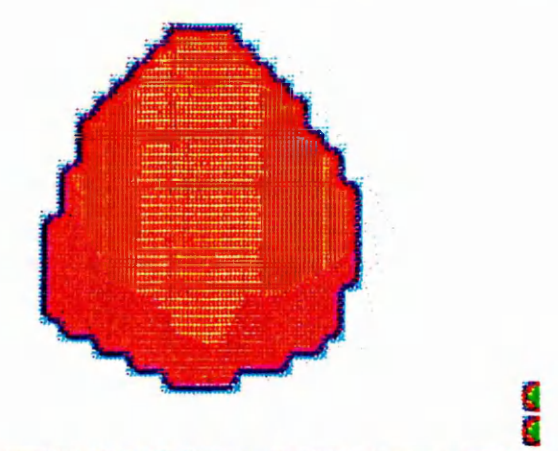
14	.30 +- .12	14	.30 +- .10
27	.44 +- .08	27	.44 +- .06
33	.28 +- .05	35	.28 +- .03
58	.16 +- .10	52	.17 +- .08

LARGE VESSEL TRANSIT TIME

14	6.47 +- .12	14	6.51 +- .09
27	6.37 +- .10	27	6.35 +- .07
33	6.24 +- .15	35	6.40 +- .10
61	6.08 +- .27	56	6.14 +- .28



L	NETT TRANSIT TIME	R	L	FRACTIONAL FLOW	R
L	5.2 +-3.6 N=127		L	.25 +-.15 N=140	
R	4.7 +-3.3 N=124		R	.26 +-.13 N=132	



L	LARGE VESSEL TT	R
L	6.2 +-.3 N=143	
R	6.3 +-.2 N=137	

INPUT FUNCTION
ARRIVAL TIME 3.0 SEC.
TRANSIT TIME 6.0 SEC.

I.D. No. 218

CORTICAL TRANSIT TIME

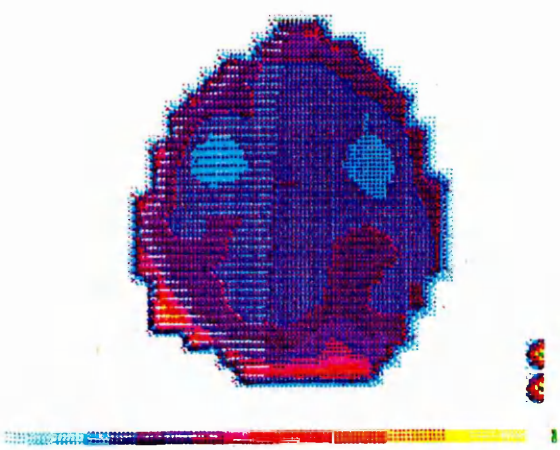
23	5.64 +- 1.04	19	5.59 +- .98
43	4.76 +- .94	35	4.47 +- .64
50	5.17 +- .88	40	4.88 +- .42
37	6.56 +- 2.02	41	6.15 +- 1.48

FRACTIONAL FLOW

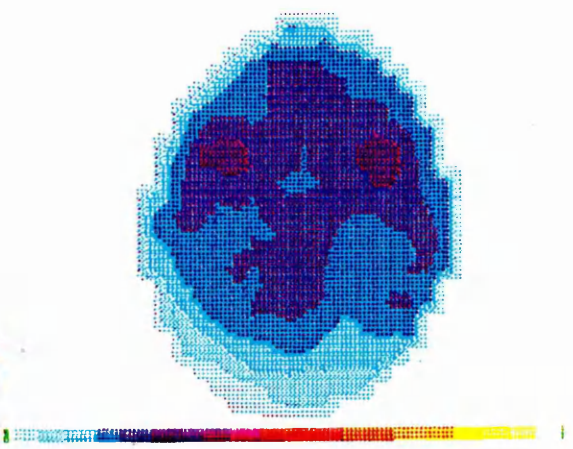
24	.18 +- .04	19	.18 +- .03
43	.22 +- .04	35	.23 +- .03
50	.20 +- .03	40	.21 +- .02
44	.15 +- .05	41	.17 +- .03

LARGE VESSEL TRANSIT TIME

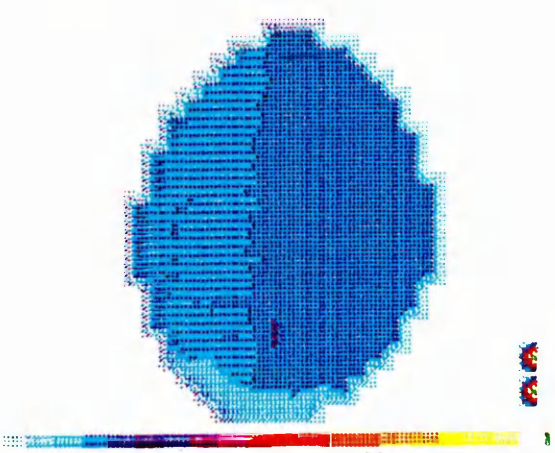
24	3.75 +- .20	19	3.74 +- .09
43	3.65 +- .12	35	3.63 +- .07
50	3.67 +- .15	40	3.63 +- .09
44	3.58 +- .32	41	3.71 +- .20



L NETT TRANSIT TIME R
L 5.5 +-1.4 N=153
R 5.3 +-1.2 N=135



L FRACTIONAL FLOW R
L .18 +-.06 N=170
R .19 +-.04 N=141



L LARGE VESSEL TT R
L 3.6 +-.3 N=170
R 3.6 +-.2 N=141

INPUT FUNCTION
ARRIVAL TIME 6.2 SEC.
TRANSIT TIME 6.2 SEC.

I.D. No 220

BASELINE

CORTICAL TRANSIT TIME

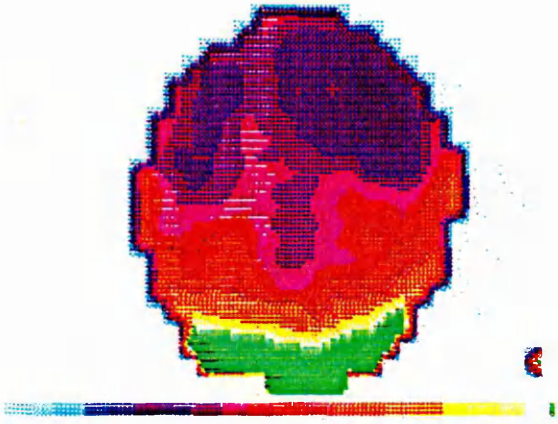
18	3.20 +- .34	15	2.83 +- .21
34	3.35 +- .42	30	2.75 +- .48
39	3.75 +- .52	35	4.01 +- 1.12
63	5.39 +- 1.51	50	5.84 +- 2.23

FRACTIONAL FLOW

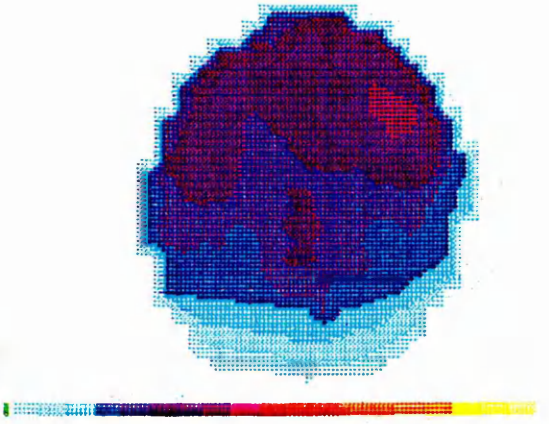
18	.32 +- .04	15	.35 +- .03
34	.30 +- .04	30	.37 +- .07
39	.27 +- .04	35	.26 +- .06
63	.20 +- .05	50	.19 +- .05

LARGE VESSEL TRANSIT TIME

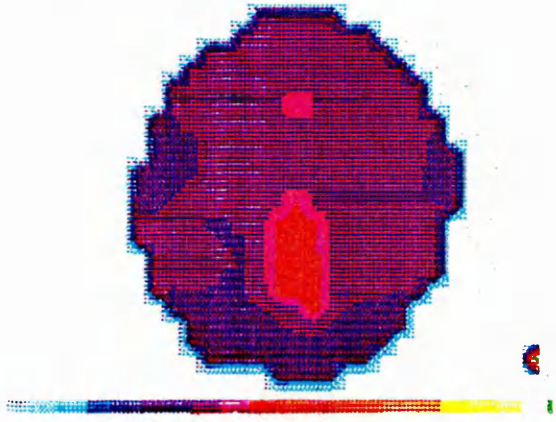
18	1.94 +- .26	15	1.96 +- .28
34	1.68 +- .32	30	1.78 +- .27
39	1.52 +- .32	35	1.53 +- .23
63	1.56 +- .42	50	1.64 +- .40



L NETT TRANSIT TIME R
L 4.2 +-.8 N=142
R 4.1 +-1.0 N=119



L FRACTIONAL FLOW R
L .22 +-.08 N=174
R .23 +-.08 N=141



L LARGE VESSEL TT R
L 3.7 +-.4 N=174
R 3.8 +-.4 N=141

INPUT FUNCTION
ARRIVAL TIME 5.0 SEC. Estimated.
TRANSIT TIME 6.4 SEC.

I.D. No. 220

GRAINE

CORTICAL TRANSIT TIME

19	4.03	+-	.28	17	3.51	+-	.21
32	4.06	+-	.47	29	3.88	+-	.54
37	5.33	+-	1.02	28	4.84	+-	.58
35	7.09	+-	2.76	25	6.76	+-	1.24

16	2.14	+-	.34
32	2.37	+-	.48
34	3.25	+-	.66
34	5.67	+-	1.65

FRACTIONAL FLOW

19	.25	+-	.02	17	.29	+-	.02
32	.25	+-	.03	29	.26	+-	.03
37	.19	+-	.03	28	.21	+-	.03
35	.16	+-	.05	25	.15	+-	.03

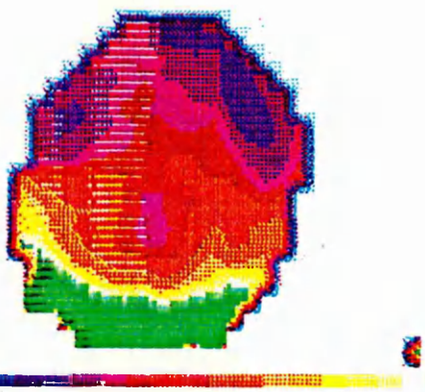
16	.48	+-	.07
32	.44	+-	.09
34	.32	+-	.07
41	.17	+-	.06

LARGE VESSEL TRANSIT TIME

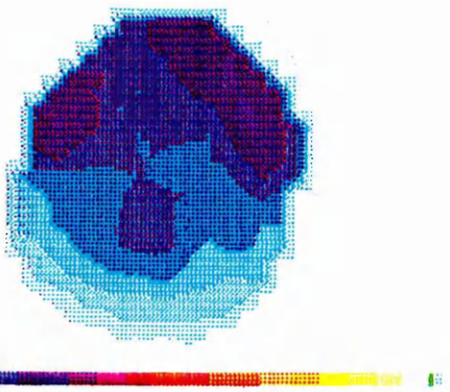
19	3.95	+-	.32	17	4.32	+-	.30
32	3.77	+-	.33	29	4.02	+-	.34
37	3.78	+-	.50	28	4.02	+-	.37
35	3.65	+-	.59	25	4.12	+-	.47

IME

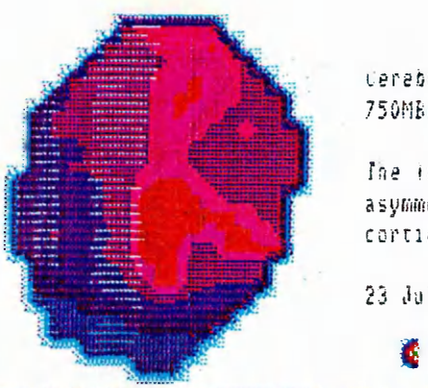
16	4.88	+-	.27
32	4.55	+-	.22
34	4.54	+-	.31
41	4.32	+-	.39



L NETT TRANSIT TIME R
L 5.0 +-1.2 N=117
R 4.7 +-1.3 N=97



L FRACTIONAL FLOW R
L .19 +-.07 N=142
R .21 +-.07 N=111



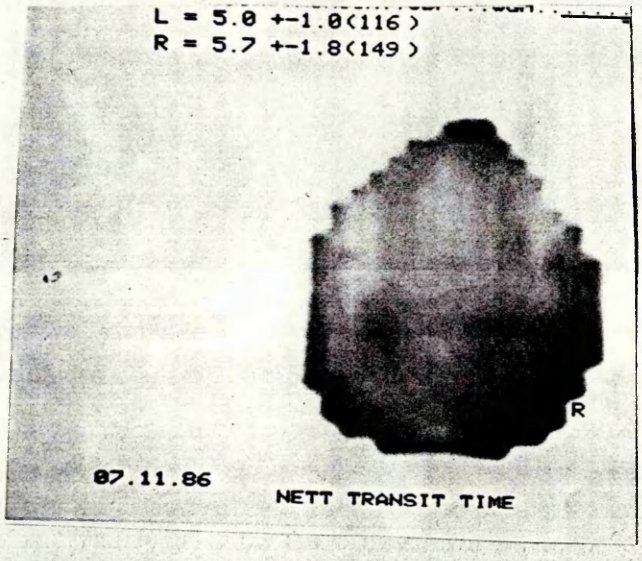
L LARGE VESSEL TT R
L 3.5 +-.6 N=152
R 3.9 +-.6 N=114

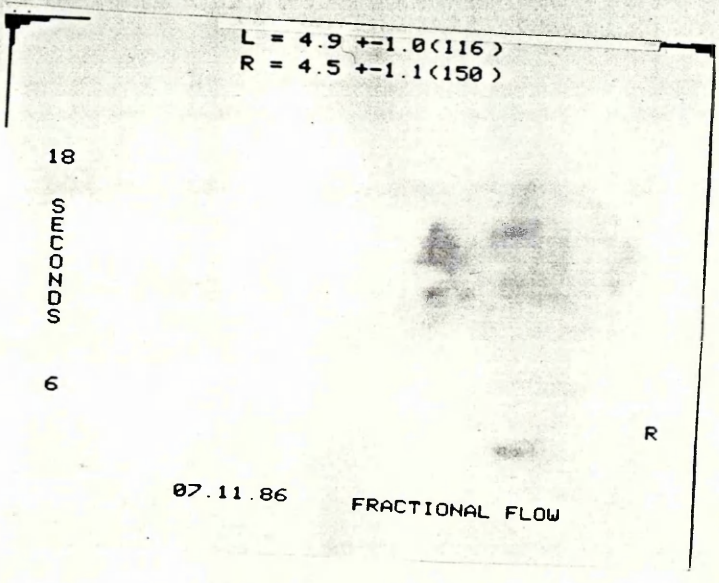
Cerebral Scintigraphy
750MBq 99mTc Pertechnetate

The large vessel transit time has become more asymmetrical than in the base line study but the cortical transit times are unchanged.

23 July 1987 M.V. MERRICK

INPUT FUNCTION
ARRIVAL TIME 7.9 SEC.
TRANSIT TIME 5.8 SEC.


L = 5.0 +-1.0(116)
R = 5.7 +-1.8(149)
R
07.11.86
NETT TRANSIT TIME


L = 4.9 +-1.0(116)
R = 4.5 +-1.1(150)
18
SECONDS
6
R
07.11.86
FRACTIONAL FLOW

I.D.No 22

L = 2.9 +-.7 (114)
R = 2.9 +-.9 (109)

R

18.02.87 FRACTIONAL FLOW

L = 2.3 +-.6 (114)
R = 2.3 +-.7 (109)

R

18.02.87 f(F)

L = 3.7 +-1.0(114)
R = 3.6 +-1.0(106)

R

18.02.87 NETT MEAN TRANSIT TIME

Cerebral Scintigraphy
750MBq 99mTc Pertechnetate

There is no evidence of abnormal perfusion or abnormal permeability.

19 Feb 1987 A. NOTGHI

I.D. No. 224

CORTICAL TRANSIT TIME

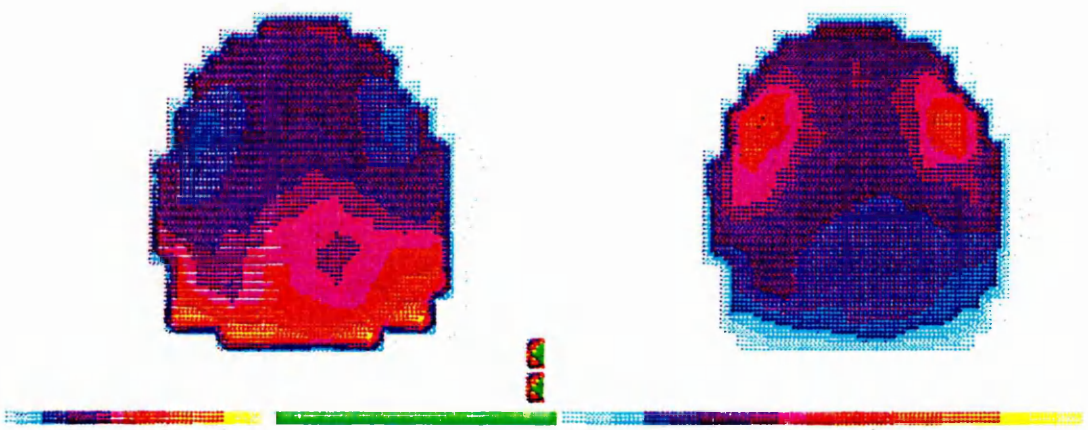
21	3.02 +- .24	16	3.11 +- .45
31	2.55 +- .46	28	2.55 +- .45
36	3.03 +- .51	32	3.33 +- .51
56	4.65 +- 1.11	49	4.83 +- 1.02

FRACTIONAL FLOW

21	.33 +- .03	16	.33 +- .05
31	.40 +- .08	28	.40 +- .08
36	.34 +- .06	32	.31 +- .05
58	.22 +- .05	51	.21 +- .04

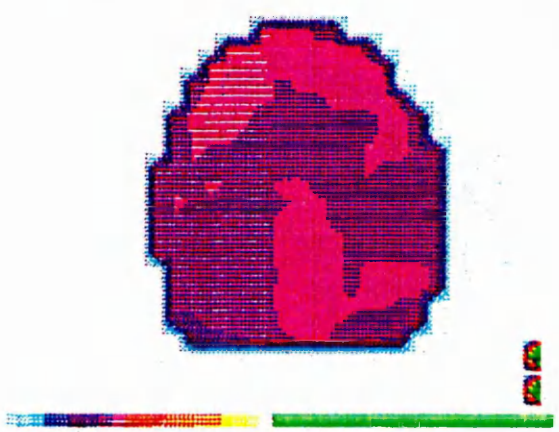
LARGE VESSEL TRANSIT TIME

21	4.18 +- .07	16	4.16 +- .06
31	4.10 +- .08	28	4.09 +- .07
36	4.06 +- .08	32	4.03 +- .06
58	3.97 +- .23	51	4.07 +- .15



L NETT TRANSIT TIME R
L 3.6 +-1.2 N=144
R 3.7 +-1.2 N=125

L FRACTIONAL FLOW R
L .31 +-.09 N=146
R .29 +-.09 N=127



L LARGE VESSEL TT R
L 4.0 +-.2 N=146
R 4.1 +-.1 N=127

INPUT FUNCTION
ARRIVAL TIME 4.8 SEC.
TRANSIT TIME 3.9 SEC.

I.D. NO 225

BASELINE

CORTICAL TRANSIT TIME

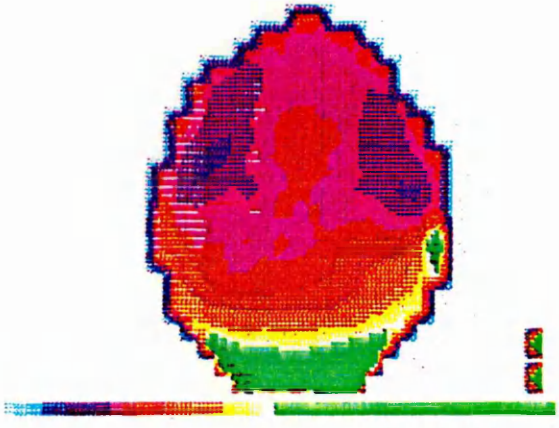
17	4.35 +- .38	10	4.47 +- .36
30	4.17 +- .48	25	4.20 +- .40
33	4.11 +- .48	34	4.10 +- .44
53	5.42 +- 1.14	57	6.36 +- 2.10

FRACTIONAL FLOW

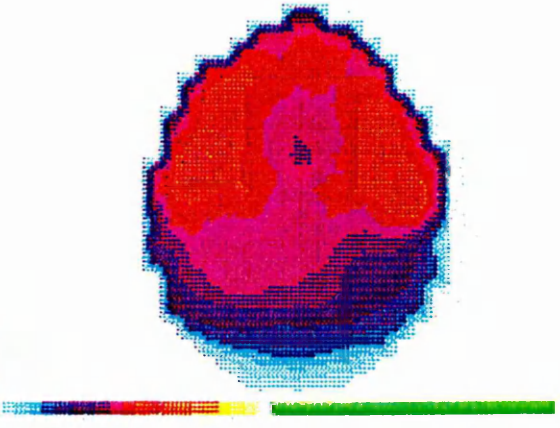
17	.23 +- .02	10	.22 +- .02
30	.24 +- .03	25	.24 +- .02
33	.25 +- .03	34	.25 +- .03
53	.19 +- .03	57	.17 +- .04

LARGE VESSEL TRANSIT TIME

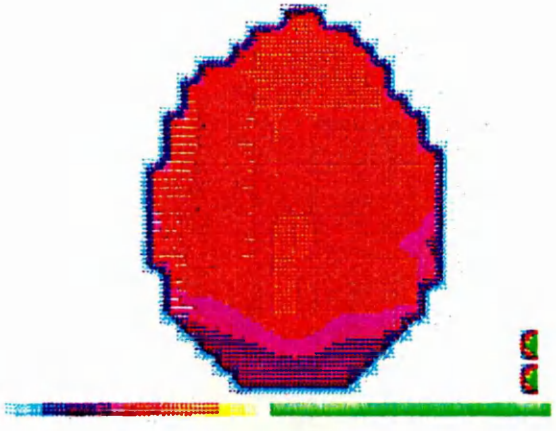
17	5.36 +- .37	10	5.41 +- .35
30	4.99 +- .25	25	5.06 +- .21
33	4.85 +- .11	34	4.89 +- .12
53	4.75 +- .27	57	4.74 +- .30



L NETT TRANSIT TIME R
L 4.5 +-.8 N=127
R 4.6 +-.8 N=110



L FRACTIONAL FLOW R
L .20 +-.06 N=150
R .20 +-.06 N=136



L LARGE VESSEL TT R
L 4.8 +-.4 N=150
R 4.8 +-.4 N=136

INPUT FUNCTION
ARRIVAL TIME 4.2 SEC.
TRANSIT TIME 4.4 SEC.

I.D. No 225

DURING MIGRAINE

CORTICAL TRANSIT TIME

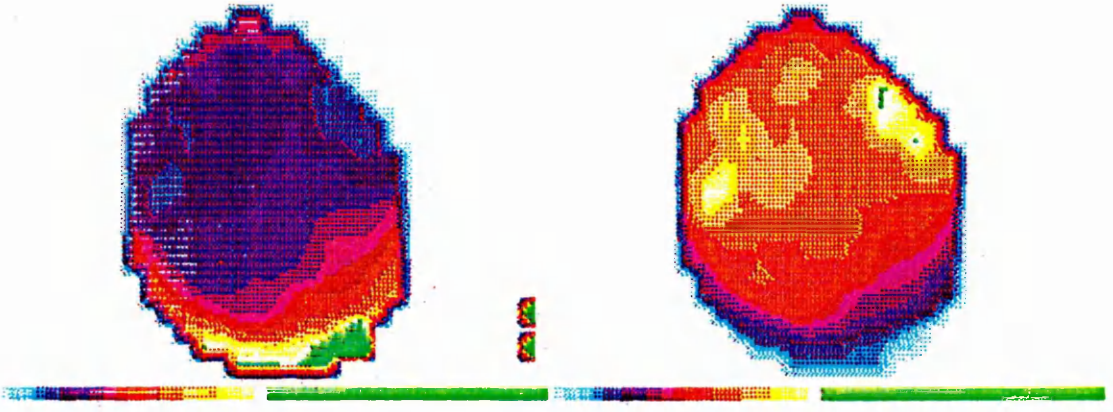
17	3.48 +- .59	9	3.30 +- .32
30	2.86 +- .24	25	2.57 +- .36
33	2.74 +- .28	31	3.15 +- .34
56	4.02 +- 1.14	46	5.18 +- 1.94

FRACTIONAL FLOW

17	.30 +- .05	9	.31 +- .03
30	.35 +- .03	25	.40 +- .06
33	.37 +- .04	31	.32 +- .03
56	.26 +- .06	46	.21 +- .06

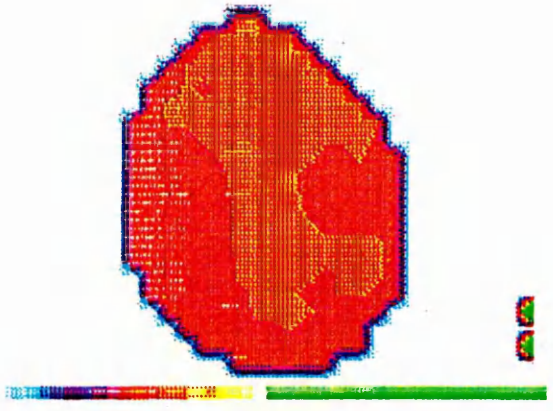
LARGE VESSEL TRANSIT TIME

17	6.17 +- .14	9	6.17 +- .06
30	6.10 +- .14	25	6.17 +- .07
33	6.01 +- .17	31	6.01 +- .13
56	5.91 +- .25	46	6.04 +- .18



L NETT TRANSIT TIME R
L 3.2 +-.7 N=130
R 3.4 +-.6 N=98

L FRACTIONAL FLOW R
L .30 +-.08 N=146
R .28 +-.10 N=117



L LARGE VESSEL TT R
L 6.0 +-.3 N=146
R 6.0 +-.2 N=117

INPUT FUNCTION
ARRIVAL TIME 4.8 SEC.
TRANSIT TIME 5.9 SEC.

APPENDIX XII

Abbreviated Case Summaries

Pilot study group

(101) This 40 year old, married, music teacher has a 10 year history of common migraine. Her headaches are bilateral and usually associated with irritability. She has had outpatient psychiatric treatment twice - (i) an episode of major depression following the death of her father when she was 19 for which she had 3-6 months of antidepressant therapy, (ii) an anxiety state treated with minor tranquillisers over a two year period 20 years later. She meets DSM-III criteria for panic disorder without phobic avoidance and has a sister who has panic attacks for which she been treated by a psychologist.

(106) This 59 year old, married, retired teacher has a 35 year history of common migraine which is usually associated with euphoria. The headaches are unilateral and affect the dominant hemisphere. Both her mother and her son also have migraine. An aunt, who has recurrent depression, has received treatment in a psychiatric hospital. Her own previous psychiatric history is of postnatal depression following the birth of a premature baby. This was treated by her GP without medication. She describes a feeling of wellbeing which occurs regularly 1-2 days prior to migraine attacks. At these times she is much more confident and active than usual.

(107) A 45 year old, single, agricultural advisory worker with a 36 year history of classical migraine. The unilateral headache usually affects the non-dominant hemisphere and rarely the dominant hemisphere. She

muddles words when speaking and also has occasional visual disturbance. The migraines are usually accompanied by feeling withdrawn, slightly anxious and irritable. This lasts approximately 24 hours. There is no personal or family history of psychiatric illness.

(111) This 43 year old, single, teacher has a 20 year history of classical migraine preceded by a visual aura. She says she also has a feeling of euphoria for up to 24 hours prior to attacks. The euphoria consists of feeling more self confident and talkative than usual and finding that her thoughts are speeded up. This has only begun in the last 1-2 years. She has a four year history of DSM-III major depression and one of her sisters also has a history of depressive illness. She also complains of perceptual distortion during migraines when her head and neck feel swollen although they look the same in the mirror.

New referrals.

Affective group (on the basis of self report at initial interview)

(102) A 44 year old, married, cashier with a 20 year history of unilateral classical migraine affecting the dominant hemisphere. She complains of euphoria and irritability on the day before a migraine attack. Her aura preceding the headache consists of sensory loss ipsilateral to the headache, scotoma and dizziness. She feels her head and neck are internally "blown out" but not enlarged in size and also had an unpleasant taste in her mouth during migraines. The euphoria prior to attacks consists of feeling more talkative, racing thoughts, distractibility and poor concentration. The euphoria has only been present for the last six years. She has had cyclothymic disorder over the same

period. Her previous psychiatric history consists of treatment with minor tranquillisers over a seven year period during her first marriage. Her husband had a serious alcohol problem.

(103) A 41 year old, married, dress shop owner with a ten year history of unilateral common migraine affecting the non-dominant hemisphere. Her migraine is always accompanied by irritability and frustration with herself for having a headache. She has seen a psychiatrist as an outpatient because of postnatal depression. At present she meets DSM-III criteria for major depression. This started four years ago after moving to Australia with her husband. At that time she felt isolated and cut off from her family. The depression has not resolved since her return to Scotland. There are marital difficulties and she feels angry with her husband for not discussing major decisions with her before making choices which affect both of them. Her husband's job in the stockmarket also causes financial insecurity for the family.

(104) This 25 year old housewife has a 15 year history of classical migraine with an aura consisting of right-sided paresis and speech disturbance. She complains of irritability which is always associated with her headaches. She meets diagnostic criteria for cyclothymic disorder and says this has been present since she was 14. However she also had a major depressive illness over a two year period following a move abroad because of her husband's job. During that episode she was charged with assaulting a neighbour and placed on six months probation. She finds her husband generally unsympathetic and unsupportive.

(105) A 34 year old, married, housewife with unilateral classical migraine involving the non dominant hemisphere. The aura consists of ipsilateral paresis and sensory loss and slurred speech. She complains of depression and anxiety lasting approximately 48 hours in association with migraines. These symptoms would meet DSM-III criteria for depression except for their brevity. She had a past episode of major depression at the age of 21 following a friend's suicide and was treated with antidepressants by her GP for a year. She has olfactory hallucinations (she smells oranges) during her migraine attacks.

(108) A 29 year old, married, housewife with unilateral classical migraine affecting the dominant hemisphere. The aura consists of ipsilateral paresis and sensory loss and speech disturbance. She says her migraines are always accompanied by irritability. She meets DSM-III criteria for bipolar illness. This started with a depressive episode when she was 18 after she broke off an engagement. She had her first hypomanic episode at the age of 25. Her most severe episode of depression occurred between 1977-79 when abroad because of her husband's job. This was accompanied by alcohol abuse which led to alcohol dependence.

(109) This 51 year old, married, housewife has a 25 year history of common migraine and says she always has a brief episode of euphoria after the headache is over. Her father had psychiatric outpatient treatment for depression and she was treated by her GP for postnatal depression for two years. Her husband had chronic osteomyelitis and was in hospital during most of this pregnancy. She has had dysthymic disorder since adolescence. Her migraine are accompanied by unpleasant olfactory and

gustatory hallucinations.

(110) This 44 year old, married, computer operator has a 10 year history of unilateral common migraine affecting the non-dominant hemisphere. She says depression and irritability always accompany migraine attacks. These symptoms would meet DSM-III criteria for major depression in all respects except duration. She had a major depressive illness at the age of 32 following the break-up of her first marriage. She is sufficiently worried that her headaches might be connected with a CVA or a tumour to justify a diagnosis of hypochondriasis. However the hypochondriacal fears are understandable in view of the increase in the frequency and severity of her migraines over the last few months and the failure of medication to control them. She was reassured to some extent by referral to the clinic and physical examination. During migraines her head feels larger than usual and she smells gas. (She has, in fact, repeatedly called out the Gas Board to investigate this with negative results. She had not recognised the connection with her migraine until the interview.)

(112) A 53 year old, married, housewife with a 17 year history of unilateral classical migraine affecting the non-dominant hemisphere. The migraines are always associated with irritability and a feeling that life is not worth living. This lasts 24-48 hours. She herself had no current or past psychiatric illness but her mother died of a CVA in a psychiatric hospital after having ECT for depression.

(113) This 51 year old, married, cleaner has a 16 year history of unilateral common migraine affecting the non-dominant hemisphere. She usually notices increased irritability (she shouts more at others) and

activity during the few hours before a migraine attack. There are no current or past psychiatric diagnoses.

(114) A 22 year old, married, housewife with a six year history of classical migraine. She has an aura of paresis and speech disturbance. She says that she always experiences depression and irritability with her migraines. She has had two episodes of major depression:-
(i) in 1981 when she was treated with antidepressant medication just after joining the RAF.
(ii) after the birth of her first child. She felt let down by her husband and they were separated for five of the nine months during which this illness was present.
She has olfactory hallucinations of an unpleasant smell in association with her migraine.

(115) A 51 year old, separated, teacher with a five year history of unilateral classical migraine affecting the non-dominant hemisphere. Attacks are associated with ipsilateral sensory loss and by visual disturbance. She complains of depression which always accompanies her migraines and lasts approximately 48 hours. She also meets diagnostic criteria for longstanding dysthymic disorder. One of her daughters was treated for suicidal ideas and agoraphobia at age 16 - this would seem most likely to have been a depressive illness.

(116) This 37 year old, married, housewife has a 1-2 year history of classical migraine. Her aura is made up of paresis, sensory loss and disturbance of speech and vision. She complains of always experiencing depression and irritability along with her migraines. She had outpatient

psychiatric contact five years ago because of depression. She feared losing her baby due to back problems and had had a miscarriage shortly before this pregnancy. She also had an episode of major depression lasting four weeks in 1983 following a move to a new home. She is currently suffering from major depression with melancholia and has hypochondriacal fears that her headaches might be caused by a brain tumour. Her husband has just lost his job and the family were intending to move to Crewe to be closer to his mother when she died two days before the removal took place. She and the family are now staying with her mother and have no clear plans for the future.

(117) A 57 year old, unmarried, clerical officer with a 15 year history of common migraine. Her episodes of migraine are always accompanied by depression. The depression consists of feeling 'fed up', poor sleep, restlessness and yet also feeling tired and poor concentration. It lasts approximately 72 hours. This lady meets criteria for the dysthymic syndrome at present.

(118) This 22 year old, unmarried, teacher has a six month history of unilateral classical migraine affecting the non-dominant hemisphere. The aura consists of contralateral hemiparesis and the attacks are always associated with depression, anxiety and irritability. She meets DSM-III criteria for major depression at present. This depressive episode seems to have been precipitated by a recent termination of pregnancy. The pregnancy resulted from an affair with a married man and she was angry that he was not more supportive towards her.

(119) A 61 year old, married, retired teacher with a 44 year history of unilateral classical migraine affecting the dominant hemisphere. The aura prior to the migraine is primarily visual (scotomata). She complains of brief episodes of euphoria prior to migraines. She also has a 16 year history of obsessive compulsive disorder and a 4-5 year history of generalised anxiety disorder. She denies any major life stresses at the moment.

(120) This 22 year old, single, surveyor has a one year history of unilateral classical migraine which usually affects the dominant hemisphere. The aura consists of speech disturbance and impairment of vision. She complains of usually experiencing depression prior to migraine. She has current generalised anxiety disorder and relates this to the stress involved in doing her final exams and dissertation at college and starting work in what is still a very male-orientated profession. She has olfactory hallucinations of an unpleasant smell during migraine attacks.

(121) This 42 year old, married, secretary has a two year history of classical migraine. There is disturbance of vision prior to attacks. She usually experiences depression and irritability associated with migraines. She meets the criteria for the dysthymic syndrome. This has been present for approximately two years and dates back to an episode of sciatica. Following this illness she was forced to reduce her physical activities and thus lost many of her interests. The sciatica coincided with her teenage children reaching the stage where she no longer felt that they needed her and her marriage is no longer offering her support. She feels she is taken for granted by her husband and children.

Non-affective Group

(201) A 20 year old, single, auxiliary nurse with a seven year history of common migraine. There is no personal or family psychiatric history and she denies ever experiencing mood change as part of her migraine other than a feeling of wanting to be left alone when she is unwell.

(202) This 20 year old, unmarried, student teacher has a four year history of unilateral classical migraine affecting the non-dominant hemisphere. She has a visual aura prior to attacks (she loses her right field of vision). There is no personal or family psychiatric history. Her main stresses are college exams and going out on teaching practice as part of her course.

(203) A 44 year old, married, housewife with a 26 year history of unilateral classical migraine affecting the dominant hemisphere. The aura consists of ipsilateral sensory loss and speech disturbance. She sometimes experiences depression prior to, and following, migraines. Prior to attacks she is 'not with it', unable to concentrate and overactive. Following the migraine she is sometimes tearful.

(204) This 46 year old, married, teacher has a 16 year history of unilateral common migraine affecting the dominant hemisphere. This is accompanied by contralateral sensory loss. She has been treated for major depression with panic attacks since 1975 and has been on antidepressants almost continuously since then. She has had two exacerbations of her illness in response to stress at school. She is

currently depressed, possibly partly due to the death of her aunt a month ago. She has numerous life stresses to contend with - her neighbour is noisy and she has quarrelled with him. Unfortunately this neighbour is also a colleague at work and this has made her professional life difficult. Her husband's elderly relatives require a lot of attention and her son, who has Down's syndrome, can be obstinate.

(205) A 25 year old, single, secretary with a 12 year history of unilateral common migraine which can affect either hemisphere. There is paresis and speech disturbance as part of attacks. She has no complaints of mood change related to her headaches. She had one session with a psychologist as an outpatient for relaxation training to help her cope with her distress after her mother was involved in a road traffic accident. She became very overdependent on her boyfriend at that time and has remained so since. She has cyclothymic disorder which has been present since adolescence.

(206) This 41 year old, divorced, cashier has a 16 year history of common migraine. She has no complaints of mood change. She feels her migraine is always triggered by emotional stress. She has had difficulty obtaining maintenance payments for herself and her two children since her divorce and six months ago her eleven year old son left to stay with his father. He had run away on two occasions before he left for good. She has been worrying about having a CVA since her boss's wife (who also has migraine) had a stroke a few months ago.

(207) A 42 year old, married, cleaner with a 10 year history of unilateral classical migraine affecting the dominant hemisphere. The

aura prior to her headaches includes ipsilateral paresis and sensory loss and disturbance of speech and vision. She sometimes has euphoria for a few hours prior to the headache. (She feels 'happy and bubbly' and without a care in the world.) She feels her migraine is always triggered by emotional stress. She had one past episode of major depression which was precipitated by the strain of her husband being off work for nine months due to a depressive illness. He has now completely recovered. She meets the criteria for generalised anxiety disorder at present. This began eight months ago when her son was made redundant.

(208) This 42 year old, single, office worker has a 20 year history of unilateral common migraine. She does not have specific mood changes related to her migraines. She has had two past episodes of major depression six years and eight months ago. There was no obvious precipitating cause for either episode. There is no family history of psychiatric illness.

(209) A 40 year old, married, clerical worker with a seven year history of bilateral classical migraine. Her aura consists of paraesthesiae which can affect either side of the body, difficulty in 'getting the words out' and disturbed vision. She has no complaints of mood change accompanying her migraines. However she has a six year history of depression and has been on antidepressant medication continuously throughout this period of time. There is no family history of psychiatric illness.

(210) This 49 year old, married, nurse has a 30 year history of common migraine. She has no complaints of mood change associated with her

headaches. There is no personal or family history of psychiatric illness.

(211) A 54 year old, married, retired teacher with a 38 year history of unilateral classical migraine affecting the dominant hemisphere. Her aura is of flashing lights. She has no complaints of mood change related to her migraine. There is no personal or family history of psychiatric illness. She has just taken early retirement because she felt under pressure at work and she also looks after her mother who has senile dementia.

(212) A 40 year old, married, lecturer with a 17 year history of unilateral classical migraine usually affecting the dominant hemisphere. She has no complaints of mood change related to her migraine. She meets DSM-III criteria for current generalised anxiety disorder. She cannot date the onset of this condition and describes it as being lifelong. She also had an illness 13 years ago, while working abroad, which was probably anorexia nervosa. Her sister has been treated by her GP for this condition.

(213) This 48 year old, married, catering assistant has a two year history of unilateral classical migraine affecting the dominant hemisphere. She has no complaints of mood change related to her headaches but is just recovering from an episode of depression and is still on antidepressant medication. There is a strong family history of depressive illness in her father and two of her sisters. Her own depressive illness was precipitated by the suicide of one of these sisters two years ago.

(214) A 27 year old, unmarried, secretary with an 11 year history of unilateral migraine affecting the dominant hemisphere. She has no complaints of mood change related to her migraine and there is no personal or family history of psychiatric illness.

(215) A 39 year old, married, telephonist with a 26 year history of unilateral classical migraine affecting the non-dominant hemisphere. Her aura consists of disturbance of speech and vision. She has no complaints of mood change related to her migraine attacks. There is no personal or family history of psychiatric illness.

(216) This 24 year old, married, teacher has a seven month history of unilateral classical migraine which can affect either hemisphere. She is sometimes irritable and short-tempered prior to migraine attacks. She was in bed with 'nerves' till two days before her wedding last July and then shortly afterwards she had what she described as a viral illness which caused her to take two months off work. This illness meets DSM-III criteria for major depression although she is extremely unwilling to consider a psychological explanation for her symptoms.

(217) This 39 year old, divorced, housewife has a ten year history of unilateral common migraine affecting the non-dominant hemisphere. She has a visual aura with attacks. She says she sometimes feels depressed and irritable in association with her migraines. She has a past history of a parasuicide attempt five years ago when her husband was having extramarital affairs. She meets DSM-III criteria for major depression which has been present for the past two weeks. Her main worry is her difficult relationship with her teenage daughter who still lives at home

with her.

(218) A 42 year old, married, sales assistant with a 17 year history of bilateral classical migraine. Her aura involves disturbance of speech and vision. She does not report mood change in association with her migraine. However she does meet DSM-III criteria for generalised anxiety disorder which she says has been present for the last five years. Her mother has had a 'nervous breakdown' i.e. she has been treated for agoraphobia, low mood and feeling unable to cope. She also has a sister who has been treated with antidepressants because of postnatal depression. At present she is worried about her daughter, who has given up a good job for no apparent reason, and about her father who has prostate problems.

(219) This 47 year old, divorced, lecturer has a 25 year history of unilateral common migraine which can affect either hemisphere. She has no complaints of mood change related to her migraines. She saw a psychiatrist as an outpatient prior to the break up of her marriage and was treated with tranquillisers and antidepressants. The marriage was a very unhappy one. After the divorce she did an Open University degree and a postgraduate diploma while bringing up her daughter. She describes herself as having to struggle with low self esteem and a poor self image during this time. She has now been successful academically and has a responsible job. Her daughter has graduated from university and left home. This leaves her feeling lonely and 'emotionally empty'.

(220) A 33 year old, separated, assistant bank manageress with a seven year history of unilateral classical migraine affecting the dominant

hemisphere. She sometimes experiences depression when she has a migraine (i.e. she feels that her mood is labile and that she is generally slowed down). She also meets DSM-III criteria for generalised anxiety disorder which has been present for 4-5 years and had a discrete episode of major depression following the break up of her marriage three years ago. She has difficulty getting on with her male colleagues at work and finds them chauvinistic in their attitude towards her.

(221) A 28 year old, divorced, shop assistant with six year history of unilateral common migraine affecting the non dominant hemisphere. Attacks are accompanied by a general feeling of weakness and dizziness. She sometimes experiences depression, anxiety and irritability in association with her headaches. She meets DSM-III criteria for both major depression and alcohol dependence - both of which have been present for the last two years. It was impossible to tell from the history which was the primary phenomenon. There is a family history of psychiatric illness.

(222) This 28 year old, divorced, secretary has a two year history of common migraine which can be both bi- and unilateral. She has no complaints of mood change in association with her headaches. She was brought up by her mother till the age of nine. Her mother then spent a year in and out of hospital before dying of cancer. She then stayed with her older brother and his new wife and baby and always felt she was unwelcome. She broke up her marriage quite abruptly after her husband confessed to a brief affair. She could not cope with the breach of trust involved even though her husband was penitent and anxious for the marriage to continue. She came to the clinic with the expectation that

she would be found to have something seriously wrong with her although, interestingly enough, she was not unduly concerned about her migraine. When Dr Price mentioned that she had a benign heart murmur these expectations were confirmed and she went on to develop obsessional ruminations about her health which her GP, Dr Price, and her family could not remove.

(223) A 32 year old, married, housewife with a nine year history of unilateral common migraine affecting the dominant hemisphere. She has no complaints of mood change associated with her migraines. She has no psychiatric history but her mother has seen a psychiatrist as an outpatient because of depression. Her only current stresses relate to her husband who is working hard to establish his own business at the same time as doing a part-time university degree. As a consequence she has recently had to give up her job as a primary school teacher to take on more responsibility for the welfare of their two young children.

(224) This 20 year old, unmarried, factory worker has a three year history of common migraine which can be bilateral or unilateral. There is no family or personal history of psychiatric illness. She had a very unhappy childhood - her father frequently physically assaulted her mother while intoxicated and they often separated. Her father would then follow the family round the country until he had persuaded his wife to take him back. Her mother died when she was 14 and her father when she was 16. She is now engaged and her migraines started after rows with her fiance's mother with whom she was staying. She and her fiance now have no contact with their families and are dependent solely on each other.

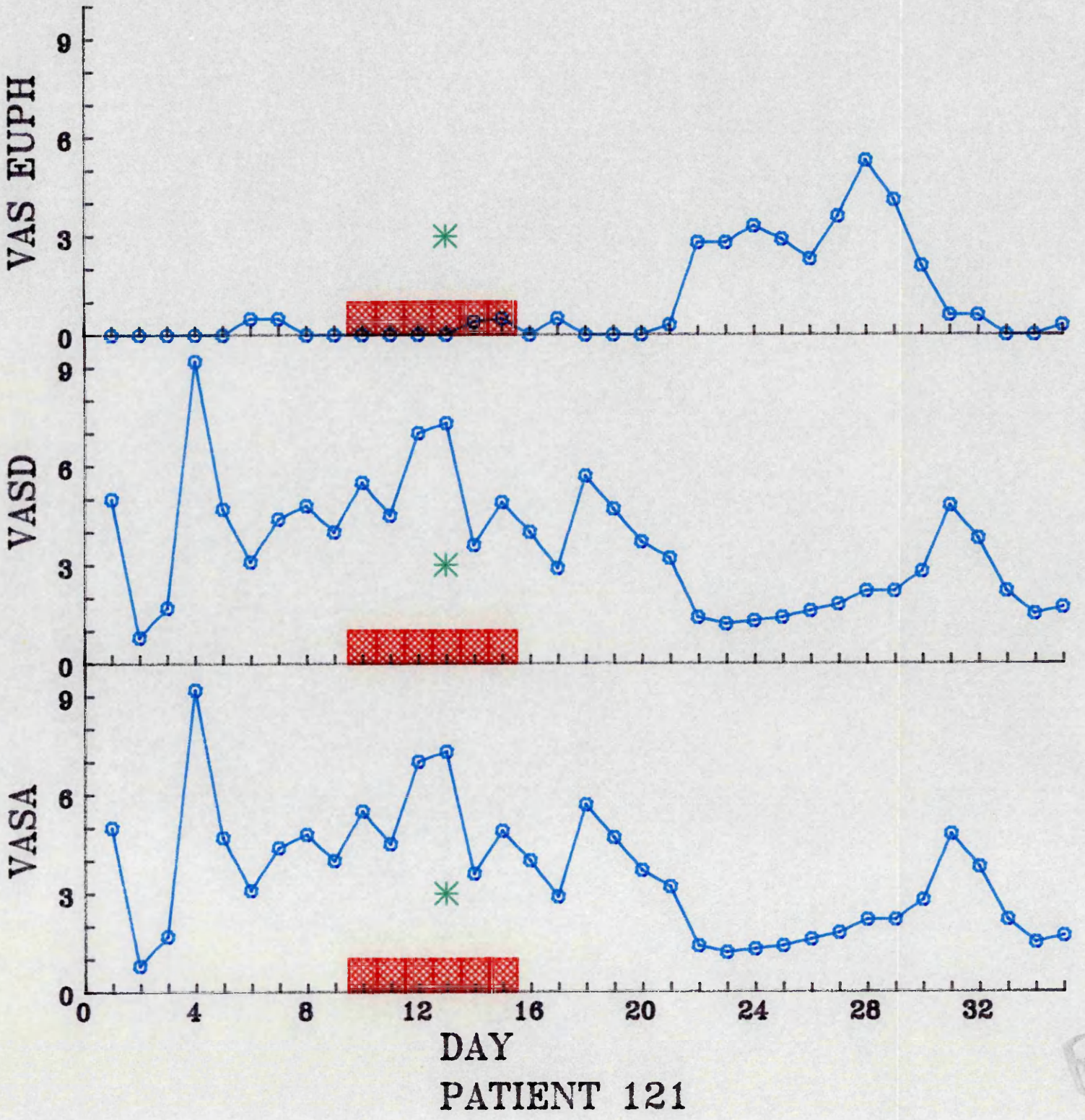
(225) A 46 year old widow who works as a market researcher. She has a ten year history of unilateral common migraine affecting the non-dominant hemisphere. She sometimes experiences euphoria for 1-2 days before a migraine attack. This euphoria consists of an increase in self confidence, increased talkativeness and more enthusiasm for doing things. It has only been present in the last year. Her main worries are her 21 year old son and 19 year old daughter - she has felt totally responsible for their welfare since the death of her husband eight years ago. Both children have had difficulties related to their jobs in the last year. She has occasionally required minor tranquillisers which she has obtained from her GP but is subthreshold for a diagnosis of generalised anxiety disorder at present and is not on any psychotropic medication.

(226) This 52 year old, married, assistant housing manager has a three year history of unilateral common migraine which almost always affects the non dominant hemisphere. She has no complaints of mood change and no personal or family history of psychiatric illness. She feels that the onset of her migraine was related to a stressful period of some months when her husband's business was failing. These business difficulties are now being resolved.

(227) A 38 year old, married, researcher with a 27 year history of classical migraine which can be both bi- and unilateral. The aura before her attacks involves paresis which can affect either or both sides of her body. She has no current or past psychiatric diagnosis and no complaints of mood change associated with her headaches.

(228) A 26 year old housewife with a two year history of unilateral common migraine affecting the non-dominant hemisphere. She has no complaints of mood change associated with her migraine and no current or past psychiatric diagnoses. There are no major stresses in her life at the moment.

(229) This 43 year old, divorced, telephonist has a seven year history of unilateral classical migraine affecting the dominant hemisphere. She has a visual aura to attacks. She has just stopped taking minor tranquillisers after being on them continuously for 20 years. She meets DSM-III criteria for past barbiturate-sedative dependence (i.e. substance abuse disorder) which was present for approximately 17 years. She also meets the criteria for current panic disorder with limited phobic avoidance over the same period of time. It is possible, but unlikely, that her panic attacks were simply withdrawal symptoms from benzodiazepines when she occasionally omitted to take the medication. She probably has two conditions with abuse of minor tranquillisers being secondary to her panic disorder. She is under considerable stress as a single parent trying to support herself and her 12 year old daughter on a low wage. She finds her job demanding and her father has just had a myocardial infarction. Her mother is her major source of emotional support.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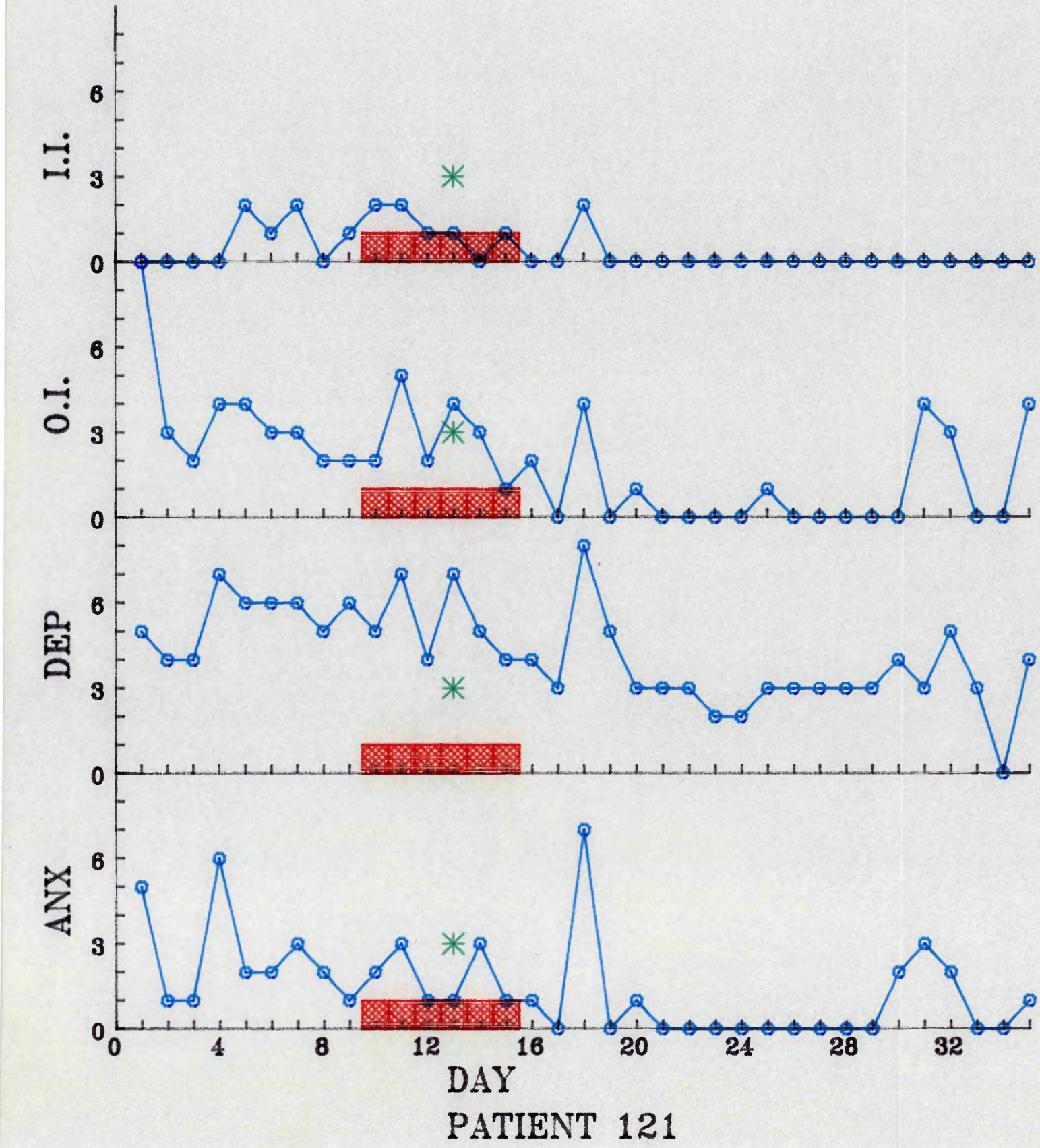
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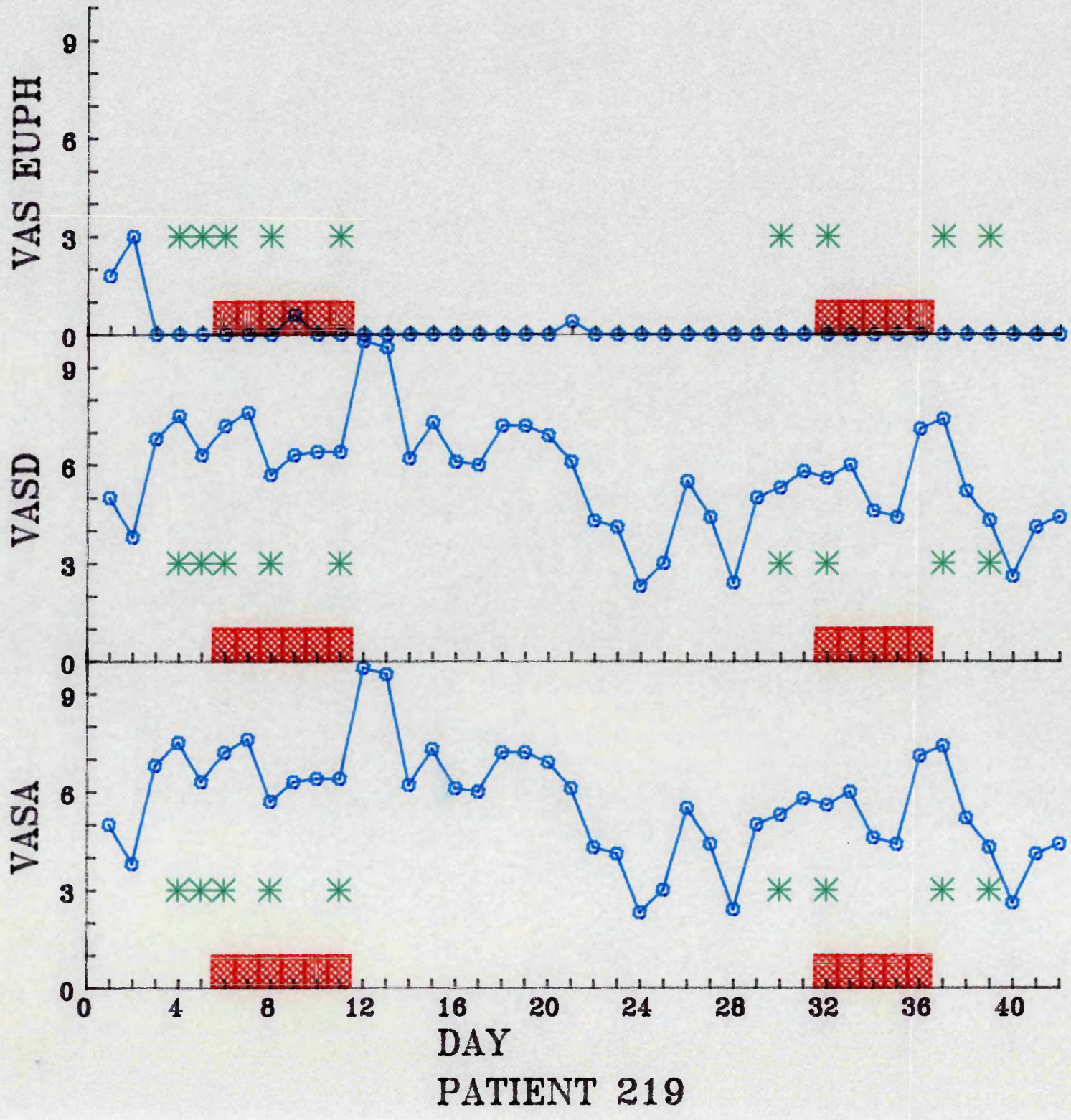
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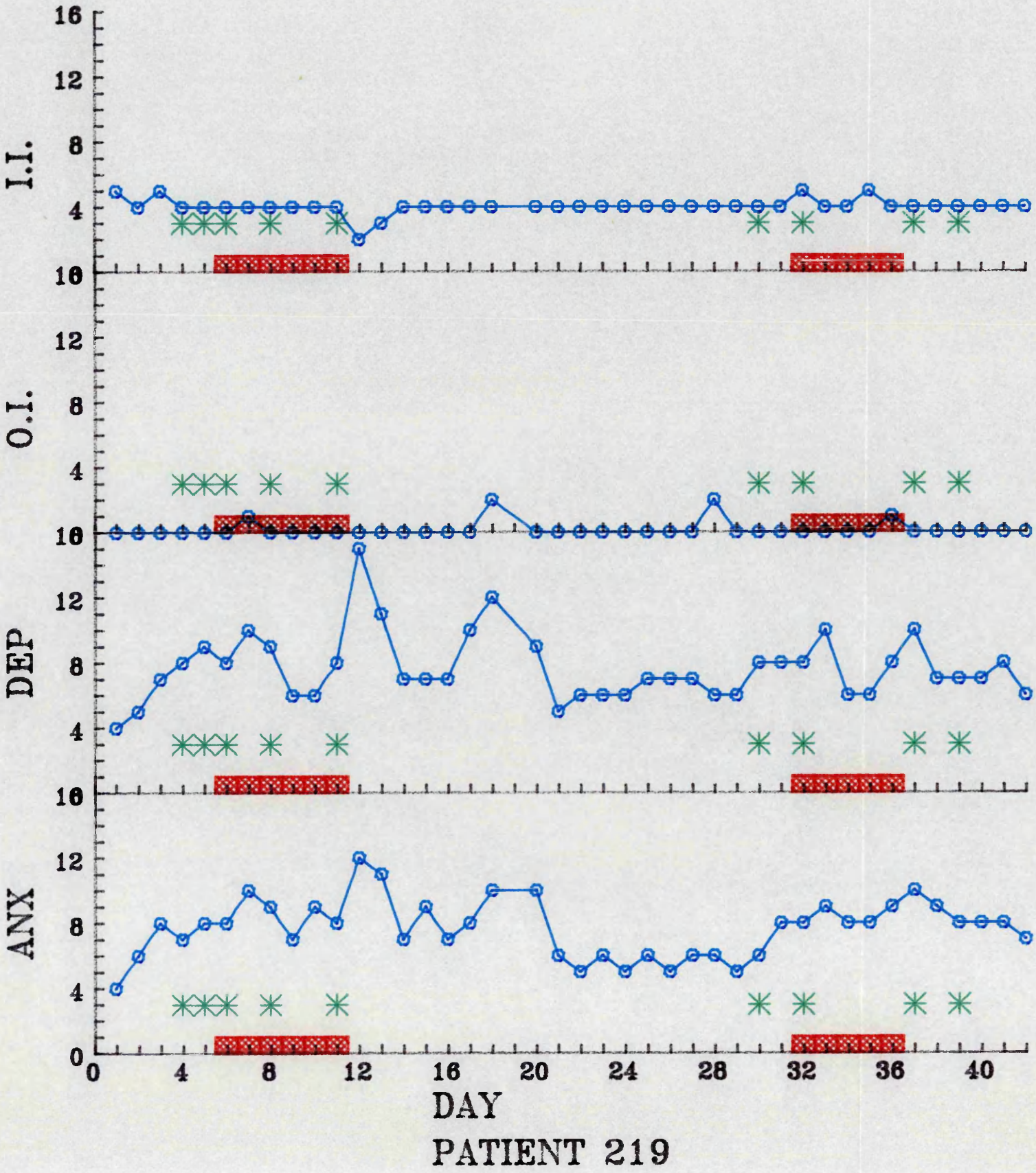
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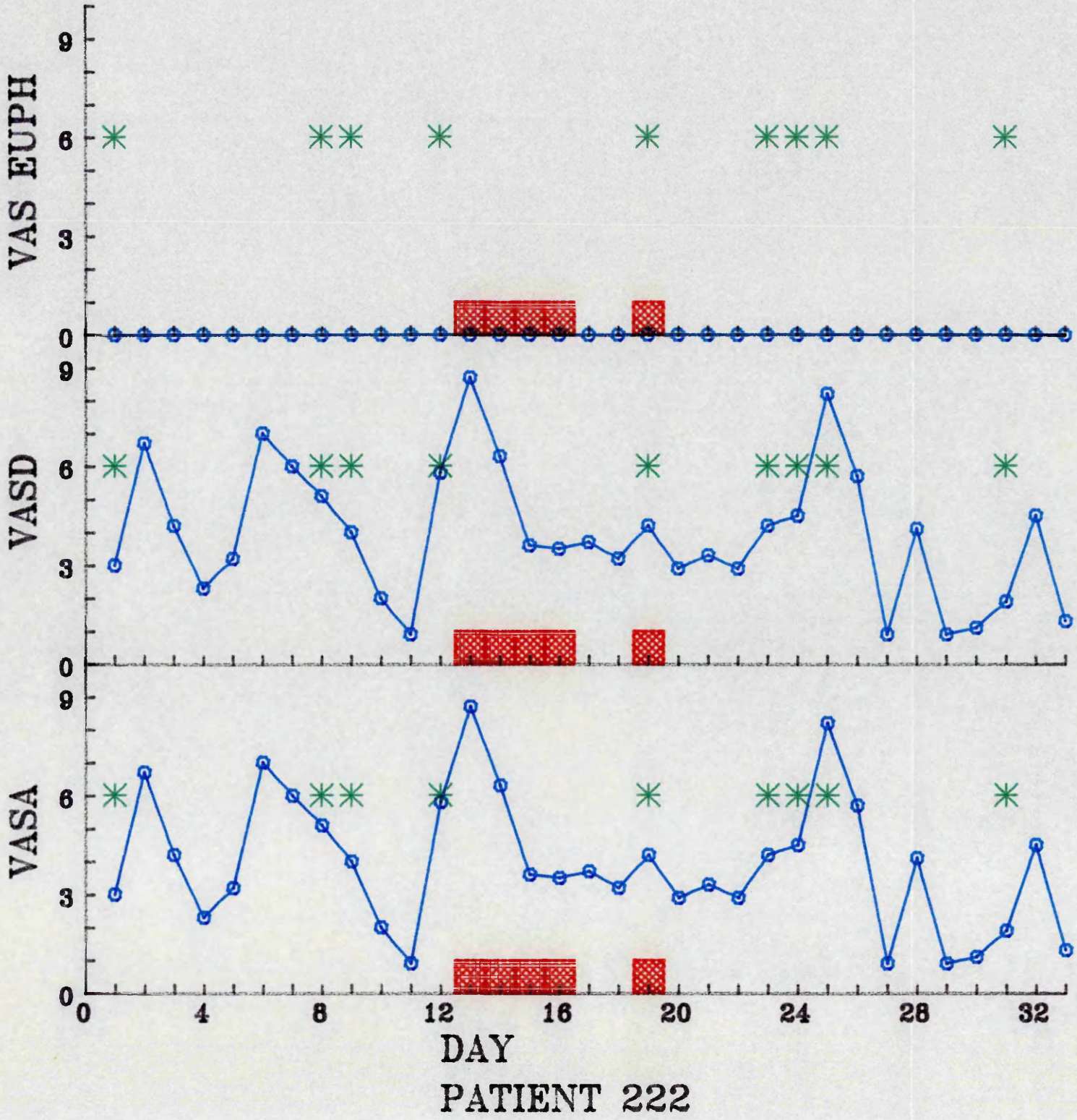
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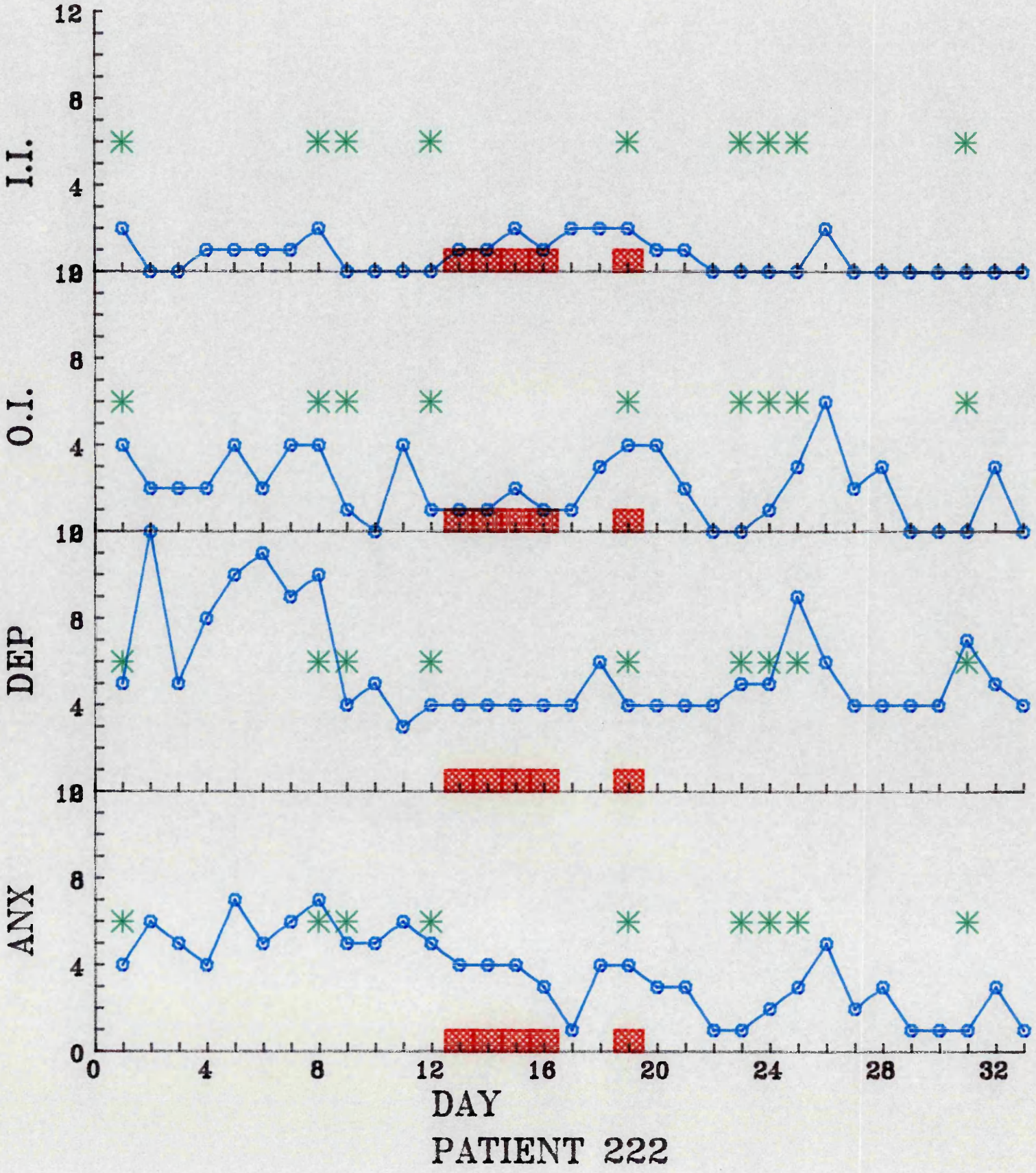
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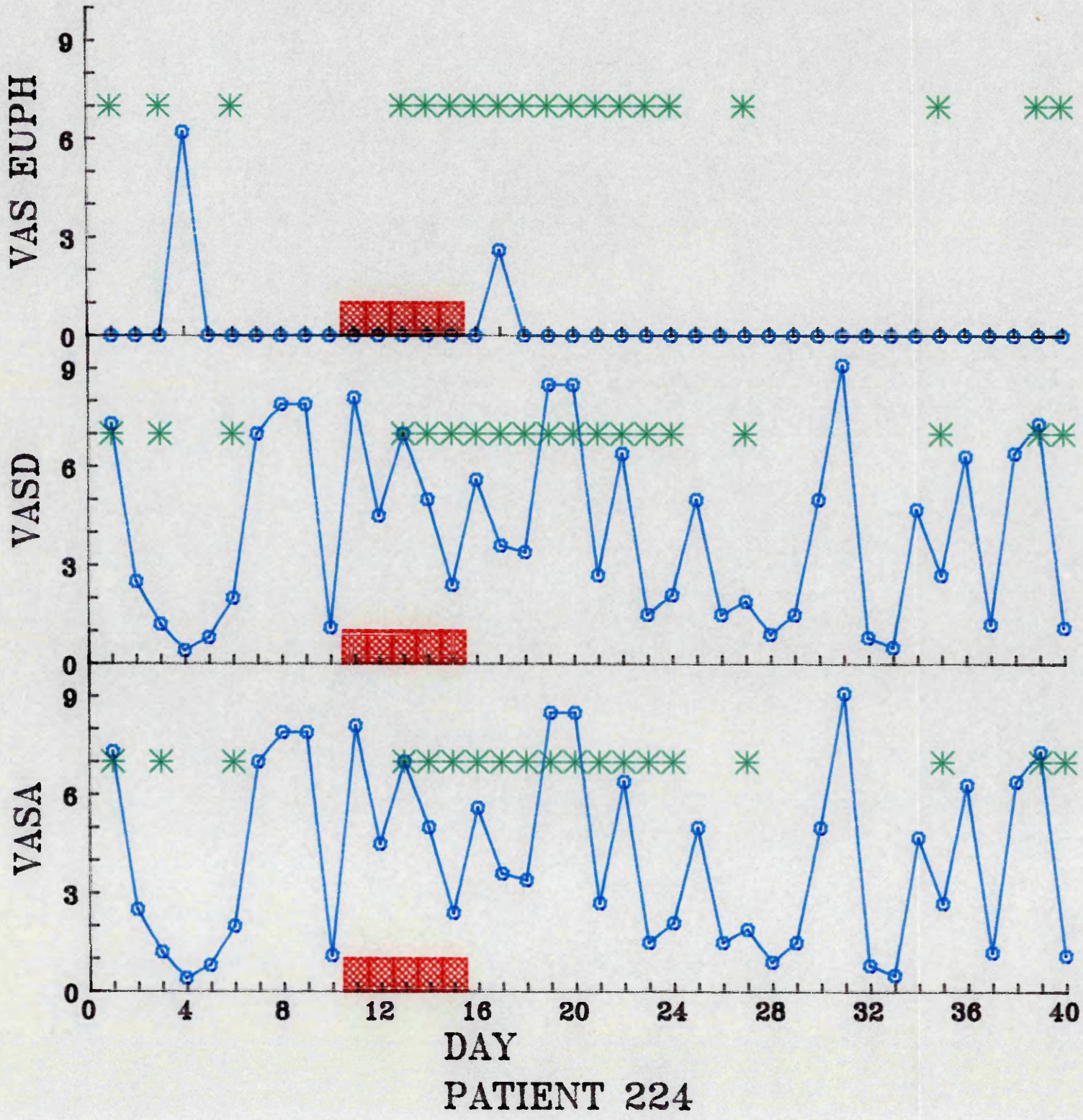
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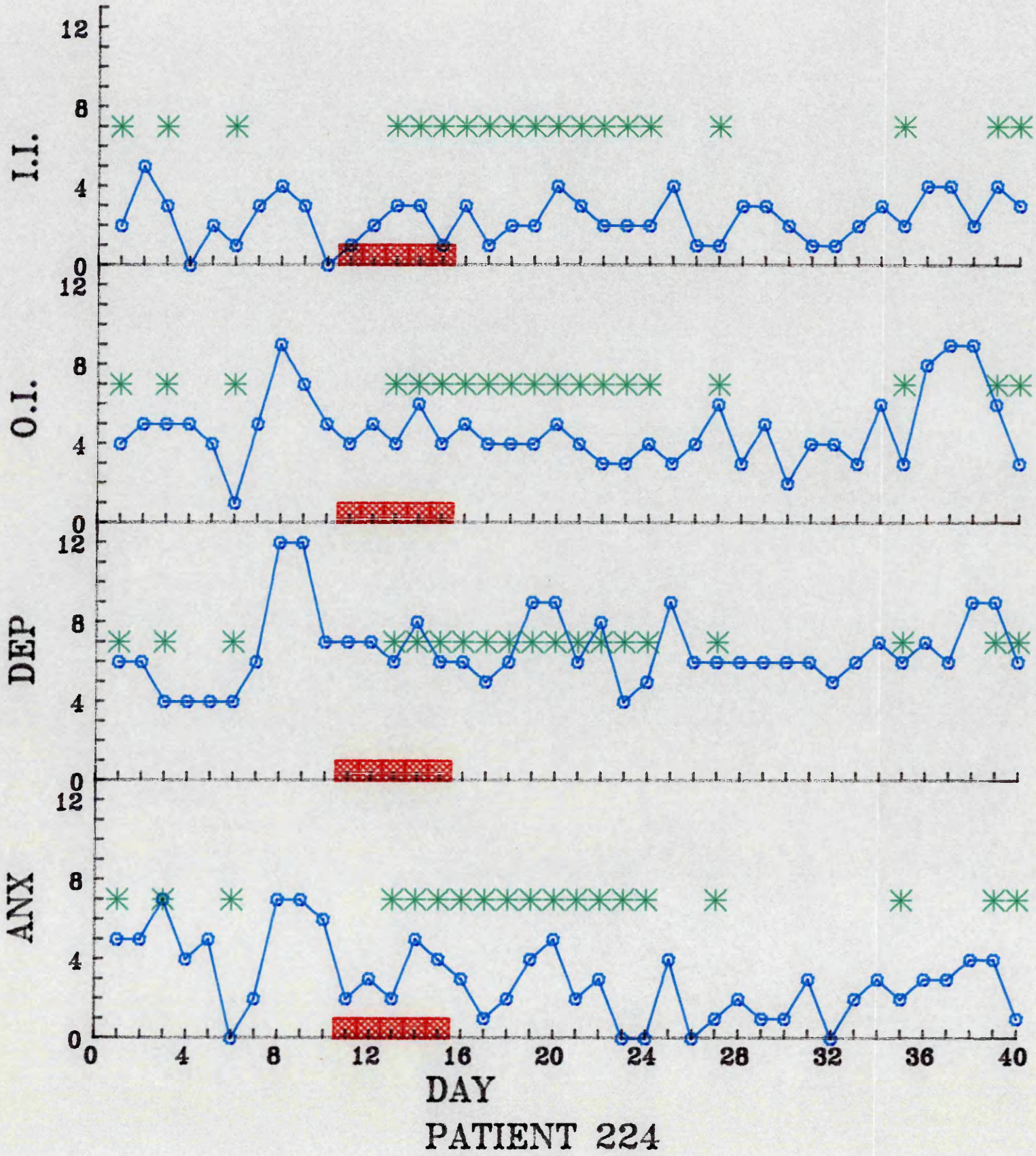
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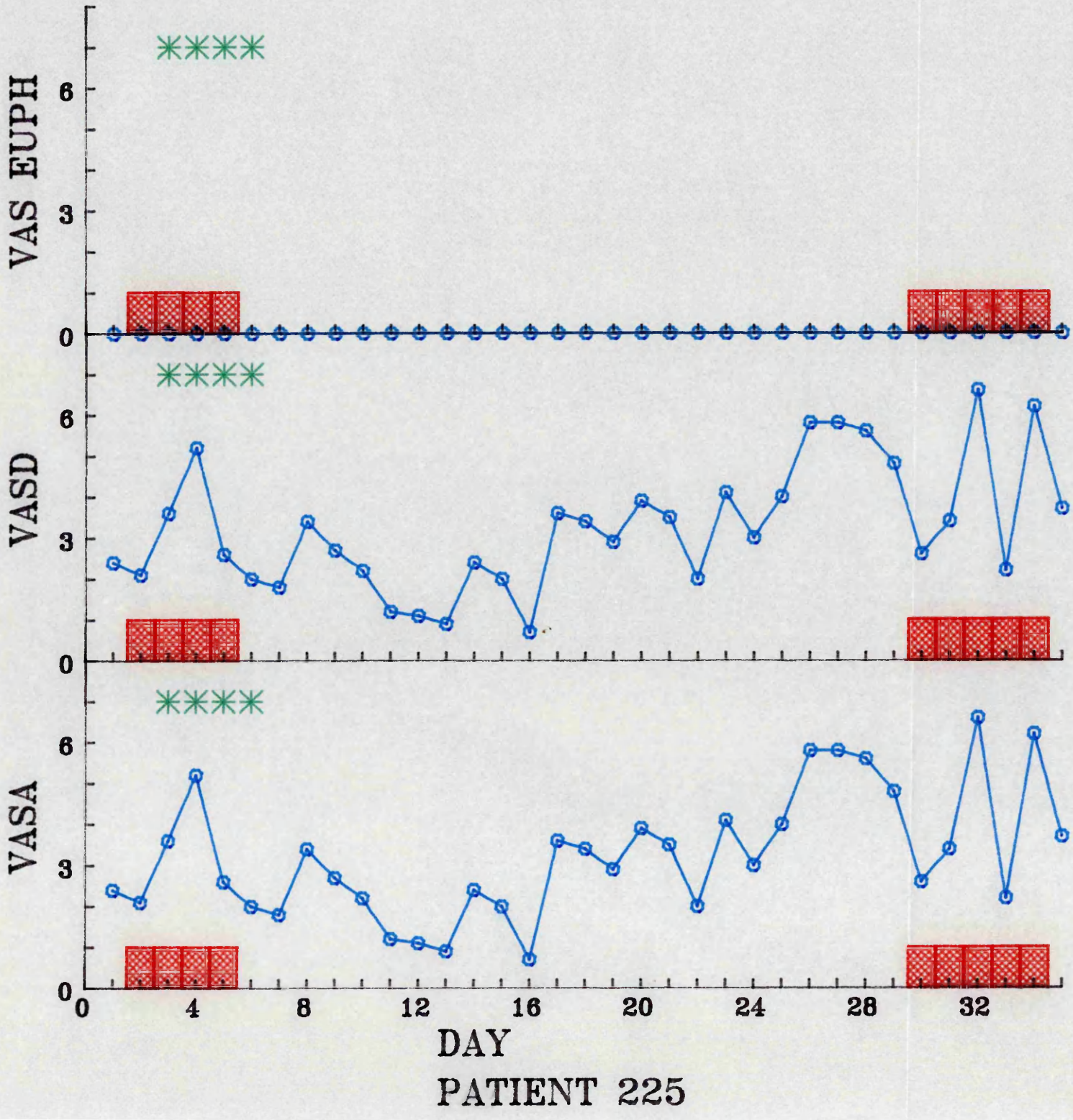
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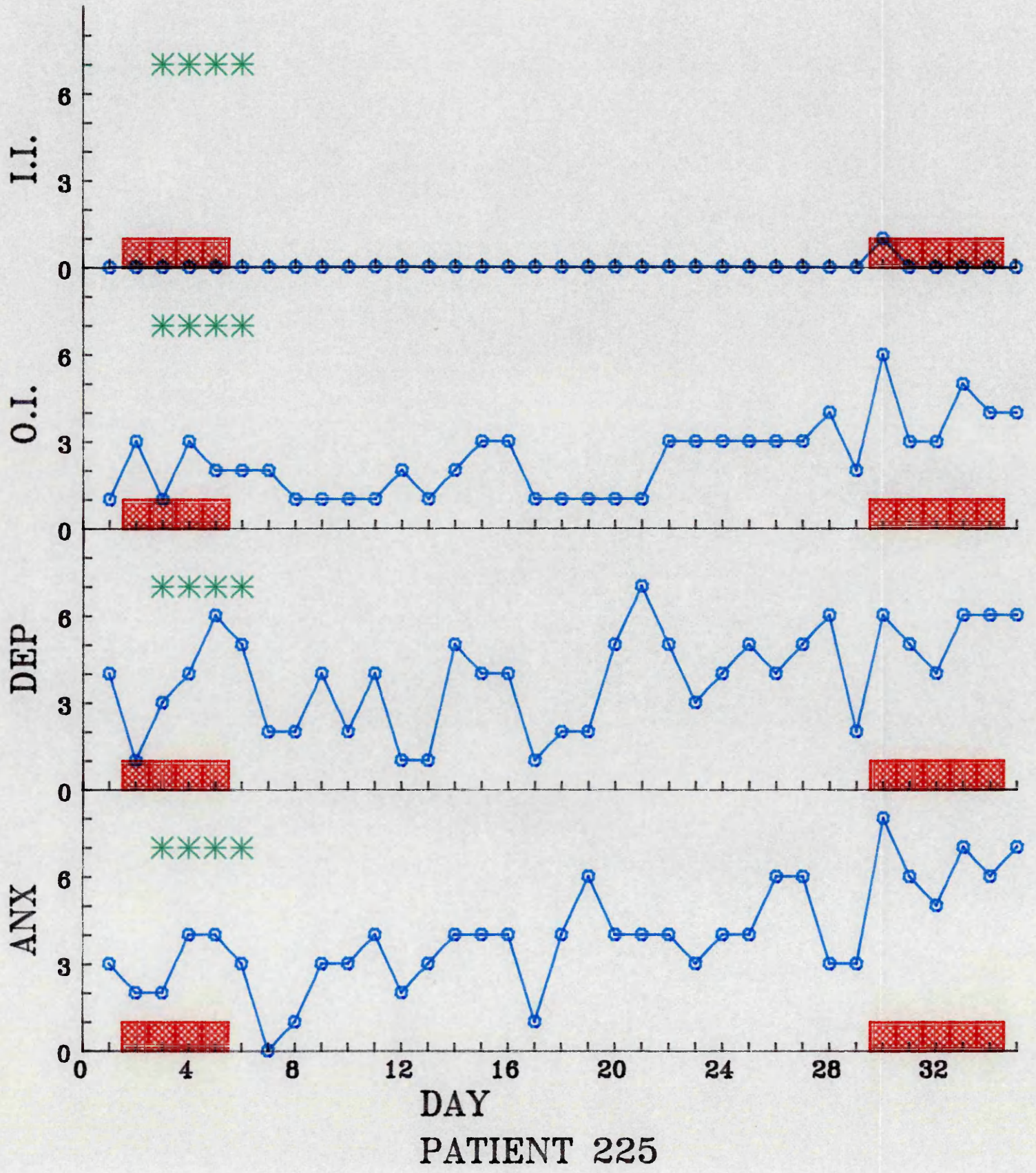
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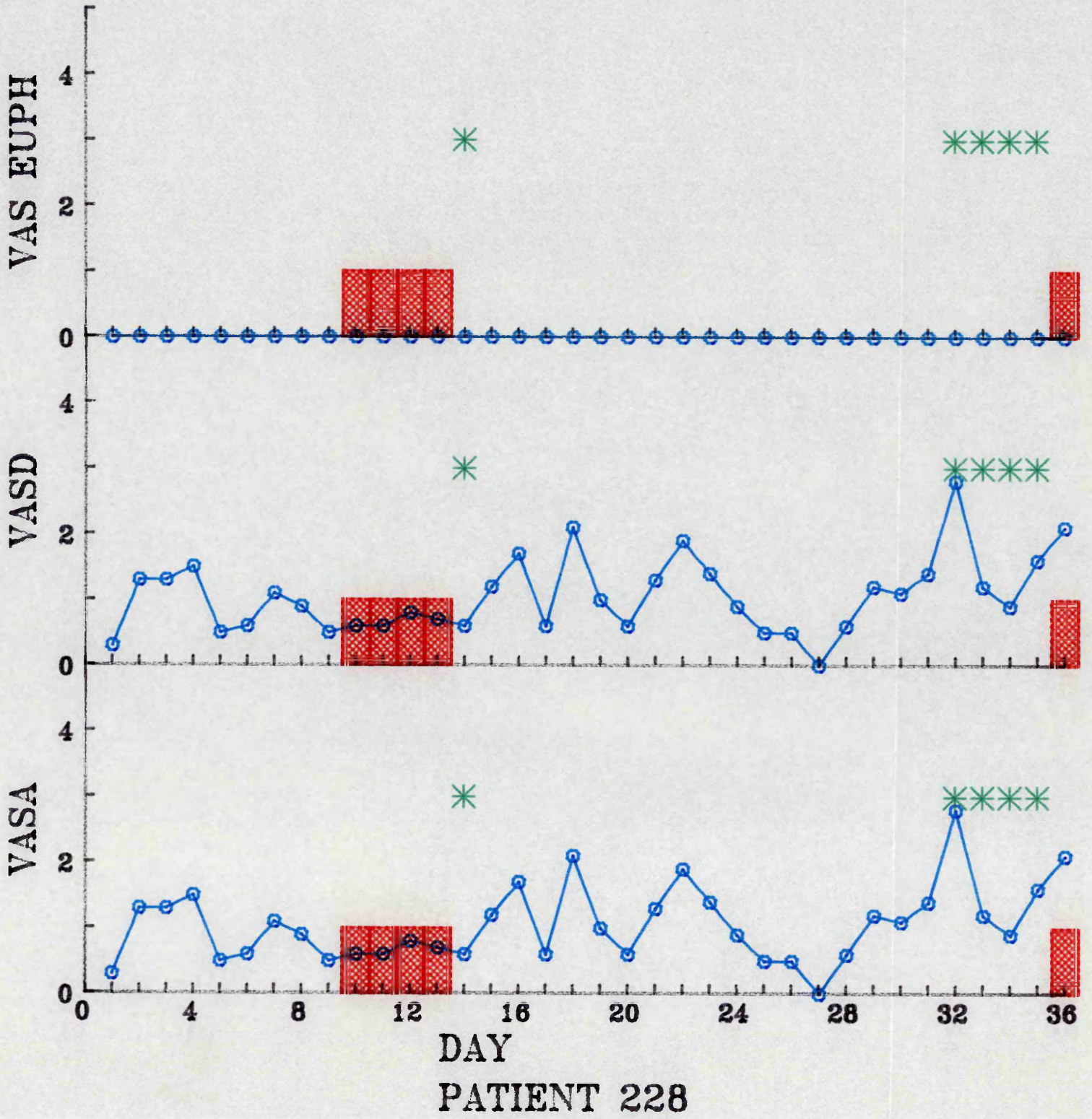
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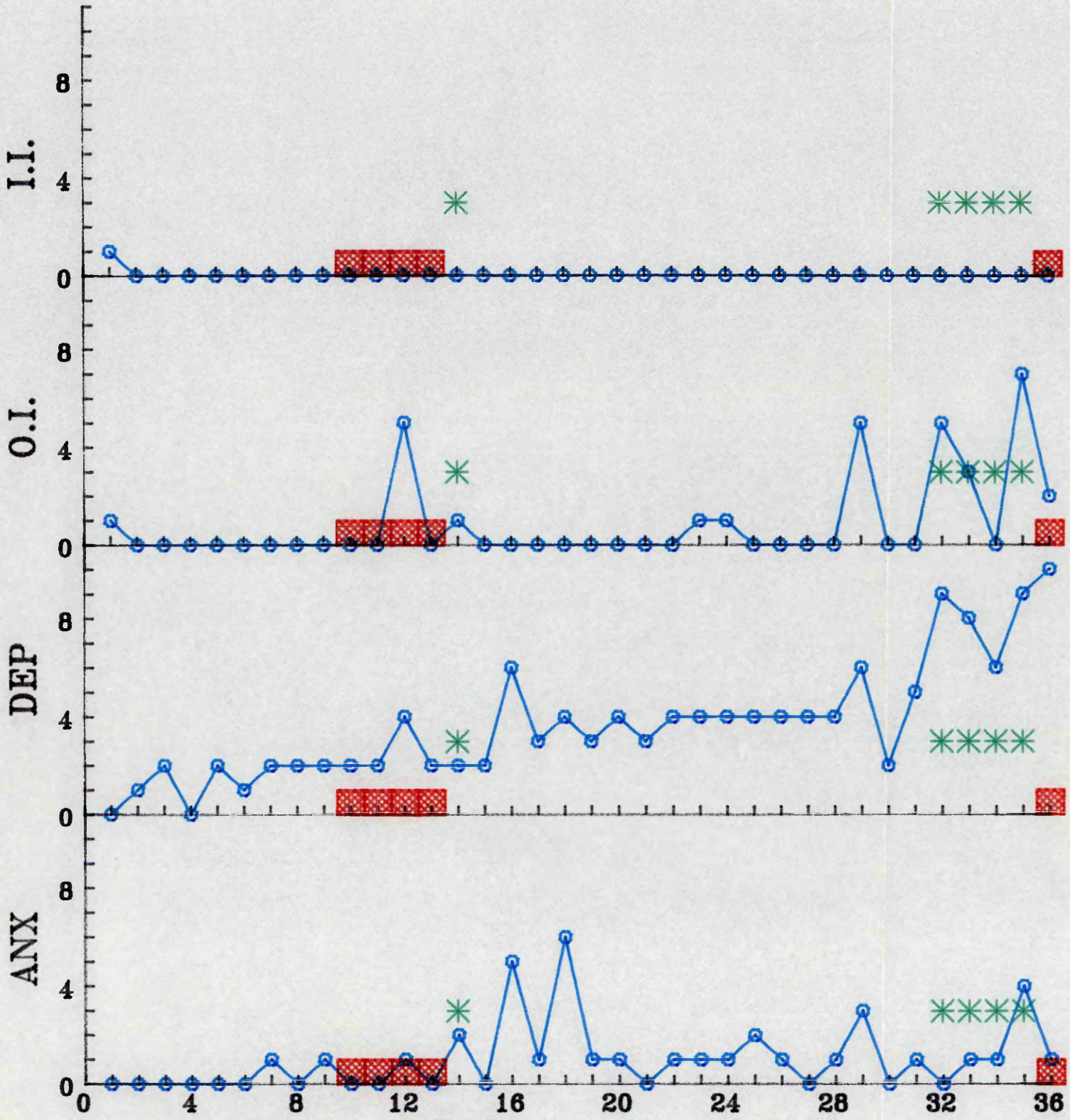
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