ASSESSMENTS OF THE PSYCHOLOGICAL SIDE-EFFECTS OF ANTIHYPERTENSIVE MEDICATION

BY JOHN SIMPSON CALLENDER

Submitted for the degree of Doctor of Medicine in the Faculty of Medicine of the University of Glasgow.

This thesis is based on research conducted in the Department of Psychological Medicine of the University of Glasgow.

August 1990

CONTENTS

LIST OF TABLES

PREFACE

The studies described in this thesis were carried out in conjunction with clinical trials of antihypertensive agents conducted under the auspices of the Glasgow Blood Pressure Clinics and the M.R.C. Blood Pressure Unit, Western Infirmary, Glasgow. The data resulting from investigations of blood pressure and related aspects have formed the basis for papers published in the journals Hypertension, the British Journal of Clinical Pharmacology and the American Journal of Medicine.

The physical investigations reported in this thesis were carried out by medical and nursing staff of the respective blood pressure clinics. The psychological investigations were organised, scored and collated by the author of the thesis. In more than ninety percent of patients the tests were administered by him. In exceptional situations in which patients would otherwise have been lost to the study the tests were administered by a research assistant who had been trained in their use by the author.

Training in the administration of the Standardised Psychiatric Interview was provided by the General Practice Research Unit, Institute of Psychiatry, London. Professor Neil Brookes of the Department of Psychological Medicine, University of Glasgow provided training and supervision in the use of the Wechsler Memory Scale and the Digit Symbol Substitution Test.

ACKNOWLEDGEMENTS

The research work which forms the basis of this thesis was carried out while the author held a post as Lecturer in the Department of Psychological Medicine, University of Glasgow. The thesis was supervised by Professor M.R. Bond, Professor of Psychological Medicine and Vice-Principal of the University of Glasgow. Professor Bond provided continual support while the work was being carried out and invaluable guidance on the design of the studies and prepraration of the thesis.

Professor Neil Brookes also of the Department of Psychological Medicine provided advice and supervision on the use of cognitive tests.

The studies described here could not have been carried out without the close cooperation of the Glasgow Blood Pressure Clinics and the Medical Research Council Blood Pressure Unit. Drs. J.I.S. Robertson and A.F. Lever provided enormous encouragement and support. The assistance and patience of clinic staff and in particular Sisters Maureen Robertson and Margaret McGowan is acknowledged.

Dr. Gordon Murray, Senior Lecturer in Medical Statistics, University of Glasgow, provided invaluable advice on statistical analysis of the data.

Ian Medley, Valerie Gray and Elizabeth Brannigan were employed as research assistants in these studies. They assisted with distribution and checking of questionnaires and acted as invaluable "understudies" when the author was unable to be present to administer the tests of cognitive functioning.

DECLARATION

I hereby declare that this thesis embodies the results of my own special work and that it has been composed by myself.

JOHN S. CALLENDER

SUMMARY

This thesis describes three studies of the effects of anti-hypertensive drugs on various aspects of psychological well-being.

The first investigation was a small pilot study of the effects of captopril on psychiatric status. This was prompted by anecdotal reports of mood elevation in hypertensive patients receiving this drug. No evidence for a euphoriant effect of captopril was found. Patients on captopril had significantly higher scores on a questionnaire of psychiatric symptoms.

The second and third trials were investigations of the effects of anti-hypertensive agents on aspects of "quality of life". In all, four drugs were assessed for effects on psychiatric well-being, social adjustment and intellectual functioning. Patients on atenolol performed less well on tests of concentration and information processing, compared to those on enalapril. Patients on nicardipine and propranolol had impairment of performance on tests of non-verbal memory. There was no demonstrable decrement in psychiatric well-being and social functioning in patients on any of the drugs.

INTRODUCTION

In adult populations living in developed societies there is a continuous distribution of levels of systolic and diastolic blood pressures. Apart from patients in whom hypertension is secondary to other disease, there is no point of discontinuity at which normal blood pressure can be said to end and high blood pressure to begin (Pickering, 1961). In people with blood pressures at the upper end of the distribution, there is an increased risk of various adverse cardiac, vascular and other events such as stroke, coronary heart disease, cardiac failure and progressive renal impairment.

The first controlled trial which demonstrated that antihypertensive drug therapy could prevent the development of complications of raised blood pressure was that of Hamilton et al (1964). This trial revealed a protective effect, particularly with regard to stroke, in adults with phase IV diastolic blood pressures of 110mmHg or above, who were free of overt cardiovascular disease at the beginning of the trial.

Large controlled trials carried out in more recent times have examined the issue of whether drug treatment of mild hypertension is of benefit in the prevention of hypertension-related morbidity.

Among the first of these were the studies carried out in the U.S.A. under the auspices of the Veterans' Administration. Two trials were carried out which examined the effects of treatment in men with phase V diastolic pressures between 90 and 114mmHg and in those with phase V diastolic pressures between 115 and 129 mmHg (Veterans Administration

Cooperative Study Group, 1967; 1970). The trials were randomised, double-blind and placebo-controlled and treatment consisted of hydrochlorothiazide and, where indicated, reserpine and hydralazine. Overall mortality was reduced when the two groups were considered in combination. There were fewer cardiac events and fewer strokes in treated patients but, in tbe case of strokes, the numbers were too small to reach statistical significance. There are, however, some problems in the analysis of the data of this trial. Approximately sixty percent of the patients had evidence of cardiovascular disease at the outset of the trial. The results of the trial were apparently inspected continually by the review committee and the trial was not terminated according to predetermined criteria (Robertson, 1987).

A large Australian study recruited 3427 men with phase V diastolic blood pressures of 95mHg or above. Subjects were randomly allocated to active treatment or to placebo and followed up for four years. The actively treated group showed a reduced mortality mainly accounted for by a two-thirds reduction in deaths from cardiovascular disease (myocardial infarction, stroke and aortic aneurysm). In addition, they experienced fewer non-fatal cerebro-vascular accidents. There was, however, little difference in the incidence of ischaemic heart disease (Australian National Blood Pressure Study Management Committee, 1980).

The Hypertension Detection and Follow-up Program (HDFP), mounted in the United States, recruited patients by population screening. Comparisons were made between patients allocated to "stepped care" with those allocated to "referred care" (Hypertension Detection and Follow -up Program Cooperative Group, 1982). Over seventy percent of patients in

each group were classified as having mild hypertension on the basis of having diastolic pressures between 90 and 104 mmHg. "Stepped care" consisted of antihypertensive drug treatment according to a set protocol along with advice on reduction of intake of alcohol, salt and cholesterol and counselling on smoking. The "referred care" group were returned to their usual medical practitioner for whatever care he considered to be appropriate. The "stepped care" group had fewer strokes and myocardial infarctions; the decrease in myocardial infarctions was also found in those whose diastolic pressure at entry was between 90 and 104 mmHg. This trial has been used to justify prophylactic treatment in those with diastolic pressures persistently equal to or greater than 90 mmHg (Moser and Gifford, 1985), although the advantages found may have been achieved by interventions other than antihypertensive therapy.

An earlier study of similar design was carried out in Gothenburg (Berglund et al, 1978). Men with hypertension were treated either at a special hospital clinic for the treatment of hypertension or by their usual medical practioner. Those attending the hypertension clinic did better and suffered fewer fatal and non-fatal myocardial infarctions. This group also experienced fewer deaths from non-cardiovascular diseases. The authors suggest that more effective control of high blood pressure and in particular greater use of beta-blockers for the treatment of hypertension may lead to reduced morbidity and mortality. It may of course be the case that the greater attention and supervision available at the clinic contributed to the favourable outcome in those attending.

A study carried out in Oslo by Helgeland et al (1980) assessed treatment of men aged 40-49 with blood pressures in the range 150-179 mm Hg systolic and/or 90-109 mm Hg phase V diastolic. Patients were randomly allocated to treatment with hydrochlorothiazide and methyldopa or propranolol or to placebo. At five-and-half year follow-up there was no difference in the number of deaths or cardiovascular events. Coronary events were more common in the treated group although this was not statistically significant. At ten year follow-up there had been a significantly greater number of deaths in the treated group (Leren and Helgeland ,1986). The authors suggested that this raised the possibility that the potential adverse cardiac effects of thiazide diuretics, such as hypokalaemia, may outweigh the benefits of lowered blood pressure.

The large trials published prior to the inception of the studies reported here suggested that there was benefit from antihypertensive therapy in patients with phase V diastolic pressures persistently above 95 mm Hg. Numerically the advantages of treatment were modest especially in the lower range of pressures and uncertain in those with diastolic pressures in the range 90-95 mmHg (Robertson, 1987).

As more trials have been completed there has been a tendency for the recommended threshold at which antihypertensive treatment should be instituted to become progressively lower (Moser et al, 1986). It was estimated in 1984 that there were thirty-five million people in the United States, and equivalent numbers in other developed countries, with blood pressures which would qualify them for treatment (Subcommittee on Definition and Prevalence, 1985). In a situation in which very large numbers of people may be subjected to long-term drug treatment, it

becomes of the utmost importance to scrutinise these treatments very closely for possible adverse effects on well-being in the psychological, as well as the physical, sphere.

PSYCHIATRIC SIDE-EFFECTS OF ANTI-HYPERTENSIVE MEDICATION

The effects of anti-hypertensive drugs on mental well-being have been studied since the earliest days of the treatment of hypertension with Rauwolfia alkaloids and the pure derivative of these, reserpine. As new drugs have been developed, case reports and systematic studies relating to psychiatric effects have appeared. The psychiatric side-effects of Rauwolfia and reserpine will be discussed in view of their historical importance. The main groups of commonly-used anti-hypertensive agents will then be considered in turn.

RESERPINE AND THE RAUWOLFIA ALKALOIDS

The Rauwolfia alkaloids were introduced into Western medicine in the early 1950s for the treatment of hypertension and various psychiatric disorders. In patients with hypertension, psychiatric side-effects were soon recognised as an important adverse conseqence of treatment.

These agents may have both central and peripheral actions. Reserpine lowers the brain content of noradrenaline, 5-hydroxytryptamine and adenosine triphosphate and has a relaxant effect on vascular smooth muscle. Arteriolar tissue and the sympathetic nervous system are depleted of noradrenaline (Laurence and Bennett, 1987).

Among the first reports of psychiatric side-effects was that of Fries (1954) who described five patients who became depressed while taking reserpine. Other symptoms which they experienced included lethargy,

poor concentration and fatiguability. One patient was troubled with drowsiness; another developed insomnia with early wakening. Symptoms had their onset at least two months after treatment was commenced. Improvement in symptoms occurred between one week and two months after withdrawal of medication. One patient with a past history of psychiatric disorder required electro-convulsive therapy (ECT). Doyle and Smirk (1954) reported that fatigue, drowsiness, depression and mental excitement were prominent in patients taking reserpine. Schroeder and Perry (1955) gave histories of five patients on reserpine who became depressed. Agitation, paranoia and suicidal tendencies were prominent in this group. Recovery occurred over a period of several weeks. Two patients were treated with ECT. Achor et al (1955) found symptoms of depression in ten out of fifty-eight patients on treatment with Rauwolfia. Three were of sufficient severity to require referral to a psychiatrist, three were "moderately depressed" and four had "mild but definite" depression. Muller et al (1955) described psychiatric symptoms in seven patients out of a group of ninety-three being treated with Rauwolfia. The most common symptoms were insomnia (present in seven patients), fatigue and lassitude (six), poor concentration (five), anxiety and apprehension (five), crying episodes (four) and drowsiness (four). Onset of symptoms was between three and six months after initiation of treatment. Patients were on higher than average doses of medication. Five out of seven were treated with ECT. Kass and Brown (1958) reported depression in four patients on either Rauwolfia or reserpine. In one patient there was clinical and EEG evidence of an acute organic brain reaction; this cleared within three weeks of drug withdrawal. Lemieux et al (1956) found symptoms of depression, lack of

energy, loss of interest, insomnia and anorexia in thirty out of 195 patients on reserpine or Rauwolfia. Ten of these patients required psychiatric hospitalisation. On average four and a half months elapsed between commencement of treatment and the onset of symptoms. Reduction of dosage or withdrawal of treatment led to improvement in most cases.

Quetsch et al (1959) compared the incidence of depression in patients being treated with Rauwolfia, alone or in combination with other drugs, with hypertensive patients on no specific therapy. Depression was found in 28% of patients on Rauwolfia alone, 21% of those on combination therapy but in only 5% of patients on no treatment. The average time to onset of depression was five months. Recovery was gradual over a period of weeks after withdrawal of medication. Nineteen patients had a past history of depression; of these eleven became depressed on Rauwolfia, none to a severe degree.

In summary, Rauwolfia and its derivative reserpine, cause psychiatric morbidity which appears on average between four and five months after starting on treatment. The most prominent symptom is depression of mood. A wide variety of accompanying symptoms is described, with fatigue and lassitude, drowsiness, insomnia and anxiety among the most common. It is possible that those with a past history of depression are more vulnerable to pychiatric morbidity. Symptoms cleared in most patients within weeks of drug withdrawal. Many patients, however, required hospitalisation and specific treatment such as ECT.

These early papers were published before the days of the widespread use of standardised psychiatric nomenclatures and no attempt is made in any

of them to come to specific diagnoses. Ratings of severity are either subjective or based on some simple criterion such as requirement for hospital care. It thus difficult to compare the syndromes described with psychiatric morbidity as found in other settings. Despite these problems, reserpine-induced depression has been an influential model for the "catecholamine hypothesis of affective disorders" which explains depressive illness in terms of a functional depletion of central catecholamines (Schildkraut,1965).

ALPHA-METHYLDOPA

Methyldopa is one of the few drugs which have passed from the design stage in the laboratory to clinical application (Sourkes, 1965). Despite this, the exact mode of action of this drug remains unclear (Laverty, 1973). One action is inhibition of dopamine decarboxylase and it was initially thought that the anti-hypertensive effect was peripheral and a result of reduced catecholamine synthesis. The drug was then shown to be metabolised to alpha-methylnoradrenaline and alpha-methyldopamine. It was thought that these substances acted as "false transmitters" which replaced noradrenaline at sympathetic synapses thus producing significant blockade in the sympathetic nervous system (Laurence and Bennett, 1987).

Central nervous system actions are now thought to be the most important in producing the hypotensive effect. Depletion of noradrenaline and serotonin in the central nervous system have been demonstrated

(Smith,1960). A centrally-mediated hypotensive effect has been demonstrated in animal studies (Henning and van Zwieten,1968; Ingenito et al,1970). Destruction of central adrenergic neurones in rats and cats reduces the hypotensive action of methyldopa.

Sedation is the most common central side-effect and has been reported in nearly every study (Paykel et al,1982). This complaint is usually transient, appearing with the initial dose and passing off within two weeks. Bulpitt and Dollery (1973) found that 56% of patients on methyldopa complained of sleepiness. Those complaining of this symptom were, on average, on a significantly higher dose of medication. Patients on methyldopa slept for more hours in a day. In a series described by Prichard et al (1968), 83% of patients on methyldopa complained of tiredness.

Sleep disturbance and insomnia have also been widely reported (Amery et al,1972; Irvine et al,1962). This symptom has sometimes necessitated withdrawal of treatment (Tuomilehto et al, 1974).

The issue of depression in methyldopa treatment has been of interest in view of its action in depleting the central nervous system of serotonin and catecholamines. Depression has been widely reported in the literature. Hamilton and Kopelman (1963) found depression in three out of sixty-nine patients on methyldopa. In two of these, both previously treated for depression, this necessitated withdrawal of medication. Prichard et al (1968) found "mild depression" in four out of thirty patients on methyldopa. Dubach (1963) described one patient who developed symptoms of depression, auditory and visual hallucinations and

psychomotor retardation. These features cleared within forty-eight hours of drug withdrawal. Mielczarek (1962) reported on a patient who became depressed and agitated after five days on methyldopa. His symptoms failed to improve and he was treated with ECT ten weeks later. Fullerton and Morton-Jenkins (1963) described a thirty-four year old woman who became acutely psychotic two days post-partum after seven days on medication. Symptoms cleared approximately one week after drug discontinuation. A case report of methyldopa-induced depression by McKinney and Kane (1967) described a depressive illness occurring in a patient who had previously suffered from depression while on reserpine. Gillespie et al (1962) described two patients, both with a past history of depression who became depressed shortly after commencing on methyldopa. In both patients depression cleared on withdrawal of medication. Raftos et al (1964) described seven patients in whom the development of depression necessitated withdrawal of methyldopa with subsequent rapid improvement. Six of these patients were considered to have a significant past psychiatric history. Igloe (1964) found no depression in a series of fifty-one patients on methyldopa.

Again, diagnoses of depression are made in these reports without reference to standard diagnostic procedures. It is always impossible to be certain that the depression was produced by medication rather than being a coincidental occurence. Three studies will be described which assessed the incidence of depression in methyldopa-treated patients, using standardised rating scales.

Snaith and McCoubrie (1974) investigated the incidence of depression in

a group of hypertensive patients drawn from a general practice population. Depression was assessed using the Wakefield Self Assessment of Depression Inventory, which had been validated by the authors. Two hundred and sixty-four hypertensive patients, including eighty-seven on methyldopa alone and forty-seven on methyldopa in combination with other drugs completed the assessment and were compared with fifty-six control patients. In patients on methyldopa, scores on the inventory did not differ significantly from controls. Depression is said to be commoner in the early in treatment with methyldopa. Patients in this study had however typically been on treatment for some years and it is possible that depression was a feature of the earlier stages of treatment.

DeMuth and Ackermann (1983) compared the incidence of depression in patients on methyldopa with that in a group of hypertensive patients on other medication. Severity of depression was assessed using the Beck Depression Inventory. The incidence of significant depression was 26% in those on methyldopa and 32% in those on other unspecified medication. The conclusion drawn from this study was that methyldopa was no more likely to cause depression than other anti-hypertensive agents.

Bant (1978) studied the incidence of depression over a year in a group of eighty-nine new referrals to a hypertension clinic and in forty-six non-hypertensive medical out-patients. Depression was assessed with a rating scale whose validation is described by the author. There was no excess of depression in the hypertensive group as a whole. The incidence of depression in patients on methyldopa was no higher than in those on other drugs.

Depression seems therefore to be no more common in patients on methyldopa than in those in various comparison groups. These comparison groups have not always been precisely described in terms of factors which may predispose their members to a higher than average rates of depression. Case reports which describe relief of depression shortly after withdrawal of the drug suggest a role for methyldopa in causing depression. In many patients suffering this side-effect there was a past history of depression suggesting the existence of pharmacological vulnerability perhaps mediated by cerebral amine depletion.

Disturbance of sexual functioning is a peripheral side-effect of methyldopa which could lead to psychiatric morbidity in the form of marital dysharmony and reactive depression. Bulpitt and Dollery (1973) found impotence in 36% and failure of ejaculation in 18.5% of men on a combination of methyldopa and diuretic. Alexander and Evans (1975) found failure of erection in 53% of methyldopa-treated men and for this reason felt that it should not be used as a first-line treatment for hypertension.

BETA-BLOCKERS

The precise mode of antihypertensive action of beta-blocking drugs remains a subject of some controversy (Laurence and Bennett, 1987). One suggestion has been that the fall in blood pressure is due to the decreased heart rate and cardiac output which follow acute administration of these drugs. A compensatory increase in peripheral

resistance occurs which declines with continued administration . It is clear however from the time course of these changes that they have little influence in lowering blood pressure. Further research has demonstrated that beta-blockers suppress release of renin from the kidney, thus producing lower circulating levels of the pressor peptide angiotensin-II. In the case of propranolol, a relationship between lower plasma renin levels and decreased blood pressure seems to occur only at low doses. A central effect, mediated by reduced sympathetic outflow, has been suggested. Against this notion is the fact that beta-blockers vary in the degree to which they penetrate the brain and despite this all reduce blood pressure to a similar degree. A final possibility is that beta-blockers act presynaptically to prevent neurotransmitter release. Administered adrenaline has been shown to have an important pressor effect (Tung et al, 1981). This is thought to be mediated by stimulation of presynaptic beta-receptors which promote release of transmitter into the synaptic cleft. Suppression of the pressor effect of exogenous adrenaline has been achieved using the beta-blocker metoprolol (Rand et al, 1983).

Beta-blockers show some variability in their pharmacodynamic and pharmacokinetic characteristics. An important pharmacokinetic variable in the present context is the degree to which a drug is lipophilic or hydrophilic. Lipophilicity is high in propranolol, intermediate in oxprenolol and others and low in atenolol and sotalol. With regard to pharmacodynamics, some beta-blockers show partial agonist activity. This is not a feature of atenolol or propranolol, the two beta-blockers which are examined in the present research. Labetalol possesses alpha-adrenergic blocking activity in addition to being a beta-blocker.

The degree to which beta-blockers penetrate the brain depends on factors such as ionization, protein binding and lipophilicity. Drugs which are highly lipid-soluble appear in the brain in higher concentrations (Patel and Turner,1981). Early studies on animals demonstrated the presence of central effects of lipophilic beta-blockers such as propranolol (Leszkovszky and Tardos, 1965). Day and Hemsworth (1977) demonstrated a high uptake into the rat brain of propranolol (blood/brain ratio 8.37) in comparison to the hydrophilic drug, atenolol where the blood/brain ratio was only 0.054. Pretreatment with atenolol however led to an increase in central nervous system (CNS) uptake of this drug. Garvey and Ram (1975) demonstrated that CNS levels in the rat brain of propranolol and pindolol were higher for a given dose than those of the more hydrophilic sotalol. The presence of central beta-adrenergic receptors was demonstrated in the mouse by Atlas et al (1977) and in the rat by Maguire et al (1976). Middlemiss et al showed that propranolol has an affinity for 5-hydroxytryptamine (5-HT) receptors in the rat brain. Green and Grahame-Smith (1977) showed that (-)propranolol inhibits the behavioural response of rats to increased 5-HT in the CNS. Bakke et al (1974) demonstrated a central hypotensive effect of propranolol in rabbits by injection of the drug into the cerebral ventricles.

In a study in man Taylor et al (1979) showed that cerebro-spinal fluid (CSF)/ plasma ratios were higher for propranolol than for atenolol. Neil-Dwyer et al (1981) carried out a study of twenty-one neurosurgical patients to determine the extent which chronically administered beta-blockers crossed the blood-brain barrier and entered brain tissue and

the CSF. Three lipophilic drugs, propranolol, oxprenolol and metoprolol and the hydrophilic drug atenolol were studied. The concentration in the CSF of the three lipophilic drugs approximated to the free drug plasma concentrations and was a poor predictor of brain concentrations. The lipophilic drugs appeared in brain tissue at concentrations between ten and twenty times greater than atenolol. The brain-plasma ratio for propranolol was 26, for oxprenolol 50, for metoprolol 12 but only 0.2 for atenolol.

Roubicek (1976; 1977) found characteristic changes in the electroencephalogram in patients given single doses of propranolol and pindolol which further confirms central penetration of these drugs. The location of the changes suggested effects on corticothalamic and deeper structures.

One of the first reports to cause concern about adverse psychiatric effects was that of Waal (1967). She became concerned when two patients taking propranolol committed suicide. She subsequently either reviewed the casenotes or interviewed a series of eighty-nine patients who were receiving propranolol for the treatment of cardiac arrythmias. Twenty-eight of this group showed some evidence of depression. Depression was commoner with prolonged administration and higher dosages. Subsequent examination of this group raised doubts about the link between propranolol and depression (Simpson and Waal-Manning, 1971). One of the suicides had a past history of depression accompanied by threats of suicide; the other was also on reserpine. In fifteen patients depression was diagnosed on the basis of "irritability, insomnia, nightmares, lack of drive and energy". Sedation and vivid dreams are recognised side-

effects of propranolol and patients may have been suffering from these symptoms rather than from a depressive illness. There was no comparison group to control for other relevant factors such as the presence of serious physical illness.

Fitzgerald (1967) reported the results of post-marketing surveillance of propranolol which suggested an incidence of drug-induced depression of only 0.1%.

Petrie et al (1982) described three patients who developed depression which met standardised criteria (DSM-III,(American Psychiatric Association, 1980)) for major depressive disorder. In all patients depression developed after an increase in dose of medication and remitted within days of withdrawal of treatment. One patient had a history of depression necessitating psychiatric treatment; another had a significant family history of depressive illness.

Avorn et al (1986) approached this issue by examining Medicaid prescribing records of a large cohort of patients, using prescription of tricyclic antidepressants as an index of depression. Tricyclic usage was compared in patients on any of seven different antihypertensive agents. In order to control for the effects of chronic illness, rates of antidepressant use were examined in patients on insulin or oral hypoglycaemic agents. Use of a tricyclic was significantly higher in patients on beta-blockers (23% in a two year period) than in those on hydralazine or hypoglycaemics (both 15%) and methyldopa or reserpine (both 10%). These differences could not be accounted for by differences

in age or sex or the co-existence of other cardiac disease. Prescription of tricyclics may not however be a true reflection of depressive illness as such but may be indicative of the presence of central nervous system side-effects such as fatigue, drowsiness and malaise which might have prompted a trial of antidepressants.

Assessment of the psychiatric effects of antihypertensive drugs was carried out by Mann (1977; 1981) as part of the Medical Research Council (MRC) study of the treatment of mild hypertension. Patients were allocated to treatment with propranolol up to a maximum dose of 240 mg/day, bendrofluazide 5 mg twice daily or placebo. The psychiatric state of the patients was assessed by the General Health Questionnaire (Goldberg,1978) on four occasions between recruitment and the completion of one year in the trial. A group of normotensive subjects acted as a control group. Trial participants were found to have lower levels of psychiatric morbidity than controls as the trial progressed. Medication, whether propranolol, bendrofluazide or placebo, had no influence on psychiatric morbidity. The improvement in psychiatric status in treated patients was thought to be due to the favourable effects on those prone to psychiatric symptoms of regular attendance at a clinic and contact with caring professional staff.

There are a number of reports of acute brain syndromes occurring in patients on beta-blockers. Fraser and Carr (1976) described two patients who became acutely unwell with symptoms of delusional thinking, auditory hallucinations and agitation. One of the patients also exhibited disorientation, ataxia and clumsiness. Symptoms had their onset within days of commencing on propranolol and cleared completely within a week

of drug withdrawal. Remick et al (1981) described a mentally retarded woman who developed symptoms of agitation, insomnia, emotional lability, disorientation and hallucinations shortly after commencing on a low dose of propranolol. Her symptoms remitted rapidly after drug discontinuation and reappeared on further administration. A similar presentation was described in a patient on propranolol by Voltolina et al (1971). Stienert and Pugh (1979) described two patients who developed schizophrenia-like symptoms shortly after their dose of beta-blocker was increased. One patient was on propranolol and the other on oxprenolol. Neither patient had a past history of mental illness, although one had a strong family history of schizophrenia. In both, symptoms remitted shortly after discontinuation of beta-blocker. A patient described by Viadero et al (1983) developed vivid dreams and lapses of short-term memory two days after commencing on atenolol. Within two weeks he became markedly confused, aggressive and violent. His symptoms settled within two days of admission to hospital. Topliss and Bond (1977) reported on a 71 year old female who became confused, paranoid and restless with jerky, involuntary movements after being given propranolol as treatment for symptoms of hyperthyroidism. Her symptoms cleared six hours after discontinuation of propranolol. There was no other apparent explanation for her mental deterioration. She had a past history of depression. Helson and Duque (1978) reported the case of a twelve year old girl suffering from both lymphoma and hypertension who became disorientated and agitated and then comatose with hyperreflexia three days after commencing on propranolol. Her symptoms cleared completely three days after the drug was stopped. Whitlock and Bonfield (1980) described a sixty year old man who developed delusions, visual hallucinations and

disturbed sleep after being on propranolol for six months. He had a long history of heavy drinking. His symptoms remitted twelve days after admission to hospital, two days after propranolol was withdrawn. Gershon et al (1979) reported on a young woman who was a volunteer in a study of the physiological effects of propranolol. As the dose of propranolol was increased her mental state deteriorated. She initially experienced irritability and vivid nightmares and then developed auditory hallucinations, delusions, depression and poor concentration. All her symptoms cleared within a day of stopping the drug. Russell et al (1979) described the case of a young man with a history of head injury and encephalitis who developed generalised seizures after being given atenolol.

Most of the cases of severe mental disorder occurred in patients in whom there were other possible predisposing or precipitating factors, such as a past psychiatric history, the presence of coincident physical disease or, in one case, a strong family history of mental illness. This suggests that the mental illness was either coincidental with no causal relationship to drug treatment or that beta- blockers rarely produce florid psychiatric or neurological symptoms in the absence of some other factor which renders the patient vulnerable to these. Although the majority of reports are concerned with patients on treatment with propranolol, it is of interest that hydrophilic beta-blockers such as atenolol may also cause acute psychiatric disorder.

An interesting side-effect of beta-blockers is the experience of visual hallucinations. Hinshelwood (1969) described the case of a fifty-three year old man who developed frightening visual hallucinations after

commencing on propranolol. These ceased ten days after drug discontinuation and reappeared on subsequent administration. Fleminger (1978) found visual perceptual disorders in eleven out of a group of sixty-three patients on propranolol. Six patients experienced visual hallucinations; visual illusions occurred in ten. All these symptoms occurred in either a hypnogogic or hypnopompic state. They were often accompanied by nightmares and vivid dreams. The onset occurred in four patients one week after an increase in dose.

Sleep disturbance has long been recognised as a side-effect of beta-blockers (Paykel et al, 1982). Betts and Alford (1983) found disturbed sleep with the lipophilic drugs propranolol, metoprolol and pindolol but not with atenolol which is hydrophilic. Subjective effects occurred without marked EEG changes.

ANGIOTENSIN CONVERTING-ENZYME INHIBITORS

The angiotensin converting-enzyme inhibitors, or A.C.E. inhibitors, are one of the most recently introduced groups of antihypertensive agents. The first drug of this group to come into clinical use was captopril (Atkinson and Robertson, 1979). Captopril contains a sulphydryl group and it is thought that this part of the molecule is responsible for some of the side-effects of captopril such as rashes, taste disturbances, proteinuria and Guillane-Barre neuropathy. This led to a search for a non-sulphydryl-containing A.C.E. inhibitor and to the development of enalapril (Gavras et al, 1981). Enalapril has subsequently been shown to

be associated with a lower incidence of taste disturbances and rash. Enalapril has not been associated with leucopenia (Todd and Heel, 1986). A recently recognised side-effect is a dry cough which has been reported with both enalapril and captopril (Coulter and Edwards, 1987). This is usually severe enough to prompt withdrawal of treatment. The mechanism is unknown but possible mediators include bradykinin and prostaglandin.

The most likely mode of antihypertensive action is inhibition of the conversion of the inactive decapeptide angiotensin I into the octapeptide angiotensin II, a potent pressor agent. This leads to increased plasma renin activity and decreased levels of angiotensin II. Reduced levels of angiotensin II will lead to decreased blood pressure mainly by decrease in total peripheral resistance. This is acheived without significant change in heart rate or cardiac output. It has been shown that cereral blood flow is preserved when arterial pressure is lowered by A.C.E. inhibitors and that this effect may be due to a shift in the limits of cerebral blood flow regulation towards lower blood pressure values (Waldemar and Paulson, 1989). Angiotensin II increases pre-junctional release of noradrenaline in response to sympathetic stimulation and the pressor effect of this can be blocked by captopril and enalapril. Captopril also leads to reduction in circulating levels of aldosterone. This effect is unlikely to be critical for the anti-hypertensive action as some studies have shown that aldosterone levels increase during prolonged captopril treatment despite continuing low levels of angiotensin-II (Edwards and Padfield, 1985).

There are to date few studies of the psychological effects of the A.C.E. inhibitors. The subject is one of great interest to psychiatry.

Angiotensin converting enzyme is present in the brain and there is evidence that it may also play a role in the metabolic degradation of met-enkephalin, one of the so-called "endogenous opiods" (Benuck and Marks ,1979; Erdos et al,1978). A study by Stine et al (1980) sugested that captopril might inhibit the in situ metabolism of met-enkephalin in rats when it is administered directly into the cerebral ventricles. The potential for central effects depends on the ability of A.C.E. inhibitors to penetrate the brain. One study in rats found no evidence that captopril administered intravenously entered the central nervous system (Heald and Ita, 1977).

With regard to observed effects in man, Zubenko and Nixon (1984) described three patients in whom elevation of mood appeared to be related to the administration of captopril. Two of the patients were elderly men suffering from congestive cardiac failure in whom captopril was substituted for hydralazine and diuretics. The first patient had been troubled with typical depressive symptoms in the weeks prior to starting on captopril. These symptoms disappeared on administration of captopril. The second patient felt better when a small dose of captopril was commenced but developed agitation, insomnia and delusional thinking on higher doses. The third patient was a forty-four year-old woman admitted to a psychiatric hospital suffering from psychotic depression. Captopril was prescribed as treatment for hypertension. This was followed by an improvement in her symptoms in the four days following commencement of the drug which was maintained despite reduction in dosage over several days and then discontinuation. Goldblatt and Bryer (1987) described the case of a patient with Huntington's disease who

became bed-bound, uncommunicative, rigid and incontinent. No other cause was found for her symptoms which remitted five days after drug discontinuation. It was suggested that inhibition of angiotensin converting enzyme in the brain may have been responsible as it is known that this enzyme is diminished in the corpus striatum and substantia nigra of patients with Huntington's disease (Arregui et al, 1979).

THIAZIDE DIURETICS

Thiazide diuretics are among the most widely used antihypertensive agents. Their hypotensive effect is acheived by lowering of intravascular volume and reduction of peripheral vascular resistance by diminishing the responsiveness of vascular smooth muscle to noradrenaline (Laurence and Bennett, 1987).

Concern has been expressed about the metabolic effects of thiazides such as potassium depletion, adverse effects on serum lipid concentrations and hyperuricaemia (Oliver, 1983). A substudy of the M.R.C. study examined the effect of bendrofluazide on ventricular ectopic beats and found a significant excess in patients who had been on treatment for an average of two years (Medical Research Council Working Party, 1983). While it has not been conclusively demonstrated that this was due to potassium depletion, this possibility remains (Robertson, 1987). Another substudy found an unexpectedly high incidence of erectile impotence in men on bendrofluazide (Medical Research Council Working Party, 1981). Perhaps in view of the peripheral actions of these drugs, there have been no listed trials examining their effects on the central nervous system.

ANTI-HYPERTENSIVE MEDICATION AND "QUALITY OF LIFE"

A recent development in the study of the psychological effects of antihypertensive drugs has been to broaden the search for adverse effects into areas which may be conceptualised in terms of impaired quality of life rather than the presence of formal psychiatric disorder. Quality of life has usually been assessed in two broad areas. The first of these is subjective well-being, which may be judged in terms of freedom from physical or mental symptoms. The second area concerns performance and satisfaction in normal social roles such as work, family life and leisure.

Quality of life is an inherently complex, nebulous and idiosyncratic entity. This is captured very well in a poem entitled "Ode to Propranolol" (Benson, 1985). The poet, who is a physician, describes how his emotional responses to the beauties of art and nature have been blunted by this drug, and goes on to question whether the benefits of medication are not outweighed by what he has lost. Assessment of all areas contributing to happiness and well-being in a group of patients would be highly laborious and research must begin by reducing the field of enquiry to areas which are of manageable proportions, broad applicability and demonstrable validity.

The largest and most comprehensive study of the effects of drug treatment of hypertension on quality of life performed to date is that of Croog et al (1986). 626 patients were recruited, of whom 486 were

followed up over twenty-four weeks of active treatment. The patients were white men in full-time employment with mild to moderate hypertension (diastolic blood pressure 92-109 mmHg). On recruitment, patients were placed on placebo for four weeks. Baseline assessment was performed at the end of this period and patients were then randomly allocated to receive therapy of standard doses of either captopril, methyldopa or propranolol. If blood pressure control was unsatisfactory after eight weeks hydrochlorthiazide was prescribed. Quality of life was assessed by well-validated rating scales relating to general well-being, physical symptoms, sleep dysfunction, sexual functioning, work performance and satisfaction, emotional state, social participation, life satisfaction and cognitive impairment. Comparisons were made between scores at baseline and at twenty-four weeks.

At the end of the study, the captopril patients were rated better than the methyldopa group in respect of general well-being, physical symptoms, sexual dysfunction, work performance and satisfaction with life. Patients on propranolol rated better than those on methyldopa in terms of work performance. Scores of the captopril group were favourable with regard to general well-being, physical symptoms and sexual dysfunction when compared to the propranolol group.

Patients receiving captopril were least likely to withdraw from treatment because of adverse effects (8% versus 20% for methyldopa and 13% for propranolol). Significantly fewer patients on propranolol (22%) required treatment with a diuretic compared to captopril (33%). 28% of the methyldopa patients required diuretic treatment which was not significantly different from the other groups.

This study entailed enormous effort. A large cohort of patients was followed up over a lengthy period of treatment. The homogeneity of the group in terms of demographic background means that the results cannot be readily extrapolated to populations dissimilar with respect to sex, race and employment status. Where statistically significant differences were found these were often small and unlikely to be of clinical importance. No effort was made to obtain an account from relatives of changes in patients' happiness and behaviour. Specific side-effects of angiotensin-converting enzyme inhibitors, such as cough, were not addressed. A recently introduced drug, captopril was compared with two old-established agents. It may have been more appropriate to compare captopril with newer and increasingly popular drugs such as the hydrophilic beta-blockers which may have less tendency to cause psychological side-effects.

Dahlof et al (1985) assessed quality of life as part of a trial of the antihypertensive effects of enalapril. Patients were withdrawn from their previous medication and placed on placebo for four weeks. They were then treated with enalapril for twelve weeks. Quality of life was assessed by a new scale devised by one of the authors. Scores on the scale improved when patient were changed to placebo and were not impaired by subsequent treatment with enalapril. Unfortunately, neither this paper nor another describing the scale contains much information about its structure and scoring (Jern, 1985). It is therefore difficult to assess what significance should be inferred from changes in scores and whether the instrument is, indeed, a valid measure of quality of life.

Jachuck et al (1982) assessed quality of life in seventy-five patients on antihypertensive medication using questionnaires given to patients, their general practitioners and a relative or close companion. Each informant was asked to assess if the patient was, overall, improved, worse or unchanged since commencing on therapy. In addition patients and relatives completed a questionnaire which inquired into important aspects of well-being.

Thirty-six patients received beta-blocking drugs (nineteen also received diuretics), eighteen received methyldopa (thirteen were also on diuretics), nine received diuretics alone and six patients were on other antihypertensive agents.

The overall assessment of the physicians was that all seventy-five patients had improved. Of the patients themselves, thirty-six felt better, seven felt worse and thirty-two rated themselves as being unchanged. In striking contrast, the assesment of relatives was that, with one exception, the patient was worse since starting on therapy.

Deteriorations highlighted by the questionnaire included undue preoccupation with sickness, irritability and decline in energy, general activity and sexual activity.

This study is interesting as it highlights large discrepancies in how the condition of the patient is perceived by different observers. Especially notable is the lack of awareness on the part of physicians of deterioration in the quality of life of their patients. A major strength

of the paper is that it sought information from an independent informant. The retrospective study design does not allow one to draw conclusions as to whether the decline in quality of life was due to treatment itself or to other factors such as illness labelling. Patients were on a variety of different drugs; the duration of treatment was not specified. The existence or otherwise of hypertension-related physical morbidity was not mentioned. There are therefore many factors which could explain a decline in quality of life in this group some of which are independent of the processes of diagnosis and treatment.

ANTIHYPERTENSIVE DRUGS AND MENTAL FUNCTIONING

Many antihypertensive drugs penetrate the central nervous system; an important potential adverse effect therefore is impairment of intellectual functioning. This issue deserves attention as patients will usually be expected to remain on treatment for many years if not for life. Small decrements in mental ability may be tolerable in short term treatment. The imposition of impairment, even of a minor nature, is less acceptable in the long term. In addition, there are certain occupations, such as airline pilots and air traffic controllers, in which it is essential to maintain optimum levels of mental functioning.

Patients whose occupation demands a high level of mental acuity may be more aware of mental impairment. Adler (1974) described five case reports of professional patients who experienced lapses of memory, problems with reading and difficulty with simple calculation while on methyldopa. In all cases symptoms disappeared promptly on discontinuation of the drug.

Most of the research done in this area has concerned the beta-blocking drugs, although a few papers also mention methyldopa and other drugs.

BETA-BLOCKERS

SINGLE DOSE STUDIES

Bryan et al (1974) examined the effects of propranolol on tests of visual function and central nervous system activity. Six normal volunteers received propranolol at doses of 40mg and 80mg. There was no effect on visual function but slowing of reaction times was found after both doses of drug.

Goldman et al (1969) studied the effects of single doses of alprenolol on simulated driving performance in six healthy volunteers. There was no difference in driving errors when performance after medication was compared with that following placebo. Bayliss and Duncan (1975) studied the effects of single doses of atenolol (50mg or 100mg) and methyldopa (250mg or 500mg) on tests of reaction time (RT) and critical flicker frequency (CFF) and on levels of drowsiness as assessed by visual analogue scale, in six normal volunteers. Methyldopa caused an increase in reaction time, this being more marked at the higher dose, and an increase in subjective drowsiness. Atenolol had no effect on any of the variables measured.

Ogle et al (1976) investigated the effects of high doses of propranolol and oxprenolol on pursuit rotor performance (PRP), reaction time and critical flicker frequency. There was no discernible effect on RT and CFF. Impairment on PRP was found but was attributed to a peripheral effect on skeletal muscle. Levander and Gillner (1982) studied the

effects of propranolol (40mg) and metipranolol (5 and 20mg) in twelve normal volunteers using a variety of assessments (digit span, perceptual maze, vigilance measures, pain perception and CFF). No decreases in performance were noted.

Similar conclusions were reached by Lader et al (1972) who found no impairment on a variety of neurophysiological and behavioural measures after administration of propranolol (120mg) or sotalol (240mg) to six normal subjects.

Salem and McDevitt (1983) studied the effects of single doses of atenolol (50mg, 100mg, 200mg and 400mg) on performance of tests of two flash fusion threshold (TFFT), simple reaction time (SRT), symbol digit modalities test (SDMT), and the Gibson Spiral Maze Test (GSMT) on six normal volunteers. In comparison with placebo, performance was poorer on all tests with the exception of the GSMT. A later study with a similar design using propranolol at doses of 40mg, 80mg, 160mgand 320mg produced comparable results (Salem and McDevitt, 1984).

STUDIES IN HYPERTENSIVE PATIENTS

Solomon et al (1983) studied the effects of propranolol and methyldopa on tests of verbal and non-verbal memory. Four groups of patients were studied; 1) hypertensive patients on methyldopa and diuretic (10 patients); 2) hypertensives on propranolol and diuretic (11 patients); 3) hypertensives on diuretic alone (12 patients) and; 4) nonhypertensives on propranolol (8 patients, on treatment for migraine,

angina, arrhythmias and familial tremor). When compared with the diuretic group patients on methyldopa and propranolol scored poorly on tests of verbal memory. Performance on tests of visual memory was not impaired. This study therefore raises the possibility that verbal memory can be impaired by propranolol and methyldopa. The diuretic-only group acted as a control for the presence of hypertension. The fact that patients in this group were adequately controlled on single drug treatment implies that their hypertension was of lesser severity. In addition some of the non-hypertensive patients had conditions such as angina which may be associated with cerebro-vascular disease. In brief, the poor performance of the propranolol and methyldopa-treated patients may be to some extent attributable to the severity of their underlying disease.

Fransceschi et al (1982) compared cognitive performance in fifteen normotensive patients, seventeen newly-diagnosed, untreated hypertensives and twenty-two treated hypertensives. Both hypertensive groups performed poorly on a variety of tests. Patients on anti-hypertensive drug treatment (diuretics plus propranolol or reserpine in four and three patients respectively) did poorly on tests of attention. This study is of interest but used a small sample and a large number of comparisons. Some of the observed differences may have arisen by chance. The design of the study does not allow exclusion of the possibility that performance of the hypertensive patients was impaired by minor cerebrovascular disease not detectable on routine neurological examination.

Madden et al (1986, 1988) studied the effects of atenolol and propranolol in a group of twenty-six men with mild hypertension. Atenolol was commenced at a dose of 50mg which was increased to 100mg if response was inadequate; propranolol was used at a dose of 40 mg increasing to 80 mg. After two weeks on medication or placebo, a test was administered which was based on a memory search paradigm. No differences were found when performance on drug treatment was compared to placebo.

A.C.E. INHIBITORS

Lichter et al (1986) examined the effects of atenolol and enalapril on memory in patients with essential hypertension. All patients completed a battery of associate learning tests after two weeks on placebo. They were then randomly allocated to receive atenolol (13 patients) or enalapril (12 patients) and retested after sixteen weeks of active treatment. When compared to placebo, the enalapril patients showed no changes in memory function, whilst there was a mild memory deficit in those on atenolol.

Olajide and Lader (1985) carried out a double -blind cross-over trial of the psychotropic effects of enalapril in twelve normal subjects treated with enalapril 20mg daily for fourteen days. Subjects were assessed by physiological measures (electroencephalogram, auditory evoked responses, skin conductance and CFF), psychological measures (digit-symbol substitution, symbol copying, auditory reaction time and tapping rate) and subjective ratings of mood and bodily symptoms. Increased alertness

on enalapril was suggested by an increase in auditory evoked responses and tapping rate. Despite this nine subjects complained of tiredness on enalapril compared to only two on placebo. No other drug effects were noted.

Frcka and Lader (1988) examined the psychotropic effects of enalapril 20mg, propranolol 160mg and atenolol 50mg each given daily for eight days to twelve normal voluteers. Assessments were similar to the preceding study with the addition of a test of verbal memory and a sleep questionnaire. Electroencephalogram changes were noted at the end of the propranolol phase but were not consistent in the case of the other drugs. Reaction time, symbol copying and verbal memory were significantly impaired with propranolol. Verbal memory was mildly affected by atenolol. Subjects showed improvements in tapping rate but impaired verbal memory on enalapril. Enalapril was associated with a feeling of calmness but also an increase in complaints of headache. Complaints of drowsiness were commoner with propranolol.

CALCIUM-CHANNEL BLOCKERS

The calcium-channel blockers are increasingly used in treatment of hypertension, effort angina and angina due to coronary artery spasm. Their mode of action is antagonism of calcium influx through the slow channel of the cell membrane. This leads to dilatation of the coronary and peripheral arteries with resulting reduction in systemic vascular resistance and improvements in myocardial oxygen supply. Cardiac pumping

ability is improved by decreased afterload (Sorkin and Clissold, 1987).

There is increasing interest in the effects of calcium channel blockers on the central nervous system. Walden et al (1985) found that verapamil could suppress epileptiform activity in an in vitro model of epilepsy. Larkin et al (1988) reported a pilot study of the use of nifedipine in a group of patients with intractable epilepsy, with approximately half of the patients achieving a greater than fifty percent decrease in seizures over a three month follow-up period.

Calcium antagonists have also been used in the treatment of various disorders characterised by abnormal movements. Barrow and Childs (1986) described a dramtic improvement in neuroleptic-induced tardive dyskinesia in two patients given verapamil. Ley et al (1988) carried out a small double-cross-over study of the effects of diltiazem on tardive dyskinesia and found a reduction of abnormal movements on active treatment. The mechanism of this effect is unknown. An anti-dopaminergic effect has been postulated although Dogget and Mercurio (1989) found no evidence for such an effect in experimental animals.

Calcium antagonists have been reported to cause cerebral vasodilatation in animal experiments (Takenaka and Handa, 1979; Yamamoto et al, 1983). Thuillez et al (1984) reported that oral nicardipine increased carotid artery diameter and blood flow in humans. There are however reports of cerebral and retinal ischaemia being caused by nifedipine (Nobile-Orazio and Sterzi, 1981; Pitlik et al, 1983). The proposed mechanism is "steal" of blood flow from areas served by atheromatous vessels which do not respond to the vasodilating effect.

It has been suggested that calcium influx to cells may produce cellular injury during reperfusion following cerebral injury (Borzeix and Cahn, 1983; Grotta et al, 1984; Gelmers, 1987). The calcium antagonist, nimodipine has been shown to improve cerebral reperfusiion and survival after ischaemic damage in cats (Kazda et al, 1979) Similar results with regard to blood flow were obtained in dogs by Iwatsuki et al (1987). Sakabe et al (1986), in a study in dogs found improvements in post-ischaemic cerebral blood flow but no associated improvement in neurological recovery. A study in patients with multi-infarct dementia using nimodipine found no evidence of benefit as assessed by clinical ratings, psychometric testing and sequential magnetic resonance imaging (Besson et al, 1988).

A large British study assessed the effect of oral nimodipine on outcome after subarachnoid haemorrhage (Pickard et al, 1989). Patients on nimodipine had a significantly lower incidence of cerebral infarction and poor outcome (death, vegetative state or severe disability). The mechanism of the beneficial effect was unclear. It was postulated that the drug may have acted to prevent vasospasm in small cerebral arterioles or had an undetermined effect on neuronal functioning which served to diminish damage.

ASSESSMENT OF PSYCHIATRIC SIDE-EFFECTS OF ANTIHYPERTENSIVE DRUGS

The realm of possible psychological effects of anihypertensives is one which is potentially very large. It ranges from formal psychiatric illness to mild effects which may be considered under the rubric of "quality of life". In addition to psychiatric well-being, quality of life embraces the areas of intellectual functioning and physical well-being. Quality of life may also be considered in terms of ability to perform satisfactorily, and derive enjoyment from, the important activities of life such as work, marriage, family life and leisure.

Assessment of psychological well-being in this situation is therefore potentially very complex. The decisions about which assessments should be performed entailed finding a compromise between the wish to be comprehensive and a recognition of constraints on the time available for both staff and patients. It was felt that assessment should cover the areas of a) psychiatric symptoms, b) social functioning and c) intellectual functioning. The patient group under study was one that was to be involved in a range of physical investigations as well as psychological assessments. It was estimated that a maximum time of around thirty minutes would be available. In addition, time spent waiting would be available for the completion of self-report questionnaires.

The studies were designed to test the following hypotheses:-
a) that antihypertensive drugs have adverse effects on mental well-being
b) that antihypertensive drugs cause impairment in functioning in normal social roles

c) that antihypertensive drugs cause decrements in mental faculties such as memory and concentration.

Psychiatric symptoms.

Psychiatric symptoms were principally assessed by the sixty-item General Health Questionnaire (Goldberg, 1978). This is a self-administered questionnaire which was developed to allow detection of psychiatric morbidity in general practice and general medical populations. Four seven-item subscales have been derived from the main questionnaire which allow examination of the areas of somatic symptoms, anxiety and insomnia, social dysfunction and severe depression.

Assessment of the validity of the questionnaire was carried out using a structured psychiatric interview. The interview used was the Clinical Interview Schedule (Goldberg et al, 1970). Again, this was developed for use in the general population. The author received special training in its use. The interview is semi-structured, is fairly brief to administer in the asymptomatic patient and is readily acceptable to non-psychiatric patient populations. It allows a reliable and valid asessment of "case" status and can be used to obtain a psychiatric diagnosis in terms of the ninth edition of the International Classification of Diseases (W.H.O., 1978).

Social functioning.

This was assessed using the self-report form of the Social Adjustment Schedule (Weissman and Bothwell, 1976; Weissman et al, 1978). This scale was developed to measure social adaptation in psychiatric populations. Cooper et al (1982) demonstrated the validity of the scale in a British population. They showed that the scale was sensitive to changes in mental state in a group of non-psychiatric patients who showed levels of psychiatric morbidity similar to the general population. Age and social class had no influence on overall scores or scores in the different subscales. The scale investigates ability to fulfil social roles in the areas of work, spare time activities and marriage and family life. Responses to questions are weighted according to level of maladjustment. The complete questionnaire is not applicable in every patient. An overall social adjustment score is obtained by calculating the average of all responses.

Intellectual Functioning.

Limitations on available time meant that assessment of intellectual functioning had to be confined to selected areas. The trial was carried out in three different hospitals thus precluding the use of non-portable equipment. It was decided to include tests of verbal memory, non-verbal memory, and attention and concentration.

The following battery of tests was performed:

a) Wechsler Memory Scale Subtests (Wechsler, 1945). i) "Logical memory" tests ability to recall verbal material, ii) "digits forward" assesses passive apprehension of new information, iii)"digits backward" tests immediate memory and iv) "associate learning" tests ability to learn new verbal material.

b) Complex Figure Test (C.F.T.) (Rey, 1942; Taylor, 1969). The subject first copies a complex abstract figure. On completion, the figure is removed and he attempts to reproduce it from memory. Reproduction is then repeated after twenty-five minutes. The test assesses constructional abilities and the ability to memorise and organise complex non-verbal information. Each component of the figure was rated according to accuracy of reproduction and position in the figure and the scores summated to yield an overall score as described in Lezak (1983).

Tests a) and b) exist in two comparable forms. Subjects were randomly allocated to receive one or the other at the time of initial testing and received the alternative form after a period of active treatment.

c) Digit Symbol Substitution Test (Wechsler, 1955). This is a subscale of the Wechsler Adult Intelligence Scale. It assesses psychomotor speed and coordination.

d) Paced Auditory Serial Addition Task (P.A.S.A.T.) (Gronwall and Sampson, 1974; Gronwall and Wrightson, 1974). The subject listens to a taped presentation of sixty randomised digits and attempts to add each digit to the one immediately preceding it. His verbal responses are

recorded by the examiner. The series of digits is presented twice. On first hearing the digits are presented at two second intervals and on second hearing at 1.6 second intervals. The test assesses speed and efficiency of information processing.

STUDIES OF THE PSYCHOLOGICAL SIDE-EFFECTS OF ANTIHYPERTENSIVE MEDICATION

Three studies performed by the author will be described. The first is a pilot study carried out to investigate the psychological effects of captopril. The results of this trial provided the stimulus for the other two. These investigations were of single drug treatment in patients with mild-moderate hypertension. The larger trial of the two looked at the effects of atenolol and enalapril on a number of measures of psychological well-being and social functioning. The smaller study was of similar design but investigated the effects of propranolol and nicardipine.

STUDY I : PSYCHIATRIC SIDE-EFFECTS OF CAPTOPRIL

INTRODUCTION

This trial was stimulated by a succession of anecdotal reports of spontaneous comments by patients of an enhanced sense of well-being after commencing on captopril as treatment for hypertension. These were usually patients previously subjected to complex drug regimes. Whilst a greater feeling of well-being may be an advantage, a definite euphoriant effect might create problems for patients.

The possibility of a mood-elevating effect is of theoretical and practical interest to psychiatry. As discussed above there is evidence

from animal studies that angiotensin converting enzyme may involved in the metabolism of met-enkephalin, one of the "endogenous opioids" and that centrally-administered captopril may inhibit breakdown of this peptide. If converting enzyme inhibitors were shown to have such an effect then further insight into the biochemical control of mood might be obtained along with the possibility of novel treatments for depression.

The hypothesis to be tested therefore was whether angiotensin-converting enzyme inhibitors create improvements in mental well-being either by relieving psychiatric symptoms or by creating an abnormal elevation of mood.

PATIENTS

Eight patients with moderately severe hypertension entered the study after informed consent was obtained. There were four women and four men; their mean age was 51 years. Patients were excluded if there was a history of cerebrovascular accident; evidence of organic brain damage or impairment; a history of schizophrenia or affective psychosis; if they had received any psychotropic medication other than benzodiazepines within three months of entry; if they had heart failure; or had severe renal impairment.

Apart from captopril, the only antihypertensive drugs used during the study were atenolol and bendrofluazide. At least four weeks before the start of the trial, antihypertensive therapy was standardised and remained fixed for each subject throughout. One patient also received

diazepam 5mg/day for four weeks before the start and throughout the study.

PROTOCOL

The study period was 12 weeks with patients seen at 0, 3, 6, 9 and 12 weeks. At the start (i.e. at least 4 weeks after standardization of atenolol and bendrofluazide doses), patients were randomly allocated to receive captopril 25 mg three times daily or matching placebo for the first 6-week period, with crossover to placebo or captopril respectively for the second 6-week period.

At each visit, supine blood pressure and pulse rate were measured. Specimens were sent for estimation of serum electrolytes, full blood count and urinary protein. At weeks 3 and 9, after 30 minutes lying supine and two hours after dosing, blood was drawn for measurement of plasma active renin concertration and angiotensin II.

Patients and observers remained unaware of the treatment code although this was available in sealed envelopes in the event of an emergency.

Psychological assesment was performed at weeks 3, 6, 9, and 12, before blood pressure measurements and blood samples were obtained. At these visits a tablet count was made to assess compliance.

Psychiatric state was assessed using the sixty-item General Health Questionnaire (Goldberg, 1978). Attention and concentration were assessed by the Paced Auditory Serial Addition Task (Gronwall and

Sampson, 1974). A mania rating scale was administered to record and quantify features of elevated mood (Young et al, 1978). Statistical analysis was by the Wilcoxon matched pairs test (Siegel, 1956).

RESULTS

Three of the patients received captopril before placebo; the other five received placebo first. No subject required intervention because of poor blood pressure control. There was no instance of proteinuria, leucopenia, electrolyte disturbance or skin rash. Taste impairment occurred in one patient at Week 11 while taking captopril.

Tablet counts were correct on all occasions. In all patients, plasma renin concentrations were higher and angiotensin II concentrations lower, during the period of captopril therapy. Comparing captopril with placebo overall, mean blood pressures were significantly lower (164/98 mm Hg + 9/3 SEM vs 176/101 + 8/2; $p < 0.05$), plasma active renin was higher (50 + 19 micro U/ml vs 23 + 7; $p < 0.05$), and angiotensin II reduced (9.3 + 1 pg/ml vs 15.1 + 3; $p < 0.05$).

PSYCHOLOGICAL TESTING

GENERAL HEALTH QUESTIONNAIRE. All except one subject had higher mean overall scores when on captopril than when on placebo. This difference was statistically significant ($p < 0.05$) (Table 1). Analysis was further pursued by considering separately those subscales addressing somatic

symptoms, anxiety and insomnia, social dysfunction and severe depression (Goldberg and Hillier, 1979). In all subgroups of questions, except those dealing with depression, average scores were higher during the captopril than the placebo phase. No particular symptom subgroup, therefore, made a disproportionate contribution to the differences in total score.

PACED AUDITORY SERIAL ADDITION TASK. No differences were found between captopril and placebo (Table 2).

MANIA RATING SCALE. No subject at any time had a score suggestive of abnormal elevation of mood (Table 3).

STUDY II: ATENOLOL AND ENALAPRIL

INTRODUCTION

The purpose of this study was to assess a recently-introduced angiotensin converting enzyme inhibitor, enalapril, and to compare it to the beta-blocker, atenolol, in terms of its efficacy in the treatment of mild-moderate hypertension and with regard to its impact on psychological and physical well-being.

Enalapril lowers peripheral vascular resistance by producing decreased plasma levels of angiotensin II. Blood pressure is lowered without causing an increase in heart rate. At doses of 10 to 40 mg per day, it is effective in lowering blood pressure in all grades of essential and renovascular hypertension (Todd and Heel, 1986). In mild to moderate hypertension, enalapril has been shown to be as effective as hydrochlorothiazide (Vidt, 1984; Bauer and Jones, 1984) and the beta-blockers propranolol, (Enalapril in Hypertension Study Group, 1984) metoprolol (O'Connor et al, 1984) and atenolol (Arr et al, 1984). Adequate control of blood pressure has been acheived in fifty to seventy-five percent of patients given enalapril alone. Adequate control in the remainder of patients can usually be attained with the addition of a diuretic.

The majority of reported side-effects are mild, transient and are often seen in similar frequencies in patients on placebo. Those most frequently reported are headache, dizziness, fatigue, diarrhoea, nausea, rash, cough, hypotension and angioneurotic oedema.

Patients

Patients were recruited in three centres covered by the Glasgow Blood Pressure Clinics namely the Vale of Leven Hospital, Glasgow Royal Infirmary and Glasgow Western Infirmary.

All patients sufferred from mild to moderate hypertension with supine blood presure of 140-220 mmHg systolic and/or 90-119mmHg diastolic on three occasions during a four week phase of treatment with placebo alone.

Patients with known secondary hypertension, accelerated phase hypertension, cerebrovascular disease, myocardial infarction within the previous six months, renal impairment (serum creatinine > 144 micromol/l), a history of psychotic or major affective illness, or any contra-indication to either of the trial treatments were excluded.

Study Design

After a four week placebo run-in period, patients whose blood pressures fulfilled the criteria stated above were randomised to receive either enalapril or atenolol in parallel groups. The use of a parallel placebo group was considered but it was judged to be ethically unacceptable to have patients on no active medication for the duration of the trial. Each centre had a separate randomisation process which was stratified for previous drug treatment. The study was conducted double-blind using a double-dummy technique. Treatment was continued for twelve weeks and

patients were reviewed at two, four, eight and twelve weeks after randomisation. The aim was to reduce systolic blood pressure to 140 mmHg or less and diastolic pressure to 90 mmHg or less.

The initial dose of medication was enalpril 20 mg or atenolol 50 mg, each taken once daily in the morning. If blood pressure did not reach the stated target at four or eight weeks after randomisation, the dose was increased to enapril 40 mg or atenolol 100 mg each taken once daily.

The full range of assessments, as described above, was performed on each subject on two occasions, firstly at the end of the four week placebo phase and secondly after twelve weeks of active treatment. The Clinical Interview Schedule was administered to a random sample of patients on the same day as they completed a General Health Questionnaire. The interviewer was blind to the result of the questionnaire. Assessments were performed at approximately the same time of day.

In addition, subjects were seen at two, four, eight and twelve weeks for physical assessment. At each visit, patients were weighed and had their blood pressures and pulse rates recorded erect and supine in the right arm after fifteen minutes of rest. Blood pressure was estimated with the arm supported at heart level using a random zero sphygmomanometer, recording phase V diastolic pressure. Tablet counts were carried out at each visit and urinary drug assay on two occasions at four and twelve weeks after randomisation. Haematological and biochemical monitoring, including measurement of plasma renin was performed at the end of the placebo phase and at the end of the active treatmnet phase. The patient was in a supine position for thirty minutes prior to blood being

withdrawn. Subjective side-effects were assessed at each visit by the response to a standard, non-leading question and by a questionnaire based on that devised by Bulpitt and Dollery (1973) which was administered at the end of the placebo and active treatment phases.

Statistical Methods

The sample size was determined by the need to provide a power of 0.8 to detect a difference between the drugs in blood pressure response of 8/5 mmHg with statistical significance at the 5% level. A single interim analysis was planned with the intention that psychological testing would be discontinued if clear differences ($p < 0.001$) between the treatment groups had emerged. Psychological data were analysed using the Mann-Whitney U test, with corresponding confidence intervals. All p values refer to the two-tailed significance of between-group differences.

Results

In all, 162 patients were randomised, to either atenolol (n = 76) or enalapril (n = 86). Their characteristics are described in Table 4. The groups were well-matched for important variables except for age, the atenolol- treated patients being on average four years older. Fifteen patients withdrew from the trial of whom seven were on atenolol and eight on enalapril. The blood pressure findings refer to the 147 patients who completed twelve weeks of active treatment. The average dose of medication being taken at twelve weeks was 91mg of atenolol and 33mg of enalapril.

Blood pressure and pulse rate

These measurements were not carried out by the author but formed part of the study of the antihypertensive effects of the drugs. They will be reported briefly as they have some relevance to the interpretation of the psychiatric data.

Decreases in supine systolic and diastolic blood pressure were significantly greater with enalapril than with atenolol. At twelve weeks the mean reduction with enalapril was 19.0 (SEM 1.6) / 12.4 (1.1) mmHg, compared to 8.8 (2.1) / 7.4 (1.2) mmHg for atenolol ($p < 0.001$ / $p < 0.005$). With regard to standing blood pressure the the mean reduction with enalapril was 20.1 (1.9) / 12.3 (1.4) compared to 13.3 (2.2) / 9.1 (1.4) mmHg for atenolol ($p = 0.02$ / $p = 0.10$). Adjustment for age had no important effect on the blood pressure responses described above. Thirty of the eighty-six patients (35%) randomised to enalapril achieved target blood pressure (140 mmHg systolic or less and 90 mmHg diastolic or less) at twelve weeks, compared to eleven of seventy- six patients (14%) randomised to atenolol ($p < 0.01$). Target blood presure was achieved by twenty-one patients taking enalapril 20 mg daily and by four patients taking atenolol 50 mg daily. Atenolol reduced the mean supine pulse rate by 16.6 (1.2) beats per minute, compared to an increase of 0.8 (1.1) beats per minute with enalapril ($p < 0.001$).

Adverse effects

Eight patients withdrew from the trial because of adverse effects which

were attributed to treatment and another seven for reasons unrelated to the trial. In the atenolol group, three patients withdrew respectively because of tirednesss, dizziness and impotence. In the enalapril group, five patients withdrew because of tiredness (two patients), chest pain, wheeze and cold extremities. The most common volunteered side-effects with atenolol were tiredness (16%) and dizziness (14%). With enalapril, the commonest volunteered side-effects were tiredness (17%), dizziness (14%) and headache (8%). Cough was reported by four patients on enalapril and by two patients on atenolol.

Symptom questionnaires showed no significant differences in the average number of symptoms reported per patient (atenolol 3.2; enalapril 3.0). Compared to placebo, patients reported an average of 0.5 symptoms less during atenolol treatment and 0.1 symptoms less with enalapril (95% C.I. for difference : -1.0, + 0.3). As assessed by volunteered information and symptom questionnaires, no particular symptom occurred significantly more frequently with either drug.

Psychological Data

Psychological testing was performed at weeks 0 and 12 in one hundred and thirty four patients; of these sixty-four were on atenolol and seventy on enalapril. Thirteen patients did not complete the psychological tests. Only one patient refused to participate. The majority of the remainder were missed for administrative reasons. Other patients were excluded if they experienced life events prior to randomisation or in the course of the active treatment phase which were considered likely to

affect their responses to testing. The results of the main comparisons are given in Table 5.

1) General Health Questionnaire (GHQ-60)

There was no significant change in GHQ-60 scores in either the enalapril or the atenolol group after twelve weeks of active treatment. There were no significant differences in scores between the groups either at baseline or at twelve weeks (Table 6).

The number of "cases" (patients with scores of 12 or more) fell from ten to four in the enalapril group and from nine to four in the atenolol group (Table 7).

The Clinical Interview Schedule was administered to a randomly selected sub-sample of twenty-seven patients. These patients had already completed the GHQ-60 on the same day. Only two cases were found to have scores at "caseness" level on interview; these patients also scored as "cases" on the questionnaire. The twenty-five interview "non-cases" were also "non-cases" by questionnaire. The small number of cases did not permit a formal analysis of validity. A significant correlation between total scores on the interview and the total GHQ score was found using the Kendall Rank Correlation Coefficient (tau = 0.457, significant at the 0.002 level) (Table 8).

Cognitive Functioning

a) Wechsler Memory Scale. In no subtest was there a significant change

between baseline scores an those obtained after twelve weeks of active treatment. There were no significant differences between groups at either baseline or twelve weeks (Tables 9-12).

b) Complex Figure Test. Again, there were no significant changes over twelve weeks and no differences between groups at either baseline or twelve weeks (Tables 13-15).

c) Digit Symbol Substitution Test. Scores in both groups increased between first and second testing. The increase in the enalapril group was significantly greater than in the atenolol group ($p < 0.005$) (Table 16).

d) Paced Auditory Serial Addition Task. Once more, scores increased in both groups with a significantly greater increase in the enalapril group ($p < 0.05$) (Table 17).

Social Adjustment

Social Adjustment Schedule (Self-Report). There was no change of note in either treatment group and no difference between groups at first or second testings (Table 18).

STUDY III. PROPRANOLOL AND NICARDIPINE

INTRODUCTION

A smaller study of similar design to Study II was carried out as part of an investigation of the antihypertensive effects of propranolol and nicardipine and of their effects on whole body electrolytes. This study allowed an examination of the psychological effects of a lipophilic beta-blocker and a calcium-channel blocker.

The calcium-channel blocker investigated in the present study is nicardipine, a recently introduced member of this group. Its usefulness in the treatment of mild-to-moderate hypertension is now well-established (Brown et al, 1986; Forette et al, 1985; Taylor et al, 1985). Side-effects are mostly mild, appear to be dose-related and are most frequent during the first few weeks of therapy. Vasodilation-related effects, such as flushing, headache and oedema, occur in approximately one third of patients. The other common group of side-effects are cardiovascular with symptoms such as increased anginal pains, exercise-induced hypotension, palpitions and dyspnoea.

Patients

Thirty patients were recruited from a population of general practice patients. Patient characteristics are described in Table 19. Exclusion criteria were similar to those described in Study II.

Design

The study employed a double-blind parallel design. Patients were taken off previous antihypertensive medication and placed on placebo for a four week washout phase. At the end of this phase and prior to starting active treatment, a baseline psychological assessment was performed. Subjects were then randomly assigned to receive nicardipine 30mg three times daily or sustained release propranolol 160 mg once daily for a twelve week period. Observer "blindness" was maintained using a double-dummy technique. Patients were seen for physical assessments on two occasions during the placebo phase and after three, six and twelve weeks of treatment. On each occasion, blood pressure was measured by clinic staff, with the patient both erect and supine, using a Hawksley random-zero sphygmomanometer. Pulse rate and weight were also recorded. Compliance was assessed by a tablet count at each visit. Adverse effects were elicited by a standard non-directive question. Statistical analysis was by the Mann-Whitney U test.

Results

Blood pressure and pulse rate

Again these were not recorded by the author but will be described as they are of relevance to interpretation of the psychiatric data.

In the nicardipine group, blood pressure supine was reduced from an

average of 165.1 (s.d. 18.9) systolic and 102.2 (6.0) diastolic to 151.5 (15.1) / 88.4 (11.0) ($p < 0.01$) and from 159.3 (20.0) / 104.1 (4.1) standing to 144.5 (15.4) / 88.2 (12.8) ($p < 0.01$). The propranolol patients showed a reduction of supine blood pressure from 177.7 (19.7) / 107.6 (7.5) to 160.8 (22.6) / 94.1 (12.1) ($p < 0.01$) and of standing pressure from 166.9 (21.2) / 108.3 (9.0) to 150.5 (24.4) / 95.6 (13.4) ($p < 0.01$). There were no significant differences between the treatment groups at baseline or after twelve weeks of treatment. Propranolol-treated patients had a significantly reduced pulse rate from baseline; pulse rate was unchanged in the nicardipine patients.

PSYCHOLOGICAL TESTING

The principal results and analyses are described in Table 20.

General Health Questionnaire

There were no significant changes from baseline and no significant differences between the treatment groups. Similar findings were obtained when the four sub-scales were examined.

Cognitive functioning

a) Wechsler Memory Scale. Significant changes were detected only in the digits forward sub-scale with the propranolol group showing an increase between weeks 0 and 12. Baseline performance was however lower in the propranolol patients in this test. In the logical memory, digits

backward and associate learning tests there were no significant differences between treatments and no changes over the active treatment phase.

b) Complex Figure Test

Copy score. There were no significant differences between the two groups or changes over time.

Immediate recall. There was a significant deterioration in both the nicardipine ($p = 0.005$) and propranolol ($p = 0.038$) groups, between weeks 0 and 12. Differences between the groups were not significant.

Delayed recall. There was a significant deterioration from baseline in the nicardipine group ($p = 0.017$) and a non-significant decline in the scores of the propranolol group.

c) Digit symbol substitution test

There was a significant improvement in the propranolol group between weeks 0 and 12 ($p = 0.015$); there was no change in the nicardipine group.

d) Paced Auditory Serial Addition Task.

Average scores on this test improved in both groups; this attained statistical significance only in the nicardipine group ($p = 0.015$).

Social Adjustment Schedule

There were no significant changes in scores in the period of active treatment and no differences between treatment groups.

DISCUSSION

STUDY I: PSYCHIATRIC SIDE-EFFECTS OF CAPTOPRIL

This small study provided no evidence for a mood-elevating effect of captopril. Indeed symptom scores on the General Health Questionnaire were significantly higher during the captopril phase of the trial, suggesting decreased psychiatric well-being. There was no change in scores on the mania rating scale.

Compliance in the trial was satisfactory as assessed by tablet counts, blood pressure reduction, elevation of plasma renin and lowering of angiotensin II.

In the absence of an intrinsic mood-elevating effect of captopril, the initial observations of increased well-being in captopril-treated patients remain unexplained. The most obvious possibility is that the increased well-being was due not to captopril but to the absence of the adverse physical or psychiatric effects of anti-hypertensive drugs which patients had been taking prior to commencing on captopril. The results of this study suggested a need to mount detailed studies of the psychiatric side-effects of commonly used antihypertensive drugs.

STUDY II: ATENOLOL AND ENALAPRIL

On psychological testing, the enalapril-treated patients performed significantly better than the atenolol-trreated patients on the Digit Symbol Substitution Test and the Paced Auditory Serial Addition Task. These findings should be interpreted cautiously as a large number of statistical comparisons were made and some nominally significant results might have been expected to occur by chance even if the drugs were truly no different. This seems less likely for the DSST finding which was highly significant statistically. Also, both tests measure alertness and mental speed and the results are in keeping with each other.

There was no evidence of impairment in tests of verbal and non-verbal memory and no differences between treatment groups.

There was no evidence of a decline in psychiatric well-being, as assessed by the General Health Questionnaire. There was no evidence of impaired social functioning after twelve weeks of treatment.

These results are in keeping with the many studies which have demonstrated mild impairment of mental functioning in patients on beta-blockers. There are however alternative explanations for the differences. The paper by Olajide and Lader (1985) described above raised the possibility that enalapril might have an alerting effect and this may explain the superior results obtained with enalapril. The absolute differences found between the effects of the two drugs were not large. In the case of the DSST, the difference was just over 5% of the average total score for the enalapril patients. The DSST has been

frequently used in the assessment of the cognitive side-effects of hypnotic drugs (Peck et al, 1976; Malpas, 1972). There have been several single-dose studies which have compared DSST performance twelve hours post-dosing in groups of patients taking either active drug and placebo. Differences comparable to those of the present study have been found when performance on placebo is compared with that on therapeutic doses of nitrazepam (Walters and Lader, 1971; Bond and Lader, 1972), flurazepam and butobarbitone (Bond and Lader, 1973). The difference in performance between the drugs thus approximates to a hypnotic "hangover" effect. Patients on antihypertensive treatment are usually on long-term medication in contrast to patients on benzodiazepines who should normally be on treatment for no more than a few months. The results in the present study are important in that they demonstrate differences in performance which are still detectable after three months of treatment.

A possible confounding effect arises from the fact that the antihypertensive effect of enalapril was superior in this study, which raises the possibility that the differences in test performances were due to blood pressure differences. The effects of elevated blood pressure on mental functioning have been assessed in several studies. One of the first was carried out by Wilkie and Eisdorfer (1971) who examined the effects of hypertension on intellectual functioning in the aged. High blood pressure was associated with poor performance on the WAIS and a subsequent decline in intellectual powers over a ten year follow-up period. No allowance was made for the effects of medication. In addition, there was evidence of end-organ damage in those with higher

diastolic pressures. Three studies of carefully treated groups of patients with moderate hypertension found no evidence of decline over lengthy follow-up periods (Costa and Shock, 1980; Elias et al, 1986; Schultz et al, 1986).

Boller et al (1977) found impaired performance on tests of test of reaction time and Digits Forward in a small group of patients with diastolic pressures greater than 105 mmHg. There was no evidence of poor performance on a large number of other tests, including the DSST. A substantial majority of the patients had hypertensive retinopathy which raises the possibility that the poor performance may in part have been due to occult cerebro-vascular disease and not simply to raised blood pressure.

Shapiro et al (1982) looked at cognitive performance in a small group of young untreated hypertensives with mild-moderate hypertension. They found impaired performance on a number of tests including the DSST. Inexplicably, female hypertensives performed less well than males. A follow-up study sought to examine the effects of treatment on these decrements (Miller et al, 1984). Some evidence of partial restitution of function was found although there were several anomalous findings. In neither study is the process of diagnosing hypertension described beyond the taking of a single blood pressure reading.

Wallace et al (1985) administered a test of verbal memory to a large group of elderly subjects. They found that diastolic hypertension was associated with impaired verbal memory. Hypertension was diagnosed on the basis of blood pressure readings in the course of a single visit.

No regard was paid to whether subjects were on antihypertensive medication and no attempt was made to control for this factor.

The largest comprehensive study of the relationship between blood pressure and cognitive performance was carried out as part of the Framingham Study (Farmer et al, 1987). A cohort of 2 123 patients aged 55-89 was examined using a test battery consisting of sub-tests of the Wechsler Memory Scale (Logical Memory, Visual Reproduction and Paired Associate Learning), sub-tests of the WAIS (Digits Forward, Digits Backward and Similarities) and Word Fluency (part of the Multilingual Aphasia Examination). Neither blood pressure nor antihypertensive treatment was significantly associated with cognitive performance. When patients on antihypertensive medication were excluded, there was still no relation between blood pressure and cognitive functioning.

In summary, no clear relationship between blood pressure and cognitive performance emerges in the studies described, particularly in non-elderly populations. In view of the fact that the present group was limited to patients under seventy with mild-moderate hypertension, it is unlikely that the blood pressure differences between the two treatment groups had a significant effect on performance.

It has generally been considered that hydrophilic beta-blockers such as atenolol are unlikely to have significant central effects in view of their poor ability to traverse the blood-brain barrier (Glaister, 1981). Recent research has confirmed that of Salem and McDevitt (1983), cited above, in suggesting that atenolol may produce detectable impairment of

cognitive functioning. Currie et al (1988), in a single dose study in healthy volunteers, found decreased alertness after atenolol. Short-term memory was impaired by propranolol. Nicholson et al (1988), in a similar study, found that body sway was increased and the EEG was influenced by both atenolol at doses of 50mg and 100mg and propranolol at doses of 40mg, 80mg and 160mg. Streufert et al (1988) studied the performance of fifty hypertensive men on tests of complex cognitive functioning after fourteen days on either atenolol or metoprolol. When compared to placebo, performance on atenolol was impaired on some of the tests whereas performance on metoprolol was superior to placebo. Gengo et al (1987) studied the effects of atenolol and metoprolol on the Stroop Word Test and CFFF. The subjects were twenty hypertensive men and testing was carried out after fourteen days of treatment. Similar depression of activity was seen with both drugs. The authors point out that the precise site of action of beta-blocker induced sedation is unknown and suggest that this may be saturated at low CNS drug concentrations.

STUDY III: NICARDIPINE AND PROPRANOLOL

The patients in the propranolol-treated group demonstrated impaired performance on tests of non-verbal memory. Again, this is in keeping with other research which points to mild memory impairment in subjects on beta-blockers. The rise in scores on the DSST between weeks 0 and 12 was similar in the propranolol patients to that obtained in the atenolol group in Study II. The absence of any rise in scores in those on nicardipine raises the possibility that performance on this test was

impaired by nicardipine. Performance on the Complex Figure Test was also diminished in the nicardipine patients. In both groups, scores on the PASAT improved by the same amount as with the atenolol patients.

As in Study II, there was no evidence of diminished mental well-being or impaired social functioning in either treatment group.

As far as the author is aware, there has been no other attempt to assess formally the psychological effects of the calcium-channel blockers in patients free of diagnosable organic brain disease. The mechanism or mechanisms producing impairment of functioning can only be a matter for speculation. The potential for the production of "steal" effects, which is discussed above, raises the possibility that these drugs may produce focal impairment of cerebral blood flow. The possible efficacy of these drugs in conditions such as epilepsy and tardive dyskinesia suggests that they may have a depressant effect on neuronal functioning which may produce mild impairment of mental functioning.

CONCLUSIONS

In the present studies, enalapril comes out as the drug on which patients performed best on the tests which were administered. The differences between enalapril and the other drugs were small in magnitude and, in the groups studied, were not of sufficient severity to produce impaired social adaptation or decreased psychological well-being. It may that they are of practical significance only in those whose occupations require high levels of mental acuity (Ledingham, 1987).

It could be argued that significant impairments of subjective well-being or social functioning might exist but that the tests used were insufficiently sensitive to detect these. The General Health Questionnaire has been very widely used to detect psychiatric morbidity in population surveys. It is commonly found in such surveys that between fifteen and twenty percent of adults score as having significant morbidity (Goldberg, 1978). The questionnaire is therefore capable of detecting common-place, low-grade psychiatric morbidity. It is unlikely that the questionnaire is missing significant morbidity in the present studies. The self-report form of the Social Adjustment Schedule was used by Cooper et al (1982), in a study of women undergoing elective sterilisation. Statistically significant improvements in scores were found when pre-operative and post-operative scores were compared. This group of women had no excess of psychiatric symptomatology at any stage of the study. The scale was thus able to detect change in a psychiatrically "normal" population which was also free of physical pathology. It may also be argued that the drugs produced impaired well-being but that this was counter-balanced by other factors such as

improvement in psychiatric symptoms as a consequence of recruitment in a drug trial as suggested by Mann (1977). The lack of a parallel placebo group as dictated by ethical considerations does not allow this factor to be excluded. The population differs from that in Mann's study in that most patients were already under treatment for hypertension prior to recruitment to the study whereas his population consisted of newly-detected hypertensives picked up by population screening. In the case of most patients in the studies described here, clinic attendance was not a new experience and significant differences between testings would be unlikely to be created by the putative psychological benefits of enrolment in a drug trial.

The results of the studies reported here are for the most part very reassuring and indicate that the antihypertensive drugs investigated do not produce detectable impairment in psychiatric well-being or social functioning. The studies are free of the methodological problems which hampered interpretation of studies such as that of Jachuck et al (1981). The results conflict with the findings of the study by Croog et al (1986) in which captopril was found to be superior to propranolol and methyldopa with regard to subjective well-being. The lack of subjective impairment is borne out by the fact that dropout rates in the atenolol/enalapril study were low with only four percent of the atenolol group and six percent of the enalapril group withdrawing because of adverse effects. This contrasts with the Croog et al study where dropout rates because of adverse effects were eight percent in the captopril patients, thirteen percent in the propranolol patients and twenty percent in those on methyldopa. The two populations were not comparable.

The Croog et al patients were all employed white males whereas the present patient groups were not restricted in this way and were therefore more representative of the population of hypertensives. This raises the possibility that sub-groups of the hypertensive population such as working males may be susceptible to subjective adverse effects which are not apparent in the population as a whole.

The absence of any effects on memory conflicts with the findings of Solomon et al (1983) with regard to their finding of impaired verbal memory in patients on propranolol. The design of their study created problems of interpretation as described above whereas the study of the effects of propranolol described was free of such handicaps. With regard to atenolol the present findings are out of keeping with those of Lichter et al (1986). Their study used tests of memory not in wide use. The cohort of patients was small (twenty-five compared to one hundred and thirty-four in the atenolol/enalapril study) and a large number of comparisons was made thereby increasing the likelihood of positive results occurring by chance.

Beta- blockers may be of positive benefit in certain situations. They have been frequently used to improve performance by reduction of autonomic response in stressful situations such as undergraduate examinations (Brewer,1972), performance on stage by professional musicians (James et al,1977; Brantigan et al,1977) and racing-car driving (Taggart and Carruthers, 1972). It may be that, in some situations or in certain personality types, the beneficial effects of beta-blockers may out-weigh the adverse effects (Hartley et al, 1983). In addition, the beta-blockers have been very widely used over many

years. Their side-effects and risks are well understood and they are of proven efficacy in prevention of the adverse consequences of raised blood pressure. The issue of cost of medication must also be taken into consideration (Milner and Johnson, 1985). The converting enzyme inhibitors are more costly than drugs such as atenolol, which in turn costs more than older drugs such as propranolol and bendrofluazide (Sahler, 1987).

In addition to the effects of treatment on quality of life, investigations have been carried out into the effects of illness "labelling". Cross-sectional studies have been published which suggest that hypertensive patients have a poorer perception of their health and decreased psychlolgical well-being (Milne et al, 1985; Monk, 1981; Soghikian, 1981). Such investigations suffer from selection bias in that those who feel unwell are more likely to seek medical help and be diagnosed as being hypertensive (Wagner and Strogatz, 1984). Two prospective studies of this issue found no evidence of significant impairment of psychological well-being as a result of diagnosis (Mossey, 1981; Mann, 1977). Effects of labelling on absenteeism have been found to be variable. One study in a large Canadian steel foundry detected increased sickness absenteeism following diagnosis of hypertension (Haynes et al, 1978). This absenteeism persisted over a four year follow-up period and was associated with decreased earnings (Taylor et al, 1981; Johnston et al, 1984). Other reports have failed to confirm this effect such as that of Alderman et al (1981). There is evidence from two studies that adverse social consequences of labelling may be largely obviated by close and systematic follow-up (Alderman et al,

1976; Polk et al, 1984).

Since the planning of the present work, several large reports have been published which have attempted to assess the benefits and risks of the drug treatment of mild hypertension.

The European Working Party on High Blood Pressure in the Elderly Trial was a double-blind, placebo-controlled trial of antihypertensive treatment in the over-sixties (European Working Party on High Blood Pressure in the Elderly, 1985). The entry criteria were elevated diastolic pressure between 90 and 119mmHg and systolic blood pressure between 160 and 239mmHg. Eight hundred and forty patients entered the trial and were randomly allocated to active treatment of hydrochlorothiazide or triamterene or to matching placebo. If blood pressure remained elevated methyldopa was added in the active treatment group. There was no significant decrease in overall mortality in the active treatment group although these patients showed a decrease in mortality due to cardiac disease. The incidence of non-fatal cardiac events was also less in the actively treated patients as was the incidence of minor (i.e. "non-terminating") cerebro-vascular events.

The Medical Research Council trial of treatment of mild hypertension was mounted to examine whether treatment of men and women aged 35-64 with Phase V diastolic blood pressures of 90-109mmHg would be effective in reducing the number of strokes and coronary events (Medical Research Council Working Party, 1985). The two agents used in the trial were the beta-blocker propranolol and the diuretic bendrofluazide. Treatment with a second drug was added if blood pressure control was inadequate. The

trial was carried out in general practice populations and was placebo-controlled. A total of 17 354 patients participated. Analysis of the results was on an "intention-to-treat" basis. Follow-up was for five years. The main benefit experienced by the active treatment group was a lowering in the rate of stroke. In the propranolol-treated group, the lower incidence of stroke was apparent only in non-smokers. There was no difference in the incidence of coronary events and no reduction in overall mortality. There was a significant difference between men and women with regard to mortality, with men gaining benefit from active treatment and women on placebo showing a lower mortality. The rather gloomy conclusion of the trial was that if 850 mildly hypertensive patients are given active treatment for one year about one stroke will be prevented, "an important but an infrequent benefit". This was acheived at the expense of subjecting patients to chronic side-effects, not all of which were minor.

This conclusion has been challenged by some authorities as being excessively cautious (Robertson, 1986; Robertson and Hansson, 1986). They argue that two factors weakened the power of the trial as initially designed. In the first place, it was considered unethical to continue patients on placebo if their blood pressures rose above 110 mmHg diastolic or 200 mmHg systolic. For this reason, a total of 1011 patients were withdrawn from placebo and given active treatment. Nevertheless, the outcomes in these patients were still analysed as if they had remained in the placebo group. It has been argued that these patients should have been regarded as having reached a trial end-point and been counted accordingly. Secondly, although patients were recruited

on the basis of having phase V diastolic pressures in the range 90-109 mmHg, approximately forty percent of patients in the placebo group had diastolic pressures lower than 90 mmHg at each annual examination.

Further analysis of the data revealed that patients who were smokers had an improved prognosis when treated with bendrofluazide but that no benefit could be expected on treatment with propranolol (Medical Research Council Working Party, 1988).

The International Prospective Primary Prevention Study in Hypertension (IPPPSH) examined the effects of beta-blocker therapy on cardiac events and stroke in patients with phase V diastolic pressure betwen 110 and 115 mm Hg (The IPPPSH Collaborative Group, 1985). Patients were randomly allocated double-blind to slow-release oxprenolol or to placebo. If blood pressure control was inadequate, the dose of the initial medication could be increased or other medication added in either the beta-blocker or the placebo group. There was no difference in rates of myocardial infarction, cerebrovascular accident and sudden death in the two groups. Male non-smokers on oxprenolol experienced half as many cardiac events as those on placebo whereas there was a an increase in coronary events in smokers on oxprenolol. Interpretation of the study is hampered by the fact that over sixty percent of the oxprenolol patients and eighty-two percent of the placebo group also received a diuretic. It is known that thiazide diuretics can cause ventricular ectopy although the significance of this is uncertain (Medical Research Council Working Party, 1983). It is possible that the cardio-protective effects of oxprenolol were partially out-weighed by the use of diuretic. The interaction of smoking and beta-blockade on

cardiac events may be related to the observation that cigarette smoking can have a pressor effect in patients on non-specific beta-blockers such as oxprenolol (Trap- Jensen et al, 1979).

The publication of these major, large-scale trials has allowed considerable clarification of the indications for antihypertensive drug treatment (Wilcox et al,1986; Beevers, 1988). A British Hypertension Society Working Party has recommended that drug treatment of hypertension is indicated if diastolic blood pressure averages 100 mmHg or more over three to four months (Swales et al, 1989). Patients with diastolic pressures between 95 and 99 mmHg should have their blood pressures checked every three to six months. Intriguing evidence has emerged to suggest that there is an optimal range of treated diastolic pressure with increased cardiac mortality both below and above this range, the so-called J-shaped relation between treated diastolic blood pressure and mortality (Cruickshank et al, 1987; Cruickshank, 1988). There is increased awareness of the importance of isolated systolic hypertension (Dustan, 1989). The potential benefits and limitations of non-drug management have also become clearer (Swales, 1987).

The reason for treating hypertension is to diminish the risks of hypertension-related morbidity and mortality. Treatment may be for life and it is very important that the impact of diagnosis and treatment on quality of life is minimal and does not outweigh the expected benefits. The existence of even small impairments in mental efficiency may be of importance in patients with intellectually demanding occupations.

It can be argued that all antihypertensive drugs in widespread use should be tested fully for effects on "quality of life" as well as for antihypertensive efficacy and their ability to prevent disease and death. With regard to intellectual functioning, computerised methods of testing this will allow more widespread use of such assessments with considerable savings in staff time. Detailed delineation of the adverse consequences of drug treatment on mental well-being and abilities should assist clinicians in choosing the medication most suited to the patient.

TABLE 1

CAPTOPRIL STUDY

MEAN GHQ TOTAL SCORES (LIKERT)

PATIENT	PLACEBO	CAPTOPRIL
1	18.0	34.5
2	30.0	44.5
3	22.5	33.5
4	61.5	85.0
5	50.0	60.5
6	68.0	71.0
7	43.0	32.5
8	22.0	68.5

TABLE 2

CAPTOPRIL STUDY

PASAT SCORES

PATIENT	PLACEBO	CAPTOPRIL
1	55.5	31.5
2	49	36
3	118.5	115.5
4	55.5	46
5	50	87
6	112	116.5
7	84.5	104.5
8	55.5	78.5

TABLE 3

CAPTOPRIL STUDY

MANIA RATING SCALE SCORES

PATIENT	PLACEBO	CAPTOPRIL
1	5	0
2	1.75	0.5
3	1.0	1.5
4	3	3
5	5.5	2
6	1	2
7	2	3.5
8	3	1

TABLE 4

ATENOLOL VS ENALAPRIL STUDY

COMPARABILITY OF THE TREATMENT GROUPS AT RANDOMISATION

	ATENOLOL (N=76)	ENALAPRIL (N=86)
Age (years)*	53.0 (1.1)	49.3 (1.3)
Sex (M:F)	45:31	48:38
Weight (kg)	74.2 (1.5)	76.4 (1.6)
Blood pressure (mmHg) supine*		
Systolic	170.8 (1.7)	167.8 (1.5)
Diastolic	98.1 (1.2)	98.2 (1.0)
Pulse rate supine	79.0 (1.4)	80.2 (1.1)
Blood pressure (mmHg) standing*		
Systolic	162.3 (1.7)	158.8 (1.5)
Diastolic	101.6 (1.2)	102.8 (1.0)
Pulse rate standing	84.2 (1.6)	86.7 (1.1)

* Values are mean (SEM)

TABLE 5

MEDIAN RESULTS OF ATENOLOL ENALAPRIL COMPARISONS

	ATENOLOL		ENALAPRIL		
	PLACEBO	CHANGE	PLACEBO	CHANGE	DIFFERENCE (95% C.I.s)
General Health Questionnaire	1.0	0.0	0.0	0.0	0.0 (0.0, +1.0)
Social Adjustment Schedule	148	0.0	140	-3.0	-3.0 (-5.0, +7.0)
Complex Figure (Copy)	33.0	0.0	33.0	0.0	0.0 (0.0, +2.0)
Complex Figure (Immediate recall)	20.0	+1.0	18.5	+1.5	+0.5 (-1.0, +2.5)
Complex Figure (Delayed recall)	18.5	0.0	16.5	+2.0	+2.0 (-1.5, +1.5)
Digit forward	7.0	0.0	7.0	0.0	0.0 (0.0)
Digit backward	5.0	0.0	4.5	0.0	0.0 (0.0)
Logical memory	10.0	+1.0	10.0	+0.5	-0.5 (-1.5, +0.5)
Paired associate learning	14.0	0.0	14.5	-0.5	-0.5 (-1.0, +1.0)
DSST	47	+2.0	49	+4.0	+2.0 (+1.0, 4.0)*
PASAT	60.5	+5.5	55.0	+10.0	+4.5 (0.0, +9.0)**

*p < 0.005 **p < 0.05

TABLE 6

ATENOLOL/ENALAPRIL STUDY

GHQ-60 TOTAL SCORES

ATENOLOL GROUP (N=64)

	PLACEBO	ATENOLOL
MEAN	3.884	3.234
MEDIAN	1.000	1.000
ST. DEV.	5.057	5.881
S.E. MEAN	0.632	0.726
MINIMUM	0.000	0.000
MAXIMUM	21	36

ENALAPRIL GROUP (N=70)

	PLACEBO	ENALAPRIL
MEAN	3.571	3.500
MEDIAN	0	0
ST. DEV.	6.682	6.524
S.E. MEAN	0.799	0.780
MINIMUM	0	0
MAXIMUM	33	39

TABLE 7

ATENOLOL/ENALAPRIL STUDY

GHQ "CASES"

WEEK	ATENOLOL	ENALAPRIL
0	9	10
12	4	4

TABLE 8

ATENONOL/ENALAPRIL STUDY

VALIDATION ASSESSMENT

SCORES ON GHQ AND CLINICAL INTERVIEW SCHEDULE

PATIENT	GHQ SCORE	CIS SCORE
1	0	4
2	5	6
3	6	11
4	0	0
5	5	8
6	22	24
7	2	3
8	9	4
9	1	8
10	0	2
11	0	12
12	1	5
13	0	5
14	0	12
15	5	6
16	0	1
17	1	5
18	18	23
19	3	6
20	1	0
21	1	6
22	0	11
23	0	0
24	0	1
25	0	0
26	0	2
27	8	15

TABLE 9

ATENOLOL/ENALAPRIL STUDY

DIGITS FORWARD

ATENOLOL GROUP (N=64)

	PLACEBO	ATENOLOL
MEAN	6.672	6.703
MEDIAN	7	7
ST. DEV.	1.16	1.366
S.E. MEAN	0.145	0.171
MINIMUM	4	0
MAXIMUM	8	8

ENALAPRIL GROUP

	PLACEBO	ENALAPRIL
MEAN	6.886	7.114
MEDIAN	7	7
ST. DEV.	1.036	0.979
S.E. MEAN	0.124	0.117
MINIMUM	4	4
MAXIMUM	8	8

TABLE 10

ATENOLOL/ENALAPRIL STUDY

DIGITS BACKWARD

ATENOLOL GROUP (N=64)

	PLACEBO	ATENOLOL
MEAN	4.992	4.953
MEDIAN	5	5
ST. DEV.	1.338	1.255
S.E. MEAN	0.167	0.157
MINIMUM	2	2
MAXIMUM	7	7

ENALAPRIL GROUP (N=70)

	PLACEBO	ENALAPRIL
MEAN	4.771	5.014
MEDIAN	4.5	4.5
ST. DEV.	1.233	1.236
S.E. MEAN	0.147	0.148
MINIMUM	2	2
MAXIMUM	7	7

TABLE 11

ATENOLOL/ENALAPRIL STUDY

PAIRED ASSOCIATE LEARNING

ATENOLOL GROUP (N=64)

	PLACEBO	ATENOLOL
MEAN	13.992	13.787
MEDIAN	14.0	14.0
ST. DEV.	3.965	3.658
S.E. MEAN	0.496	0.457
MINIMUM	5.5	5.5
MAXIMUM	21.0	21.0

ENALAPRIL GROUP (N=70)

	PLACEBO	ENALAPRIL
MEAN	14.614	14.643
MEDIAN	14.5	14.0
ST. DEV.	3.489	3.655
S.E. MEAN	0.417	0.437
MINIMUM	7.0	6.0
MAXIMUM	21.0	21.0

TABLE 12

ATENOLOL/ENALAPRIL STUDY

LOGICAL MEMORY

ATENOLOL GROUP (N=64)

	PLACEBO	ATENOLOL
MEAN	9.881	10.797
MEDIAN	10	11
ST. DEV.	3.688	3.783
S.E. MEAN	0.461	0.473
MINIMUM	1.0	0
MAXIMUM	18.5	18.5

ENALAPRIL GROUP (N=70)

	PLACEBO	ENALAPRIL
MEAN	10.257	10.751
MEDIAN	10	10.5
ST. DEV.	3.498	3.504
S.E. MEAN	0.418	0.419
MINIMUM	4.5	1.0
MAXIMUM	22.0	18.0

TABLE 13

ATENOLOL/ENALAPRIL STUDY

COMPLEX FIGURE TEST -COPY

ATENOLOL GROUP (N=63)

	PLACEBO	ATENOLOL
MEAN	32.25	32.22
MEDIAN	33	33
ST.DEV.	4.046	4.007
S.E. MEAN	0.510	0.515
MINIMUM	16.0	16.5
MAXIMUM	36.0	36.0

ENALAPRIL GROUP (N=69)

	PLACEBO	ENALAPRIL
MEAN	31.44	31.88
MEDIAN	33	33
ST. DEV.	4.323	5.054
S.E. MEAN	0.520	0.608
MINIMUM	14.5	14.0
MAXIMUM	36.0	36.0

TABLE 14

ATENOLOL/ENALAPRIL STUDY

COMPLEX FIGURE TEST -IMMEDIATE RECALL

ATENOLOL GROUP (N=62)

	PLACEBO	ATENOLOL
MEAN	19.75	20.90
MEDIAN	20.0	21.5
ST. DEV.	7.404	7.381
S.E. MEAN	0.940	0.937
MINIMUM	2.0	3.0
MAXIMUM	32.0	34.0

ENALAPRIL GROUP (N=69)

	PLACEBO	ENALAPRIL
MEAN	17.94	19.80
MEDIAN	18.5	20.0
ST. DEV.	6.699	7.244
S.E. MEAN	0.807	0.872
MINIMUM	4.5	0.0
MAXIMUM	31.0	32.0

TABLE 15

ATENOLOL/ENALAPRIL STUDY

COMPLEX FIGURE TEST -DELAYED RECALL

ATENOLOL GROUP (N=62)

	PLACEBO	ATENOLOL
MEAN	17.73	19.61
MEDIAN	18.5	18.5
ST.DEV.	9.05	8.15
S.E. MEAN	1.16	1.04
MINIMUM	0.0	0.0
MAXIMUM	32.0	34.0

ENALAPRIL GROUP (N=69)

	PLACEBO	ENALAPRIL
MEAN	16.06	18.49
MEDIAN	16.5	18.5
ST. DEV.	7.536	7.738
S.E. MEAN	0.942	0.967
MINIMUM	0.0	0.0
MAXIMUM	31.0	31.0

TABLE 16

ATENOLOL/ENALAPRIL STUDY

DIGIT SYMBOL SUBSTITUTION

ATENOLOL GROUP (N=64)

	PLACEBO	ATENOLOL
MEAN	47.58	49.59
MEDIAN	47	49
ST. DEV.	13.16	14.03
S.E. MEAN	1.64	1.75
MINIMUM	16	14
MAXIMUM	82	85

ENALAPRIL GROUP (N=70)

	PLACEBO	ENALAPRIL
MEAN	48.41	52.50
MEDIAN	49	53
ST. DEV.	12.18	12.55
S.E. MEAN	1.46	1.50
MINIMUM	19	23
MAXIMUM	75	79

TABLE 17

ATENOLOL/ENALAPRIL STUDY

PACED AUDITORY SERIAL ADDITION TASK

ATENOLOL GROUP (N=60)

	PLACEBO	ATENOLOL
MEAN	60.98	66.60
MEDIAN	60.5	66
ST. DEV.	22.11	26.43
S.E. MEAN	2.72	3.41
MINIMUM	6	9
MAXIMUM	109	114

ENALAPRIL GROUP (N=63)

	PLACEBO	ENALAPRIL
MEAN	58.58	68.90
MEDIAN	55	65
ST. DEV.	22.60	26.02
S.E. MEAN	2.65	3.28
MINIMUM	9	6
MAXIMUM	105	117

TABLE 18

ATENOLOL/ENALAPRIL STUDY

SOCIAL ADJUSTMENT SCALE -TOTAL SCORES

ATENOLOL GROUP (N=64)

	PLACEBO	ATENOLOL
MEAN	155.20	150.05
MEDIAN	148	148
ST. DEV.	31.44	29.44
S.E. MEAN	3.93	3.68
MINIMUM	111	105
MAXIMUM	236	250

ENALAPRIL GROUP (N=70)

	PLACEBO	ENALAPRIL
MEAN	145.73	142.80
MEDIAN	140	137
ST. DEV.	29.45	26.91
S.E. MEAN	3.52	3.22
MINIMUM	105	108
MAXIMUM	241	239

TABLE 19

NICARDIPINE/PROPRANOLOL TRIAL

DEMOGRAPHIC CHARACTERISTICS

	NICARDIPINE	PROPRANOLOL
AGE (S.D.)	52.5 (11.9)	55.9 (6.6)
SEX		
Male	8	8
Female	7	7
EDUCATION		
Special school	0	1
Secondary school to age 15	10	12
Secondary school to age 18	4	1
Higher education	1	1
OCCUPATION/SOCIAL CLASS		
I	1	0
II	1	1
III (i)	1	2
III (ii)	1	0
IV	4	1
V	1	0
Unemployed/retired	6	11

TABLE 20

NICARDIPINE AND PROPRANOLOL STUDY

RESULTS AND COMPARISONS

WEEK	NICARDIPINE	PROPRANOLOL
GHQ-60 (Total scores and ranges)		
0	5.9 (0-19)	11.1 (0-49)
12	10.1 (0-48)	10.9 (0-50)
Social Adjustment (Total scores and s.d.)		
0	1.59 (0.43)	1.69 (0.35)
12	1.68 (0.63)	1.66 (0.33)
Logical memory		
0	9.8 (3.2)	9.8 (3.0)
12	9.8 (3.9)	9.6 (3.3)
Digits forward		
0	6.9 (1.0)	6.1 (1.5)
12	6.8 (1.1)	6.8 (1.2)*
Digits backward		
0	4.8 (1.4)	4.6 (1.4)
12	5.1 (1.3)	4.8 (1.4)
Associate learning		
0	13.3 (3.2)	12.2. (4.9)
12	13.9 (5.1)	11.7 (3.9)

*Significant increase Week 0-12 (p=0.033)

TABLE 20 (continued)

DSST		
0	43.0 (16.2)	44.3 (13.1)
12	42.9 (14.6)	47.9 (13.6)*
CFT (Copy)		
0	29.6 (5.6)	30.0 (3.4)
12	27.4 (7.9)	30.1 (5.4)
CFT (Immediate recall)		
0	19.1 (8.4)	19.2 (6.0)
12	14.4 (9.2)**	16.3 (7.7)***
CFT (Delayed recall)		
0	17.7 (8.5)	17.6 (5.9)
12	14.3 (9.0)+	16.0 (7.6)
PASAT		
0	64.0 (18.4)	60.8 (25.2)
12	70.1 (24.9)++	66.1 (28.0)

*Significant increase Week 0-12 (p=0.015)

**Significant decrease Week 0-12 (p=0.005)

***Significant decrease Week 0-12 (p=0.038)

+Significant decrease Week 0-12 (p=0.017)

++Significant increase Week 0-12 (p=0.038)

REFERENCES

ACHOR R.W.P., HANSON N.O. & GIFFORD R.W. (1955). Hypertension treated with Rauwolfia Serpentina (whole root) and with reserpine. *Journal of the American Medical Association*, **159**, 839-840.

ADLER S. (1974). Methyldopa-induced decrease in mental activity. *Journal of the American Medical Association*, **230**, 1428-1429.

ALDERMAN M.H. & DAVIS T.K. (1976). Hypertension control at the work-site. *Journal of Occupational Medicine*, **18**, 793-796.

ALDERMAN M.H., CHARLSON M.E. & MELCHER L.A. (1981). Labelling and absenteeism: the Massachusetts Mutual Experience. *Clinical and Investigative Medicine*, **4**, 165-171.

ALEXANDER W.D. & EVANS J.I. (1975). Side-effects of methyldopa. *British Medical Journal*, i, 501.

AMERY A.K.P.C., BOSSAERT H., FAGARD R.H. & VERSRAETE M. (1972). Clonidine versus methyldopa. *Acta Cardiologica*, **27**, 82-99.

AMERY A., BIRKENHAGER W., BRIXKO P., BULPITT C., CLEMENT D., DERUYTERRE M, et al. (1985). Mortality and morbidity results from the European Working Party on High Blood Pressure in the Elderly Trial. *Lancet*, i, 1349-1355.

ARR S.M., BURGESS J., COOPER W.D., CURRIE W.J.C. & DAVIDSON C. (1984). A comparative study of enalapril and atenolol in moderate to severe hypertension. *British Journal of Clinical Pharmacology*, **18**, 292P- 298P.

ARREGUI A., IVERSEN L.L., SPOKES E.G.S. & EMSON P.C. (1979). Alterations in post-mortem brain angiotensin-converting enzyme activity and some neuropeptides in Huntington's disease. *Advances in Neurology*, **23**, 517-525.

ATKINSON A.B. & ROBERTSON J.I.S. (1979). Captopril in the treatment of clinical hypertension and cardiac failure. *Lancet*, ii, 836-839.

ATLAS D., TEICHBERG V.I. & CHANGEUX J.P. (1977). Direct evidence for beta-adrenoreceptors on the Purkinje cells of mouse cerebellum. *Brain Research*, **128**, 532-536.

AUSTRALIAN NATIONAL BLOOD PRESSURE STUDY MANAGEMENT COMMITTEE. (1980). The Australian therapeutic trial in mild hypertension. *Lancet*, i, 1261-1267.

AVORN, J., EVERITT, D. & WEISS, S. (1986). Increased Antidepressant Use in Patients Prescribed Beta-Blockers. *Journal of the American Medical Association*, **255** ,357-360

BANT W.P. (1978). Antihypertensive drugs and depression. *Psychological Medicine*, **8**, 275-283.

BAKKE O.M., DOLLERY C.T., LEWIS P.J., MYERS M.G. & REID J.L. (1974). Regional brain concentration of propranolol and its hypotensive effect in the concious rabbit. *British Journal of Pharmacology*, **51**, 148P.

BARROW N. & CHILDS A. (1986). An anti-tardive-dyskinesia effect of verapamil. *American Journal of Psychiatry*, **143**, 1485.

BAUER J.H. & JONES L.B. (1984). Comparative studies: enalapril versus hydrochlorothiazide as first-step therapy for the treatment of primary hypertension. *American Journal of Kidney Diseases*, **4**, 55-62.

BAYLISS P.F.C. & DUNCAN S.M. (1975). The efects of atemolol (Tenormin) and methyldopa on simple tests of central nervous system function. *British Journal of Clinical Pharmacology*, **2**, 527-531.

BEEVERS D.G. (1988). Overtreating hypertension. *British Medical Journal*, **297**, 1212-1213.

BENSON A. (1985). Ode to propranolol. *New England Journal of Medicine*, **313**, 123.

BENUCK M. & MARKS N. (1979). Co-identity of brain angiotensin converting enzyme with a membrane bound dipeptidyl carboxypeptidase inactivating met-enkephalin. *Biochemical and Biophysical Research Communications*, **88**, 215-220.

BERGLUND G., WILHELMSEN L., SANNERSTEDT R., HANSSON L., ANDERSSON D. & SIVERTSSON R. (1978). Coronary heart disease after treatment of hypertension. *Lancet*, i, 1-5.

BESSON J.A.O., PALIN A.N., EBMEIER K.P., EAGLES J.M. & SMITH F.W. (1988). Calcium antagonists and multi-infarct dementia: a trial involving sequential NMR and psychometric asessment. *International Journal of Geriatric Psychiatry*, **3**, 99-105.

BETTS T.A. & BLAKE A. (1977). The psychotropic effects of atenolol in normal subjects. Preliminary findings. *Postgraduate Medical Journal*, **53**, (Suppl 3), 151-156.

BETTS T.A. & ALFORD C. (1983). Beta-blocking drugs and sleep. A controlled trial. *Drugs*, **25**, (Suppl. 2) 268-272.

BOLLER F., VRTUNSKI B., MACK J.L. & KIM Y. (1977). Neuropsychological correlates of hypertension. *Archives of Neurology*, **34**, 701-705.

BOND A.J. & LADER M.H. (1972). Residual effects of hypnotics. *Psychopharmacologia (Berl.)*, **25**, 117-132.

BOND A.J. & LADER M.H. (1973). The residual effects of flurazepam. *Psychopharmacologia (Berl.)*, **32**, 223-235.

BORZEIX M.G. & CAHN J. (1983). The effect of the calcium entry blockers nimodipine and nicardipine on the sub-acute biochemical and functional consequences of transient cerebral oligaemia in the rat. *Naunyn-Schmiedeberg's Archives of Pharmacology*, **324** (Suppl), R46.

BRANTIGAN T.A., BRANTIGAN C.O. & JOSEPH N.H. Beta-blockade and musical performance. *Lancet*, i, 896.

BREWER C. (1972). Beneficial effect of beta-adrenergic blockade on "exam. nerves". *Lancet*, ii, 435.

BRITISH HYPERTENSION SOCIETY WORKING PARTY (1989). Treating mild hypertension. *British Medical Journal*, **298**, 694-698.

BROWN III S.T.,FREEDMAN D., DeVAULT G.A., SLAY L., ELDERLY MULTICENTER STUDY GROUP (1985). Safety, efficacy and pharmacokinetics of nicardipine in elderly hypertensive patients. *British Journal of Clinical Pharmacology*, **22** (Suppl), 289S-295S.

BRYAN P.C., EFIONG D.O. & STEWART-JONES J. (1974). Propranolol on tests of visual function and central nervous system activity. *British Journal of Clinical Pharmacology*, **1**, 82-84.

BULPITT C.J. & DOLLERY C.T. (1973). Side-effects of hypotensive agents evaluated by a self-administered questionnaire. *British Medical Journal*, iii, 485-490.

CLAYTON A.B., HARVEY P.G. & BETTS T.A. (1977). The psychomotor effects of atenolol and other antihypertensive agents. *Postgraduate Medical Journal*, **53**, Suppl. 3, 157-161.

COOPER P., OSBORN M., GATH D. & FEGETTER G. (1982). Evaluation of a modified self-report measure of social adjustment. *British Journal of Psychiatry*, **141**, 68-75.

COSTA P.T. & SHOCK N.W. (1980). New longitudinal data on the question of whether hypertension influences intellectual performance. In: *Cognitive processes and Hypertension.* ed. Elias M.F. and Streeten D.H.P. Beech Hill. Mount Desert, ME.

COULTER D.M. & EDWARDS I.R. (1987). Cough associated with captopril and enalpril. *British Medical Journal*, **294**, 1521-1523.

CROOG S.H., LEVINE S., TESTA M.A., BROWN B., BULPITT C.J., JENKINS C.D., KLERMAN G.L. & WILLIAMS G.H. (1986). The effect of antihypertensive therapy on quality of life. *New England Journal of Medicine*, **314**, 1657-1664.

CRUICKSHANK J.M., THORP J.M. & ZACHARIAS F.J. (1987). Benefits and potential harm of lowering high blood pressure. *Lancet*, i, 581-584.

CRUICKSHANK J.M. (1988). Coronary flow reserve and the J curve relation between diastolic blood pressure and myocardial infarction. *British Medical Journal*, **297**, 1227-1230.

CURRIE D., LEWIS R., McDEVITT D.G., NICHOLSON A.N. & WRIGHT N.A. (1988). Central effects of the beta-receptor antagonists propranolol and atenolol. *British Journal of Clinical Pharmacology*, **25**, 124P.

DAHLOF B., ANDREN L., EGGERTSEN R., JERN S., SVENSSON A. & HANSSON L. (1985). Potentiation of the antihypertensive effect of enalapril by randomized addition of diferent doses of hydrochlorothiazide. *Journal of Hypertension*, 3 (suppl 3), S483-S486.

DAY M.D., HEMSWORTH B.A. & STREET J.A. (1977). The central uptake of beta-receptor antagonists. *Journal of Pharmacy and Pharmacology*, **29**, 52P.

DeMUTH G.W. & ACKERMANN, S.H. (1983). Alpha-methyldopa and depression: a clinical study and review of the literature. *American Journal of Psychiatry*, **140**, 534-538.

DOGGET S. & MERCURIO G.G. (1989). Calcium blockers in tardive dyskinesia. *American Journal of Psychiatry*, **146**, 121-122.

DOYLE,A.E. & SMIRK, F.H. (1954). Hypotensive Action of Reserpine. *Lancet*, i, 1096-1097.

DUBACH U.C. (1963). Methyldopa and depression. *British Medical Journal*, i, 261-262.

EDWARDS C.R.W. & PADFIELD P.L. (1985). Angiotensin converting enzyme inhibitors: past, present and bright future. *Lancet*, i, 30-34.

ELIAS M.F., ROBBINS M.A., SCHULTZ N.R. & STREETEN D.H.P. (1986). A longitudinal study of neuropsychological test performance for hypertensive and normotensive adults: Initial findings. *Journal of Gerontology*, **41**, 503-505.

ENALAPRIL IN HYPERTENSION STUDY GROUP (1984). Enalapril in essential hypertension: a comparative study with propranolol. *British Journal of Clinical Pharmacololgy*, **18**, 51-56.

ERDOS E.G., JOHNSON A.L. & BOYDEN N.T. (1978). Hydrolysis of enkephalin by cultured human endothelial cells and by purified dipeptidyl dipeptidase. *Biochemical Pharmacology*, **27**, 843-848.

FARMER M.E., WHITE L.R., ABBOTT R.D., KITTNER S.J., KAPLAN E., WOLZ M.M., BRODY J.A. & WOLF P.A. (1987). Blood pressure and cognitive performance. The Framingham Study. *American Journal of Epidemiology*, **126**, 1103-1114.

FITZGERALD, J.D.(1967). Propranolol-induced depression. *British Medical Journal*, ii, 372-373.

FLEMINGER R. (1978). Visual hallucinations and illusions with propanolol. *British Medical Journal*, i, 1182.

FORRETTE F., BELLET M., HENRY J.F., HERVY M.P., POYARD-SALMERON C. et al. (1985). Effect of nicardipine in elderly hypertensive patients. *British Journal of Clinical Pharmacology*, **20** (Suppl. 1), 125S-129S.

FRANCESCHI M., TANCREDI O., SMIRNE S., MERCINELLI A. & CANAL N. (1982). Cognitive processes in hypertension. *Hypertension*, **4**, 226-229.

FRASER H.S. & CARR A.C. (1976). Propranolol Psychosis. *British Journal of Psychiatry*, **129**, 508-509.

FRCKA G. & LADER M.(1988). Psychotropic effects of enalapril, propranolol and atenolol in normal subjects. *British Journal of Clinical Pharmacology*, **25**, 67-73.

FRIES, E.D. (1954). Mental Depression in Hypertensive Patients Treated for Long Periods with Large Doses of Reserpine. *New England Journal of Medicine*, **251**, 1006-1008.

FULLERTON, A.G. & MORTON-JENKINS, D.(1963). Methyldopa and Depression. *British Medical Journal*, i, 538-539.

GARVEY H.L. & RAM N. (1975). Comparative antihypertensive effects and tissue distribution of beta-adrenergic blocking drugs. *Journal of Pharmacology and Experimental Therapeutics*, **194**, 220-223.

GAVRAS H., BIOLLAZ J., WAEBER B., BRUNNER H.R., GAVRAS I. & DAVIES R.O. (1981). Antihypertensive effect of the new oral angiotensin converting enzyme inhibitor "MK-421". *Lancet*, ii, 543-547.

GELMERS H.J. (1987). Effect of calcium antagonists on the cerebral circulation. *American Journal of Cardiology*, **59**, 173B-176B.

GENGO F.M., HUNTOON L. & McHUGH W.B. (1987). Lipid-soluble and water-soluble beta-blockers. Comparisons of the central nervous system depressant effects. *Archives of Internal Medicine*, **147**, 39-43.

GERSHON E.S., GOLDSTEIN R.E., MOSS A.J. & VAN KAMMEN D.P. (1979). Psychosis with ordinary doses of propranolol. *Annals of Internal Medicine*, **90**, 938-939.

GILLESPIE L., OAKES J.A., CROUT J.R. & SJOERDSMAN T. (1962). Clinical and chemical studies with alpha-methyldopa in patients with hypertension. *Circulation*, **25**, 281-291.

GLAISTER D.H. (1981). Effects of beta-blockers on psychomotor performance: a review. *Aviation, Space and Environmental Medicine*, **52**, (No. 11 Part 2), S23-S30.

GOLDBERG D.P., COOPER B., EASTWOOD M.R., KEDWARD H.B. & SHEPHERD M. (1970). A standardised psychiatric interview for use in community surveys. *British Journal of Preventive and Social Medicine*, **24**, 18-23.

GOLDBERG D. (1978). *Manual of the General Health Questionnaire*. Windsor: NFER Publishing Company.

GOLDBERG D.P. & HILLIER V.F. (1979). A scaled version of the General Health Questionnaire. *Psychological Medicine*, **9**, 139-145.

GOLDBLATT J. & BRYER A. (1987). Huntingdon's disease: deterioration in clinical state during treatment with angiotensin converting enzyme inhibitor. *British Medical Journal*, **294**, 1659-1660

GOLDMAN V., COMERFORD B., HUGHES D. & NYBERG G. (1969). Effect of beta-adrenergic blockade and alcohol on simulated car driving. *Nature*, **224**, 1175-1178.

GREEN A.R. & GRAHAME-SMTH D.G. (1976). (-)-Propranolol inhibits the behavioural responses of rats to increased 5-hydroxytryptamine in the central nervous system. *Nature*, **262**, 594-596.

GRONWALL D.M.A. & SAMPSON H. (1974). *The psychological effects of concussion.* Auckland. Auckland University Press.

GRONWALL D. & WRIGHTSON P. (1981). Memory and information processing after closed head injury. *Journal of Neurology, Neurosurgery and Psychiatry*, **44**, 889-895.

GROTTA J.C., OSTROW P., SPYDELL J. & HUNTER D. (1984). Calcium entry blocker therapy in acute cerebral ischaemia. *Annals of Neurology*, **16**, 111

HAMILTON M. & KOPELMAN H. (1963). Treatment of severe hypertension with methyldopa. *British Medical Journal*, i, 151-155.

HAMILTON M., THOMPSON E.N. & WISNIEWSKI T.K.M. (1964). The role of blood pressure control in preventing complications of hypertension. *Lancet*, i. 235-238.

HARTLEY L.R., UNGAPEN S., DAVIE I. & SPENCER D.J. (1983). The effect of beta adrenergic blocking drugs on speakers' performance and memory. *British Journal of Psychiatry*, **142**, 512-217.

HAYNES R.B., SACKETT D.L., TAYLOR D.W., GIBSON E.S. & JOHNSON A.L. (1978). Increased absenteeism from work after detection and labelling of hypertensive patients. *New England Journal of Medicine*, **299**, 741-744.

HEALD A.F. & ITA C.E. (1977). Distribution in rats of an inhibitor of angiotensin converting enzyme, SQ 14225, as studied by whole body autoradiography and liquid scintillation counting. *The Pharmacologist*, **19**, 129.

HELGELAND A. (1980). Treatment of mild hypertension: a five year controlled drug trial. The Oslo Study. *American Journal of Medicine*, **69**, 725-732.

HYPERTENSION DETECTION AND FOLLOW-UP PROGRAM COOPERATIVE GROUP (1982). The effect of treatment on mortality in 'mild' hypertension. *New England Journal of Medicine*, **307**, 976-980.

HENNING M. & VAN SWIETEN P.A.(1968). Central hypotensive effect of alpha-methyldopa. *Journal of Pharmacy and Pharmacology*, **20**, 409-417.

HINSHELWOOD, R.D. (1969). Hallucinations and Propranolol. *British Medical Journal*, ii, 445.

IGLOE M.C. (1964). Effects of methyldopa in hypertension. *Journal of the American Medical Association*, **189**, 188-190.

INGENITO A.J., BARRETT J.P. & PROCITA L. (1970). A centrally mediated peripheral hypotensive effect of alpha-methyldopa. *Journal of Pharmacology and Experimental Therapeutics*, **175**, 593-599.

IRVINE R.O.H., O'BRIEN K.P. & NORTH J.D.K. (1962). Alpha methyldopa in the treatment of hypertension. *Lancet*, i, 300-303.

IWATSUKI N., ONO K., KOGA Y. & AMAHA K. (1987). Prevention of postischaemic hypoperfusion after canine cardiac arrest by nicardipine. *Critical Care Medicine*, **15**, 313-317.

JACHUCK S.J., BRIERLEY, H., JACHUCK S. & WILLCOX P.M. (1982). The efect of hypotensive drugs on the quality of life. *Journal of the Royal College of General Practioners*, **32**, 103-105.

JAMES I.M., PEARSON R.M., GRIFFITH D.N.W. & NEWBURY P. (1977). Effect of oxprenolol on stage-fright in musicians. *Lancet*, i, 952-954.

JERN S. (1985). Assessment of psychic side-effects of antihypertensive drugs. *Acta Medica Scandinavica*, **693** (suppl), 103-106.

JOHNSTON M.E., GIBSON E.S., TERRY C.W., HAYNES R.B., TAYLOR D.W., GAFRIN A., SICURELLA J.I. & SACKETT D.L. (1984). Effects of labelling on income, work and social function among hypertensive employees. *Journal of Chronic Diseases*, **37**, 417-423.

KASS I. & BROWN E.C. (1955). Treatment of hypertensive patients with rauwolfia compounds. *Journal of the American Medical Association*, **159**, 1513-1516.

KAZDA S., HOFFMEISTER F., GARTHOFF B. & TOWART R. (1979). Prevention of post-ischaemic impaired reperfusion of the brain by nimodipine. *Acta Neurologica Scandinavica,* **60**, Suppl. 72, 358-359.

LADER M. & TYRER P.J. (1972). Central and peripheral efects of propranolol and sotalol in normal human subjects. *British Journal of Pharmacology,* **45**, 557-560.

LANDAUER A.A., POCOCK D.A. & PROTT F.W. (1979). The effects of propranolol and atenolol on human performance and subjective feelings. *Psychopharmacology,* **60**, 211-215.

LARKIN J.G., BUTLER E. & BRODIE M.J. (1988). Nifedipine for epilepsy? A pilot study. *British Medical Journal,* **296**, 530-531.

LAURENCE D.R. & BENNETT P.N. (1987). *Clinical Pharmacology.* Sixth edition. London: Churchill Livingstone.

LAVERTY R. (1973). The mechanism of action of some antihypertensive drugs. *British Medical Bulletin,* **29**, 152-157.

LEDINGHAM J.G. (1987). Personal communication.

LEMIEUX G., DAVIGNON A. & GENEST J. (1956). Depressive states during Rauwolfia therapy for arterial hypertension. *Canadian Medical Association Journal,* **74**, 522-526.

LEREN P. & HELGELAND A. (1986). Oslo hypertension study. *Drugs,* **31**, (suppl. 1), 41-45.

LESZKOVSZKY G. & TARDOS L. (1965). Some effects of propranolol on the central nervous system. *Journal of Pharmacy and Pharmacology,* 17, 518-519.

LEVANDER S. & GILLNER A. (1982). Metipranolol and propranolol: no C.N.S. effects of a single oral dose. *Psychopharmacology,* **76**, 359-366.

LEYS D., VERMERSCH P., DANEL T., COMAYRAS S., GOUDEMAND M., CARON J. & PETIT H. (1988). Diltiazem for tardive dyskinesia. *Lancet,* i, 250-251.

LEZAK M.D. (1983). *Neuropsychological Assessment.* Second edition. New York: Oxford University Press.

LICHTER I., RICHARDSON P.J. & WYKE M.A. (1986). Differential effects of atenolol and enalapril on memory during treatment for essential hypertension. *British Journal of Clinical Pharmacology,* **21**, 641-645.

McKINNEY W.T. & KANE F.J. (1967). Depression with then use of alpha-methyldopa. *American Journal of Psychiatry,* **124**, 80-81.

MADDEN D.J., BLUMENTHAL J.A., EKELUND L-G., KRANTZ D.S. LIGHT K.C. & McKEE D.C. (1986). Memory performance by mild hypertensives following beta-adrenergic blockade. *Psychopharmacology,* **89**, 20-24.

MADDEN D.J., BLUMENTHAL J.A. & EKELUND L-G. (1988). Effects of beta-blockade and exercise on cardiovascular and cognitive functioning. *Hypertension,* 11, 470-476.

MAGUIRE M.E., WIKLUND R.A., ANDERSON H.J. & GILMAN A.G. (1976). Binding of [125 I] Iodohydroxybenzylpindolol to beta-adrenergic receptors of rat glioma and other cell clones. *Journal of Biological Chemistry,* **251**, 1221-1231

MALPAS A. (1972). Subjective and objective effects of nitrazepam and amylobarbitone sodium in normal human beings. *Psychopharmacologia (Berl.),* **27**, 373-378.

MANN A.H. (1977). The psychological effects of a screening programme and clinical trial for hypertension upon the participants. *Psychological Medicine*, **7**, 431-438.

MANN A.H. (1981). Factors affecting psychological state during one year on a hypertension trial. *Clinical and Investigative Medicine,* **4**, 197-200.

MEDICAL RESEARCH COUNCIL WORKING PARTY (1981). Adverse reactions to bendrofluazide and propranolol following treatment of mild hypertension. *Lancet,* ii, 539-543.

MEDICAL RESEARCH COUNCIL WORKING PARTY (1983). Ventricular extrasystoles during thiazide treatment: substudy of the MRC Mild Hypertension Trial. *British Medical Journal*, **287**, 1249-1253.

MEDICAL RESEARCH COUNCIL WORKING PARTY (1985). MRC trial of treatment of mild hypertension: principal results. *British Medical Journal,* **291**, 97-104.

MEDICAL RESEARCH COUNCIL WORKING PARTY (1988). Stroke and coronary heart disease in mild hypertension: risk factors and the value of treatment. *British Medical Journal,* **296**, 1565-1570.

MIDDLEMISS D.N., BLAKEBOROUGH L. & LEATHER S.R. (1977). Direct evidence for an interaction of beta-adrenergic blockers with the 5-HT receptor. *Nature,* **267**, 289-290.

MIELCZAREK J. (1962). Methyldopa and depression. *British Medical Journal,* ii, 1471.

MILLER R.E., SHAPIRO A.P., KING H.E., GINCHEREAU E.H. & HOSUTT J.A. (1984). Effect of antihypertensive treatment on the behavioral consequences of elevated blood pressure. *Hypertension,* **6**, 202-208.

MILNE B.J., LOGAN A.G. & FLANAGAN P.T. (1985). Alterations in health perception and life-style in treated hypertensives. *Journal of Chronic Diseases,* **38**, 37-45.

MILNER P.C. & JOHNSON I.S.(1985). Treating mild hypertension. *Lancet,* ii, 1364.

MINER J.B. & BREWER J.F. (1976). The management of ineffective performance. In: *Handbook of Industrial and Organisational Psychology,* edited by Dunette M. pp 995-1029. Chicago: Rand McNally.

MONK M. (1981). Blood pressure awareness and psychological well-being in the Health and Nutrition Examination Survey. *Clinical and Investigative Medicine,* **4**, 183-189.

MOSER M. & GIFFORD R.W. (1985). Why less severe degrees of hypertension should be treated. *Journal of Hypertension,* **3**, 437-447.

MOSER M., BLACK H. & STAIR D. (1986). The dilemma of mild hypertension. *Drugs,* 31, 279-287.

MOSSEY J.M. (1981). Psychosocial consequences of labelling in hypertension. *Clinical and Investigative Medicine,* 4, 201-207.

MULLER J.C., PRYOR W.W., GIBBONS J.E. & ORGAIN E.S. (1955). Depression and anxiety occurring during Rauwolfia therapy. *Journal of the American Medical Association,* **159**, 509-522

NATIONAL HEART, LUNG AND BLOOD INSTITUTE. (1973). *The public and high blood pressure: a survey.* Washington DC: DHEW Publication No. 74-356.

NEIL-DWYER G., BARTLETT J., McAINSH J. & CRUICKSHANK J.M. (1981). Beta-adrenoceptor blockers and the blood-brain barrier. *British Journal of Clinical Pharmacology,* 11, 549-553.

NICHOLSON A.N., WRIGHT N.A., CURRIE D. & McDEVITT D.G. (1988). Effects of the beta-adrenoceptor antagonists propranolol and atenolol on the EEG and body sway. *British Journal of Clinical Pharmacology,* **24**,125P.

NOBILE -ORAZIO E. & STERZI R. (1981). Cerebral ischaemia after nifedipine treatment. *British Medical Journal,* **283**, 948.

O'CONNOR D.T., MOSLEY C.A., CERVENKA J. & BERNSTEIN K.N. (1984). Contrasting renal haemodynamic responses to the angiotensin converting enzyme inhibitor enalapril and the beta-adrenergic antagonist metoprolol in essential hypertension. *Journal of Hypertension,* **2** (Suppl. 2), 89-92.

OGLE C.W., TURNER P. & MARKOMIHELAKIS H. (1976). The effects of high doses of oxprenolol and of propranolol on pursuit rotor performance, reaction time and critical flicker frequency. *Psychopharmacologia (Berlin),* **46**, 295-299.

OLAJIDE D. & LADER M. (1985). Psychotropic effects of enalapril maleate in normal volunteers. *Psychopharmacology,* **86**, 374-376.

OLIVER M.F. (1983). Risks of correcting the risks of coronary disease and stroke with drugs. *New England Journal of Medicine,* **306**, 297-298.

PATEL L. & TURNER P. (1981). Central actions of beta-adrenoceptor blocking drugs in man. *Medicinal Research Reviews,* Vol.1, 4, 387-410.

PAYKEL E.S., FLEMINGER R. & WATSON J.P. (1982) Psychiatric Side Effects of Antihypertensive Drugs Other Than Reserpine. *Journal of Clinical Psychopharmacology,* **2**, 14-38

PECK A.W., ADAMS R., BYE C. & WILKINSON R.T. (1976). Residual efects of hypnotic drugs. *Psychopharmacology,* **47**, 213-216.

PETRIE, W.M., MAFFUCCI, R.J., WOOSLEY & R.L. (1982). Propranolol and Depression. *American Journal of Psychiatry,* **139**, 92-94.

PICKARD J.D., MURRAY G.D., ILLINGWORTH R., SHAW M.D,M., et al. (1989). Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British aneurysm niomodipine trial. *British Medical Journal,* **298**, 636-642.

PICKERING, G.W. (1961). *The nature of Essential Hypertension.* London: Churchill.

PITLIK S., MANOR R.S., LIPSHITZ I., PERRY G. & ROSENFELD J. (1983). Transient retinal ischaemia induced by nifedipine. British Medical Journal, **287**, 1845-1846.

POLK B.F., HARLAN L.C., COOPER S.P., STROMER M., IGNATIUS J., MULL H. & BLASZKOWSKI T.P. (1984). Disability days associated with detection and treatment in a hypertension control program. *American Journal of Epidemiology,* **119**, 44-53.

PRICHARD B.N.C., JOHNSTON A.W., HILL D. & ROSENHEIM M.L. (1968). Bethanidine, guanethidine and methyldopa in treatment of hypertension: a within-patient comparison. *British Medical Journal,* i, 135-144.

QUETSCH R.M., ACHOR R.W.P., LITIN E.M. & FAUCETT R.L. (1959). Depressive reaction in hypertensive patients. *Circulation,* **19**, 366-375.

REMICK R.A., O'KANE J. & SPARLING T.G. (1981). A case report of toxic psychosis with low-dose propranolol therapy. *American Journal of Psychiatry,* **138**, 850.

REY A. (1941). L'examen psychologique dans les cas d'encephalopathie traumatique. *Archives de Psychologie,* **28**, 286-340.

RAND M.J., MAJEWSKI H. & TUNG L-H. (1983). Activation of prejunctional beta-adrenoceptors by adrenaline acting as a co-transmitter. A possible cause of hypertension. *Drugs,* **25**, (Suppl 2), 65-68.

ROBERTSON J.I.S. (1983). State-of-the-art review: Beta-blockade and the treatment of hypertension. *Drugs,* **25**, (Suppl 2), 5-11.

ROBERTSON J.I.S. (1986). The 1985 trials of hypertension treatment. In *ISH Hypertension Yearbook,* edited by Hansson L., pp 3-25. London: Gower Academic Journals, 1986.

ROBERTSON J.I.S. (1987). The large studies in hypertension: What have they shown? *British Journal of Clinical Pharmacology,* **24**, 3S-14S.

ROBERTSON J.I.S. & HANSSON L. (1986). How well is hypertension treated? *Journal of Hypertension,* **4** (suppl 6), S638-S641.

ROUBICEK J. (1976). Effect of beta-adrenoceptor blocking drugs on EEG. *British journal of Clinical Pharmacology,* **3**, 661-665.

ROUBICEK J. (1977). The EEG profile of beta-adrenoceptor blockers. *Electroencehalography and Clinical Neurophysiology,* **42**, 438-439.

RUSSELL D., VEGER T., BUNAES U.B. & EFSKIND P.S. (1979). Epileptic seizures precipitated by atenolol. *Journal of Neurology, Neurosurgery and Psychiatry,* **42**, 484.

SAHLER C.P. (1987). Antihypertensive therapy and quality of life. *New England Journal of Medicine,* **315**, 52.

SAKABE T., NAGAI I., ISHIKAWA T., TAKESHITA H., MASUDA T., MATSUMOTO M. & TATEISHI A. (1986). Nicardipine increases cerebral blood flow but does not improve neurological recovery in a canine model of complete cerebral ischaemia. *Journal of Cerebral Blood Flow an Metabolism,* **6**, 684-690.

SALEM S.A. & McDEVITT D.G. (1983). Central effects of beta-adrenoceptor antagonists. *Clinical Pharmacology and Therapeutics,* **33**, 52-57.

SALEM S.A.M. & McDEVITT D.G. (1984). Central effects of single oral doses of propranolol in man. *British Journal of Clinical Pharmacology,* **17**, 31-36.

SCHILDKRAUT J.J. (1965). The catecholamine hypothesis of affective disorders. *American Journal of Psychiatry,* **122**, 509-522.

SCHROEDER H.A., PERRY H.M. (1955). Psychosis apparently produced by reserpine. *Journal of the American Medical Association,* **159**, 839-840.

SCHULTZ N.R., ELIAS M.F., ROBBINS M.A., STREETEN D.H.P. & BLAKEMAN N. (1986). A longitudinal comparison of hypertensives and normotensives on the Wechsler Memory Scale: Initial findings. *Journal of Gerontology,* **41**, 169-175.

SHAPIRO A.P., MILLER R.E., KING H.E., GINCHEREAU E.H. & FITZGIBBON K. (1982). Behavioral consequences of mild hypertension. *Hypertension,* **4**, 355-360.

SIEGEL S. (1956). *Non-parametric statistics for the behavioral sciences.* New York: McGraw-Hill

SIMPSON, F.O. & WAAL-MANNING,H.J.(1971). Hypertension and Depression: Interrelated Problems in Therapy. *Journal of the Royal College of Physicians of London,* **6**, 14-24.

SMITH S.E. (1960). The pharmacological actions of 3,4-dihydroxyphenyl-alphamethylalamine (alpha-methyldopa), an inhibitor of 5-hydroxy-tryptophan decarboxylase. *British Journal of Pharmacology,* **15**, 319-327.

SNAITH R.P. & McCOUBRIE M. (1974). Antihypertensive drugs and depression. *Psychological Medicine,* **4**, 393-398.

SOGHIKIAN K., FALLICK-HUNKELER E.M., URY H.K. & FISHER A.A. (1981). The effect of high blood pressure awareness and treatment on emotional well-being. *Clinical and Investigative Medicine,* **4**, 191-196.

SOLOMON S., HOTCHKISS E., SARAVAY S.M., BAYER C., RAMSEY P. & BLUM R.S. (1983). Impairment of memory function by antihypertensive medication. *Archives of General Psychiatry,* **40**, 1109-1112.

SORKIN E.M. & CLISSOLD S.P. (1987). Nicardipine. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy, in the treatment of angina pectoris, hypertension and related cardiovascular disorders. *Drugs,* **33**, 296-345.

SOURKES T.L.(1965). The Action of Alpha-methyldopa in the Brain. *British Medical Bulletin,* **21**, 66-69.

STEINERT J. & PUGH C.R. (1979). Two patients with schizophrenic-like psychosis after treatment with beta-adrenergic blockers. *British Medical Journal,* i, 790.

STINE S.M., YANG H-Y. T. & COSTA E.(1980). Inhibition of in-situ metabolism of [3H][met5]-enkephalin and potentiation of [met5]-enkephakin by captopril. *Brain Research,* **180**, 295-299.

STREUFERT S., DePADOVA A., McGLYNN T., POGASH R. & PIASECKI M. (1988). Impact of beta-blockade on complex cognitive functioning. *American Heart Journal,* **116**, 311-315.

SUBCOMMITTEE ON DEFINITION AND PREVALENCE OF THE 1984 JOINT NATIONAL COMMITTEE (1985). Hypertension prevalence and the status of awareness of treatment, and control in the United States: final report. *Hypertension*, 7, 457-468.

TAGGART P. & CARRUTHERS M. (1972). Suppression by oxprenolol of adrenergic response to stress. *Lancet*, ii, 256-258.

TAKENAKA T. & HANDA J. (1979). Cerebrovascular effects of YC-93, anew vasodilator in dogs, monkeys and human patients. *International Journal of Clinical Pharmacology and Biopharmacy*, **17**, 1-11.

TAYLOR L.B. (1969). Localisation of cerebral lesions by psychological testing. *Clinical Neurosurgery*, **16**, 269-287.

TAYLOR D.W., HAYNES R.B., SACKETT D.L. & GIBSON E.S. (1981). Long-term follow-up of absenteeism among working men following detection and treatment of their hypertension. *Clinical and Investigative Medicine*, **4**, 173-177.

TAYLOR E.A., CARROLL D. & JEFFERSON D. (1979). C.S.F./plasma ratios of propranolol and pindolol in man. *British Journal of Clinical Pharmacology*, **8**, 381P-382P.

THE IPPPSH COOLLABORATIVE GROUP (1985). Cardiovascular risk and risk factors in a randonized trial of treatment based on the beta-blocker oxprenolol: the International Prospective Primary Prevention Study in Hypertension. *Journal of Hypertension*, **3**, 379-392.

TODD P.A. & HEEL R.C. (1986). Enalapril: A review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in hypertension and congestive heart failure. *Drugs*, **31**, 198-248.

THUILLEZ C., GUERET M., DUHAZE P., LHOTSE F., KIECHEL J.R., et al (1984). Nicardipine: pharmacokinetics and effects on carotid and brachial blood flows in normal volunteers. *British Journal of Clinical Pharmacology*, **18**, 837-847.

TOPLISS D. & BOND R. (1977). Acute brain syndrome after propranolol treatment. *Lancet*, **2**, 1133-1144.

TRAP-JENSEN J., CARLSEN J.E., SVENDSEN T.L. & CHRISTENSEN N.J. (1979). Cardiovascular and adrenergic effects of cigarette smoking during immediate non-selective and selective beta-adrenoceptor blockade in humans. *European Journal of Clinical Investigation*, **9**, 181-189.

TUOMILEHTO J., PUSKA P. & MUSTANIEMI H. (1974). A comparative study of alprenolol and alpha-methyldopa respectively in combination with chlorthalidone in hypertension. *Acta Medica Scandinavica [Suppl]*, **554**, 47-54.

TUNG L.H., RAND M.J. & MAJEWSKI H. (1981). Adrenaline-induced hypertension in rats. *Clinical Science*, **61** (Suppl 7), 191-193.

VETERANS ADMINISTRATION COOPERATIVE STUDY GROUP (1967). Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressures averaging 115 through 129mmHg. *Journal of the American Medical Association*, **202**, 1028-1034.

VETERANS ADMINISTRATION COOPERATIVE STUDY GROUP (1970). Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressures averaging 90 through 114 mmHg. *Journal of the American Medical Association,* **213**, 1143-1152.

VIADERO J.J., WONG S.H. & WHITE W.B. (1983). Acute psychotic behaviour assiciated with atenolol. *American Journal of Psychiatry,* **140**, 1382

VIDT D.G. (1984). A controlled multiclinic study to compare the antihypertensive effects of MK-421, hydrochlorothiazide, and MK-421 combined with hydrochlorothiazide in patients with mild to moderate essential hypertension. *Journal of Hypertension,* **2** (Suppl. 2), 81-88.

VOLTOLINA E.J., THOMPSON S.I. & TISWE J. (1971). Acute organic brain syndrome with propranolol. *Clinical Toxicology,* **4**, 357-359.

WAAL, H.J. (1967). Propranolol-induced depression. *British Medical Journal*, ii, 50.

WAGNER E.H. & STROGATZ D.S. (1984). Hypertension labelling and well-being: alternative explanations in cross-sectional data. *Journal of Chronic Diseases,* **37**, 943-947.

WALDEMAR G. & PAULSON O.B. (1989). Angiotensin converting enzyme inhibition and cerebral circulation -a review. *British Journal of Cliniucal Pharmacology*, **28**, 177S-182S.

WALDEN J., SPECKMANN E-J. & WITTE O.W. (1985). Suppression of focal epileptiform discharges by intraventricular perfusion of calcium antagonists. *Electroencephalography and Clinical Neurophysiology*, **61**, 299-309.

WALLACE R.B., LEMKE J.H., MORRIS M.C., GOODENBERGER M., KOHOUT F. & HINRICHS J.V. (1985). Relationship of free recall memory to hypertension in the elderly. The Iowa 65+ Rural Health Study. *Journal of Chronic Diseases,* **38**, 475-481.

WALTERS A.J. & LADER M.H. (1971). Hangover effects of hypnotics in man. *Nature,* **229**, 637-638.

WECHSLER D. (1945). A standardised memory scale for clinical use. *Journal of Psychology,* **19**, 87-95.

WECHSLER D. (1955). *Wechsler Adult Intelligence Scale Manual.* New York: The Psychological Corporation.

WEISSMAN M.M. & BOTHWELL S. (1976). Assessment of social adjustment by patient self-report. *Archives of General Psychiatry,* **33**, 1111-1115.

WEISSMAN M.M., PRUSOFF B.A., THOMPSON W.D., HARDING P.S. & MYERS J.K. (1978). Social adjustment by self-report in a community sample and in psychiatric outpatients. *Journal of Nervous and Mental Disease,* **166**, 317-326.

WHITLOCK F.A. & BONFIELD A.R. (1980). Propranolol Psychosis. *Medical Journal of Australia,* i, 184-185.

WILCOX R.G., MITCHELL J.R.A. & HAMPTON J.R. (1986). Treatment of high blood pressure: should clinical practice be based on results of clinical trials? *British Medical Journal,* **293**, 433-437.

WILKIE F. & EISDORFER C. (1971). Intelligence and blood pressure in the aged. *Science,* **172**, 959-962.

WORLD HEALTH ORGANISATION (1978). *Mental disorders: Glossary and guide to their classification in accordance with the Ninth Revision of the International Classification of Diseases.* W.H.O. Geneva.

YAMAMOTO M., OHTA T. & TODA N. (1983). Mechanisms of relaxant action of nucardipine, a new calcium antagonist, on isolated dog cerebral and mesenteric arteries. *Stroke,* **14**, 270-275.

YOUNG R.D., BIGGS J.T., DIEGLER V.T. & MAYER D.A. (1978). A rating scale for mania. Reliability, validity and sensitivity. *British Journal of Psychiatry,* **133**, 429-434.

ZUBENKO G.S., NIXON R.A. (1984). Mood-elevating effect of captopril in depressed patients. *American Journal of Psychiatry,* **141**, 110-111.

GENERAL HEALTH QUESTIONNAIRE

GHQ-60

Please read this carefully:

We should like to know if you have had any medical complaints, and how your health has been in general, *over the past few weeks.* Please answer ALL the questions on the following pages simply by underlining the answer which you think most nearly applies to you. Remember that we want to know about present and recent complaints, not those that you had in the past.

It is important that you try to answer ALL the questions.

Thank you very much for your co-operation.

HAVE YOU RECENTLY:

1	**– been feeling perfectly well and in good health?**	Better than usual	Same as usual	Worse than usual	Much worse than usual
2	**– been feeling in need of a good tonic?**	Not at all	No more than usual	Rather more than usual	Much more than usual
3	**– been feeling run down and out of sorts?**	Not at all	No more than usual	Rather more than usual	Much more than usual
4	**– felt that you are ill?**	Not at all	No more than usual	Rather more than usual	Much more than usual
5	**– been getting any pains in your head?**	Not at all	No more than usual	Rather more than usual	Much more than usual
6	**– been getting a feeling of tightness or pressure in your head?**	Not at all	No more than usual	Rather more than usual	Much more than usual
7	**– been able to concentrate on whatever you're doing?**	Better than usual	Same as usual	Less than usual	Much less than usual
8	**– been afraid that you were going to collapse in a public place?**	Not at all	No more than usual	Rather more than usual	Much more than usual
9	**– been having hot or cold spells?**	Not at all	No more than usual	Rather more than usual	Much more than usual
10	**– been perspiring (sweating) a lot?**	Not at all	No more than usual	Rather more than usual	Much more than usual
11	**– found yourself waking early and unable to get back to sleep?**	Not at all	No more than usual	Rather more than usual	Much more than usual
12	**– been getting up feeling your sleep hasn't refreshed you?**	Not at all	No more than usual	Rather more than usual	Much more than usual
13	**– been feeling too tired and exhausted even to eat?**	Not at all	No more than usual	Rather more than usual	Much more than usual

PLEASE TURN OVER

HAVE YOU RECENTLY:

14 – **lost much sleep over worry?**	Not at all	No more than usual	Rather more than usual	Much more than usual
15 – **been feeling mentally alert and wide awake?**	Better than usual	Same as usual	Less alert than usual	Much less alert
16 – **been feeling full of energy?**	Better than usual	Same as usual	Less energy than usual	Much less energetic
17 – **had difficulty in getting off to sleep?**	Not at all	No more than usual	Rather more than usual	Much more than usual
18 – **had difficulty in staying alseep once you are off?**	Not at all	No more than usual	Rather more than usual	Much more than usual
19 – **been having frightening or unpleasant dreams?**	Not at all	No more than usual	Rather more than usual	Much more than usual
20 – **been having restless, disturbed nights?**	Not at all	No more than usual	Rather more than usual	Much more than usual
21 – **been managing to keep yourself busy and occupied?**	More so than usual	Same as usual	Rather less than usual	Much less than usual
22 – **been taking longer over the things you do?**	Quicker than usual	Same as usual	Longer than usual	Much longer than usual
23 – **tended to lose interest in your ordinary activities?**	Not at all	No more than usual	Rather more than usual	Much more than usual
24 – **been losing interest in your personal appearance?**	Not at all	No more than usual	Rather more than usual	Much more than usual
25 – **been taking less trouble with your clothes?**	More trouble than usual	About same as usual	Less trouble than usual	Much less trouble
26 – **been getting out of the house as much as usual?**	More than usual	Same as usual	Less than usual	Much less than usual
27 – **been managing as well as most people would in your shoes?**	Better than most	About the same	Rather less well	Much less well
28 – **felt on the whole you were doing things well?**	Better than usual	About the same	Less well than usual	Much less well
29 – **been late getting to work, or getting started on your housework?**	Not at all	No later than usual	Rather later than usual	Much later than usual
30 – **been satisfied with the way you've carried out your task?**	More satisfied	About same as usual	Less satisfied than usual	Much less satisfied
31 – **been able to feel warmth and affection for those near to you?**	Better than usual	About same as usual	Less well than usual	Much less well
32 – **been finding it easy to get on with other people?**	Better than usual	About same as usual	Less well than usual	Much less well
33 – **spent much time chatting with people?**	More time than usual	About same as usual	Less than usual	Much less than usual

GO ON TO THE NEXT PAGE

HAVE YOU RECENTLY:

34 – **kept feeling afraid to say anything to people in case you made a fool of yourself?**	Not at all	No more than usual	Rather more than usual	Much more than usual
35 – **felt that you are playing a useful part in things?**	More so than usual	Same as usual	Less useful than usual	Much less useful
36 – **felt capable of making decisions about things?**	More so than usual	Same as usual	Less so than usual	Much less capable
37 – **felt you're just not able to make a start on anything?**	Not at all	No more than usual	Rather more than usual	Much more than usual
38 – **felt yourself dreading everything that you have to do?**	Not at all	No more than usual	Rather more than usual	Much more than usual
39 – **felt constantly under strain?**	Not at all	No more than usual	Rather more than usual	Much more than usual
40 – **felt you couldn't overcome your difficulties?**	Not at all	No more than usual	Rather more than usual	Much more than usual
41 – **been finding life a struggle all the time?**	Not at all	No more than usual	Rather more than usual	Much more than usual
42 – **been able to enjoy your normal day-to-day activities?**	More so than usual	Same as usual	Less so than usual	Much less than usual
43 – **been taking things hard?**	Not at all	No more than usual	Rather more than usual	Much more than usual
44 – **been getting edgy and bad-tempered?**	Not at all	No more than usual	Rather more than usual	Much more than usual
45 – **been getting scared or panicky for no good reason?**	Not at all	No more than usual	Rather more than usual	Much more than usual
46 – **been able to face up to your problems?**	More so than usual	Same as usual	Less able than usual	Much less able
47 – **found everything getting on top of you?**	Not at all	No more than usual	Rather more than usual	Much more than usual
48 – **had the feeling that people were looking at you?**	Not at all	No more than usual	Rather more than usual	Much more than usual
49 – **been feeling unhappy and depressed?**	Not at all	No more than usual	Rather more than usual	Much more than usual
50 – **been losing confidence in yourself?**	Not at all	No more than usual	Rather more than usual	Much more than usual
51 – **been thinking of yourself as a worthless person?**	Not at all	No more than usual	Rather more than usual	Much more than usual
52 – **felt that life is entirely hopeless?**	Not at all	No more than usual	Rather more than usual	Much more than usual
53 – **been feeling hopeful about your own future?**	More so than usual	About same as usual	Less so than usual	Much less hopeful

PLEASE TURN OVER

HAVE YOU RECENTLY:

54	– **been feeling reasonably happy, all things considered?**	More so than usual	About same as usual	Less so than usual	Much less than usual
55	– **been feeling nervous and strung-up all the time?**	Not at all	No more than usual	Rather more than usual	Much more than usual
56	– **felt that life isn't worth living?**	Not at all	No more than usual	Rather more than usual	Much more than usual
57	– **thought of the possibility that you might make away with yourself?**	Definitely not	I don't think so	Has crossed my mind	Definitely have
58	– **found at times you couldn't do anything because your nerves were too bad?**	Not at all	No more than usual	Rather more than usual	Much more than usual
59	– **found yourself wishing you were dead and away from it all?**	Not at all	No more than usual	Rather more than usual	Much more than usual
60	– **found that the idea of taking your own life kept coming into your mind?**	Definitely not	I don't think so	Has crossed my mind	Definitely has

Published by The NFER-Nelson Publishing Company Ltd.
Darville House, 2 Oxford Road East, Windsor, SL4 1DF, Berks.

First published 1978. Reprinted 1982.

ISBN 07005 0212 2
Printed in Great Britain.

Code 4075.04.4

STANDARDISED PSYCHIATRIC INTERVIEW

Matched with [ ] Serial Number [ ]

C O N F I D E N T I A L THE INFORMATION IN THIS SCHEDULE IS CONFIDENTIAL. IT WILL BE SEEN ONLY BY AUTHORISED MEMBERS OF THE RESEARCH SURVEY TEAM. INDIVIDUAL INFORMATION WILL NOT BE DISCLOSED AND WILL BE USED FOR STATISTICAL PURPOSES ONLY.

NAME: _____ FAMILY DOCTOR: _____

ADDRESS: _____

_____

Complete before Interview	Check at Interview
YEAR OF BIRTH	
SEX	
MARITAL STATUS	
NO. OF CHILDREN	
NO. IN HOUSEHOLD	
OCCUPATION (self/husband/father)	
SOCIAL CLASS	

HOME VISIT:

Signature of Interviewer: _____ Date of Interview _____

NOTES:

GENERAL PRACTITIONER'S NOTES ON INDEX CONSULTATION

HISTORY OF PRESENT CONDITION

I understand you saw Dr ..... on .....

Would you mind telling me about that?
(give brief history of present complaint, including samples of patient's account verbatim.)

Try to elicit a) date of onset (as near as possible)

b) mode of onset (whether sudden, gradual, etc)

(For working patients) Have you had to take any time off work because of this trouble (i.e. in the past 3 months)?

(For all others, incl. housewives) Has this trouble interfered with any of your normal activities (i.e. in the past 3 months)?

IF YES, ascertain details

GENERAL MEDICAL HISTORY

Now I'd like to ask you about your previous health. Have you had any serious illnesses?

What about operations?

(check the following):-

Chronic chest condition (e.g. bronchitis, asthma)?

High blood pressure?

Heart trouble?

Stomach or bowel trouble (e.g. stomach ulcers, gastritis)

Jaundice?

Kidney or bladder disease?

Diabetes?

Any serious skin trouble?

Arthritis (stiffness, pain in the joints)?

Any kind of growth or tumour?

Anything else?

Do you suffer from any kind of ill-health now (apart from what you came to see Dr ..... about)?

Have you ever had a nervous breakdown, or suffered from bad nerves?

Were you ever a patient in a hospital for nerves (Mental Hospital)?

Did anyone in your family suffer from nervous trouble?

- or have treatment in a hospital for nerves (Mental Hospital)?

How long has Dr ..... been your doctor now?

(If a new episode)
When was the last time you saw him before this recent trouble?

What was that for?

(If not a new episode)
How long have you been seeing him for this trouble?

During the past year, have you been under any other doctor?

- have you been in hospital or attended hospital?

ADDITIONAL NOTES ON MEDICAL HISTORY
(Including any special points from patient's medical notes)

ANY SPECIAL COMMENTS ON MEDICAL HISTORY BY PATIENTS'S G.P.

Have you noticed anything else wrong with your health apart from the things that you've already told me?

(Anything else?)

In the past week, have you been troubled with a) headache

b) indigestion

c) backache

If the rater suspects that psychological mechanisms may be implicated in any of the somatic symptoms described, elicit more details as follows:-

How long have you had this trouble?

Does it seem to get worse when your nerves are bad?

How much does it upset you?

How often have you had it in this past week?

SOMATIC SYMPTOMS	4	3	2	1	0

ALL PATIENTS:- Are you at all worried about your health at the moment?

Do you find yourself thinking a lot about your health, or about the workings of any part of your body?

Do you every worry about having cancer? or heart disease?

(The following Part 2 rating may be made at this point if the rater wishes)

EXCESSIVE CONCERN WITH BODILY FUNCTIONS	4	3	2	1	0

Have you noticed that you get tired easily?

Or tht you seem to be lacking in energy?

<u>If the patient's replies indicate excessive fatigue or lethargy, go on as follows</u>:-

How long have you noticed this?

Do you feel tired the whole time, or just now and then?

What sort of things do you find most tiring?

Do you feel completely tired out in the evening?

How has it been this past week?

Has it stopped you from doing anything you've wanted to do?

FATIGUE 4 3 2 1 0

What about your sleep?

(If reply indicates difficulties, ask for details):-

Do you have difficulty dropping off?

Are you restless at night?

Do you wake early?

Have you lost any sleep in the past week?

If the patient's replies indicate loss of sleep in the past week, go on as follows:-

How long have you had this trouble?

Have you any idea why you can't sleep?

How many nights in the past week have you lost sleep?

How many hours sleep do you think that you miss on a bad night?

SLEEP DISTURBANCE	4	3	2	1	0

ALL PATIENTS:-

Do you take any sleeping pills?

If YES, o on to ask:-

Do you get them from your doctor?

Do you know what they are called?

Do you take them every night, or just now and again?

How many have you had in the past week?

HYPNOTICS	2	1	0

Do you find that you are easily upset or irritable with those around you?

If the patient's reply indicates irritability, go on as follows:-

How long have you been like this?

Are you like it all the time or just occasionally?

What sort of things upset you?

How has it been in the past week?

Have you had any rows with anyone in this past week?

Are there still any hard feelings?

IRRITABILITY	4	3	2	1	0

Do you find it difficult to concentrate?

Do you get muddled or forgetful?

If replies indicate impairment, go on as follows:-

How long have you noticed this trouble?

Do you notice it all the time or just now and then?

Has it caused any difficulty at home?

at work?

Can you concentrate on a newspaper or on a play on T.V.?

How bad has it been in this past week?

Has it stopped you from doing anything?

How many of your activities are affected?

LACK OF CONCENTRATION 4 3 2 1 0

How have you been feeling in your spirits in the past week?

Have you had spells of feeling sad or miserable?

If the patient's replies indicate despondency or sadness, go on as follows:-

Have you felt low the whole time or just occasionally?

Does it seem connected with anything that happens?

How bad does it get?

Do you ever get weepy?

Can you snap out of it?

Do you sometimes feel hopeless?

Have you felt like making an end to it all?

DEPRESSION	4	3	2	1	0

If indicated, ask the following questions for the Part 2 rating of depressive thoughts:-

Do you every blame yourself for being like this?

Do you ever find yourself feeling guilty?

Do you sometimes feel inferior to other people?

How do you feel about the future?

Would you say that you are a highly-strung or nervous person?

Do you ever find that you get anxious or frightened for no good reason?

Do you worry a lot about things?

If the patient's replies indicate anxiety and worrying, go on and ask more:-

What sort of things do you chiefly worry about?

Have you always been like this, or is it something that has only started recently?

Do you worry all the time, or only now and then?

Do you find yourself worrying more than you need about little things?

Have you been upset by worries in the past week?

ANXIETY 4 3 2 1 0

Are there any special things or situations that you find frightening or upsetting?

What about being alone in the house?

- going out by yourself?

- travelling on buses or trains?

- animals? insects? heights? the dark?

If patient's replies indicate any phobias, go on to elicit details, viz:-

How severe is this?

Do you get it all the time or just now and again?

How bad has it been in this past week?

Do you have to go out of your way to avoid or alter your usual activities in any way?

PHOBIAS 4 3 2 1 0

Do you ever find that you have to do things over and over to make sure that you've done them right?

Or that you keep having unwelcome thoughts that you can't get rid of? (If patient asks what is meant, Well any sort of unpleasant thought that comes into your mind against your will).

Do you find it hard to make decisions?

If the patient's replies indicate possible obsessions or compulsions, ask appropriate questions from the following:-
(CHECKING)

How many times do you find yourself checking your work?

Do you check it even thought you know that it's right really?

Are there any other things that you find yourself having to do a number of times?

UNWELCOME THOUGHTS

Can you describe them to me?

DIFFICULTY WITH DECISIONS

Is this something that you've always had or is it something new?

Is it just over important issues or does it affect trivialities as well?

ALL PHENOMENA

Do you try and struggle against it?

Is it very distressing?

Does it take up much of your time?

How bad has it been in this past week?

OBSESSIONS 4 3 2 1 0

Do you ever get the feeling that you're not really there. Or that everything around you seems unreal?

<u>If patient's replies indicate possible depersonalisation, go on to elicit details, viz</u>:-

Can you describe the feeling?

Do you find it unpleasant or frightening?

Do you get it every day or just now and again?

How long does it last when you get it?

How bad has it been just lately (e.g. in this past week)?

DEPERSONALISATION 4 3 2 1 0

Is there anything else to do with your health that you think might be important?

- or anything I haven't asked you about?

FAMILY PSYCHIATRIC HISTORY

BRIEF PERSONAL AND SOCIAL HISTORY

PART TWO RATINGS

Evidence for Psychiatric Disturbance Noted at Interview

Name of Rating:	Reason for Morbid Rating:	Rating Assigned:
SLOW, lacking spontaneity		4 3 2 1 0
SUSPICIOUS, defensive		4 3 2 1 0
HISTRIONIC		4 3 2 1 0
DEPRESSED		4 3 2 1 0
ANXIOUS, TENSE AGITATED		4 3 2 1 0
ELATED, euphoric		4 3 2 1 0
FLATTENED, INCONGRUOUS		4 3 2 1 0
DELUSIONS, Misinterpretations THOUGHT DISORDER		4 3 2 1 0
HALLUCINATIONS		4 3 2 1 0
INTELLECTUAL IMPAIRMENT		4 3 2 1 0

The following ratings may already have been made:-

EXCESSIVE CONCERN with BODILY FUNCTIONS		4 3 2 1 0
DEPRESSIVE THOUGHTS		4 3 2 1 0

Interviewer's notes

Summary and Formulation

Assessment of the Reliability of the Information

GOOD / FAIR / POOR

I.C.D. DIAGNOSIS

Principal Diagnosis .....

Ancillary Diagnosis .....

D.S.M. DIAGNOSIS

OVERALL SEVERITY RATING

4 3 2 1 0

SOCIAL ADJUSTMENT - SELF REPORT QUESTIONNAIRE

I am interested in finding out how you have been doing in the last two weeks. We would like you to answer some questions about your work, your spare time and your family life. There are no right or wrong answers to these questions. Please tick the answer that best describes how you have been in the last two weeks.

WORK OUTSIDE THE HOME

Please tick the situation that best describes you.

I am
1) .... a worker for pay
2) .... a housewife
3) .... a student
4) .... retired
5) .... unemployed

Do you usually work for more than 15 hours per week?

1) .... YES 2) .... NO

Did you work any hours for pay in the last two weeks?

1) .... YES 2) .... NO

Tick the answer that best describes how you have been in the last two weeks.

1. How many days did you miss from work in the last two weeks?

1) .... No days missed
2) .... One day.
3) .... I missed about one week
4) .... I missed more than a week but managed to work at least one day.
5) .... I did not work any days.
6) .... I was on holiday all of the last two weeks.

If you have not worked any days in the last two weeks, please go on to Question 7.

2. Have you been able to do your work in the last two weeks?

1) .... I did my work very well.
2) .... I did my work well but had some minor problems.
3) .... I needed help with work and did not do well about half of the time.
4) .... I did my work poorly most of the time.
5) .... I did my work poorly all the time.

3. Have you been ashamed about how you did your work in the last two weeks.

   1) .... I never felt ashamed.
   2) .... Once or twice I felt a little ashamed.
   3) .... About half of the time I felt ashamed.
   4) .... I felt ashamed most of the time.
   5) .... I felt ashamed all of the time.

4. Have you had any arguments with people at work in the last two weeks?

   1) .... I had no arguments and got along very well.
   2) .... I usually get along well but had minor arguments.
   3) .... I had more than one argument.
   4) .... I had many arguments.
   5) .... I was consistently involved in arguments.

5. Have you felt upset, worried or uncomfortable while doing your work during the last two weeks.

   1) .... I never felt upset.
   2) .... Once or twice I felt upset.
   3) .... Half of the time I felt upset.
   4) .... I felt upset most of the time.
   5) .... I felt upset all of the time.

6. Have you found your work interesting in these last two weeks.

   1) .... My work was almost always interesting.
   2) .... Once or twice my work was not interesting.
   3) .... Half of the time my work was uninteresting.
   4) .... Most of the time my work was uninteresting.
   5) .... My work was always uninteresting.

WORK AT HOME - HOUSEWIVES ANSWER QUESTIONS 7 - 12. OTHERWISE, GO TO QUESTION 13.

7. How many days did you do some housework in the last two weeks?

   1) .... Every day.
   2) .... I did housework almost every day.
   3) .... I did housework about half of the time.
   4) .... I usually did not do housework.
   5) .... I was completely unable to do housework.
   6) .... I was away from home all of the last two weeks.

8. During the last two weeks, have you kept up with your housework. This includes, cooking, cleaning, laundry, shopping and messages.

   1) .... I did my work well.
   2) .... I did my work well but had some minor problems.
   3) .... I needed help with my work and did not do it well about half the time.
   4) .... I did my work poorly most of the time.
   5) .... I did my work poorly all of the time.

9. Have you been ashamed about how you did your housework during the last two weeks?

   1) .... I never felt ashamed.
   2) .... Once or twice I felt a little ashamed.
   3) .... About half the time I felt ashamed.
   4) .... I felt ashamed most of the time.
   5) .... I felt ashamed all of the time.

10. Have you had any arguments with salespeople, tradesmen or neighbours in the last two weeks.

   1) .... I had no arguments and got along very well.
   2) .... I usually got along well but had minor arguments.
   3) .... I had more than one argument.
   4) .... I had many arguments.
   5) .... I was constantly involved in arguments.

11. Have you felt upset while doing your housework during the last two weeks.

   1) .... I never felt upset.
   2) .... Once or twice I felt upset.
   3) .... Half the time I felt upset.
   4) .... I felt upset most of the time.
   5) .... I felt upset all the time.

12. Have you found your housework interesting in these last two weeks?

   1) .... My work was almost always interesting.
   2) .... Once or twice my work was not interesting.
   3) .... Half the time my work was uninteresting.
   4) .... Most of the time my work was uninteresting.
   5) .... My work was always uninteresting.

FOR STUDENTS

ANSWER QUESTIONS 13 - 18 if you attend school, college or University for half of your time or more, if not please go on to QUESTION 19.

What best describes your study programme? (choose one)

1) .... Full time.
2) .... 3/4 time.
3) .... Half time.

Tick the answer that best describes how you have been in the last two weeks.

13. How many days of classes did you miss in the last two weeks?

1) .... No days missed
2) .... A few days missed.
3) .... I missed about half the time.
4) .... I missed more than half the time but did attend at least one day.
5) .... I did not go to classes at all.
6) .... I was on holiday during the last two weeks.

14. Have you been able to keep up with your class work in the last two weeks?

1) .... I did my work very well.
2) .... I did my work well but had minor problems.
3) .... I needed help with my work and did not do well about half the time.
4) .... I did my work poorly most of the time.
5) .... I did my work poorly all of the time.

15. During the last two weeks, have you been ashamed of the way you did your school/college/University work?

1) .... I never felt ashamed.
2) .... Once or twice I felt ashamed.
3) .... About half the time I felt ashamed.
4) .... I felt ashamed most of the time.
5) .... I felt ashamed all of the time.

16. Have you had any arguments with people at school/college/University in the last two weeks?

1) .... I had no arguments and got along very well.
2) .... I usually got along well but I had minor arguments.
3) .... I had more than one argument.
4) .... I had many arguments.
5) .... I was constantly involved in arguments.
6) .... Not applicable; I did not attend school/college/University.

17. Have you felt upset at school/college/University during the last two weeks?

1) .... I never felt upset.
2) .... Once or twice I felt upset.
3) .... Half the time I felt upset.
4) .... I felt upset most of the time.
5) .... I felt upset all of the time.
6) .... Not applicable; I did not attend school/college/University.

18. Have you found school/college/University work interesting these last two weeks?

1) .... My work was almost always interesting.
2) .... Once or twice my work was not interesting.
3) .... Half the time my work was uninteresting.
4) .... Most of the time my work was uninteresting.
5) .... My work was always uninteresting.

SPARE TIME - EVERYONE PLEASE ANSWER QUESTIONS 19 - 27.

Tick the answer that best describes how you have been in the last two weeks.

19. How many friends have you seen or spoken to on the telephone in the last two weeks?

1) .... Nine or more friends.
2) .... Five to eight friends.
3) .... Two to four friends.
4) .... One friend.
5) .... No friends.

20. Have you been able to talk about your feelings and problems with at least one friend during the last two weeks?

1) .... I can usually talk about my innermost feelings.
2) .... I usually can talk about my feelings.
3) .... About half of the time I felt able to talk about my feelings.
4) .... I usually was not able to talk about my feelings.
5) .... I was never able to talk about my feelings.
6) .... Not applicable; I have no friends.

21. How many times in the last two weeks have you gone out socially with other people? For example, visited friends, gone to the cinema, football, church, restaurants, invited friends to your home?

1) .... More than 3 times.
2) .... Three times.
3) .... Twice.
4) .... Once.
5) .... None.

22. How much time have you spent on hobbies or spare time interests during the last two weeks? For example, football, sewing, gardening, sport and reading?

1) .... I spent most of my spare time on hobbies almost every day.
2) .... I spent some spare time on hobbies some of the days.
3) .... I spent a little spare time on hobbies.
4) .... I usually did not spend any time on hobbies but I did watch T.V.
5) .... I did not spend any spare time on hobbies or watching T.V.

23. Have you had open arguments with your friends in the last two weeks?

1) .... I had no arguments and got along very well.
2) .... I usually got along well but had minor arguments.
3) .... I had more than one argument.
4) .... I had many arguments.
5) .... I was constantly involved in arguments.
6) .... Not applicable; I have no friends.

24. If your feelings were hurt or offended by a friend during the last two weeks, how badly did you take it?

1) .... It did not affect me or it did not happen.
2) .... I got over it in a few hours.
3) .... I got over it in a few days.
4) .... I got over it in a week.
5) .... It will take me months to recover.
6) .... Not applicable; I have no friends.

25. Have you felt shy or uncomfortable with people in the last two weeks?

1) .... I always felt comfortable.
2) .... Sometimes I felt uncomfortable but could relax after a while.
3) .... About half the time I felt uncomfortable.
4) .... I usually felt uncomfortable.
5) .... I always felt uncomfortable.
6) .... Not applicable; I was never with people.

26. Have you felt lonely and wished for more friends during the last two weeks?

1) .... I have not felt lonely.
2) .... I have felt lonely a few times.
3) .... About half the time I felt lonely.
4) .... I usually felt lonely.
5) .... I always felt lonely and wished I had more friends.

27. Have you felt bored in your spare time during the last two weeks?

1) .... I never felt bored.
2) .... I usually did not feel bored.
3) .... About half the time I felt bored.
4) .... Most of the time I felt bored.
5) .... I was constantly bored.

Are you a Single, Separated, or Divorced Person not living with a person of the opposite sex; please answer below -

1) .... YES If YES, answer questions 28 and 29.

2) .... NO If NO, please go on to question 30.

28. How many times have you gone out socially with a member of the opposite sex during the last two weeks?

1) .... More than 3 times.
2) .... Three times.
3) .... Twice.
4) .... Once.
5) .... Never.

29. Have you been interested in going out socially with members of the opposite sex during the last two weeks. If you have not gone out with a member of the opposite sex would you have liked to?

1) .... I was always interested in going out with a member of the opposite sex.
2) .... Most of the time I was interested.
3) .... About half of the time I was interested.
4) .... Most of the time I was not interested.
5) .... I was completely uninterested.

FAMILY

Answer questions 30 - 37 about your parents, brothers, sisters, in-laws, and children not living at home. Have you been in contact with any of them in the last two weeks?

1) .... YES. If YES, please answer questions 30 - 37.

2) .... NO. If NO, please go on to question 36.

30. Have you had open arguments with your relatives in the last two weeks?

1) .... We always got along very well.
2) .... We usually got along very well but had some minor arguments.
3) .... I had more than one argument with at least one relative.
4) .... I had many arguments.
5) .... I was constantly involved in arguments.

31. Have you been able to talk about your feelings and problems with at least one of your relatives in the last two weeks?

1) .... I can always talk about my feelings with one relative.
2) .... I usually can talk about my feelings.
3) .... About half of the time I felt able to talk about my feelings.
4) .... I usually was not able to talk about my feelings.
5) .... I was never able to talk about my feelings.

32. Have you avoided contacts with your relatives during these last two weeks?

1) .... I have contacted relatives regularly.
2) .... I have contacted a relative at least once.
3) .... I have waited for my relatives to contact me.
4) .... I avoided my relatives but they contacted me.
5) .... I had no contacts with any relatives.

33. Did you depend on your relatives for help. advice, money or friendship during the last two weeks?

1) .... I never needed to depend on them.
2) .... I usually did not need to depend on them.
3) .... About half the time I needed to depend on them.
4) .... Most of the time I depended on them.
5) .... I depended completely on them.

34. Have you wanted to do the opposite of what your relatives wanted in order to make them angry during the last two weeks?

1) .... I never wanted to oppose them.
2) .... Once or twice I wanted to oppose them.
3) .... About half the time I wanted to oppose them.
4) .... Most of the time I wanted to oppose them.
5) .... I always opposed them.

35. Have you been worried about things happening to your relatives without reason in the past two weeks?

1) .... I have not worried without reason.
2) .... Once or twice I was worried.
3) .... About half the time I was worried.
4) .... Most of the time I was worried.
5) .... I have worried the entire time.
6) .... Not applicable; my relatives are no longer living.

EVERYONE please answer QUESTIONS 36 and 37, even if your relatives are not living.

36. During the last two weeks have you been thinking that you have let any of your relatives down or have been unfair to them at any time?

1) .... I did not feel that I let them down at all.
2) .... I usually did not feel that I had let them down.
3) .... About half the time I felt that I had let them down.
4) .... Most of the time I felt that I let them down.
5) .... I always felt that I let them down.

37. During the last two weeks have you been thinking that any of your relatives have let you down or have been unfair to you at any time?

1) .... I never felt that they let me down.
2) .... I felt that they usually did not let me down.
3) .... About half the time I felt they let me down.
4) .... I usually felt that they let me down.
5) .... I am very bitter that they let me down.

Are you living with your spouse or have been living with a person of the opposite sex in a permanent relationship?

1) .... YES. If YES, please answer questions 38 to 46.

2) .... NO. If NO, please go on to question 47.

38. Have you had open arguments with your partner in the last two weeks?

1) .... We had no arguments and we got along well.
2) .... We usually got along well but had minor arguments.
3) .... We had more than one argument.
4) .... We had many arguments.
5) .... We were constantly involved in arguments.

39. Have you been able to talk about your feelings and problems with your partner during the last two weeks?

1) .... I could always talk freely about my feelings.
2) .... I usually could talk about my feelings.
3) .... About half the time I felt able to talk about my feelings.
4) .... I usually was not able to talk about my feelings.
5) .... I was never able to talk about my feelings.

40. Have you been demanding to have your own way at home during the last two weeks?

1) .... I have not insisted on always having my own way.
2) .... I usually have not insisted on having my own way.
3) .... About half the time I insisted on having my own way.
4) .... I usually insisted on having my own way.
5) .... I always insisted on having my own way.

41. Have you been bossed around by your partner during these last two weeks?

1) .... Almost never.
2) .... Once in a while.
3) .... About half the time.
4) .... Most of the time.
5) .... Always.

42. How much have you felt dependent on your partner during these last two weeks?

1) .... I was independent.
2) .... I was usually independent.
3) .... I was somewhat dependent.
4) .... I was usually dependent.
5) .... I depended on my partner for everything.

43. How have you felt about your partner during these last two weeks?

1) .... I always felt affection.
2) .... I usually felt affection.
3) .... About half the time I felt dislike and half the time affection.
4) .... I usually felt dislike.
5) .... I always felt dislike.

44. How many times have you and your partner had sexual intercourse?

1) .... More than twice a week.
2) .... One or twice a week.
3) .... Once every 2 weeks.
4) .... Less than once every two weeks but at least once in the last month.
5) .... Not at all in a month or longer.

45. Have you had any problems during sexual intercourse, such as pain, during these last two weeks?

1) .... None.
2) .... Once or twice.
3) .... About half the time.
4) .... Most of the time.
5) .... Always.
6) .... Not applicable, no sexual intercourse took place in the last two weeks.

46. How have you felt about sexual intercourse during the last two weeks?

1) .... I always enjoyed it.
2) .... I usually enjoyed it.
3) .... About half the time I did and about half the time I did not enjoy it.
4) .... I usually did not enjoy it.
5) .... I never enjoyed it.

CHILDREN

Have you had unmarried children, stepchildren or foster children living at home during the last two weeks?

1) .... YES. If YES, please answer questions 47 - 50.

2) .... NO. If NO, please go on to question 51.

47. Have you been interested in what your children are doing - school, play or hobbies during the last two weeks?

1) .... I was always interested and actively involved.
2) .... I usually was interested and involved.
3) .... About half the time interested and half the time not interested.
4) .... I usually was disinterested.
5) .... I was always disinterested.

48. Have you been able to talk and listen to your children during the last two weeks? Include only children that are over the age of 2 years.

1) .... I always was able to communicate with them.
2) .... I usually was able to communicate with them.
3) .... About half the time I could communicate with them.
4) .... I usually was not able to communicate with them.
5) .... I was completely unable to communicate with them.
6) .... Not applicable; no children over the age of 2 years.

49. How have you been getting along with the children during the last two weeks?

1) .... I had no arguments and got along very well.
2) .... I usually got along well but had minor arguments.
3) .... I had more than one argument.
4) .... I had many arguments.
5) .... I was constantly involved in arguments.

50. How have you felt towards your children during these last two weeks?

1) .... I always felt affection.
2) .... I mostly felt affection.
3) .... About half the time I felt affection.
4) .... Most of the time I did not feel affection.
5) .... I never felt affection towards them.

FAMILY UNIT

Have you every been married, ever lived with a person of the opposite sex or ever had children? Please tick the response which is most suited to you.

1) .... YES. If YES, please answer questions 51 to 53.

2) .... NO. If NO, please go on to question 54.

51. Have you worried about your partner or any of your children without any reason during the last two weeks, even if you are not living together now?

1) .... I never worried.
2) .... Once or twice I worried.
3) .... About half the time I worried.
4) .... Most of the time I worried.
5) .... I always worried.
6) .... Not applicable; partner and children are not living.

52. During the last two weeks, have you been thinking that you have let your partner or any of your children down at any time?

1) .... I did not feel I let them down at all.
2) .... I usually did not feel that I let them down.
3) .... About half the time I let them down.
4) .... Most of the time I felt that I let them down.
5) .... I let them down completely.

53. During the last two weeks, have you been thinking that your partner or any of your children have let you down at any time?

1) .... I never felt they let me down.
2) .... I felt they usually did not let me down.
3) .... About half the time I felt they let me down.
4) .... I usually felt they let me down.
5) .... I felt bitter that they should have let me down.

FINANCIAL EVERYONE PLEASE ANSWER QUESTION 54.

54. Have you had enough money to take care of your own and your children's financial needs during the last two weeks?

1) .... I had enough money for needs.
2) .... I usually had enough money with minor problems.
3) .... About half the time I did not have enough money but did not have to borrow money.
4) .... I usually did not have enough money and had to borrow from others.
5) .... I had great financial difficulty.

WAIS RECORD FORM

Wechsler Adult Intelligence Scale

Name _____

Birth Date _____ Age _____ Sex _____ Marital: S M D W (CIRCLE ONE)

Nat. _____ Colour _____ Tested by _____

Place of Examination _____ Date _____

Occupation _____ Education _____

TABLE OF SCALED SCORE EQUIVALENTS*

Scaled Score	RAW SCORE											Scaled Score
	Information	Comprehension	Arithmetic	Similarities	Digit Span	Vocabulary	Digit Symbol	Picture Completion	Block Design	Picture Arrangement	Object Assembly	
19	29	27-28		26	17	78-80	87-90					19
18	28	26		25		76-77	83-86	21		36	44	18
17	27	25	18	24		74-75	79-82		48	35	43	17
16	26	24	17	23	16	71-73	76-78	20	47	34	42	16
15	25	23	16	22	15	67-70	72-75		46	33	41	15
14	23-24	22	15	21	14	63-66	69-71	19	44-45	32	40	14
13	21-22	21	14	19-20		59-62	66-68	18	42-43	30-31	38-39	13
12	19-20	20	13	17-18	13	54-58	62-65	17	39-41	28-29	36-37	12
11	17-18	19	12	15-16	12	47-53	58-61	15-16	35-38	26-27	34-35	11
10	15-16	17-18	11	13-14	11	40-46	52-57	14	31-34	23-25	31-33	10
9	13-14	15-16	10	11-12	10	32-39	47-51	12-13	28-30	20-22	28-30	9
8	11-12	14	9	9-10		26-31	41-46	10-11	25-27	18-19	25-27	8
7	9-10	12-13	7-8	7-8	9	22-25	35-40	8-9	21-24	15-17	22-24	7
6	7-8	10-11	6	5-6	8	18-21	29-34	6-7	17-20	12-14	19-21	6
5	5-6	8-9	5	4		14-17	23-28	5	13-16	9-11	15-18	5
4	4	6-7	4	3	7	11-13	18-22	4	10-12	8	11-14	4
3	3	5	3	2		10	15-17	3	6-9	7	8-10	3
2	2	4	2	1	6	9	13-14	2	3-5	6	5-7	2
1	1	3	1		4-5	8	12	1	2	5	3-4	1
0	0	0-2	0	0	0-3	0-7	0-11	0	0-1	0-4	0-2	0

*Clinicians who wish to draw a "psychograph" on the above table may do so by connecting the subject's raw scores. The interpretation of any such profile, however, should take into account the reliabilities of the subtests and the lower reliabilities of differences between subtest scores.

SUMMARY

TEST	Raw Score	Scaled Score	
Information			
Comprehension			
Arithmetic			
Similarities			
Digit Span			
Vocabulary			
Verbal Score			
Digit Symbol			
Picture Completion			
Block Design			
Picture Arrangement			
Object Assembly			
Performance Score			
Total Score			

VERBAL SCORE _____ IQ _____

PERFORMANCE SCORE _____ IQ _____

FULL SCALE SCORE _____ IQ _____

1. INFORMATION	SCORE 1 or 0		SCORE 1 or 0		SCORE 1 or 0
1. Flag		11. Height		21. Members of Parliament	
2. Ball		12. Italy		22. Genesis	
3. Months		13. Clothes		23. Temperature	
4. Thermometer		14. Valentine's Day		24. Iliad	
5. Rubber		15. Hamlet		25. Blood vessels	
6. Prime Ministers		16. Vatican		26. Koran	
7. Longfellow		17. New York		27. Faust	
8. Weeks		18. Egypt		28. Ethnology	
9. Gibraltar		19. Yeast		29. Apocrypha	
10. Brazil		20. Population			

OBSERVATIONS:

The NFER-NELSON Publishing Company Ltd., Darville House, 2 Oxford Road East, Windsor, Berks SL4 1DF, England.

Code 1102 05 4

2 (6.85)

2. COMPREHENSION	SCORE 2, 1 or 0
1. Clothes	
2. Engine	
3. Envelope	
4. Bad company	
5. Cinema	
6. Taxes	
7. Iron	
8. Child employment	
9. Forest	
10. Deaf	
11. Town land	
12. Marriage	
13. Still waters	
14. Swallow	

4. SIMILARITIES	SCORE 2, 1 or 0
1. Orange—Banana	
2. Coat—Dress	
3. Axe—Saw	
4. Dog—Lion	
5. North—West	
6. Eye—Ear	
7. Air—Water	
8. Table—Chair	
9. Egg—Seed	
10. Poem—Statue	
11. Wood—Alcohol	
12. Praise—Punishment	
13. Fly—Tree	

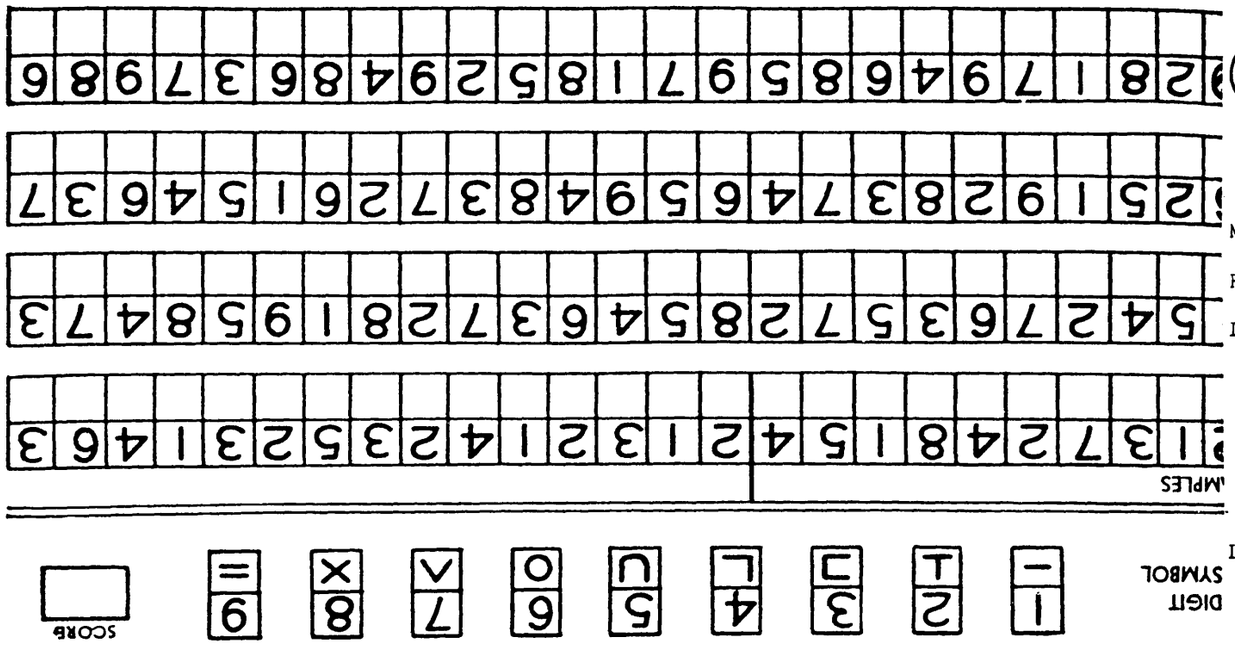
3. ARITHMETIC			
	R. W.	Time	SCORE
1. 15″			0 1
2. 15″			0 1
3. 15″			0 1
4. 15″			0 1
5. 30″			0 1
6. 30″			0 1
7. 30″			0 1
8. 30″			0 1
9. 30″			0 1
10. 30″			0 1
11. 60″			0 1 2 (1-10)
12. 60″			0 1 2 (1-10)
13. 60″			0 1 2 (1-15)
14. 120″			0 1 2 (1-20)

5. DIGIT SPAN	SCOR
Digits Forward	Circle
5-8-2	3
6-9-4	3
6-4-3-9	4
7-2-8-6	4
4-2-7-3-1	5
7-5-8-3-6	5
6-1-9-4-7-3	6
3-9-2-4-8-7	6
5-9-1-7-4-2-8	7
4-1-7-9-3-8-6	7
5-8-1-9-2-6-4-7	8
3-8-2-9-5-1-7-4	8
2-7-5-8-6-2-5-8-4	9
7-1-3-9-4-2-5-6-8	9
Digits Backward	Circ
2-4	2
5-8	2
6-2-9	3
4-1-5	3
3-2-7-9	4
4-9-6-8	4
1-5-2-8-6	5
6-1-8-4-3	5
5-3-9-4-1-8	6
7-2-4-8-5-6	6
8-1-2-9-3-6-5	7
4-7-3-9-1-2-8	7
9-4-3-7-6-2-5-8	8
7-2-8-1-9-6-5-3	8

F____+B_____ = ___

Highest numbers circle

6. VOCABULARY	SCORE 2, 1 or 0
1. Bed	
2. Ship	
3. Penny	
4. Winter	
5. Repair	
6. Breakfast	
7. Fabric	
8. Slice	
9. Assemble	
10. Conceal	
11. Enormous	
12. Hasten	
13. Sentence	
14. Regulate	
15. Commence	
16. Ponder	
17. Cavern	
18. Designate	
19. Domestic	
20. Consume	
21. Terminate	
22. Obstruct	
23. Remorse	
24. Sanctuary	
25. Matchless	
26. Reluctant	
27. Calamity	
28. Fortitude	
29. Tranquil	
30. Edifice	
31. Compassion	
32. Tangible	
33. Perimeter	
34. Audacious	
35. Ominous	
36. Tirade	
37. Encumber	
38. Plagiarize	
39. Impale	
40. Travesty	



WECHSLER MEMORY SCALE FORM I

David Wechsler
Bellevue Hospital, New York

NAME _____ AGE ____ SEX _____

REFERRED FOR _____ DATE ____ EXAMINER _____

	Score
I. Information	___
II. Orientation	___
III. Mental Control	___
IV. Memory Passages	___
V. Digits Total	___
VI. Vis. Reprod.	___
VII. Associate Lng.	___
Total Raw Score	___
Age Correction	___
Corrected Score	___
MQ (Table 3)	___

I. PERSONAL AND CURRENT INFO.

	Score
1. Age	___
2. When born	___
3. President of U.S.	___
4. Before him	___
5. Governor	___
6. Mayor	___
Total	___

II. ORIENTATION

	Score
1. Year	___
2. Month	___
3. Day	___
4. Where now	___
5. City in	___
Total	___

III. MENTAL CONTROL (Circle omits; cross out errors.)

		Time	Errors	Score	Total Score
1.	(30") 20 19 18 17 16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1	___	___	___	
2.	(30") A B C D E F G H I J K L M N O P Q R S T U V W X Y Z	___	___	___	
3.	(45") 1 4 7 10 13 16 19 22 25 28 31 34 37 40	___	___	___	

IV. LOGICAL MEMORY

(A) Anna Thompson/ of South/ Boston/ employed/ as a scrub woman/ in an office building/ reported/ at the City Hall/ Station/ that she had been held up/ on State Street/ the night before/ and robbed/ of fifteen dollars/. She had four/ little children/ the rent/ was due/ and they had not eaten/ for two days/. The officers/ touched by the woman's story/ made up a purse/ for her/.

(B) The American/ liner/ New York/ struck a mine/ near Liverpool/ Monday/evening/. In spite of a blinding/ snowstorm/ and darkness/ the sixty/ passengers including 18/ women/ were all rescued/ though the boats/ were tossed about/ like corks/ in the heavy sea/. They were brought into port/ the next day/ by a British/ steamer/.

(A) Number of Memories ____ (B) Number of Memories ____ Average Score = $\frac{(A+B)}{2} = \frac{\quad}{2} = \quad$

V. (A) DIGITS FORWARD

	Score
6-4-3-9	4
7-2-8-6	4
4-2-7-3-1	5
7-5-8-3-6	5
6-1-9-4-7-3	6
3-9-2-4-8-7	6
5-9-1-7-4-2-3	7
4-1-7-9-3-8-6	7
5-8-1-9-2-6-4-7	8
3-8-2-9-5-1-7-4	8

Draw a line through any series failed. Circle score for maximum number repeated correctly.

(B) DIGITS BACKWARD

	Score
2-8-3	3
4-1-5	3
3-2-7-9	4
4-9-6-8	4
1-5-2-8-6	5
6-1-8-4-3	5
5-3-9-4-1-8	6
7-2-4-8-5-6	6
8-1-2-9-3-6-5	7
4-7-3-9-1-2-8	7

Forward Score ____ Backward Score ____ Digits Total ____

8. PICTURE COMPLETION

	SCORE 1 or 0
1. Knob	
2. Tail	
3. Nose	
4. Handles	
5. Diamond	
6. Water	
7. Nose piece	
8. Peg	
9. Oar lock	
10. Base pins	
11. Union Jack	
12. Dog tracks	
13. Cornwall	
14. Funnels (Stacks)	
15. Leg	
16. Arm image	
17. Finger	
18. Shadow	
19. Stirrup	
20. Snow	
21. Eyebrow	

9. BLOCK DESIGN

	Time	SCORE
1. 60"	1 / 2	0 2 4
2. 60"	1 / 2	0 2 4
3. 60"		0 4
4. 60"		0 4
5. 60"		0 4
6. 60"		0 4
7. 120"		0 4 31-40 5 1-30 6
8. 120"		0 4 46-70 5 1-45 6
9. 120"		0 4 61-80 5 1-60 6
10. 120"		0 4 61-80 5 1-60 6

10. PICTURE ARRANGEMENT

		Order	Time	SCORE
1. Nest	60"	1 / 2		0 2 4 WXY
2. House	60"	1 / 2		0 2 4 PAT
3. Hold up	60"			0 4 ABCD
4. Louie	60"			0 4 ATOMIC
5. Enter	60"			0 4 OPENS
6. Flirt	60"			0 2 4 JNAET JANET AJNET
7. Fish	120"			0 2 4 5 6 26-40 1-25 EGFNIJ EFGHIJ EJFGHI
8. Taxi	120"			0 2 4 5 6 16-25 1-15 SALNUE SAMUEL AMUELS

11. OBJECT ASSEMBLY

		Time	SCORE
Manikin	120"		0 1 2 3 4 5 16-20 6 11-15 7 1-10 8
Profile	120"		0 1 2 3 4 5 6 7 8 9 36-45 11 26-35 12 1-25 13
Hand	180"		0 1 2 3 4 5 6 7 41-50 9 31-40 10 1-30 11
Elephant	180"		0 1 2 3 4 5 6 7 8 31-50 10 21-30 11 1-20 12

Printed in U. S. A.
The Psychological Corporation, New York, N. Y. 10017
72-245AS 9-987306

VI-A

VI-B

VI C-1. C-2

WECHSLER MEMORY SCALE FORM II

Calvin P. Stone
Stanford University, California

David Wechsler
Bellevue Hospital, New York

Name_____ Age_____ Sex_____ Date_____

I. PERSONAL AND CURRENT INFORMATION — Score

1. Age . . . . . ____
2. When born . . . . . ____
3. President of the U.S. . . . . ____
4. Before him . . . . . ____
5. Governor . . . . . ____
6. Mayor . . . . . ____

Score . . . . . ____

Referred for_____

Total Raw Score . . . . . ____
Score Correction for Age . . . . . ____
Corrected Score . . . . . ____
MQ(Table 3) . . . . . ____

Examined by:

NOTES:

II. ORIENTATION

1. Year . . . . . ____
2. Month . . . . . ____
3. Day . . . . . ____
4. Where now . . . . . ____
5. City in . . . . . ____

Score . . . . . ____

III. MENTAL CONTROL — Time — Errors — Score

1. Alphabet (30") ____ ____ ____
2. 20 to 1 (30") ____ ____ ____
3. Counting by 4's (45") (1-5-9 up to 53) ____ ____ ____

Score . . . . . ____

IV. (A) Dogs/are trained/to find/the wounded/in war time./ Police dogs/are also trained/ to rescue/drowning people./ Instead of running/down to the water/and striking out,/ they are taught/to make/a flying leap,/ by which they save/many swimming strokes/ and valuable/seconds of time./ The European sheep dog/makes the best/police/ dog./

Number of Memories ____

(B) Many/school/children/in northern/France/ were killed/or fatally hurt,/ and others/ seriously injured/when a shell/wrecked/ the schoolhouse/in their village./ The children/were thrown/down a hillside/and across/a ravine/a long distance/from the schoolhouse./ Only two/children/escaped uninjured./

Number of Memories ____

Average Score = $\frac{(A+B)}{2}$ = ____ = ____

V. (A) DIGITS FORWARD — Total Digits Score____

4) 2 8 6 1 / 5 3 9 4 ____
5) 7 4 2 9 6 / 8 5 1 6 4 ____
6) 8 4 2 7 5 1 / 7 2 9 5 3 6 ____
7) 7 4 8 2 5 9 1 / 8 3 9 6 1 5 2 ____
8) 2 6 9 5 8 3 7 1 / 3 7 2 9 4 1 5 8 ____
9)*(5 9 4 8 2 7 3 1 6) / (4 2 9 3 8 6 1 7 5) ____
10)*(5 2 7 1 8 4 9 3 6 2) / (4 9 7 3 6 1 5 8 4 7) ____

Score____

(B) DIGITS BACKWARD

3) 7 5 1 / 2 9 6 ____
4) 3 5 8 2 / 9 6 1 7 ____
5) 4 7 1 8 6 / 3 9 2 6 1 ____
6) 6 3 9 1 5 8 / 4 8 1 6 3 7 ____
7) 5 4 9 2 7 3 6 / 2 5 1 9 4 7 3 ____
8)*(2 7 1 5 3 9 6 4) / (3 8 5 9 4 7 1 6) ____
9)*(9 1 6 4 8 3 7 5 2) / (5 2 7 1 8 4 9 3 6) ____

Score____

*Not counted in score if used.

VI. VISUAL REPRODUCTION

1____ 2____ 3-L____ 3-R____

Score____

Printed in U. S. A.

48-102 AS

Fold Part VII under on broken line before giving paper to subject for drawing in Part VI.

VI. VISUAL REPRODUCTION A____ B____ C-1____ C-2____ Total____

VII. ASSOCIATE LEARNING

First Presentation

Metal - Iron
Baby - Cries
Crush - Dark
North - South
School - Grocery
Rose - Flower
Up - Down
Obey - Inch
Fruit - Apple
Cabbage - Pen

Second Presentation

Rose - Flower
Obey - Inch
North - South
Cabbage - Pen
Up - Down
Fruit - Apple
School - Grocery
Metal - Iron
Crush - Dark
Baby - Cries

Third Presentation

Baby - Cries
Obey - Inch
North - South
School - Grocery
Rose - Flower
Cabbage - Pen
Up - Down
Fruit - Apple
Crush - Dark
Metal - Iron

First Recall	Easy	Hard
North	____	
Fruit	____	
Obey		____
Rose	____	
Baby	____	
Up	____	
Cabbage		____
Metal	____	
School		____
Crush		____
TOTAL	____	____

Second Recall	Easy	Hard
Cabbage		____
Baby	____	
Metal	____	
School		____
Up	____	
Rose	____	
Obey		____
Fruit	____	
Crush		____
North	____	
TOTAL	____	____

Third Recall	Easy	Hard
Obey		____
Fruit	____	
Baby	____	
Metal	____	
Crush		____
School		____
Rose	____	
North	____	
Cabbage		____
Up	____	
TOTAL	____	____

Easy 1)____
2)____
3)____
(A)Total____
A÷2 ____
Hard 1)____
2)____
3)____
(B)Total____

SCORE
$\frac{A}{2}$ + B=____

VI. 1

VI. 2

VI. 3-L; 3-R

Fold Part VII under before giving paper to subject for drawing in Part VI.

VII. ASSOCIATE LEARNING

First Presentation	Second Presentation	Third Presentation
Come - Go	Knife - Sharp	Country - France
Lead - Pencil	Jury - Eagle	Necktie - Cracker
In - Although	Country - France	Murder - Crime
Country - France	Lead - Pencil	Dig - Guilty
Dig - Guilty	Necktie - Cracker	Come - Go
Lock - Door	Murder - Crime	In - Although
Jury - Eagle	Lock - Door	Lock - Door
Murder - Crime	Come - Go	Jury - Eagle
Knife - Sharp	Dig - Guilty	Lead - Pencil
Necktie - Cracker	In - Although	Knife - Sharp

First Recall	Easy	Hard	Second Recall	Easy	Hard	Third Recall	Easy	Hard
Knife	___		Lock	___		Lead	___	
Lead	___		Dig		___	Lock	___	
Jury		___	Come	___		Necktie		___
Country	___		Jury		___	Come	___	
In		___	Knife	___		Dig		___
Murder	___		Country	___		Country	___	
Necktie		___	In		___	Jury	___	
Lock	___		Murder	___		Knife	___	
Come	___		Necktie		___	In		___
Dig		___	Lead	___		Murder	___	
Total	___	___	Total	___	___	Total	___	___

Easy 1) ___
2) ___
3) ___

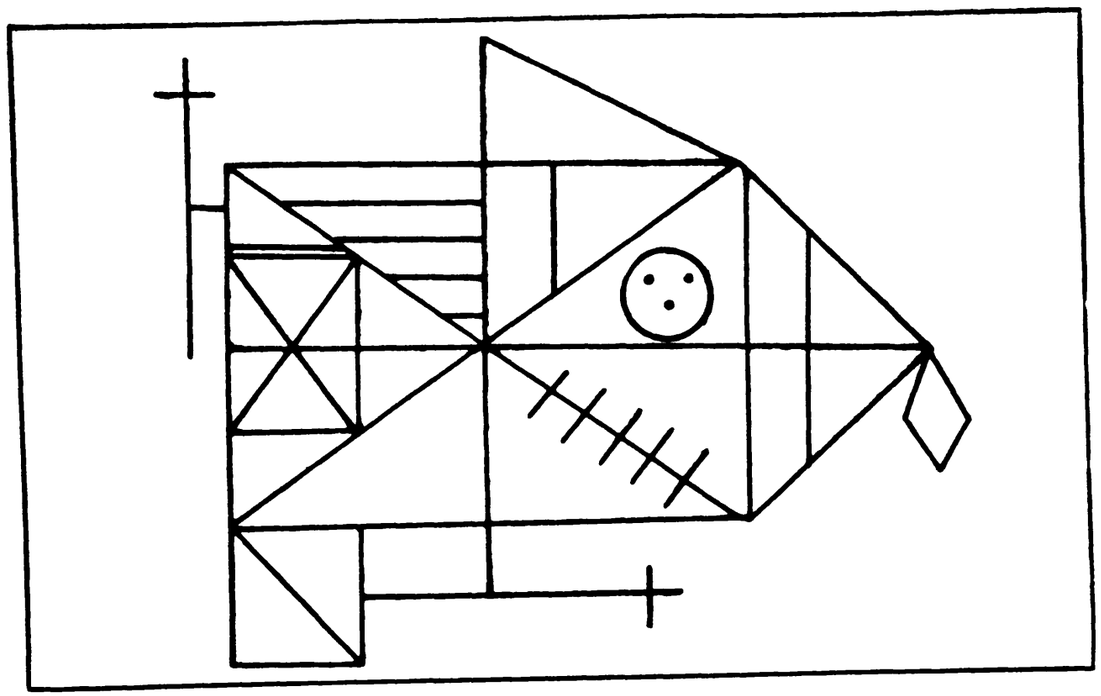
(A) Total ___
A ÷ 2 ___

Hard 1) ___
2) ___
3) ___

(B) Total ___

SCORE
$\frac{A}{2} + B =$ ___

COMPLEX FIGURE TEST I



COMPLEX FIGURE TEST II