THE ALLERGIC FACTOR IN IDIOPATHIC EPILEPSY.

by

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Nature of Allergy.

The term allergy was first coined by Von Pirquet whilst engaged in investigations of the infectious disease cow pox. He used it to indicate the altered reaction from a second innoculation as compared with a first. During the past thirty years a more restricted usuage of the term has been introduced and it has now come to be associated with a specific group of diseases. Nevertheless there has been and still is much confusion over the term and what it signifies. Many designations such as Anaphylaxis, Hypersensitiveness, Idiosyncrasy, and Atopy have been indiscriminately used. Perhaps one of the best definitions ever given was that of Jonathan Hutchinson who described it as "Individuality run mad." It is now agreed that the term Anaphylaxis should be applied to the specific hypersensitiveness which is experimentally induced in animals and that Allergy be reserved for the numerous manifestations of hypersensitiveness occurring in man either spontaneously or induced. Allergy in brief is a state of heightened susceptibility to certain specific agents usually proteins and symptoms may be initiated by inhalents, contactants or ingestants.

It should be noted, however, that although proteins are usually responsible for bringing on attacks, non-proteins may also precipitate them. This is true of alcohol and certain drugs. The fact that heredity plays a part is universally recognized and in this relation Coca (1), who divides allergy into Serum sickness, bacterial allergy, contact dermatitis and atopy writes "By atopy is meant a group of clinical conditions (bronchial asthma, hay-fever, eczema, gastro-intestinal hypersensitiveness and others), which effect a relatively small proportion of the population, about 7% according to Cooke and his

co-workers, and which have been shown to be subject strictly to a mendelian hereditary influence." Cooke himself states "The constitutional peculiarity which makes probable the development of hypersensitiveness is transmitted according to mendelian laws as a dominant characteristic," while Kennedy (2) also mentions the fact that we may inherit as a dominant mendelian characteristic the tendency to become sensitized or allergic to some foreign substance. He, however, stresses the point that sensitiveness to particular substances does not appear to be inherited but is determined by environmental chance.

It must be emphasized that in addition to the hereditary predisposition, the nature of the exciting factor, the degree and frequency of exposure and the vulnerability of the shock organ, be it skin or nasal mucous membrane, must be taken into consideration. And even then we have not explained the mechanism of sensitization. The fundamental nature of allergy, this capacity to develop sensitiveness and then to react to the specific substance is still unknown. Should a condition of hypersensitiveness be present then the introduction of the specific allergen will give rise to shock phenomena and that is the limit of our absolute knowledge. It has naturally been suggested that the allergic sufferer has a constitutional modification which renders him peculiarily liable to sensitization and it is stated that all grades exist from those that are extremely susceptible to those that are extremely unsusceptible. Some writers go further and state that everyone is potentially allergic. Vaughan (3) suggests that given sufficiently heavy exposure 100% of the population is capable of responding abnormally. The person with high susceptibility may become sensitive to any substance with which he comes in frequent or constant contact, while the mildly allergic individual only becomes sensitized towards relatively rare or new allergens. If allergic susceptibility varies from 0-100% then one would expect to find people who are allergic to practically everything, and it is a fact that such cases do unfortunately occur. Thus one may state that individuals differ only in

degree of manifestation and that the mechanism of the allergic response is essentially a purposeful and protective one; and that the presenting symptoms are significant of the body's attempt to neutralize offending irritants. It is to be explained as an integrated reaction complex, fundamentally protective in nature but defective in execution, since it has neither co-ordination or directing influence.

It can be accepted that sensitization is a fairly universal phenomenon. Furthermore workers of international repute such as Rackemann (4), Lintz (5), and Eyermann (6) are agreed that multiple manifestations of allergy are the rule rather than the exception and occur in from one third to one half of their cases. Smyth (7) on the other hand casts some doubt on this generalization. However contraversal the point may be in adults it is certain that in children symptoms are often manifold and transitory; but here again opinion differs on whether specific sensitizations are inherited or acquired shortly after birth, say on weaning. The weight of evidence seems to favour the latter suggestion. In this respect Kern (8) offers it as his opinion that the majority of sensitivities are acquired post-natally not intrauterine, that intrauterine sensitization is not a major factor, and if and when it is present it has more to do with foods than with other substances. On the other hand Stuart and Farnham (9) summarise by stating "The inference is drawn that hypersensitivity to food proteins tends to be present at birth and to be gradually lost during childhood, whereas hypersensitivity to inhalent proteins tends to be acquired and is more resistant to change."

It would appear that there is to be expected a changing state of sensitization during childhood especially towards food proteins, and statistics bear out this fact. It must, however, be recognized that sensitivities also wax and wane in adult life and that old susceptibilities may at any time be exchanged for new. Environmental and occupational factors play a big part in this change. Again it has been found that offending proteins have been carefully isolated and removed and symptoms temporarily ameliorated only

to return too frequently in greater severity in response to hitherto innocuous substances. It seems that in some people there is an inherent idiosyncrasy which must express itself and if one channel is blocked another will be found. The actual expression of that idiosyncrasy may not change - an asthmatic will continue to have his attacks of asthma, a stomach sufferer his billiousness, - but it is the means to that end that is altered. On the other hand "to assume that an allergic is born hypersensitive to every known protein but that only a few are at any time above the threshold of reactivity, is simply considering that person fundamentally different from the normal."

At all events it seems to be the case that many food sensitivities, be they inherited or acquired, are present in childhood and in most children and that they tend to form a constantly changing background during the early years of life. As the child grows older there is an ever increasing tendency for food idiosyncrasies to disappear and by the time puberty is past the great majority have left their early sensitivities far behind. How this is accomplished is not too evident but it is generally accepted that a process of passive desensitization following minute doses of the allergic substance has been steadily at work; or it may be that active elimination of the offending protein has been undertaken. Some, however, are not so fortunate and in them convulsions, following discontinued breast-feeding, may lay the foundation for future catastrophe; or if they escape convulsions, eczema, or later migraine and asthma may well make life burdensome. Sensitivities acquired in later life are much more difficult to remove, and unless active treatment is initiated they have a strong tendency to remain permanent. Hence the advisability of energetic and prolonged attempts to desensitize in childhood when there is a simplicity of diet and environment that can bear no comparison to the variabilities and complexities of later years.

During the past decade an enormous amount of

research work has been done on allergy mostly in America, and many writers have endeavoured to find in it a universal panacea for the relief of various diseases of obscure etiology. It is not the burden of this thesis to discuss or criticize these conditions and conclusions as a whole but it has as its purpose the systematic investigation of idiopathic epilepsy from the viewpoint of its being a sensitization disease.

There are several conditions which are now recognized as having a definite allergic basis and many more that are suspected of being closely associated. These latter may be merely isolated instances or form groups of cases occurring in the routine examination of still larger groups of a similar symptom - complex. The literature for some time past has been laden with such references, but it will be sufficient if here only a few are mentioned. All manner of gastro-intestinal manifestations have been encountered such as abdominal pain, chronic indigestion, constipation and vomiting. In several instances operative procedure has been instituted for what was later determined to be severe colic of allergic origin. Both Rowe (10) and Vaughan (11) describe numerous unusual instances of food sensitization and the former writes "The various alimentary symptoms probably arise from oedema of the mucous membrane and spasm of the smooth muscle, which produce disturbances in peristalsis and in function." Gastric ulceration and muco-membranous colic are described by Klein (12), Vaughan (13) and Kern (14). Retrobulbar neuritis, transient palsies and maladies of peripheral nerves and spinal roots have been recorded by Kennedy (2), Levy (15) and others; while tuberculosis, scarlet fever, purpura, and acne are among a few of the many conditions that are said to have an allergic connection.

Epilepsy also has been studied and treated from this stand point and with encouraging frequency a definite connection has been

demonstrated between protein sensitization and fit incidence. Before going on to enumerate and discuss these instances, however, it might be beneficial to undertake a general survey of the analagous states of epilepsy and migraine and to compare and contrast their etiology; the rationale for this proceeding resting on their undoubted similarity and the now established fact that migraine is almost 100% allergic.

According to Goltmann (16) attacks of migraine have three stages (1) Vasomotor spasm causing ischaemia of part of the brain. (2) Vascular dilitation with oedema of the affected brain tissue and (3) temporary hypersecretion followed immediately by hyperabsorption of cerebro-spinal fluid. He asserts that migraine has often been successfully treated on the basis of food allergy and that conditions which precipitate attacks, such as excitement, exertion, fatigue and menstruation may be contributory factors which disturb the allergic mechanism.

Kennedy (2) states "The analogy of urticaria and migraine gives one to think in terms of a similar morbid process in two widely separated ectodermic tissues. Such a local skin dropsy translated to the intracranial cavity would make us visualize focal areas of oedema inflicting painfully the meninges and especially their foldings and angled reflections emanating probably from the brain itself. Such localized swellings could form rapidly; the meninges are sensitive to pulling or stretching. It is not necessary here to enlarge on the phenomena of migraine but it would be well to remember they are not confined simply to localized periodic headache lasting several hours and ending in nausea. The most typical attacks are associated with events characteristic of focal cerebro-meningeal irritation or transient injury." It may well be that in some cases of idiopathic epilepsy areas of severe focal oedema may play at least a contributory part in producing convulsions.

It has been pointed out by Miller and

Raulston that migraine and the diseases classed as clinical anaphylaxia have in common periodicity, heredity, temporary disappearance of symptoms after severe injections, eosinophilia and frequent favourable influence by pregnancy. Besides the common characteristics enumerated above by Miller and Raulston there are some additional factors of mutual significance that should be mentioned. The onset of each may coincide with the development of an acute infective condition, while symptoms are definitely modified by the often pre-existing neurotic background. Migraine has been described as sensory epilepsy. Diet again plays an important part and it has been shown that the ketogenic diet exerts a favourable influence on both epilepsy and migraine.

Lennox (17) concisely lists the differences and similarities of migraine and epilepsy. He states that - socially epilepsy is an outcast, migraine respectable. Epilepsy is scattered at random between the sexes while migraine is twice as common in females. Epilepsy developes most frequently in infancy, migraine in adolescence and beyond. Epilepsy often leads to mental deterioration, migraine does not. Epilepsy usually appears in the muscle using, migraine in the brain using members of society. Emotional disturbances are usually a result of epilepsy and a cause of migraine. Epileptics will readily undergo all manner of examinations and treatments; migraine sufferers are evasive and cling to their disability. Both epileptic and migraine seizures come in attacks with periods of normality between, but this does not prove a generic relationship. The best evidence is that of a common inheritance. Suggestive are the occasional patients whose bouts of epilepsy seem to give place to bouts of migraine or vice versa, and whose convulsions are preceded by scintilating scotomota. Epilepsy occurs more frequently in migraine patients and migraine more frequently in epileptic patients than in the general population. Again it is found that migraine and epilepsy tend to appear in the same

family and that among the immediate relatives of epileptics and migraine patients there is a greater percentage of migraine and epilepsy respectively than among the general population. If migraine bears a generic relationship to epilepsy the incidence of migraine among the relatives of patients should be greater in the so called idiopathic epileptic than in the symptomatic epileptic and this has been shown to be the case.

This evidence would seem to establish a definite relationship between migraine and epilepsy. "Obviously the two conditions are not twins, or perhaps even brothers, but they are cousins not many times removed and knowledge of one should throw light on the other. It is suggested that migraine and epilepsy may each be likened to a reservoir which periodically fills and overflows its banks, the overflow representing the attacks. These reservoirs are fed from underground streams which may represent the fundamental and the contributory causes of the attacks. In any individual patient the cause is probably never single, but two or more combine to produce the seizure, In both migraine and epilepsy an inborn tendency plays a considerable part." (Lennox.)

As previously mentioned some considerable research has been carried out of recent years on the possibility of idiopathic epilepsy having an allergic basis. The writer would now like, before proceeding to discuss his own work, to review critically the literature, but first just one word on skin testing. Many of the writers to be quoted refer to the results they have obtained on testing the skin for protein sensitivity. This whole problem of skin testing is one which will be examined later at some length, but meanwhile it will suffice to state that this commonly employed diagnostic procedure, although it has been subjected to much adverse criticism from time to time, is recognized by those most competent to judge, as one of the principal keys in the interpretation of the mystery of allergy.

Without it much vauluable information would be lost and many unsuspected protein problems never brought to light. And although at times false results or erroneous interpretations may side-track the investigator it must still remain the most estimable guide to diagnosis and treatment.

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THE ASSOCIATION OF ALLERGY AND EPILEPSY

Review of Literature.

It has long been known that Epilepsy is favourably influenced by acute infective diseases and that temporary disappearance of fits often follows, but Turnowsky (18) in 1901 reported three cases in which the seizures subsided permanently following pneumonia and scarlatina. A number of years later Tinel (19) confirmed this, recording the disappearance of epilepsy following pneumonia and typhoid-fever; while in 1909 Hamilton (20) referred to twelve epileptic patients who contracted typhoid and of whom nine made a great improvement, one remaining free of seizures for four years. Pearce, Gudder, Chambrelet and Weir Mitchell (21) recorded similar findings, the latter stating that in his experience pregnancy has a very beneficial effect on fit incidence. Spangler in 1908 reported the results of giving a course of non-specific treatment to a series of thirty six epileptics by means of subcutaneous injections of crotalin (snake venom), and found that every patient treated reacted favourably.

Several years previously Spratling had noted that patients who acquired tuberculosis frequently showed a lessening or a disappearance of fits and in this respect Crockett's experience of tuberculin is interesting. He observed that if tubercular epileptics were treated with tuberculin the seizures usually disappeared. He treated twenty three cases,

giving eight to ten weekly injections, and always tried to avoid a reaction. Eleven of his patients were freed from attacks for more than three months and one patient who had had three hundred major and minor fits in the month preceding treatment was free for nineteen months.

Most of the above findings might be explained on the gound that desensitization has taken place, but such conclusions would be purely speculative were it not for the fact that there is a great mass of therapeutic evidence which supports it. The theory that epilepsy and allergy are related finds some confirmation in the work of Van Leeuwen and Zeyder (22) who isolated a toxic substance from the blood of epileptic patients. This they found to be a muscle - stimulating substance and following careful research they proved it to be present also in the blood of patients afflicted with asthma, migraine and urticaria, but absent in all other diseases and in normal individuals. It was their considered view that this substance was related in some way to the allergic disposition of the patients affected; and according to Miller (23) would seem to indicate an intimate connection between epilepsy and the accepted group of allergic diseases.

It was in 1915 that Osler remarked on the similarity of migraine and epilepsy and suggested that, "Certain types of epilepsy result as a continuation of the pathologic process causing some migraine headaches." Clarke (24) elaborated this idea and stated that it was his belief that acute allergic oedema was the cause of both migraine and epilepsy; that both conditions had a similar pathology viz. cerebral oedema; that they had the common criteria of headache, dizziness and vomiting; and that it was only the convulsions that distinguished them. He reported two cases treated from an allergic view point with complete alleviation of symptoms.

Kennedy (2) writing two years later in 1936 supports in some measure Clarke's hypothesis when he speaks of focal areas of oedema involving the meninges and being a possible cause of migraine. Kennedy is convinced that many cases of epilepsy are built up on a basis of protein susceptibility and urges that full investigation should be made in every instance where there is the least likelihood of success. He records two cases of epilepsy who were also allergic subjects, and in whom appropriate treatment completely controlled the convulsions. The first was a girl of two years who had always been subject to attacks of giant urticaria. In time screaming attacks followed by convulsions appeared and after several associations of this nature a search for a possible convulsing agent was instituted. This was found in milk to which, by good fortune, she gave a positive skin test. When it was discontinued the seizures disappeared and she has had none since during the past twelve years. The other was the case of a boy aged thirteen, a subject of asthma and hay-fever who was also found sensitive to milk and in whom seizures likewise ceased when the offending substance was removed from his diet. He sums up by saying, "The evidence that many cases of epilepsy constitute a sensitization disease cannot be safely ignored; family histories for allergic inheritance must be investigated, sensitization tests made, and elimination diets and dehydration experimented with before we can decently resign ourselves in the case of the idiopathic epileptic to the therapeutic despair of increasing doses of the barbituric series."

Food hypersensitivity and epilepsy were first bracketed by Spratling (25) in 1904 who wrote, "The individual susceptibility to certain foods, harmless in themselves, but poisonous to others should not be overlooked as a factor in causing epilepsy." But it was not till 1919 that Pagniez (26) and Lieutaud reported the first authentic cases of epilepsy that were definitely

traceable to a specific substance namely chocolate. These occurred in two young men, who in addition to epilepsy suffered from migraine, and one of whom had himself noted some relationship between his migraineous attacks and the consumption of chocolate. This gave the authors the idea that possibly his epilepsy likewise rested on a food basis and they tested their theory by giving him chocolate alone and with his meals. Epileptic seizures were inevitably produced soon after the ingestion of the chocolate and the withholding of it prevented their onset. Similar findings were recorded in the other young man's case.

Since then there has been an ever increasing accumulation of clinical material and writers have recorded numerous instances where protein sensitization was proved to be the main factor in the causation of convulsions. The work of Pagniez and Lieutaud was followed three years later by the publication of Weschler's (27) paper dealing with the examination and treatment of a group of fifty eight epileptics. He suggested that the periodicity of some of the epilepsies might be and, in his opinion, were due to the deleterious action of certain foods which produced something akin to a sensitization or an anaphylactic reaction, which resulted in convulsive phenomena. He detailed specific diets which tended to produce convulsions in different individual patients, but was unable to prove his conclusions.

Thompson (28) reported in the same year that in his study of two hundred cases of infantile convulsions he had come to believe that a possible relationship existed between poisoning by common food stuffs and the anaphylactic phenomena common in infancy. In the following year (1922) Ward (29) of New York wrote a very illuminating paper on protein sensitization as a possible cause of epilepsy. He prefaced his remarks by saying, "The disturbances which we know as hay-fever and

and asthma are supposed to be brought about by the action of the split proteins demonstrated by Vaughan, the presence of which is due to imperfect assimilation in the digestive tract. These poisons seek exit through the mucosa of the nasal and bronchial passages, there producing a condition which remains latent until the individual in question inhales some exciting agent - such as plant pollen or animal emanation - whereupon a typical attack is manifested, the severity of the attack depending upon the hypersensitiveness of the individual. Reasoning by analogy it would appear by no means unlikely that a similar etiology might be attributed to epilepsy. It seems possible that epileptic seizures might be the result of exciting agents acting upon the brain through the intermediacy of the nasal sinuses..... and through ingested food." He recounts two cases of epilepsy associated with protein sensitization. The first was a girl then aged fifteen who after convulsions in childhood, developed typical major epileptic seizures between eight and twelve years of age and from then onwards took them regularly. She was put on a non-meat diet and the fit incidence improved, but following a rebellion against the restricted diet fits again appeared. Protein skin tests were now undertaken and the bovine products of milk, cheese and meat recognized as being inimical to her well-being. On a strictly enforced and rearranged diet complete cessation of fits quickly took place and since then she has remained free. The second was a patient who was found sensitive to milk and cheese, and when these two articles were eliminated from the diet the epilepsy disappeared.

Ward maintains that the relationship between food poisoning and epilepsy is clear and says that if an effort was made in every case of infantile convulsions to find the offending protein many future cases of epilepsy would be aborted. He believes that the periodicity of attacks is due to accumulation of protein poisons in the organism and that the

precipitation of fits varies according to the sensitiveness of the nerve centres and the amount of foreign protein gaining entrance to the circulation.

Further work along similar lines was carried out in 1923 by Wallis and Nichol (30) and their results corroborated and elaborated the findings of Ward. They carried out examinations at Hanwell on a series of One Hundred and Twenty two epileptics using as controls a group of One Hundred non-epileptics, composed of staff and other patients. Skin tests were carried out on each by the scratch method and the readings taken after an interval of ten minutes. There were forty-six positive reactors in the epileptic group, with four slight positives among the controls. The authors found that sensitivity varied according to the time tests were carried out, and that the best time to do them was when the patient was not fatigued; and furthermore that after a bout of fits sensitivity to a particular protein may disappear but that the time elapsing before the onset of this desensitization varies. They affirm that "In those patients who have a series of fits over some days we have found that at the commencement of the attack they remain sensitive, but at the end of the attack they no longer react." They postulate a particular type of epileptic whom they believe especially suitable for treatment and of this type they declare "They appear to be quite healthy persons, usually inclined to obesity, and not excitable or markedly unstable." They describe thirteen such cases, in each of which the detection and removal of the offending proteins either abolished or greatly reduced the number of fits and they conclude by stating, "The diagnosis and treatment by means of skin tests, peptone and diet, applies only to one special type, and we do not wish to convey the impression that we have a panacea for all types of epilepsy..... The result of these observations has shown conclusively that in some cases where it has been possible to adjust the diet on the basis of skin tests, no

further treatment has been necessary." Shortly before Wallis and Nichols' paper had appeared and in the same year, Howell (31) published what was really the first complete study of epilepsy from an allergic viewpoint. He reported on fourteen cases of epilepsy whom he skin tested, and who either gave positive cutaneous reactions to certain food proteins or were seized with fits on eating certain articles. He found that all the cases were relieved by removing the offending protein and that convulsions recurred when they were ingested.

In 1924 Mc Cready and Ray (32) cited seven cases in whom convulsions were apparently due to a definite sensitivity to food. They maintained that convulsions in infancy often dated from the introduction of foods other than breast milk into the dietry, and further that they sometimes persisted into later life despite modification of diet. They "postulate an intimate connection between the phenomena of anaphylaxis and allergy and the phenomena of idiopathic epilepsy."

Three years later a very interesting and informative article was presented by Ward and Patterson (33). They studied the occurrence of protein hypersensitibility in One Thousand epileptic patients and in One Hundred non-epileptic controls. They found that 46.9% of the epileptics manifested sensitization, while only 8% of the control group were positive reactors. They did not undertake any form of treatment but suggested that it should consist in either restriction of the diet or desensitization. They concluded that the percentage of patients hypersensitive to protein is higher in epileptic than in non-epileptic groups and stressed the early recognition of the hypersensitive state as important from the standpoint of possible prophylaxis. They believed that many cases of adult epilepsy had their origin buried deep in infantile convulsions and that if appropriate steps had been taken at the

time to uncover the guilty substance much future unhappiness would have been avoided.

In the same year Rowe (34) reported two authentic cases where fits were controlled by diet plus desensitization to inhalants. These were the first two cases where such a combination in treatment had ever been attempted. The first case was that of a boy of four who was found on skin testing to be sensitive to twelve Spring and Autumn pollens and in whom pollen desensitization completely cured the convulsions. The second case was that of a girl of eleven who suffered from petit mal and whose skin gave positive results to cat, horse and rabbit hair. In her case also desensitization banished the attacks. Rowe sums up by saying, "Allergy undoubtedly is the cause of certain cases of epilepsy, especially in children. The percentage of cases due to protein sensitization may not be large, but in the investigation of epileptics allergy should certainly be seriously considered."

Again in 1927 Spangler (35) writing in the Journal of Laboratory and Clinical Medicine says "..... the fact that allergy results in attacks of epilepsy in some individuals cannot be denied and certainly is worthy of consideration when we come to the treatment of this little understood and perplexing 'symptom-complex of disturbed metabolism ' - the epileptic individual." He made a detailed analysis of One Hundred cases of epilepsy and found that 88% of them showed a history of allergy in their ancestors and that 54% had other signs of allergy themselves. In several of his cases he was able to demonstrate a connection between food and fits, but admits that he was unfortunate with skin tests in food sensitivities. Independently Rowe also came to this conclusion and professed little faith in skin testing, at any rate for foods and especially in adults.

In 1930 Felsen (3 6) writing on epilepsy

states "Clinically, the sudden change from comparative normality to a condition of violent physical distress and as sudden return to normality with little or no knowledge of what has happened suggests the liberation of some toxic substance possibly cumulative in its effect. According to present knowledge, if this is the nature of a simple food idiosyncrasy, the most likely element at fault is protein." In his investigations, however, he was unable to obtain even one positive reaction to many food and bacterial extracts and stated that there was no evidence on which he could personally base any connection between allergy and epilepsy. Cohen and Lichtig's (37) findings agree with those of Felsen. They tested each of ten epileptic children with one hundred and twenty-eight proteins, but found that no reactions that could be said to have any bearing on the convulsions. Bray (38) also is extremely sceptical as to the efficacy of the skin test in epileptics and states that among thirty epileptic children in whom he has carried out routine skin reactions he has failed to obtain a single positive. He has never been able to substantiate the view that idiopathic epilepsy is or might be a sensitization disease.

On the other hand Levin 1931 (39) reports the cases of two children which arose in his practice, one of whom was found to be sensitive to cat's hair and the other strongly sensitive to American cheese and slightly so to Swiss and Roquefort. In the first instance removal of a cat from the patient's environment banished the epileptiform attacks, while careful control of the diet had a likewise curative effect in the second. Levin is convinced that some cases of allergy are undoubtedly of allergic origin and strongly recommends an investigation along these lines, especially in those cases presenting a past or present history of other allergic manifestations or a positive family history of allergy.

Three years later Forman (40) described ten cases of epilepsy, each giving an allergic history and in each of whom various skin tests were carried out and a number of positive results obtained. Elimination diets were prescribed and offending proteins excluded. His results were very satisfactory, complete cessation of fits occurring in many of the cases, providing the incriminated foods were rigorously avoided. One interesting feature was the fact that he demonstrated an eosinophilia in several of his cases. Forman, like Levin and other workers, believe that there is a small but definite group of essential epileptics who have an inherited tendency towards sensitization, and in whom certain other evidence of allergy will be found if a search is made. Forman follows Cocoa in recognizing Atopy as that part of allergy which is controlled by inheritance and states that it is the primary duty of the allergist before investigating further to classify cases of idiopathic epilepsy as atopic or non-atopic. Should they prove to be atopic then a thorough allergic review is indicated; if they are non-atopic then an explanation should be sought elsewhere. His four criteria for the recognition of Atopy are :- (1) A familial and (2) a personal history of asthma, hay-fever, vasomotor rhinitis, hives, eczema, migraine-like headaches and other allied conditions; (3) eosinophila in the blood preceding and during the attacks, and (4) positive reactions to cutaneous tests for sensitiveness to protein.

In 1934 Wilmer and Miller (41) reported an interesting case, of what they believed to be, allergic epilepsy. This occurred in a college student aged nineteen, who was suddenly seized with headache, dizziness and mental confusion. Two months later the first convulsive seizure appeared. During the next two years the seizures increased in frequency and depression and fatigue were manifest. Temporary paralysis in groups of

muscles and skin hypersensitivity to external stimuli were fleeting and incordinated symptoms. Finally a detailed allergic study was undertaken and he was found to be sensitive to a variety of foods. Rowe's elimination diets were tried in turn and a combination arrived at to which the patient was non-sensitive, and on this modified diet he ceased to have fits. Since then (he is now thirty-two) he has been free from seizures and most of the associated symptoms have long disappeared. This case exhibits several characteristic features of allergy, such as the multiple hypersensitiveness, the periodicity and the reaction to protein elimination. It seems possible that focal areas of oedema may have been responsible for the temporary and localized palsies.

Similar isolated instances thought to have an allergic basis were reported in 1936 by Costello and Fox (42) and by Oriel (43) These writers point out the apparent dependency of the idiopathic convulsions on the preceding exacerbation of the underlying allergic disease. Costello and Fox record the case of a girl who began to suffer from asthma, bronchitis and epilepsy at the age of ten. From the first the fits always occurred at the end of the asthmatic attack. She continued to have a number of these attacks and each ended up, when the patient was very cyanosed, with typical epileptic fits. Eventually, under treatment directed towards the chest condition, the asthma and bronchitis cleared up and co-incident with this improvement the epilepsy disappeared. They conclude, "A good deal has been written about the connection between epilepsy and asthma, and it has often been suggested that they are both allergic manifestations. In some cases where they co-exist it seems that the two types of attacks may replace each other." Oriel's case was that of a woman of twenty-two who had suffered from migraine and epilepsy for many years. There was no allergic family history and skin tests to foods etc. were negative. Her attacks of migraine culminated invariably in a

few hours in either petit or grand mal, on the occurrence of which her migraine ceased.

Both of the above demonstrate the close affinity existing between epilepsy and other allergic diseases. In these two instances the steadily progressive symptoms dramatically resolved themselves in a sudden convulsive attack. Cases are also known where asthma, hay-fever or migraine have actually been replaced by epilepsy, and conversely where the latter has been replaced by either of the former. This substitution is not uncommon about the time of puberty, but no satisfactory explanation for it has so far been offered.

In 1937 Clein (44) reported the successful treatment of six cases of epilepsy, three of grand mal and three of petit mal. They were each entirely or greatly relieved by treatment on the basis of an allergic etiology. He gives two case reports in detail where the patients were found to be sensitive not only to foods but also to dust. The first was a case of allergic rhinitis, asthma and grand mal; the second of eczema, urticaria and petit mal. In each instance elimination of the offending foods was associated with desensitization to dust, to which they had both given strongly positive reactions. Clein is of the opinion that allergy should always be kept in mind when considering the etiology of epilepsy and like Forman suggests certain criteria which are necessary in order to make a diagnosis of allergy regardless of symptoms. These are (1) A positive family history of allergy (2) Previous allergy in the same individual such as eczema, pyloro-spasm or certain types of gastro-intestinal distress in infancy, and later, urticaria, hay-fever, asthma, "chronic nose catarrh" or "sinus trouble," migraine type headaches, canker sores, mucous colitis, and vague gastro-intestinal complaints. (3) The presence of active allergy manifested chiefly by recurrent, frequent colds and chronic coughs, and other manifestations as previously mentioned. He further says, "Once it has been determined that the patient and his family are at least suggestive of an allergic background, a thorough study, including skin and intradermal tests, is indicated.

This is particularly desirable in those cases which have been thoroughly studied for epilepsy and which have not shown improvement."

In the same year (1937) Singer (45) reported the case of a boy who had suffered from epilepsy for four years and whose attacks occurred at intervals of abour four weeks and only towards mid-night or in the early hours of the morning. He never had a seizure during the day. After prolonged and fruitless investigation the boy's father recalled the fact that it was only when pork, eggs or cheese had been eaten at mid-day or for supper that attacks appeared. If the boy consumed any of these foods at mid-day the attack occurred about mid-night and after a similar supper, early the next morning. The interval between eating the food and the onset of convulsions was almost exactly twelve hours. Once this connection was recognized appropriate steps were taken to remove the guilty substances from the diet, and further to desensitize the patient. This desensitization was carried out by means of Propeptane and Polypropeptane and was completely successful. During the past few years the patient has had only one attack and that was caused by an indiscretion of diet.

The above extracts cover most of the literature that has been published to date. It will be obvious that the association of epilepsy and allergy is no new one, but it is surprising, in view of some of the striking results obtained, that more systematic investigation along similar lines has not been attempted. On the contrary the whole subject seems to have been largely neglected, particularly in this country. Furthermore some investigators have merely recorded the incidence of positive skin reactions in epileptics as compared with control groups, and gone no further. Others have confined themselves to the elimination of the specific foods, occasionally, be it admitted, with outstanding success. Specific desensitization, with one or two marked exceptions, has not been even attempted; and in those few recorded instances where it has

been the subject was invariably a child. Indeed the bulk of the work done on allergic epilepsy and the successes achieved have been with children.

There is no doubt that the outlook in childhood is more hopeful and sensitivities more readily detected and influenced, but that does not seem to the writer any reason to condemn without trial the adult idiopathic epileptic who after all forms by far the greater bulk of the epileptic population. The picture may be more obscure in later life, but the essential outlines are there, can the detail be but filled in. A systematic examination of the personal and family history may reveal unrecognized or long forgotten allergic traits, and by careful elimination skin reactions may be correlated with food difficulties or fit incidence.

Because most of the research carried out has been on epileptic children, it does not follow that the conclusions drawn have been in agreement. Indeed there are very sharp differences of opinion regarding their allergic sensitivity. As already pointed out some writers have failed to find on extensive and repeated attempts any evidence of protein hypersensitiveness in young epileptics, while others have demonstrated it successfully and effectively controlled it. The whole subject is a highly controversal one and seems bristling with portentous possibilities.

Several investigations have been carried out on institutionalized adult epileptics and interesting facts been recorded, but as usually little specific desensitization has followed the disclosure of the hidden sensitivities the results have often been incomplete and inconclusive. It would appear that there is here a field of fruitful potentialities, ripe and ready to be garnered by the first physician who is so minded. It is to this field that the present writer has attempted to apply himself. It will be his task to substantiate or criticize the work already done, to follow up and further

that work and finally to suggest and assess new lines of treatment.

As a preliminary to describing the first steps in the present investigation it would be convenient at this stage to give a comprehensive survey of the science of skin testing. Since this naturally plays such an important part in the study of allergy it will be described in some detail.

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SKIN TESTING.

Skin sensitivity had been mentioned and demonstrated in isolated instances over a long period of years before Schloss in 1912 extended and described its usage and established it as a definite means of detecting hypersensitiveness. Since then it has been universally recognized as a most useful adjunct to the study of the etiological problems of allergy. At first it seemed that there had been found a miraculous means of explaining both the cause and the reason for the recurrence of certain common disorders of obscure etiology in widely separated organs. It promised to show how totally different symptoms could be attributed to a common agent. It was such a simple matter to make a scratch on the skin, apply some of the suspected substance and then wait quietly for ten minutes or so for the appearance or the non-appearance of a wheal. The very fact that the skin was sensitive but that the only clinical evidence of disease was, say in the lungs, gave the impression that all the organs of the body must be in a like state of sensitivity. This has since been disputed and denied and to quote Alexander (46) on this subject, "Clinically at least, this assumption is a fallacy. Man may be sensitive all over and exhibit general hypersensitivity if a huge dose of a protein is introduced. From the common clinical standpoint he is not sensitive throughout, but in spots. There are three

particular tissues affected, namely the mucosa of the gastro-intestinal and the respiratory tracts and the skin."

If then it is the case that hypersensitiveness is localized in certain tissues, it follows that the skin may or may not be sensitive at any given time. In other words because the ingestion of a specific food leads to colic or urticaria it does not necessarily follow that the skin will give a positive reaction to an extract of that food at all times or indeed at any time. This limitation of the skin tests has now been accepted; but even allowing that only 50% - 60% of allergics, (and that is not an over generous estimate), give positive results it still remains a very valuable aid to diagnosis.

TESTING MATERIALS.

One of the first and most important considerations in skin testing is that the testing materials should be potent and trustworthy. Many workers use the dry protein extracts exclusively; others prefer standardized solutions of the extracts, and for this purpose many different extracting fluids may be used such as saline, dextrose, glycerine and alcohol. Should solutions be employed a careful watch must be kept for deterioration and frequent control tests performed on known allergic subjects. Some solutions are prone, in time, to develop histamine and the mere presence of this renders results useless by producing inevitable positives; on the other hand negative findings may arise through a gradual loss of potency.

It is of primary importance that one should be thoroughly familiar with the extracts employed and that a reliable source be found and maintained, as they differ so much in their effectiveness and uniformity. Indeed this lack of uniformity is such a disturbing factor that several allergists now produce the required allergens in their own laboratories. The standardization of extracts is

usually determined on the basis of total nitrogen or protein nitrogen. According to Simon (47) two essential factors are involved, (1) What will the extract do when injected into the skin of a clinically sensitive patient? (2) What will it do in a normal and non-sensitive person? No interpretation of tests is possible unless an answer to each of these questions can be given, since the first must ensure its potency and the second provide a control.

Furthermore certain vegetable and fruit extracts which contain non-specific irritating properties and which will produce erythema and wheal formation in normal persons, must be so diluted that these non-specific reactions disappear before they are suitable for testing. In short it is evident that the chief tool of the allergist is his extract and should its qualities be unknown or unreliable he cannot be expected to achieve results, be his technique ever so perfect.

THE DIFFERENT METHODS EMPLOYED IN SKIN TESTING.

Several distinct methods exist of testing the skin for protein sensitivity, but the only two that will be discussed at length are the Dermal or, Scratch method, and the Intradermal... Other methods less often employed are firstly the Patch Test which is largely used to detect sensitivity in dermatitis due to external irritants. The suspected substance in relatively large quantity is applied on gauze to the back and three readings taken at twenty-four hour intervals. It is not applicable to the present study.

Secondly there is the Ophthalmic Test which is usually used as a means of determining the exciting or causative factor of pollen sensitiveness. It may be performed by dropping a

quantity of pollen equal to the amount used for a scratch test into the conjunctival sac. A positive reaction is indicated by reddening of the inner canthus. According to Peshkin (48), - "The main purpose of the ophthalmic test with dry pollen is to determine, not the degree of sensitivity, but rather, the absence or presence of sensitization when skin sensitization is absent."

A third method occasionally used is the method of Passive Transfer or the Prausnitz-Kustner reaction. The rationale of this procedure lies in the fact that if the serum of a protein sensitive person be injected into the skin of one who is non-sensitive, the latter becomes sensitized at the site of inoculation to those allergens to which the former is normally positive. A few hours after injection it is possible to carry out intradermal tests on the prepared area, and this acquired sensitivity may persist for many weeks. Should the site become desensitized to one allergen it will still react to others, provided the original serum was multiple sensitive.

According to Becker and Black (49) passive transfer may or may not be obtainable with the serum of patients with positive skin reactions together with marked clinical manifestations; also skin sensitive individuals who never have had clinical manifestations may give a positive passive transfer. Passive transfer is not dependent on the degree of skin sensitivity, on clinical manifestations, on a temporary allergic state, or on previous desensitization treatment. The method has a limited field of application and is chiefly useful when it is difficult or impossible to perform skin tests in the usual way, as in infants, extensive skin disease, or dermographia. Like the Ophthalmic and Patch Tests it has no useful significance in the present study of allergic epilepsy and will not be further mentioned. The same applies likewise to subcutaneous, nasal and

other tests.....

THE DERMAL OR SCRATCH METHOD.

This method is more widely used than the intradermal and has the initial advantage of being simpler to perform and thus requiring no particular experience. Once the site has been selected a series of small scratches is made by a scarifier, a scalpel or something similar. The scratches should all be of equal length (about a quarter of an inch long), and made across the lines of the skin and not parallel to them. It is important that no blood be drawn. The extracts to be tested are then applied to the prepared surface, directly if in solution, or with a drop of decinormal soda solution if dry. The substance is then gently rubbed into the scarified area with a clean glass rod and the result noted in ten to twenty minutes. Before reading each site should be lightly wiped with moistened cotton wool.

THE INTRADERMAL METHOD.

Some little preliminary experience is necessary to master the technique of intradermal testing and the novice should acquire this before investigations are seriously undertaken. This method is a much more sensitive and delicate one and presents serious pitfalls to the unitiated both from the point of view of interpretation of results and from the possible sudden appearance or exacerbation of existing clinical phenomena. A tuberculin syringe is often used and should preferably be composed entirely of glass. The point of the fine intradermal needle is introduced between the layers of the skin with the bevelled surface upwards and a small quantity, about one fiftieth of a cubic centimetre, of the solution carefully injected. Great care must be taken to ensure that the total amount of solution introduced gets between the layers of the skin

and that none is given subcutaneously or escapes to the surface on withdrawal of the needle. Should such errors go uncorrected uniformity of results cannot be expected.

INTERPRETATION OF RESULTS.

Reactions begin to appear in approximately five minutes, reach their maximum in twenty minutes, and then fade rapidly. The recorded reading is usually the one taken at the end of twenty minutes and it must be carefully compared with the control reaction which is generally produced by injecting a like quantity of normal saline. Some writers believe that positive reactions may be delayed and only appear after several hours. Vaughan, who found skin tests a reliable lead in 50% of his cases reports this phenomenon in his treatise on migraine and suggests that this delayed reaction is characteristic of the condition. If this is so it may partly explain Foran's (50) lack of success with skin tests in migraine. Rowe (51) records similar findings to Vaughan in food hypersensitivities. Parlato (52) takes an opposite view and says, "Food reactions are important only when they are immediately positive I think that we should be very careful when we speak of delayed reactions.

The actual findings may be tabulated as true positives, pseudo-positives, traumatic-positives or negatives. A true positive consists of a clearly defined wheal of appreciable size with a white pitted centre, or with irregular outgrowths (the so called pseudopodia) reaching from its margin. Again there may be simply a pronounced area of erythema without wheal formation, or any combination of the above pattern types may occur. It should be noted that the size of the skin reaction bears no relationship to the degree of sensitivity.

Some considerable experience is obviously necessary to interpret readings correctly; to distinguish strongly positive reactions from

moderately positive and both from pseudo- or traumatic. It may at first be impossible to differentiate a true positive from a pseudo but if doubt exists repeated trials will show a lessening effect if due to hypersensitiveness and an ever increasing one if the reaction is non-specific. It is suggested that these non-specific positive recordings are due to the liberation of histamine at the site of the innoculation. Some people have a skin unusually responsive to slight irritation and some have one that is frankly dermographic. In both these types the mere introduction of the needle or application of the scarifier is sufficient to set up a reaction, and the final result may be difficult if not impossible to assess owing to wide - spread erythema. Such incalculable results show the desirability of reciprocally relating the apparent causative agent with a history of recent contact or ingestion.

Various standards are employed in estimating skin tests. Results may be classified as one plus, two plus, three plus, four plus or negative. The area of erythema may be gauged roughly or measured in centimetres. Berkoff (53) has produced a scale with four eye-holes whose respective diametres grade the positive reactions as above. More recently Abramson and Gorin (54) (1939) have described the construction and operation of a simple contour gauge, by means of which the rate of growth of the height and cross section of allergic wheals may be measured and recorded.

CHOICE OF APPLICATION SITE.

The site usually chosen for skin testing is either the forearm or the upper arm but if the intention is to perform a large number of tests at one sitting then the back offers

the more convenient area. The anterior surface of the thigh can also be successfully utilized. Different areas of skin have different sensitivities in the same individual, and according to Alexander (45) and others the subject may manifest varying degrees of positiveness in different sites or may be negative in one place and markedly positive in another. He maintains that this variability reduces the worth of the test, as the investigator cannot know which finding is the true one. On the other hand if the best reacting site be chosen and tests be confined to this area then uniformity should result. This point will be discussed later.

According to Bowman (55) the whealing process to pollen extracts is better in the upper part of the arm than the lower and better on the medial side than on the lateral. She adds, "Tests inserted in rows vertically on the arm influence each other more than those inserted in horizontal rows. This point should be taken into consideration in routine cutaneous testing for hypersensitivity."

FACTORS MODIFYING RESULTS IN BOTH THE SCRATCH & INTRADERMAL METHODS.

As already stressed at the beginning of this section skin testing is far from being infallible, but once its limitations and pitfalls are properly appreciated it can prove in the hands of a competent and impersonal observer a most helpful and suggestive diagnostic procedure. But certain facts to be now sumarized must be carefully kept in mind.

Because a person gives a positive reaction to a skin test it does not necessarily follow that he is presently allergic to that substance. It may simply be the expression of a former or a future sensitivity, or desensitization may have been achieved. Clinical

symptoms may never have been present or the condition may have long disappeared or there may as yet have been insufficient contact to produce it. The same applies to negative results. Here also an absence of reaction does not prove the person immune. It may indicate that sensitivity is not sufficiently established to respond to a locally administered allergen, although the shock organ will readily react to a small amount. Negatives may occur in cases with marked clinical signs of disease or where there is other evidence to strongly suggest the negative reacting allergen as the primary cause.

An accurate diagnosis can only be arrived at when a correlation of positive results with the history or with the present condition is possible. Variations in technique may account for the anomalous findings of different workers, as may also the potency of reagents. The location of the injection site has already been shown to have an influence. Age is a determining factor and children are infinitly greater reactors than adults. Bray states that eight or nine out of every ten asthmatic children will give a positive result. Food sensitization rapidly declines towards the end of infancy and inhalant sensitization rapidly rises.

Multiple sensitiveness is the rule rather than the exception (Eyermann (56)), but it must be remembered that because a person reacts to a number of allergens it does not follow that his clinical symptoms are due to their joint action. His condition may be due to only one of the suspected substances. Again sensitivities may be lost and gained from time to time or during treatment. Variations also occur with the time of performance of the tests, and results that are strongly positive just prior to or immediately following an allergic flare-up may be only mildly positive or even negative at other times.

Finally negative results, it should be noted, are especially common after specific treatment or the administration of adrenaline, or following severe allergic attacks or prolonged lack of contact with the offending protein. In respect to treatment Levin (57) reported that energetic desensitization reduced the skin response and obliterated it in 14.9% of his cases. He believed the reduction in the skin test paralleled the clinical improvement.

COMPARISON OF SCRATCH & INTRADERMAL METHODS.

For some time past there has been violent controversy over the relative merits of the scratch and intradermal methods of skin testing. According to Coca (1) the differences in the results can be almost eliminated by the use of reliable extracts and a proper technique. He maintains that the increased number of non-specific reactions usual with intracutaneous testing results from the injection of too large a volume of the extract and that they can almost always be avoided if the injected volume does not exceed 0.02 c.c. On the other hand the scratch method often fails when the intradermal is successful and he attributes this failure to the relative inactivity of the material used. "If the extract contains the specific excitant in sufficient concentration, that is, many times that used for the injection test, the results of the two tests will be practically the same."

Whether this explanation is accepted or not it is an admitted fact that many more positives are obtained by the intradermal method and that much valuable information would be lost if diagnosis was solely based on the scratch. Simon (46) states that results indicate the intracutaneous to be from one hundred to ten thousand times more sensitive than the scratch. Tuft (58) maintains that, " ..... the

important advantage of the intracutaneous test lies in its greater sensitiveness and in its ability to uncover positive reactions that may not be detected by the scratch."

It is, however, generally recognized that the intradermal is more difficult to perform and the results to interpret and that it is more dangerous and gives more false positives. If a strong extract be given intradermally to a highly susceptible patient a general reaction may occur; while a weak extract or one slightly sensitive may give a false negative. Hence once more the absolute necessity of standardization. It is better to have two extracts, one strong and one weak, than to test with a single one of varying efficiency. If two extracts are used the weak can be applied first and then, if the results are negative the other may be tried. Or even better a scratch test may first be performed using the strong extract and if negative, then the same solution may be tried intradermally. This method would combine the simplicity, rapidity and safety of the scratch method with the increased sensitivity of the intradermal, while at the same time eliminating the disadvantages of the lesser sensitivity of the scratch and the danger of a general reaction with the intracutaneous.

Rowe (34) writing in 1927 said that he favoured the scratch test and only used the alternative method when the former had completely failed and then only in cases of pollen and dust sensitizations. But by 1934 his views had changed somewhat and in the Journal of Allergy of that year he remarks, "The scratch test with active allergens well executed will demonstrate in most patients those foods to which skin sensitizing bodies exist. The intradermal test should then be done with active extracts of those important foods to which negative scratch reactions have

occurred." And again, "The activity of a food extract for intradermal testing should be determined by definite intradermal reactions obtained in a patient who is clinically sensitive to such a food and who gives a good scratch reaction to that food." He found that a 1 : 200 dilution of a 2% extract of an active dry food allergen in glycerine-salt solution useful for testing intradermally those patients who were scratch negative. The change of view expressed by Rowe is largely indicative of the present trend of thought which during the past few years has rather favoured a combination of the two methods.

And finally one last word - It has already been pointed out that most people are potentially allergic to some substance or other at some period of their lives, but that only a few develop symptoms. In this connection, Colmes, Guild and Rackemann (59) write, "To become skin sensitive is a common property of mankind; while the capacity to express the sensitivity clinically is the property of those in whom the intrinsic, factor the activator, is operative." And again in 1935 Rackemann and Simon (60) studying reactions in a group of sixty normal individuals found quite a large percentage positive; and in the following year Grow and Herman (61) examined one hundred and fifty adults and reported that 55.5% showed positive reactions to one or more allergens. They, however, included in their positives a number of faint reactions. These figures are much in excess of those given by Row, Vaughan, and others, but nevertheless are enlightening and serve to show that the omnipotence of the skin tests, as originally conceived was not justified.

It should be pointed out that the Authors quoted do not wish to discredit the test but merely to demonstrate that it is far from being an infallible guide to allergy. It should be always associated with a history of symptoms or

contact. The fact that normal individuals may display skin sensitiveness is far from condemming it. The positiveness may be due to any one of the several factors previously mentioned. In any case it must be obvious that where clinical symptoms exist its use will narrow the field and suggest a possible causal agent that might otherwise go unsuspected.

It is a most illuminating sign that despite the levelling of destructive criticism and the production of disparaging evidence the limits of application continue to widen year by year. Occasional brilliant results in obscure cases encourage research, as witness the many victims of epilepsy, dubbed incurable, who owe their deliverance to the happy combination of an astute physician and a sensitive skin.

GENERAL LINES OF INVESTIGATION.

A study of the literature bearing on the subject of allergy and epilepsy had convined the writer that here was a problem, almost unexplored, that promised wide opportunities for research and offered hope where hitherto none seemed to exist. True, most of the work done and successes achieved had been with children; but it was thought that a useful addition to existing knowledge might be contributed by selecting a number of so called chronic idiopathic epileptics, at present undergoing hospitalization and subjecting them to an intimate allergic review. Treatment along specifically directed lines would be instituted and maintained following an assessment of the results of that review. At the same time it was considered that an informative comparison might be obtained by contrasting the incidence of protein sensitization in epileptics with that in ordinary psychotics and in normal individuals.

Accordingly the first step taken was the formation of three numerically similar but

otherwise distinct groups. The first was carefully chosen and consisted of twenty-four adult epileptics in whom no history of birth or subsequent head injury could be ascertained, and to the presence of whose disability no known cause could be attributed. They were, in short, members of that large and unfortunate class of epileptic collectively styled idiopathic. The second and third groups were picked at random from the non-epileptic psychotics and the staff respectively. The only common factor stressed was an approximation, as far as possible, in the average age of the three groups.

A careful enquiry was then instituted into the personal and family history of each of the seventy-two selected individuals with a view to uncovering any clinical manifestations of allergy. The results of this investigation were summarised as follows:-

GROUP	PERSONAL HISTORY	FAMILY HISTORY	NO. OF POSITIVES.
Epileptic	Positive	Positive	5
	Positive	Negative	4
	Negative	Positive	7
Psychotic	Positive	Positive	0
	Positive	Negative	2
	Negative	Positive	4
Control	Positive	Positive	0
	Positive	Negative	1
	Negative	Positive	3

From the above it can be seen that the presence of allergic phenomena was a marked feature of the epileptic group, the figure being almost double that of the combined results of the other two classes. Actually 66% of the epileptics gave either a positive personal or a positive family history of allergy, while in 20% of the cases positive findings occurred in both instances. These figures contrasted strikingly with 25% and 0% for the Psychotics and 17% and 0% for the control group.

The above figures seriously suggested the existence of some close association linking epilepsy with the recognized allergic disorders although the actual nature of that association was difficult to assess. In any event the main issue remained the frequent and convincing combination of seizures and clinical hypersensitivity in both the epileptic and his family.

Despite the difficulty of obtaining satisfactory histories in all cases the writer's results bore out to some extent the findings of Spangler (35) who in an analysis of one hundred epileptics reported that in the ancestors there was a history of allergy in 88% of the cases while the patients' personal history revealed a figure only slightly less.

CHOICE OF TESTING MATERIALS.

The next step was to skin test the different groups for protein sensitiveness. Before this was practical, however, several preliminary but nevertheless important details had to be considered. The first was the choice of the testing material to be employed. As already pointed out one had to be found that would fulfil certain fundamental conditions. It had to be carefully standardized, of known potency and free from irritating substances, while supplies of identical material had to be readily accessible.

It was not found convenient to use dry protein extracts, owing to the time and labour involved in standardizing solutions for intradermal purposes. After a survey of available sources it was decided to accept Bray's recommendation and use the preparations marketed by Messrs. C. L. Bencard (1934) Ltd. of London, whose products Bray maintained gave thoroughly reliable specific reactions.

The next question to be settled was the nature and number of the allergens to be employed. It is an expensive and laborious, not to say dangerous procedure to routine test each individual for a hundred or more allergens, with many of which he could never possibly have come in contact, and which in consequence could never be even remotely suspect. It must be accepted as an axiom that if convulsions are due to a hypersensitivity to a particular allergen, that allergen must be sought somewhere in the environment of the patient. It is true that the present environment may apparently differ radically from that in which the fits first had their being; but sensitivities may have changed with the years or the situation; multiple sensitivity may have been an early feature; or most likely the offending protein may be so common-place that it finds itself invariably present irrespective of time and locality.

It was obvious that a judicious selection of proteins should be attempted and that such a selection to be comprehensive without being cumbersome should contain only those extracts present in the commoner foods and pollens. Additional allergens might be suggested by individual histories or circumstances but for practical purposes this generalization seemed a sound one. Nevertheless such a restriction while eliminating much needless testing still meant a considerable number of allergens had to be investigated, and it was felt that a further

simplification of procedure was required. It was found in the use of the Group Reagent. This term signifies the testing extract resulting from the grouping together of approximately some half dozen distinct but biologically related allergens. Vaughan (62) favours such a grouping although other competent authorities insist on individual testing. The present writer employed group reagents initially in every case and found them most helpful and labour saving. It was only when a group gave a positive reaction that separate testing of its component allergens became necessary.

Group Reagents are prepared by Bencard and were used in this investigation. These combined proteins are in solution and are put up in twelve groups as follows:-

1. MIXED INHALANTS, STANDARD. Mixed feathers, horse dander and hair, cats' fur, mixed dog hair, mixed house dust, orris.

2. OTHER INHALANTS. Rabbit fur, sheeps' wool, furs (fine), cow dander, human hair, goats' hair, camel hair.

3. CEREALS. Wheat, oats, barley, maize, mixed flour, rye.

4. EGGS, MILK, etc. Egg while, egg yolk, milk, cheese, chocolate.

5. VEGETABLES. Mixed beans, mixed peas, cabbage, spinach, carrot, potato.

6. MEATS. Beef, mutton- lamb, pork - bacon, veal.

7. FRUITS. Apple, banana, orange, tomato, strawberry.

8. FISH. Cod, salmon, herring, sardine.

9. SHELL- FISH. Lobster, crab, mussel, oyster.

10. FABRICS. Silk, cotton - flock, kapok, wool.

11. NON- CLASSIFIED. Tobacco, yeasts, mushroom.

12. POLLENS. Grasses, shrubs, trees.

The procedure adopted was to test each person first with all twelve group reagents, and should he show a positive reaction to any of the groups then the individual proteins of that group were separately investigated, until the positively reacting allergen or allergens were finally isolated. This method was considered to be as effective, speedier and less irritating to the patient, than the laborious method of systematic individual testing. In addition to the above group reagents all were tested for such articles of food as appeared either periodically or frequently in the hospital dietry and which did not appear in any of the groups. These articles comprised onion, parsley and turnip; rice; lemon and pear ; chicken; herring, halibut and haddock. Finally if there was a history of a particular hypersensitiveness, either early or recent, that specific substance was tested for whether its group reagent was positive or not.

CHOICE OF TESTING METHOD.

It was clearly recognized that care and accuracy of performance were essential to a proper interpretation of results, and that for a similar reason the evolution of a standard technique became a necessity. This involved the performance of some preliminary work on skin testing. It was imperative before the investigation could be seriously commenced to decide on the method to be employed and the

site of application. A series of experiments was therefore conducted on two groups of patients, each twenty in number and containing ten epileptics and ten psychotics. These groups were named A and B. Group A was then divided into two halves, each half containing five epileptics. The first half of group A was scratch tested with twelve extracts and a similar number then given intradermally to the second half. Two days later the procedure was reversed and the first half was now tested intradermally and the second half dermally. On each of the two following weeks this whole operation was again repeated. The same site, namely the anterior surface of the forearm being used throughout. Separate standardized scratch and intradermal solutions were used.

The findings may be tabulated thus:-

GROUP	INTRADERMAL		MULTIPLE SENSITIVITY	SCRATCH		MULTIPLE SENSITIVITY.
	Positive	Negative		Pos.	Neg.	
Epileptic	7	3	5	4	6	3
Psychotic	2	8	1	1	9	0

The main points determined were recorded as follows:-

1. The original number of positive findings obtained by (1) the Scratch (2) the Intradermal method did not change on

subsequent testings.

2. The specificity of the positive allergens did not vary.

3. The Intradermal method gave almost double the number of positive reactors.

4. Multiple sensitivity was twice as common with the intradermal method.

5. In several members of the epileptic group the scarifying of the skin produced of its own accord some whealing and considerable erythema which made satisfactory interpretation of results impossible.

6. No general reactions of any kind were experienced.

One week following the commencement of the above experiment, and immediately it had become apparent that the intradermal method was producing more positives than the scratch, location tests were instituted with group B. This group was likewise divided into two equal divisions or sub-groups each containing five epileptics and five psychotics. One division was given a series of twelve injections using the anterior aspect of the forearm and the patient's back, while in the other the surfaces employed were the upper arm and the anterior and medial aspect of the thigh. The method of testing favoured throughout was the intradermal. The injections were repeated after an interval of two days and then the sites employed were reversed in the two divisions and another two series of injections given. This reversal of procedure was carried out until each sub-group had been tested eight times on each of four distinct sites.

Results were summarised as follows:-

	FOREARM		UPPER ARM		BACK		THIGH.	
	Pos.	Neg.	Pos.	Neg.	Pos.	Neg.	Pos.	Neg.
EPILEPTIC GROUP	6	4	6	4	4	6	5	5
PSYCHOTIC GROUP	2	8	2	8	0	10	1	9

The main inferences drawn were the following:-

1. The largest number of positives was obtained on the forearm and upper arm.
2. The lowest number obtained was on the back.
3. No positives were present on any of the sites that were not also present on the forearm.
4. The positives present on each of the four sites neither changed their number or specificity on any of the eight occasions.
5. A difference in degree of positiveness was noted between the forearm reactions and those on other sites, the former being definite and distinct, the latter, especially on the back, being often of less intensity and ill defined.
6. No general reactions of any kind occurred.

Two general conclusions were drawn from the above preliminary investigations:-

1. If a method was desired of ensuring the greatest possible number of positive reactions then that method must of choice be the intradermal and the site must be the forearm.

2. Provided the site remained the same, uniformity of results could be expected.

There appeared every justification to the writer for adopting that method which would give the biggest positive recording. Admittedly such a method involved a greater danger of false positives and a correspondingly greater difficulty in tracking down offending allergens. It was clear, however, that the extra labour necessitated, was in every way preferable to the constant uncertainity of results that must attach itself to another method. For example many sensitivities would successfully remain unsuspected should reliance be placed exclusively on the scratch test, or the back be utilised in preferenc e to the forearm. At the same time it was recognized that the literature contained many references to the serious consequences not infrequently following the indiscriminate use of the intradermal test, and stressing the fact that caution should be the key note in all investigations. After a careful consideration of all the facts and although no systemic disturbances of any kind had been encountered in the present series of cases, it was considered wiser to err on the side of safety. Accordingly it was decided to adopt a system of dual testing and the method finally chosen was a slight modification of that recommended by Simon. Each person was first scratch tested and then a day later intradermally tested, irrespective of results. The scratch test gave a useful clue to general hypersensitiveness, and, at the same time, a warning of any alarming sensitivity. Thus was one enabled to modify the strength of the intradermal injection of any specific allergen and so avoid the possibility of a general reaction. Scratch

testing was employed solely as a precautionary expedient and the writer believes no untoward results would have occurred had it been omitted altogether.

EXAMINATION OF SELECTED GROUPS.

Once the choice of testing materials, method and site had been established, work was begun on the testing of the three previously selected groups of epileptics, psychotics and controls. Each of the seventy-two individuals involved was scratch tested on the forearm with the twelve group reagents mentioned above. Two days later they were further scratch tested on the forearm for onion, parsley and turnip; rice; lemon and pear; chicken; herring, halibut and haddock. In performing the scratch test the procedure described earlier in this thesis was closely followed and all recognized precautions observed. An interval of one week was allowed to elapse after the scratch tests had been completed before the skin of the forearm was considered to be again in a fit condition for further testing by the intradermal method. This delay was occasioned by the fact that a certain amount of discolouration persisted for several days at the site of the tests and was apt to confuse readings and also because of the possibility, however remote, of local desensitization having been temporarily produced.

The intradermal testing was then carried out, strict attention to practical details being again observed. The dose injected was 0.2 c.c. of a solution specially prepared by Bencard and of a proportionately modified strength as compared with the scratch solution. This modified solution could be further reduced to one half or one quarter of its normal potency by the addition of carbol-saline

and used for investigating especially marked sensitivites as indicated by scratch reactions.

The final recording of positive results was based entirely on intradermal testing irrespective of whether the corresponding scratch reaction was negative or positive. Incidentally a positive scratch reaction in no instance was negative on intradermal testing. Results were tabulated as follows:-

GROUP	AVERAGE AGE	POSITIVE	NEGATIVE	MULTIPLE SENSITIVITY
Epileptic	38	14	10	11
Psychotics	36	7	17	2
COntrols	29	1	23	-

In the epileptic group there were fifteen males and nine females but in the other two groups the sexes were equally represented. Of the nine females five were positive and four negative, and of the fifteen males nine were positive and six negative. The average age of positive reactors among the epileptics was thirty-six and of negative reactors forty.

The obvious contrast in the degree of

sensitivity in the groups was self evident and not unexpected but the multiple sensitivity of the epileptics was a striking feature. A positive correlation between the comparative incidence of hypersensitiveness in the members of the three groups and the presence of allergic phenomena in their personal and family histories was readily demonstrated. It will be recalled that 66% of the epileptics now under investigation had previously given either a positive personal or family history of allergy, while the figures for the psychotics and the control group were 25% and 17% respectively. From the above table it was found that 58% of the epileptics had positive skin reactions, 29% of the psychotics and only 4% of the control group. These figures were sufficiently arresting to apparently bear out the ascertion that some undoubted interconnection existed between allergy and epilepsy. It was particularly encouraging to note that such results had been possible with chronic adult epileptics, although it remained to be seen whether specifically directed treatment would be as successful in benefitting the epileptic condition as the history and the intradermal test had been in suggesting it as an expression of allergy.

The findings recorded above may be compared with those of Beauchemin (63) who in 1936 skin tested a group of one thousand individuals. They comprised one hundred cases of epilepsy, two hundred of manic-depressive insanity, six hundred of Dementia Praecox and one hundred normal controls. He found 80% of the epileptics positive to one protein or another while only occasional hypersensitiveness was encountered amoung the psychotics. Among the controls the percentage of positive reactions was between 1 and 2% Each individual was tested against sixty-four food, bacterial and plant proteins, the method employed being the scratch and the site the

back. High as his figures were he mentioned the presence of many doubtful positives that were classed as negatives and it would appear possible that had another method and site been used his final results might have shown a still greater percentage of positives. As previously mentioned, in their study of one thousand epileptics and one hundred non-epileptic controls, Ward and Patterson (33) found 46.9% had evidence of protein sensitization while only 8% were positive in the non-epileptic group.

It would appear that patients suffering from epilepsy exhibit an allergic phenomenon common to them as a group. Nevertheless it remains extremely doubtful whether convulsions arise from the actual presence of this hypersensitiveness or whether, as Van Leeuwen thinks, there is a primary factor which predisposes the brain centres so that the allergic reaction acts merely as a secondary stimulus. Or again it may well be that the circulating protein picks out, for choice, the weakest structure in the individual's economy which in the case of the potential epileptic will be the central nervous system, and by producing irritation of it initiate convulsions. At all events it seems abundantly clear to the writer, both from his own work and from the work of others, that this powder and match partnership linking epilepsy and allergy is an established fact and no mere coincidence.

Only a brief comment on the skin results as recorded in the psychotic and control groups is necessary. The psychotics displayed a mild degree of allergic response, not comparable with the epileptics, but sufficiently strong for comment and certainly much more evident than that of the controls. Whether the occurrence of this sensitivity in so large a proportion of the psychotics was purely accidental and would not have maintained itself had a further number been tested, or whether there is indeed a certain amount of

heightened susceptibility are questions that require closer investigation. At least an interesting hypothesis is offered by the suggestion that institutionalized psychotics have the tendency to develop similar sensitivities owing to similar environment. Of the seven positives recorded in the above table four were sensitive to cheese or milk and three to fish. The psychotic group however, was not chosen on account of length of residence but with a view to the approximation of their average age to that of the epileptics. The mean length of residence of the psychotics was 2.6 years and of the positive section of the group 3.8 years. It is impossible to assess results on such meagre data but the point is nevertheless one of interest.

The incidence of positive reactors in the control group, which was drawn from the nursing staff, was small and resembled the findings obtained from time to time in non-allergic groups of the general population. This latter figure is variously stated at anything from 1 - 8%.

As previously indicated fourteen epileptics gave positive reactions either to the group reagents or to the specially selected group of common foods, not incorporated in those reagents. Each of these epileptics was now finally subjected to skin tests with individual allergens in an attempt to isolate the offending protein or proteins. Before, however, tabling these last results this would seem an appropriate moment to detail the histories of these fourteen cases whose examination and treatment forms the main basis of this thesis.

CASE RECORDS.

(1)

Aet. 32.

T.L. - The seizures commenced when he was one month old and at first they averaged about ten per day. To begin with they were very mild in character. At the time they commenced, an epidemic of cerebro-spinal meningitis was raging and two of his brothers, aged two and a half and six years, died of it. He himself was not infected, He was brought up on the bottle and no connection was noticed between the feeds and the fits. He went to an ordinary public school about the usual age but was unable to learn to any extent. He left school when he was thirteen and after a spell at home was sent to an Epileptic Colony, where he remained for almost four years. According to his sister the only thing learned there was how to tell the time.

During his childhood and youth the fit incidence had fallen considerably, first to approximately one per day, and later to about ten per month. The individual fits, however, greatly increased in severity. He was removed from the Colony to an Asylum where he remained for ten years until his transfer here on the outbreak of war.

It was consistently noted that a s a child and as a youth fits often occurred after eating ham. This fact slowly became evident to his family and it was found that when ham was eliminated from his diet the number of fits was diminished. During his four years at the Colony this connection continued to be observed. When he was allowed home occasionally on vacation it was again noted that severe convulsions followed the consumption of ham.

As a child he was said to suffer from skin trouble which cleared up when he was a few years old. This was probably some form of infantile eczema. There was no further

history of allergy either in the patient or in his immediate relatives.

Mentally he is dull, rather listless but accessible and co-operative. He has occasional attacks of mild excitement. Under supervision he can perform simple tasks about the ward.

The average monthly number of fits during the years 1937 - 1939 was 8.5 detailed as follows:- 1937 - 9.2; 1938 - 7.7; 1939 - 8.6.

On group testing he was found sensitive to:- Standard Mixed Inhalants and Meats. On individual testing to:- Mixed house dust and Pork.

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(2)

G.K. Aet. 41. - He was the youngest of a large family and owing to the early death of his mother was neglected as a baby. He was brought up on the bottle. When he was six months old he had a severe convulsions lasting for three and a half hours. He developed catarrh of the stomach at twelve months old, and for the next three years was brought up on proprietary foods, such as Horlicks.

He was much neglected during all this time. He did not walk until he was over two years. Epileptic seizures commenced when he was approximately six years of age. From this time onwards he took them fairly regularly with occasional longish intervals between. He would take several consecutively and then be free for months. They were not

very severe when he was a boy and if seized with one while out playing, he would immediately get up when it was over and go on with his game. He attended school and proved a clever scholar, being particularly smart at arithmetic. Later he worked in an office and then joined the Marines. Finally the fits became so frequent and incapacitating that he was forced to give up an active life.

He has been an inmate of this Institution for over twelve years and during that time has continued to take fits regularly. His eldest sister volunteed the information that seizures were more prone to occur after a meal containing porridge or potatoes. When these articles of diet were restricted he would go free from fits for a long period.

It has been observed in this Hospital that he frequently takes a fit in the early forenoon and this following a breakfast consisting chiefly of porridge.

As a child he suffered from urticaria for several years but this condition left him when he was about nine. His mother was said to have been very sensitive to fish and following an injudicious meal containing fish was subject to sick headaches often lasting for days.

He is painstakingly bright and punctuates his remarks with allegedly witty sallies. He has a good conceit of his own ability and tackles a job with great determination, but as he lacks application and staying power he quickly discards it for another. He is mischievous and delights in the discomforture of others. He is quick tempered, irritable and suspicious. Following a fit there is a period of deep confusion lasting several hours.

The average monthly number of fits

during the years 1937 - 1939 was 11.6 detailed as follows:- 1937 - 12.4; 1938 - 10.8 ; 1939 - 11.6.

On group testing he was found sensitive to:- Standard Mixed Inhalants and cereals. On individual testing to:- Mixed Feathers and Oats.

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(3)

M.M. Aet. 27. - Convulsions commenced when she was about eight months old and continued with frequency for two years, when they disappeared until the onset of puberty at sixteen. She was breast fed for the first six months and then put on the bottle. It was thought at the time that the convulsions may have been due to teething or to poisoning from an infected bottle. She suffered from gastro-intestinal irritation for several years but this finally left her about the age of seven.

She was never able to learn and had to be specially cared for. Since sixteen she has been taking seizures regularly. No history of allergy, either personal or family, could be obtained.

She is confused, inaccessible and resistive. An appreciable degree of dementia is evident. She is confined to bed and totally unemployable.

The average monthly number of fits during the years 1937 - 1939 was :- 4.9 detailed as follows:- 1937 - 5.5 ; 1938 - 4.5 ; 1939 - 4.6.

On group testing she was found sensitive to:- Egg, Milk, etc. On individual testing to:- Egg White.

Although whe was found to demonstrate skin sensitivity as recorded above no attempt was made to desensitize her. This was owing to the weakness of her general condition. She suffered from phthisis and has since died.

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(4)

J.R. Aet. 44. - Her infancy and girlhood were uneventful. She attended school and proved herself to be quite an average scholar. She suffered from the usual childish ailments but, on the whole, always enjoyed good health. She became increasingly stout after puberty, and this stoutness has persisted. She is slightly sub-thyreodic.

Fits commenced when she was twenty and were of the major variety from the beginning. At first they were infrequent, averaging one every three or four months, and she was able to retain her situation in a warehouse. By the end of five years, however, they had become sufficiently frequent to compel her to leave this position. Following this she was cared for at home until owing to her rapidly deteriorating mental condition and violent nature it became essential to remove her under certificate to an Asylum. She remained there until her transfer here on the outbreak of war.

As a young woman she suffered from periodical attacks of migraine. These attacks had no observed connection with the epileptic

seizures, and have now been absent for several years. One of her brothers suffered badly as an infant from eczema, and still continues to have occasional acute exacerbations of what has become a chronic condition.

Since her removal to this Institution she has been rather dull, peevish and petulant, constantly finding fault, and complaining about her environment. She is evasive and suspicious, and looks with extreme disfavour on her fellow patients. She is lazy and indolent. The history from her former Institution adds that she was frequently aggressive, abusive and threatening.

The average monthly number of fits during the years 1937 - 1939 was 6.1. detailed as follows:- 1937 - 4.5 ; 1938 - 7; 1939 - 8.

On group testing she was found sensitive to:- Fish.

On individual testing to:- Haddock and Herring.

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(5)

J.J. Aet. 39. He was the youngest of a family of ten, and infancy and early childhood were normal. His parents died when he was seven and he was boarded out. He left school at fourteen where he had a normal scholastic career. Fits first appeared at the age of eleven but were mild and very few in number to begin with. This state continued until after puberty when there was a rapid and progressive increase in their number and severity. At first he did not quite lose consciousness and

and was given plenty of warning of their approach; later loss of consciousness was complete; the fits became typically major in character and mental disturbance displayed itself. He has been an inmate of this Institution for the past fourteen years.

No personal history of allergy was obtainable but a strong family history was present. His father suffered from asthma for many years, dying from associated complications. One sister suffers from pruritis and another from migraine.

His temperament is characteristically epileptic. He is suspicious and irritable, querulous and aggressive. He is inquisitive, persistently interfering in the affairs of others but bitterly resenting reciprocation in kind. He freely exudes false accusations and general dissatisfaction. At times he is confused, impulsive, and dangerous.

The average monthly number of fits during the years 1937 - 1939 was 6.7. detailed as follows:- 1937 - 6.5; 1938 - 7.2 ; 1939 - 6.6.

On group testing he was found sensitive to:- Egg, Milk, etc. and Fish.

On individual testing to:- Cheese and Salmon.

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(6)

Mrs. B. Aet. 33. - She was born into a family of fourteen, and her early environment was one of sordidness and poverty. She

suffered from rickets as a child, and had intermittent attacks of billiousness over a period of some years. Towards puberty her physique improved and she eventually became strong and robust. She was at school until she was fourteen and was quite a fair scholar.

Fits commenced between the ages of eighteen and nineteen and were severe from the start. They were never frequent and showed a predilection to occur at or near to the menstrual period. She retained her employment, only leaving to get married. Following the birth of her first child she took several severe seizures, became violent and homicidal and was certified insane. After some months she was discharged, only to be readmitted during her second pregnancy in a similar state of acute mania. She has been an inmate of this Institution since then - that is for the past nine years.

No personal history of allergy was obtained, but two of her sisters suffered from infantile eczema and her paternal grandfather was subject to frequent attacks of 'summer-colds,' probably of the nature of hay-fever.

When free of fits her mental condition is comparatively normal and she then works consistently in the Laundry. At such times she is bright, acessible and fairly rational in outlook. Every now and again however, she has an attack of acute excitement, usually but not always, associated with seizures. She is then completely unmanageable, dangerously impulsive and lost to all sense of decency. Mental deterioration is not a marked feature of the case.

The average monthly number of fits during the years 1937 - 1939 was 5.1 detailed as follows:- 1937 - 4.2 ; 1938 - 5.9 ; 1939 - 5.1.

On group testing she was found sensitive to:- Eggs, Milk, etc.

On individual testing to:- Cheese.

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(7)

W.S. Aet. 37. - As a baby he was brought up on the breast, but proved a weakly child and fell victim to every prevalent infective disease. Mentally however, he was alert and did well at school, till fits commenced at the age of fourteen. No reason could be attributed for their commencement, but it was noted that about this time he contracted 'bronchitis.' This 'bronchitis' was of a recurrent nature and was later diagnosed as asthma. He has continued to suffer from periodical attacks of asthma ever since. The fits, once established, became frequent and of a very severe nature. Five years after their first appearance he had become so unmanageable at home that he was certified and sent to this Institution. He has been an inmate here for eighteen years. No food idiosyncrasies have been noted.

As mentioned above he is subject to asthmatical attacks, averaging one or two yearly. No correlation between seizures and asthma has been observed. There is a strong family history of allergy on the paternal side, his father suffering from asthma and two of his aunts from urticaria.

When first admitted here fits occurred as often as fifteen times per month but for the past dozen years they have been reduced in number. He is rather facile but not lacking in insight. He is bright and willing and a good worker, being allowed many privileges. He is not given to interfering with others or causing trouble. He is very amenable to discipline. A certain degree of mental weakness is evident.

The average monthly number of fits during the years 1937 - 1939 was 3.1 detailed as follows:- 1937 - 2.1 ; 1938 - 3.4 ; 1939 - 3.8 .

On group testing he was found sensitive to:- Standard Mixed Inhalants.

On individual testing to:- Mixed House Dust, Mixed Feathers.

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(8)

G.R. Aet. 44 - He was breast fed during a period of several weeks and from then onwards reared on the bottle. When about one year old he had a series of convulsions and these were repeated at intervals over a number of months. An older brother died of meningitis about this time. The convulsions finally disappeared and he continued free till twelve when typical major epileptic seizures made their appearance. They were severe from the beginning but infrequent. He had a normal schooling and left when he was fourteen. After one or two short lived attempts at obtaining and keeping employment it was realised that he would never be able to maintain himself. His parents were now dead and he was sent to a Colony for Epileptics. Eventually the increasing number and the severity of the fits affected his behaviour and he became noisy and troublesome. He was removed to this Institution where he has remained during the past eighteen years.

No personal history of allergy was obtainable, but his mother was said to suffer from migraine as a young woman and one of his sisters from a recurring skin condition of the

hands, most noticeable each Spring, when she worked in the garden. It was probably some form of urticaria.

Mental deterioration is a marked feature and insight is lacking. He is exalted in his ideas, superior in his manner and avidly religious. At times he is intensely confused, restless and impulsive. He is unemployable.

The average monthly number of fits during the years 1937 - 1939 was 21.7, detailed as follows:- 1937 - 25.4 ; 1938 - 19.7 ; 1939 -20.2.

On group testing he was found sensitive to:- Egg, Milk, etc. and Onion.

On individual testing:- Cheese and Onion.

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(9)

J.McK. Aet. 32. - Seizures commenced when she was about six years of age. No known cause could be ascribed to their incidence, as up to this time she had been a normal child in every way. The fits were of a very severe character from the first although only occurring at the rate of one or two monthly. Her capacity for learning was early affected and she was sent to a special school, but she could never master either reading or writing. As she grew older she became impulsive and difficult to control, especially following a fit, and finally required certification. She has been a patient here for eight years.

No allergic history of any kind was obtainable and there has never been any

apparent connection between fits and food, either at home or in this Hospital.

She is typically epileptic in that she is lazy, sulky and discontented, quarrelsome, unpleasant and importunate in her demands. Her outlook is apathetic and her reactions lethargic, but on occasion she can be impulsive and destructive. She is unfriendly and disinterested. She is capable of useful employment but consistently refuses.

The average monthly number of fits during the years 1937 - 1939 was 1.7, detailed as follows:- 1937 - .8; 1938 - 1.2 ; 1939 - 2.2.

On group testing she was found sensitive to:- Standard Mixed Inhalants, Eggs, milk, etc.

On individual testing to Mixed Feathers, and Egg White.

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(10)

H. McA. Aet. 32. - He was one of a family of six, of whom four died in infancy. He developed meningitis at the age of twelve months. He was reared on the breast. Twelve months after weaning convulsions developed and persisted during a period of two years. Typical major epileptic fits followed at the age of ten. They were comparatively few and mild in character, to begin with, but rapidly increased in number and intensity. He was unable to learn and was sent to a special school. He was totally unemployable. His mental condition worsened; he became troublesome, unruly and landed in the hands of the police. He was transferred to a state

institution and later here, where he has been for the past nine years.

As an infant he suffered from severe facial eczema and later from pruritis. Both conditions had left him before puberty. It was noted that convulsions often followed a heavy meal or heavy smoking. This has been borne out to some extent by observations in this Hospital. His mother was sensitive to fish and sickness and urticarial wheals occasionally developed as a result of eating certain varieties.

He is simple minded and facile, but capable of performing light tasks under supervision. He displays the typical epileptic habitus:- sulkiness, suspicion, irritability and obstinacy. After a bout of seizures he is excited, treacherous and impulsive.

The average monthly number of fits during the years 1937 - 1939 was 9.1 detailed as follows:- 1937 - 7.2 ; 1938 - 9.6 ; 1939 - 10. 5.

On group testing he was found sensitive to:- Egg, Milk, etc., Fish, Rice.

On individual testing to:- Cheese, Milk, Sardine and Rice.

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(11)

J.L. Aet. 36. - It was found impossible to obtain accurate information concerning his infancy and childhood, but apparently he had always been rather simple minded and childish in his outlook. He had only two epileptic

seizures prior to admission here; the first when he was fourteen years of age and the second about one month before certification and removal here. He has been an inmate at this Hospital for the past nineteen years. For the first few years after admission fits occurred irregularly and at intervals of many months but their incidence greatly increased as time went on and especially during the past six or seven years has this been so. No connection between fits, food or environment was ever noted. No allergic history of any kind was admitted.

His mental condition has deteriorated with the increase in the number of fits. He is shiftless, indolent and uncertain, suspicious and easily annoyed. He lacks insight, He gives no thought to the comfort of others but is most solicitous of his own.

The average monthly number of fits during the years 1937 - 1939 was 5.1 detailed as follows:- 1937 - 6.2 ; 1938 - 4.6; 1939 - 4.4.

On group testing he was found sensitive to:- Standard Mixed Inhalants and Egg, Milk, etc.

On individual testing to:- Mixed House Dust and Cheese.

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(12)

A.E. Aet. 36. - He was the third child of six siblings. There was no family history of epilepsy or insanity on either side, and his brothers and sisters were all perfectly normal children. As a child he was delicate and suffered from gastro-intestinal irritation. He was breast-fed. He was said to have had several 'turns' during the period of dentition,

but it could not be clearly ascertained whether these were actual convulsions or not. He was at school until eleven at which age epileptic seizures first made their appearance. They were very severe and necessitated his almost immediate withdrawal from school. Attempts were later made to teach him at home but unsuccessfully and he has never been able to learn to any extent. As he grew older the fits became more frequent and incapacitating. He eventually became noisy and destructive, was certified and sent to this Institution, where he has been for seventeen years.

In addition to the early gastro-intestinal disturbances, which may possibly have been of an allergic nature, he suffered from nettle-rash, frequently traceable to the eating of unripe fruit. One of his sisters also suffered from nettle-rash but no causal agent could be ascribed. His father was said to be 'asthmatic' as a young man.

He is usually cheery and affable and displays an active interest in his surroundings. He is childish in thought and speech. He craves the limelight and resents being overlooked. At times he is querulous and complaining, at other times hectoring and overbearing. He is occasionally impulsive but on the whole easily managed. He is capable of performing simple supervised tasks.

The average monthly number of fits during the years 1937 - 1939 was 6.9 detailed as follows:- 1937 - 8.1 ; 1938 - 6.2 ; 1939 - 6.4 .

On group testing he was found sensitive to:- Egg, Milk, etc. and Fish.

On individual testing to:- Cheese and Herring.

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(13)

M.L. Aet. 36. - She was a normal baby and was breast fed. Two of her sisters died in early life from tuberculosis, but she herself, excepting the usual childish illnesses was always strong and healthy. Her schooling was without incident and her ability average. She left school at fourteen and it was about this time and almost coincident with the onset of puberty, that the first epileptic seizures commenced. They were major in character and severe, but at first only occurred at intervals of two months or longer. As time passed they became increasingly frequent until as many as twenty would be present in one month. She was forced to give up her employment and live at home, but became so difficult to manage that she was sent to this Hospital. She was here for four years.

All her life she was subject to attacks of urticaria and several of those attacks occurred while she was an inmate here. She had a strong antipathy towards cheese, but circumstances occasionally induced her to partake of it and it seems reasonably certain that at least some of her urticarial attacks were thus explained. No connection between cheese consumption and fit incidence was ever noticed. Such a connection may have existed without its being detected. No family history of allergy was obtainable.

For the most part she was quiet, docile and childish, but on occasion could be sulky and very difficult. Following a fit she was quarrelsome and confused. She died during desensitization, and her case will be more fully discussed under the heading of treatment.

The average monthly number of fits during the years 1937 - 1939 was 7.4. detailed as

follows:- 1937 - 5 ; 1938 - 8.7 ; 1939 - 8.6.

On group testing she was found sensitive to:- Egg, Milk, etc.

On individual testing to:- Egg White and Cheese.

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(14)

R.L. Aet. 53. - So far as could be ascertained his infancy and childhood were normal and uneventful. He appeared to be a healthy child and was at school until he was thirteen. He was rather below average scholastically. On leaving school he followed various occupations until the outbreak of the last war. He joined the army and it was while serving abroad that seizures first made their appearance. For many years they were mild and very few in number, occurring only at intervals of many months. More recently they increased in number and severity, and following an unusually severe attack he became outrageous and confused. His sister, with whom he lived, was unable to manage him and he was certified and removed here. That was two years ago.

He has always had a thick, scaly ichthyotic skin, but beyond this no personal history of allergy was elicited. His sister had suffered all her life from chronic eczema affecting both her legs.

He is quiet, sociable and simple minded. He is capable of partially supervised employment. He is lacking in the aggressiveness, cunningness and irritability of the average epileptic. He is confused and depressed following a bout of fits.

The average monthly number of fits during the years 1937 - 1939 was 4.7 detailed as follows:- 1937 - ? ; 1938 - 4.8. ; 1939 - 4.6

On group testing he was found sensitive to:-Egg, Milk, etc.

On individual testing to:- Cheese.

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In none of the above cases was any seasonal variation noted in the number of fits over the past three years.

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The remaining ten epileptics under investigation gave negative skin reactions and as the history in no instance offered a clue to any demonstrable sensitivity it was impossible to subject them to specific treatment. Incidentally a positive personal history of allergy occurred in two of the cases and a positive family history in three.

In several of those negatively reacting epileptics an attempt was made to induce and maintain a lowering of the alkaline reserve of the blood, by giving large doses of ammonium chloride either alone or in combination with acid sodium phosphate. A weekly estimation of the total carbon dioxide content of the blood was made during treatment, but although an initial fall was noted, it was not maintained. The body seemed to adapt itself to the altered conditions, and it was found impracticable to sufficiently increase the dosage without causing serious gastro-intestinal upset. The rationale of the procedure was based on the hope of producing a

systemic reaction similar to that following starvation or the ketogenic diet.

It is a widely recognized fact that both epilepsy and allergy are often benefitted in a remarkable degree by either starvation or a diet which is rich in fats, both conditions tending to induce a state of acidosis. Nevertheless is it not possible that in at least some cases of allergy and epilepsy the improvement noted may be due, not to the production of an acidosis with its attendant dehydration, but to the accidental elmination of the offending proteins? It was thought that if an acidosis was successfully produced by chemical means, the diet remaining unaltered, any improvement in fit incidence must be due to protein elimination. Following satisfactory conclusions with non-allergic epileptics, a series of investigations would then have been instituted with those epileptics showing skin sensitivity, and a comparison of the individual and combined effects of acidosis and desensitization on fit incidence thus made possible. However the difficulties of medication proving unsurmountable, this particular line of investigation has been suspended for the present.

The following table briefly summarises those specific allergens which gave positive results and indicates the comparative strength of the resulting reaction in each instance.

CASE	POSITIVE ALLERGENS.
1	Mixed House Dust + Pork +
2	Mixed Feathers + Oats +
3	Egg White ++
4	Haddock + Herring +
5	Cheese ++ Salmon ++
6	Cheese ++
7	Mixed House Dust +++ Mixed Feathers +++
8	Cheese ++ Onion +
9	Egg White ++ Mixed Feathers ++
10	Cheese +++ Milk ++ Rice ++ Sardine +
11	Mixed House Dust ++ Cheese +++
12	Cheese + Herring ++
13	Egg White + Cheese ++
14	Cheese ++

It was evident that in eleven cases sensitivity existed to more than one protein, ten cases showing positive results towards two extracts while one case reacted to four. Most of the cases displayed well marked positiveness with large areas of erythema and pseudopodia. These were expressed as double plus, while the single and treble plus were used to indicate respectively lesser and greater degrees of reaction. Three distinct groups of allergens were mainly involved, namely eggs, milk and cheese; the common inhalants, mixed house dust and feathers; and fish. One noteworthy feature was the disproportionately large percentage (57%) sensitive, in some degree, to cheese.

The main facts can now be re-summarized, thus:- Of an available total of twenty-four idiopathic epileptics who were skin tested on the forearm by the intradermal method, one displayed sensitivity to four allergens, ten to two allergens, three to a single allergen

and ten were negative. Of the fourteen showing positive reactions, five had a positive personal and family history of allergy, two a positive personal history only, and four a positive family history only. In the remaining three instances no allergic history of any kind could be elicited. Of the ten skin negative cases, two gave a personal history and three a family history of hypersensitivity.

T R E A T M E N T .

Treatment of all allergic conditions may be grouped under the three main headings of Elimination, Non-specific desensitization and Specific desensitization. These three methods will be briefly discussed in turn.

Elimination.

Elimination is, as a rule, only possible where the existing sensitivity is towards foods. In most cases of dust and pollen allergy the difficulties of withdrawal are too great to be overcome, although occasional instances are recorded. Some of these have followed a change of environment, the removal of a pet from the family circle or the replacement of a hair mattress or a feather pillow. Such cases, sufficiently rare, and depending so obviously on chance, are to be regarded as offering no real solution to the problem of treatment.

In the case of foods the situation is somewhat different. Here, as a result of skin testing it may be possible to eliminate certain suspected foods, especially should they be of an uncommon nature or only appear rarely in the dietry. Often, however, the offending protein is one in general use, such as milk or wheat; or multiple sensitivity with reactions to both usual and unusual allergens may complicate the

picture. In such cases elimination becomes so difficult as to be impracticable.

It is also recognised that diets based solely on skin reactions will not always con--trol symptoms, and in such instances it is advised that trial diets be used to aid diagnosis. These trial diets may also be used for treatment. Rowe (64) is a firm advocate of this method and has established a series of what he terms "Elimination diets." These diets, or modifications, are in universal use in the diagnosis and treatment of allergy. Each diet is suitably balanced and on it a normal average activity may be maintained for long periods. Should one diet not succeed in allaying symptoms, then another is tried and so on until one is found that gives relief. Articles from other diets in the series may be added every few days, a close watch being kept meanwhile for any return of symptoms.

Vaughan's "Food diary" is conducted along broadly similar lines. On a skeleton diet the patient is encouraged to keep a daily record of his physical condition and of any symptoms that may appear from time to time. He must also carefully note the effect of adding new foods or of eliminating any that do not agree with him. In other words the observations are the patient's own and only their interpretation lies in other hands. This demands some measure of co-operation and is hardly suitable for institutionalized epileptics.

Waters (65) of New York, an authority on food sensitivity, also lays great stress on elimination diets. She presents in tabular form seven elimination diets for the diagnosis and treatment of food allergy in people eating at home, and four for those eating in restaurants. Her method is to give the diets successively until one is found on which symptoms improve or disappear, and then, using this diet as a basis, to add one new food at intervals of four days. Fruits and vegetables are added first, then meats and cereals, and lastly the remaining common allergens. Should one of the added foods cause a return of symptoms, it is excluded and no more additions made until the patient is so improved that any recurrence of symptoms resulting from

still another food can be immediately noted.

One of the chief difficulties with food elimination is the fact that hypersensitivity usually occurrs to common allergens, and it is difficult to eradicate these indefinitely. Nevertheless if this form of treatment is once commenced it should be persevered with, and especially so in young subjects, for in them prolonged elimination may eventually lead to desensitization. In brief elimination has a restricted field of application, chiefly confined to food allergy, and especially where the offending food is relatively unusual and easily avoided.

Non-Specific desensitization.

The underlying conception of this line of treatment is the supposition that by the injection of one type of protein, the tendency to react to the specific protein will be diminished. Many attempts have been made by different workers to produce desensitization by this means, but results, on the whole, have not been good, despite the variety of substances employed and the variations in technique. It cannot be recommended, except as a last resort, on account of the large element of chance involved.

Peptone has been employed in numerous allergic conditions and may be given orally, intramuscularly or intravenously. Wallis and Nichol (30) and other writers report good results following its use. Propeptane and Polypropetane have been both successfully used by Singer (45) in epilepsy of allergic origin, while the case for Tuberculin has been supported by such authorities as Crocket, Simpson and Stone (66) and Maxwell (67). It is an accepted fact that good results are usually temporary and that relapse, partial or complete may be expected, but Spangler did not find this so in his experience with crotalin (snake venom). He employed it over a number of years in epilepsy and other allergic conditions with marked success.

Sterile milk has been given intradermally by Loeper (68) in the treatment of asthma, while vaccines of every discription have been systematically injected in all forms of allergy.

Rackemann and Graham (69) suggested that stock vaccines possibly produced results by establishing a specific immunity or, more probably, by their non-specific local reactions. This latter supposition has found some support in recent work.

Specific Desensitization.

The principle of desensitization lies in the endeavour to lessen sensitivity or to raise the tolerance level, either by oral administration ~~of~~ of graduated doses of the specific food, or by injecting a standardized solution of the specific food, extract or pollen. Unlike desensitization in anaphylaxis, the induced tolerance in the human being requires relatively long time for its establishment.

Four routes may be employed in specific desensitization, namely the oral, the intradermal, the subcutaneous and the intramuscular. The oral route is widely recommended when dealing with food sensitivities. In this method the offending food or its specific peptone is given in small but gradually increasing doses in an attempt to abolish sensitivity. In children desensitization to common foods was successfully accomplished by Schofield and Schloss in three to eight months by administering increasing amounts of the suspected protein in capsules until tolerance was established. In 1935, Keston, Waters and Hopkins (70) discussing oral desensitization wrote "Oral desensitization was instituted if the patient was found to be sensitive to one of the common foods ..... With the exception of egg, the initial desensitizing dose contained under a milligram of protein..... The protein content of the dilution was increased every four days so that at the end of a few months the patient was eating, without ill effects, a normal daily portion."

Bray finds that with such common factors as egg and milk, desensitization is more readily induced if pepsin and H.C.L. are added to the small doses of the foods being given. On the other hand Forman is severely critical and describes the whole procedure of oral desensitization

as being worthy of trial only as a sort of "last straw."

Intradermal desensitization has occasionally been employed in dust and pollen hypersensitivity, but results are not encouraging, and the subcutaneous route is the one more commonly used, especially in mild allergic conditions. The method here employed is to prepare standardized solutions of the specific substance in various dilution strengths and to give them at weekly intervals, the dose being doubled with each injection.

In constant and severe allergy, or where the occupation of the patient makes it impossible to avoid contact with the specific substance, a modification of the above technique, known as the "Rush" method of Freeman, is commonly employed. This method, conducted in hospital, only occupies from five to seven days and consists of giving graduated doses of solutions of increasing potency. Injections are given daily every two hours from 8 a.m. to 10 p.m., and each day a stronger solution is employed till at the end of a week the patient can stand huge quantities of the specific allergen. He can then be safely returned to his usual environment.

Taub and Friedman discussing specific desensitization state, "Treatment is usually begun with a small injection, usually 0.05 to 0.1 cc. of the highest dilution which provokes a positive intracutaneous reaction. This dilution may vary from 1:5000 to 1:50000. The injections are usually given at five to seven day intervals and the size of the dose is never increased if it produces either a large local reaction manifesting itself as edema and erythema and itching at the site, or if it should cause systemic reactions such as generalized urticaria or pruritus or hay fever or asthma. The appearance of these signs necessitates a repetition of the dose which produced the symptoms instead of an increase at the next injection. In some patients it may even be necessary to decrease the amount given. The treatment is given as an ordinary subcutaneous injection."

The intramuscular route, like the subcutaneous, has been widely employed in most allergic diseases but it frequently happens that either route may be used with equal success in the same patient, according to the inclination of the physician. Intramuscular medication has the advantage of bringing the patient more intimately into contact with the desensitizing solutions and more quickly under their influence. Solutions of greater potency are given intramuscually and subcutaneously, and their effect is considered to be less transient. At the same time there is an increased danger of general reactions taking place, and careful technique and observation are essential.

No recorded instance could be found in the literature of allergic epilepsy having been treated by intramuscular desensitization. Usually where specific treatment had been attempted in such cases it was by means of eliminating the suspected article, although a few workers such as Rowe (10), Clein (44) and Singer (45) had given specific subcutaneous injections for sensitivity to dust, pollens and foods.

Such good results have followed intramuscular desensitization in most other forms of allergy that it seemed strange no effort had been made to employ it in epilepsy. I therefore appeared to the writer that intramuscular injections of potent and specifically prepared solutions offered a means of bringing the allergic state of the organism quickly and effectively under control.

PREPARATORY STEPS IN SPECIFIC TREATMENT

The writer had already formed the opinion that any form of treatment to be really effective would require to be specific and that probably the best method to adopt was one which embraced both specific elimination and specific desensitization. Furthermore it appeared preferable to make use of the intramuscular route in view of the strong desensitizing solutions to be used, and the fact that this route, while so successful in other forms of allergy, had never been tried in epilepsy. Here,

as in skin testing the first main difficulty to be overcome was that of establishing a technique ensuring maximum efficiency without risk of possible disaster. On enquiry Bencard expressed themselves willing to produce desensitizing solutions according to prescription, and availing himself of the offer, the writer had a series of thirteen prepared.

Each of these was separately dispensed in strict accordance with the tabulated results of the skin testing, due attention being paid to varying degrees of positiveness. As previously indicated no attempt was made in one instance to establish desensitization, on account of rapidly increasing debility, and the consequent dangers that might ensue.

Two solutions of graded potency were employed, one of moderate strength and constituting an Ordinary Desensitization Course, the other, more concentrated, and to be used with discretion, as a Continuation Course. The supplied solutions contained in addition to the specific allergens, Adrenaline Chloride of a strength of 1 in 4,000. The injections were given deep into the gluteal muscles near the junction of the outer and middle thirds of the line joining the Anterior Superior Spine of the Ilium to the top of the natal cleft. The initial dose given was 1 minim of the Ordinary strength plus two minims of Adrenaline 1 in 1,000.

A preliminary test-treatment was undertaken on six selected epileptics of the group under review. This was done so that some idea might be gained of their reactions before the whole group commenced the regular course of injections. No local or general reactions were noted in any instance after the first injection and on the following day two minims of the same solution with two minims of adrenaline were injected into the opposite gluteal region. On each succeeding day, for a total of five days, this procedure was adopted, increasing the desensitizing solution by 1 minim daily and continuing with the two minims of adrenaline.

After the fifth injection two patients

M.L. and Mrs. B., both sensitive to cheese began taking fits. The latter had three severe seizures within twelve hours. On the sixth day instead of giving her six minims of the solution, four were injected. No further fits occurred and she appeared none the worse. In the case of M.L., however, status epilepticus intervened. This patient took eight seizures in the interval between her fifth and sixth injections, each fit being, for her, severe in character. As with Mrs. B. she was given for her sixth injection four minims instead of six, but the fits persisted and increased in severity and it was decided to discontinue the injections. Despite every effort, however, she continued to take fits and passed into a state of coma. She died approximately seventy-two hours following the first seizure, having taken in all thirty-seven.

It was, of course, impossible to state definitely whether this sudden accession of fits was due to the injection and possible concentration of the specific allergen, or whether it was purely coincidental and would have occurred in any case. Nevertheless, one suggestive fact was that although she took fits comparatively frequently - from seven to eight monthly - she had never previously had an attack approaching this in either number or severity. The outlook was disquieting as it was felt possible that a similar increase in fit incidence might be induced in other subjects, unless some method of gauging dosage could be found. In the case of M.L. there had been no outward indication, either local or general, of overdosage, until the sudden appearance of the convulsions, if indeed they were to be regarded as a sequel to treatment and not as arising spontaneously.

For that matter no outward evidence existed in any of the other cases as to the dosage given being adequate or excessive. Daily minim increases were employed by such authorities as Bray and Paterson (73) to produce desensitization, but on the other hand,

they were dealing with forms of allergy such as asthma and hay-fever. It was possible that a dosage suitable for such cases might require adjustment for epileptics. Furthermore where, in the case of asthma and hay-fever, an overdosage might cause an increase in the severity of the specific symptoms or even general symptoms of oedema and collapse, in epileptics the first or only response to overdosage might well be one or more seizures.

It was clear that more harm than good might easily result if the present line of approach was persisted in. Indiscriminate dosage was unsatisfactory, not to say dangerous. Accordingly a further survey of the literature on allergy and epilepsy was undertaken, and some useful information obtained from work performed, over a number of years, by the American allergist, Spangler. The work referred to included a method, conceived and advocated by him, of checking dosage in non-specific therapy. The rationale was based on changes in the number of eosinophil cells in the differential blood count following the injection of desensitizing solutions. A modification of this procedure was evolved and used in the present work. A brief discription now follows:-

THE EOSINOPHILIC INDEX.

One factor common to most allergic conditions is an increase in the eosinophil cells of the blood. This eosinophilia is usually present in asthma, hay-fever and eczema, less frequently in urticaria and migraine, and more rarely in other allergic conditions. Its presence has been noted in epilepsy of allergic origin by Spangler (71), Forman (40) and others. Spangler writing on this subject says, "Since migraine, epilepsy, certain rheumatic conditions and some of the digestive disturbances have been investigated with reference to a possible allergic etiology, an increase of the eosinophils in the peripheral blood is being reported with more frequency."

In addition, however, to noting an

occasional eosinophilia in epileptics Spangler (72) found that in treatment by non-specific means the relative number of eosinophils in the differential count could be employed as an indicator of the degree of hypersensitivity and as a means of regulating amount and frequency of dosage. This he designated the "Eosinophilic Index."

In recommending this index as a guide to dosage, more particularly in bronchial asthma, he states that "As a rule the highest rise in the percentage of eosinophils, following venom protein injections occurs by the second or third day. In from five to seven days after injection, the eosinophil cells will, as a rule, have dropped to 4 per cent. or under (unless a higher percentage range of eosinophils had been present in the patient before the first injection was given,) and the patient may be given another injection. It has been my practice not to repeat an injection if the percentage of eosinophil cells by the fifth day has not dropped to within the normal range, or at least as low as they were before starting the protein injections. Moreover, it has not seemed wise to increase the strength of the dose if any given strength is producing an increase of from 8 to 10 per cent. of eosinophils by the second or third day after an injection." He concludes that "The varying percentage of eosinophil cells (the eosinophilic index) has been found a valuable guide in regulating the strength of dose and frequency of administration of venom protein when it has been used as a non-specific desensitizing agent in allergic asthma."

However, he later found that the eosinophilic index was of equal value in the non-specific treatment of allergic epilepsy and in his paper on "Allergy and Epilepsy" (35) states "I would emphasize again the need of a scientific method for regulating the strength of dose and for determining the frequency with which both specific and non-specific agents should be administered..... Following intramuscular injections of crotalin solution, ... I have found the degree of

eosinophilia produced in the differential blood counts to be of prognostic value as well as a very satisfactory guide to dosage."

In epilepsy as in other forms of allergy he found that the highest percentage of eosinophils occurred within forty-eight hours following injection and that normal counts were again present in from five to eight days. He did not repeat an injection unless the percentage of eosinophil cells had by the fifth day dropped to at least 4 per cent. Furthermore, he did not increase the strength of the dose so long as any given strength produced an 8 - 10 eosinophilia on the second or third day after an injection.

THE EOSINOPHILIC INDEX APPLIED TO THE PRESENT SERIES OF CASES.

Spangler's work appeared to have a direct bearing on the present problem and to offer considerable opportunity for comparison and elaboration. His technique had been developed in conjunction with non-specific treatment, namely the intramuscular injection of small doses of crotalin. It remained to be seen whether similar reactions to those he recorded would result from the injection of specific desensitizing solutions. His results had established a definite connection between the degree of eosinophilia produced and the margin of effective dosage. If this factor held good with specific desensitization then one of the main problems would be solved.

It was decided to divide the group of twelve available epileptics into two subgroups (A) and (B) of six each. The first group was submitted to specific treatment, controlled, as far as possible, by systematic eosinophil counts; the second was given a similar course of injections to the first, modified in respect of dosage, in the light of recent experience, but otherwise uncontrolled.

During treatment each of the twelve patients was permitted to follow very much his usual routine, the only restrictions laid down having reference to diet. Wherever a patient displayed sensitivity to a particular food, as indicated by his history or the results of skin testing, that food or foods was rigorously excluded from his diet. The active co-operation of the nursing staff was essential and proved willing and effective. It can be stated with some assurance that from beginning to end of treatment no patient gained access to food proteins other than those permitted in his dietry. The majority of the patients were actively interested in the proceedings and submitted cheerfully to all temporary discomfort in the hope of permanent benefit.

Before commencing active treatment a preliminary period of ten days was employed in making a series of differential blood counts on the members of Group A. This preparatory work was done to determine the average number of eosinophil cells normally present in the blood. In all fifteen counts were performed on each patient during this ten day period, and these results, along with those of succeeding counts during treatment, were arranged in graph form.

On the eleventh day Group A commenced treatment. At ten a.m. one minim of the ordinary desensitizing course along with two minims of adrenaline 1 in 1,000 was injected into the gluteal muscles of the right side. Just previously blood was obtained from the right ear and two blood films made of each patient. A differential count was then made of the twelve slides thus prepared. To ensure accuracy two hundred cells in each slide were counted, making a total of four hundred cells counted for each person. At 5 p.m. the same day another two films from each patient were prepared and results recorded, while a third count was read at 10 a.m. on the following morning, namely the 12th. A final and fourth reading took place twenty-four hours later at 10 a.m. on the thirteenth day and this was followed immediately by the second injection

of two minims of solution plus two minims of adrenaline into the left gluteal region.

This whole procedure was repeated until a total of fourteen injections had been reached, injections being increased by one minim on each occasion and spaced at intervals of forty-eight hours. When fourteen injections of the ordinary solution had been administered, and irrespective of the actual dosage then reached, the patient was changed to the concentrated course and to begin with given one minim of this and two of adrenaline. (An exception was made in one instance where it was thought advisable to commence the concentrated course with half a minim). Forty-eight hours later two minims were injected and so on until a total of twelve injections had been administered. In all each epileptic thus received twenty-six desensitizing injections. Throughout the course differential blood counts were made at 7, 24 and 48 hour periods following each injection.

The method employed in staining the blood film was the Giemsa Rapid, while Schillings "meander" method was used in making the differential count. The work involved was quite considerable, but with a little practice it became possible to make an accurate estimation of each slide in approximately fifteen minutes. The ears were used alternately for obtaining the blood, and no difficulty was experienced. Treatment commenced on the 11th of March and ended on the 30th of April.

One of the first points noted as treatment proceeded was the fact that although a degree of eosinophilia usually occurred after each injection, the percentage increase did not, in any way, approach that recorded by Spangler. In no instance did the differential count show an eosinophilia higher than 8.5%. Furthermore the eosinophilia produced was less persistent than Spangler's and by the end of forty-eight hours had invariably disappeared, except in a very few instances where the cell level was persistently raised over several days. In such cases it was generally associated with a bout of fits. As stated, an increase in eosinophils

usually followed an injection but occasionally id did not, or was too small to be of practical significance. After such a negative or mild reaction a seizure never occurred. A slight but definite eosinophilia, was nevertheless the rule, while exceptionally marked and suggestive counts occurred from time to time.

As already mentioned readings were recorded after each injection at the end of seven, twenty-four and forty-eight hours. It was found, generally speaking, that the eosinophilia had appeared by the time the first count was recorded, had reached a maximum by the end of twenty-four hours, and had disappeared by the end of forty-eight.

Another fact soon evident was the relatively larger increase in the eosinophilia invariably associated with the onset of a seizure. From a daily study of the Eosinophilic Index, as it was charted, it was seen that one or more convulsions were bracketed with most of the higher elevations in the graph curve. It appeared as though a marked eosinophilia, following an injection, could be regarded as either the accompaniment to, or the forerunner, of a fit.

Whether such an eosinophilia had, prior to treatment, accompanied a fit in any of the cases under review could not be, of course, stated with certainity. There had been nothing, however, in the results of the preliminary examination period of ten days to suggest that it did so. Furthermore, to the writer's knowledge, the literature on epilepsy gave no indication that such a reaction had ever been recorded in epileptics in general.

If, as appeared, such a fit only occurred when the degree of eosinophilia reached a certain peak level, then it was obvious that some fixed increase in eosinophils must be set as the margin of safety above which there was a likelihood of seizures and below which there was not. Only thus could the rate of dosage increase be regulated.

This standard was determined as follows:- The mean eosinophilic count of each patient was ascertained for the ten days prior to treatment and this was accepted as his or her normal level. An increase in eosinophils above this by 2% or over was considered to be significantly high and the next injection was accordingly modified. This figure was purely an arbitrary one, arrived at by noting, during the first days of treatment, the association of seizures with counts at least 2% above the average range. It was felt that some connection existed between these two factors, and subsequent findings in course of treatment tended to confirm this.

Admittedly fits did occur without a corresponding increase in eosinophils, and an occasional eosinophilia of over 2% above average was unaccompanied by a seizure, but nevertheless a high reading, on the whole, signified a convulsion. If one accepted the view that convulsions were incited by overdosage as evidenced by an eosinophilia of more than average degree, then by suitably restricting that dosage so that the said degree of eosinophilia was prevented from occurring, it should be possible to control the seizures.

Such was the ideal aimed at, but in point of fact it could not be achieved. The main reason was that an injection would frequently produce a seizure when the previous count gave no indication that a normal increase of one minim in dosage was at all likely to do so. Certainly, in such a case, the imminence of a fit would be indicated by the rise in the current count, but unfortunately the fit would often occur before the seven hour reading had been taken. Nevertheless the reading did give a good indication of the severity of the reaction, and was of value in deciding what particular modification of dosage should be instituted. If the count was unusually high, that is appreciably over 2% above the normal mean for the individual, then a grave danger existed of still further fits, should an increase in dosage, or even a repetition of

the last injection be attempted. If the eosinophilia was less evident but still 2% above normal, then the last injection might be repeated, but not increased.

Dosage control was summarised thus - (1) provided the Eosinophilic Index remained below the agreed maximum increase of 2% on the individual mean, the dosage of each injection was regularly increased by one minim. (2) Should the Eosinophilic Index show a 2% increase or slightly over, then whether a seizure had taken place or not, the previous injection was repeated. (3) Should the Eosinophilic Index show an increase considerably over 2% the next injection was decreased by from 1 - 3 minims according to the severity of the last reaction.

Co-incident with the treatment of Group A, Group B was likewise given a series of injections. These also were administered at intervals of forty-eight hours, the same dosage and rate of increase being followed in the two groups. In this group, however, eosinophil counts were omitted and dosage was uncontrolled. A series of twenty-six injections was given and the same precautions observed as in the other group.

In this group the question of dosage was naturally unsatisfactory. As no means existed of foretelling the likelihood of a convulsion, it was impossible to anticipate by cutting down quantity; the seizure had occurred before overdosage was recognized.

It was naturally borne in mind when dealing with either group that seizures during treatment were not in any way necessarily due to desensitization. Nevertheless it was felt of some significance that, in Group A, they were usually accompanied by an eosinophilia, and further if that eosinophilia could be prevented from reaching too high a level, they were not likely to occur. One could not state conclusively that had the eosinophilia not been controlled they would have occurred, but it seemed reasonable to infer that such was the case.

Again it was recognized that a seizure would often take place before the current count could be read, or at least before anything could be done to arrest it; but on the other hand, increased counts were not always followed by fits and by modifying the next injection were invariably prevented. Another important factor in regulating the treatment of Group A was the measure of the severity of the reaction on the organism as reflected in the degree of eosinophilia.

None of these advantages was enjoyed by Group B, but nevertheless with careful observation, no untoward results were experienced. The principle applied here was purely one of caution. Whenever a fit occurred, in course of treatment, the last dose was repeated, and if there was a series of fits over some days this same dose was repeated every forty-eight hours until the patient was free of fits. The usual routine increases were then resumed.

SKIN SENSITIVITY FOLLOWING DESENSITIZATION

One week following the course of specific desensitization, the two groups were subjected to a series of skin tests. Each patient was only tested against those substances to which he or she had formerly given a positive reaction. Three months later, at the beginning of August, they were again tested towards the same substances. The reason for this dual testing was to ascertain, (1) Whether desensitization had had any effect on the skin reactions, and, (2) Whether this effect was temporary or relatively permanent. If it could be shown that former positives were rendered negative it was evidence, although not absolute, that desensitization had been successful. Furthermore it might be possible to demonstrate a correlation between change in skin reaction and fit incidence.

The results of both investigations were tabled as below and should be compared with the original findings as shown on page sixty-eight.

TABLE 1.

CASE	IMMEDIATELY AFTER TREATMENT.			
1	Mixed House Dust	—	Pork	—
2	Mixed Feathers	—	Oats	—
4	Haddock	—	Herring	—
5	Cheese	+ +	Salmon	—
6	Cheese	+		
7	Mixed House Dust	+	Mixed Feathers	+
8	Cheese	+ +	Onion	—
9	Egg White	—	Mixed Feathers	+
10	Cheese + Milk — Rice — Sardine —			
11	Mixed House Dust	+ +	Cheese	+ + +
12	Cheese	+	Herring	—
14	Cheese.	—		

TABLE 2.

CASE	THREE MONTHS AFTER TREATMENT.			
1	Mixed House Dust	—	Pork	—
2	Mixed Feathers	—	Oats	—
4	Haddock	—	Herring	—
5	Cheese	+ +	Salmon	—
6	Cheese	+		
7	Mixed House Dust	+	Mixed Feathers	+
8	Cheese	+ +	Onion	—
9	Egg White	+	Mixed Feathers	+
10	Cheese + Milk — Rice — Sardine —			
11	Mixed House Dust	+ +	Cheese	+ + +
12	Cheese	+	Herring	—
14	Cheese	—		

Conclusions were summarised as follows:-

(1) In four instances (33 %) all reactions were negative in both tables.

(2) In five of the remaining eight cases (Table 1) negative reactions occurred towards one of two or more formerly positive allergens; in table 2 this number had fallen to four.

(3) Four cases showed a lessened degree of positiveness; similar findings occurred in both tables.

(4) In one patient the original sensitivities remained unaltered.

(5) Negativeness once established was not quickly unaltered.

(6) In several instances the decrease in skin sensitivity paralleled the improvement in fit incidence.

(7) It might be inferred that desensitization had taken place in those cases where an improvement in fit incidence and mental condition was accompanied by negative skin reactions. In five instances (42%) these three factors were present.

(8) Where improvement was less evident, or was absent, there was, approximately, a corresponding lack of alteration in the skin reaction. In such cases a lesser degree of desensitization, or a failure to desensitize might be inferred.

RESULTS OF TREATMENT.

Results were assessed according to two main factors namely (1) Decrease in the fit incidence and (2) Improvement in the mental health.

On the whole results were encouraging without being spectacular. It was rather too much

to hope for complete remission of fits in confirmed epileptics of many years standing, nor was it reasonable to expect a normality of thought and action in minds long disordered. It was sufficient to hope, if not for cure, at least for a degree of improvement. Could it be shown that some had improved, no matter to what small extent, then the work done was justified and was not without value. If others displayed a decided or permanent benefit as expressed by a significant fall in fit incidence and a more rational outlook, then the allergic approach to epilepsy would have fulfilled its promise and would be advocated with conviction.

As previously stated specific desensitization commenced on the 11th of March and was complete by the end of April. Observations were continued until the 11th day of September. During this time specific food elimination was maintained. By the 11th of September an interval of six months had elapsed since the beginning of treatment, and one of four months and eleven days since its completion.

While this period was not so long, as perhaps desirable, it was sufficiently long to make a very fair estimation of results. Before this was done, however, each individual case was carefully reviewed in all its aspects both during and after treatment, and the salient facts summarized as follows:-

CASE RECORDS.

1.

T.L. Group A. Mean eosinophilic count before treatment - 3.7% ; mean eosinophilic count during treatment - 4.2% ; mean eosinophilic count of twenty-four hourly readings - 5%.

In this instance, as in five of the six cases investigated the average range of eosinophils before treatment was less than the average range during treatment, and considerably less than that at the twenty-four hour periods.

The Eosinophilic Index showed a greater degree of response than in most cases, rising in one instance to 8.5%. This reading was associated with two fits.

During treatment there were four seizures, and since then to date (September 11) there have been an additional twenty-two. This gives an average of 4.3 per month since treatment commenced. This figure compares very favourably with the monthly average of 8.5 for the past three years.

Mentally this patient has improved. He is brighter and displays more initiative. The lethargy, formerly a marked feature, has largely disappeared. He has had no attacks of excitement during the past three or four months. He admits feeling better and more alert. His general condition shows improvement and he has put on weight.

On skin testing he was found to have become negative to both Mixed House Dust and Pork. A similar reading was recorded three months later.

Result. A marked fall in fit incidence associated with general mental and physical improvement.

2.

G.K. Group A. Mean eosinophilic count before treatment - 3.9% ; mean eosinophilic count during treatment - 4.5% ; mean eosinophilic count of twenty-four hour readings - 5.4%.

The Eosinophilic Index showed seven considerable elevations. In six of these the crest

corresponded to a twenty-four reading, and in one instance to a seven hour reading. Four of these elevations were associated with seizures and in each instance the dosage was modified with good results.

During treatment ten seizures occurred and since then another twenty-one have been recorded. This gave an average of 5.1 monthly which was less than half the average monthly figure of 11.6 for the past three years.

Unfortunately his mental condition has not improved concurrently with the fall in the number of fits. There is, perhaps, less tendency to be quarrelsome but he remains mischievious and self-centred. In time a greater improvement might reasonably be expected, provided the fit incidence remains at its present level.

On skin testing he was found to have become negative to Mixed Features and Oats. A similar reading was recorded three months later.

Result. A marked fall in fit incidence, unassociated with any appreciable change in the mental condition.

4.

J.R. Group B. Dosage uncontrolled by eosinophilic count.

Treatment ran a normal course and there were no undesirable symptoms of any kind. One seizure was recorded during treatment, but since then none have occurred. This highly satisfactory result is particularly striking in view of the fact that there had been a monthly average of eight fits during the past three years. In other words in the last six months only one fit has occurred in place of a previous forty-eight.

Corresponding to the fall in fit incidence

there has been an encouraging improvement in her mental condition. Certainly, this has not been so dramatic, but it has been appreciable and continues to progress favourably. She is no longer sulky and petulant and her former suspicion and aggressiveness have largely disappeared. She is now co-operative and productive and displays a new interest and initiative.

On skin testing she gave negative responses to Haddock and Herring, to both of which she had previously been positive. A similar reading was recorded three months later.

Result. A great decrease in fit incidence amounting to a virtual cessation of fits, with some considerable associated mental improvement.

5.

J.J. Group B. Dosage uncontrolled by eosinophilic count.

Early in treatment a series of severe seizures occurred. The normal dosage increment was suspended until fits had been absent for twenty-four hours. During this time the original dosage, which had been followed by the first convulsion, was repeated twice at forty-eight hourly intervals. Thereafter normal minim increases in dosage were resumed.

In all ten fits took place during treatment, and since then a further twenty-three. This gave a monthly average of 5.5 over the whole period. This figure was approximately the same as the monthly average of 6.6 for the past three years, and consequently no improvement in fit incidence could be said to have occurred.

His mental condition likewise shows no change. He continues to be troublesome,

aggressive and interfering. He is morbidly suspicious and irritable.

On skin testing he displayed the same degree of sensitivity towards Cheese as he originally did, but was negative towards Salmon. A similar reading was recorded three months later.

Result. No improvement in either fit incidence or mental condition.

6.

Mrs. B. Group A. Mean count before treatment - 3% ; mean count during treatment - 3.8% ; mean of twenty-four hour readings 4.5%.

On the Eosinophilic Index there were only two elevations of any magnitude and these were both associated with seizures - three in either case. On both occasions the highest point of each curve corresponded to the readings recorded at the end of twenty-four hours. The dose injected just previously to the onset of the fits was repeated and there was no recurrence.

During treatment there were six fits and since then ten have occurred. This gave a monthly average of 2.6, and showed a distinct improvement on the monthly average of 5.1 during the past three years.

Mentally she has shown no improvement. In any event no spectacular change was likely, as at all times her outlook was fairly rational, except at odd intervals when she became confused and violent. She still continues to have impulsive outbursts and to be most unmanageable at such times.

On skin testing she gave a lessened degree of positiveness towards Cheese. A similar reading was recorded three months later.

Result:- Some considerable improvement in fit incidence, unassociated with any mental improvement.

7.

W.S. Group B. Dosage uncontrolled by eosinophilic count.

Treatment ran a normal course and was uninterrupted in any way. Three seizures occurred during this period and these were later followed by another ten. This gave a monthly average of 2.1 which was slightly below the average of 3.1 for the past three years. This was not considered sufficient justification for claiming an improvement in fit incidence.

Mentally he is possibly somewhat brighter and certainly feels better in himself. There is, however, comparatively little change to be noted. He continues to be mild mannered and rather facile. He works about the Institution and interferes with no one.

On skin testing positive reactions of a lessened intensity were recorded towards Mixed House Dust and Mixed Feathers. A similar reading was recorded three months later.

Result:- No improvement in fit incidence, but some slight improvement mentally.

8.

G.R. Group A. Mean count before treatment 1.5% ; mean count during treatment 3.9% ; mean of twenty-four hour periods 3.1%.

The Eosinophilic Index rose rapidly after the second injection and following the third injection reached its extreme height of 8.5%.

During this period of abnormal reaction fifteen fits occurred. The marked elevations in the eosinophil counts would probably never have been recorded had prompt steps been taken to ensure control of treatment. As it was, however, the emergency was the first of its kind, occurring as it did in the early days of treatment and consequently adequate counter measures were not applied as quickly as they might. A drastic reduction in dosage was deemed necessary and proved effective, the count falling steadily within the next two forty-eight hour periods. Later in treatment five further well marked elevations in the counts occurred, the highest, however, only reaching 6.5%.

Four of these increases were associated with fits. During treatment there was a total of thirty-seven fits and since then eighty-five have taken place. This gave a monthly average of 20.1, approximately the same as the average of 21.7 for the past three years.

Not only has there been no improvement in the fit incidence, but his mental condition likewise shows no change. He continues to be confused, irritable and aggressive. He lacks initiative, is unemployable and in need of constant supervision.

Results were somewhat disappointing, as judging by the activity of the eosinophil reactions one would have believed desensitization possible. Apparently the case was too established and the seizures too frequent to admit of improvement.

On skin testing he was found still positive to cheese, but had become negative to onion. Three months later a similar reading was recorded.

Result:- No improvement in either fit incidence or mental condition.

9

J. Mc. K. Group B. Dosage uncontrolled by eosinophilic count.

Treatment ran a normal course, except on two occasions when a total of three fits occurred. Dosage was modified in the usual manner during those periods.

Since completion of treatment there have been no fits. This gave a monthly average of 0.5 slightly better than 1.7, the average for the past three years.

Corresponding to the minor degree of improvement in the fit incidence, there has been noted lately a slight change in her mental outlook. She has, if anything, been more approachable and more amenable to discipline. She remains, however, indolent and unproductive.

On skin testing she showed lessened sensitivity to Mixed Feathers and was negative to Egg White. Three months later the same degree of sensitivity was expressed towards Mixed Feathers but she had again become positive to Egg White.

Result:- - A slight improvement in fit incidence associated with a minor degree of mental improvement.

10.

H. Mc A. Group A. Mean reading before treatment 1.4% ; mean reading during treatment 2.8% ; mean of the twenty-four hour periods 3.1%.

The Eosinophilic Index showed two main elevations, each of which were associated with

a seizure. Some lesser elevations, although greater than 2% above the average range, were also present, and two of these likewise corresponded to seizures.

The mean of the twenty-four hour readings was not so noticeably higher in this instance as it was in several of the others. No apparent reason for this could be found.

Seven fits took place during treatment and since then nineteen, which gave a monthly average of 4.3, appreciably less than half the average of 9.1 for the past three years.

Recently there has been a distinct improvement in his mental condition. He is much brighter and more accessible and nothing like so quarrelsome. He is less interfering and cleaner in his habits. The degree of mental deterioration in his case was such that any improvement had, of necessity, to be purely comparative. Bearing this in mind one is justified in laying claim to a distinct improvement.

On skin testing he showed lessened sensitivity to Cheese and gave negative reactions to Milk, Rice and Sardine. A similar reading was recorded three months later.

Result:- A distinct improvement in fit incidence associated with a similar improvement in mental condition.

11.

J.L. Group B. Dosage uncontrolled by eosinophilic count. Treatment was uninterrupted except for the occurrence of eight fits which necessitated dosage adjustment according to plan.

From the beginning of May to date (Sept. 11) there were a further eighteen fits. This gave a monthly average of 4.2, only slightly less than

the monthly average of 5.1, over the past three years.

The mental condition, like the fit incidence, shows no change of any significance. He continues to be lazy, irritable and uncertain. He displays no interest in anything outside his own immediate wants.

On skin testing no alteration in the original sensitivities was found. This reading was confirmed three months later.

Result:- No improvement in either fit incidence or mental condition.

12.

A.E. Group A. Mean reading prior to treatment 4.4% ; mean reading during treatment 4.4% ; mean reading of twenty-four hour periods 5.1%.

As in the case of H. Mc A (10), the mean of the twenty-four hour periods was not significantly higher than the other two readings. Nevertheless, the four elevations of more than 2% above the normal range occurring during treatment were all recorded at twenty-four hour periods. Three of these same elevations were associated with fits.

The total number of fits during treatment was five and since then twenty-three have occurred. This gave a monthly average of 4.6, somewhat better than the average of 6.9 for the past three years.

Mental deterioration was too established in this case to admit of much change, and there has been none appreciable. He continues to be, on the whole, bright and cheery, with occasional noisy and impulsive interludes.

On skin testing he was found to have retained his sensitivity towards Cheese, but to have become negative to Herring. Three months

later a similar reading was recorded.

Result:- Some improvement in fit incidence unassociated with mental improvement.

14.

R.L. Group B. Dosage uncontrolled by eosinophilic count.

Treatment was uneventful. Early in March three fits occurred but there were none in April or May. About the middle of June a bout of fifteen seizures occurred within the space of twelve hours. They could not be attributed to anything in the environment. Since then to date there have been no further seizures.

The monthly average was thus 3, or somewhat less than 4.7, the average for the past three years. Had it not been for the sudden accession of fits in June this case would have been considered to have shown an appreciable benefit. As it is it will be interesting to note the fit incidence over the next few months. There would seem every likelihood of a distinct eventual improvement.

Mentally there has been a quickening of intelligence and a display of initiative that is very encouraging. He appears to have greater confidence in himself and employs himself usefully about the Institution. His skin condition, likewise has improved, being much less harsh and scaly.

On skin testing he gave a negative reaction to Cheese. This reading was confirmed three months later.

Result:- An improvement in fit incidence associated with distinct mental improvement.

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The above results in the twelve epileptics can be finally summarised as follows:-

(1) A distinct improvement in fit incidence and mental condition. (4 cases.)

(2) A lesser degree of improvement in fit incidence and mental condition. (1 case.)

(3) An improvement in fit incidence alone. (3 cases.)

(4) An improvement in mental condition alone. (1 case.-)

(5) No improvement. (3 cases.)

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CONCLUSIONS.

In nine of the twelve patients treated the results of desensitization were indicative of some degree of response, while in four instances this response amounted to a definite improvement. In only one instance, however, could a claim be laid to anything approaching complete elimination of seizures. The fact was striking that, in this case the average monthly figure of eight had fallen to the extremely small one of 0.2. Furthermore, should this improvement continue the prospects of ultimate recovery appeared likely.

It was impossible to state that the same good end result would be achieved with the others, on account of the difficulty of assessing the effect of a lowered fit incidence over a period of years. Nevertheless, it was not improbable that should the present lowered incidence persist that it might eventually permit of some cases being cared for outside a certified institution.

Meanwhile the main points elicited were:-

(1) Most of the epileptics were now taking fewer

fits. (2) Several admitted to feeling better in themselves. (3) They were, generally speaking, quieter and conducting themselves more rationally. (4) In consequence, there was a noticeable easing of strain on the nursing staff and a lessening of friction with other patients. These two factors alone would have justified the effort expended.

The whole series of investigations, from start to finish, tends to confirm the close relationship existing between allergy and epilepsy. These facts are mainly as follows:- (1) The obvious preponderance of allergic manifestations in the epileptic's personal and family history as compared with the psychotics and controls. (2) On skin testing the epileptics displayed, as a group, a much more evident sensitivity to food and other allergens. (3) Following desensitization skin sensitivities were lost or lessened in degree in all but one instance. This change, in dermal responsiveness was accompanied in four cases by a decrease in seizures and a corresponding increase in mental acuity. (4) In four patients the personal history suggested a linking of seizures with a specific protein. It was interesting to note that in each instance a positive reaction resulted when skin testing the subject for that particular substance. (5) Specifically directed treatment by elimination and desensitization was successful, in nine patients, in alleviating symptoms.

In short, the writer was convinced that allergy played an important part in the etiology of his particular series of cases.

With regard to treatment it was felt that injections given by the intramuscular route and controlled by frequent reference to the Eosinophil count, was a preferable method to a similar, but uncontrolled, line of treatment. It was not a question of the end result being more satisfactory in the former method but rather that the element of risk and uncertainity was the more successfully eliminated or overcome.

The use of the Eosinophil Index, in treatment,

as applied here was new, and the number of cases small. Further research along similar lines might suggest modifications of technique, such as an alteration in the fixed increase level of 2%. Had time permitted or, the services of a technician been available, the counts would have been recorded two hourly, in order that a closer watch might have been kept on the rising tide of cells. However, despite the absence of these refinements, the method appeared to offer a reliable guide to dosage and fit control.

It is the writer's intention to follow up the present series of cases with the object of determining, (1) The effect of time on the fit incidence and (2) the effect of a permanent lowering in fit incidence on the mental condition. As a result of these observations it may be deemed advisable to give a second desensitizing course of treatment. Furthermore, as other material becomes available it is hoped to institute investigations along similar lines.

In conclusion, one would like to see the significant connection of allergy and epilepsy more widely considered and more effectively investigated. Early idiopathic epileptics should be prevented, if possible, from joining the ranks of the chronic, by a timely allergic examination, while even those cases, chronic and institutionalized, should not be despaired of or drug-saturated, without every effort being first made to trace sensitivities and institute desensitization.

SUMMARY.

1. The nature of allergy and its possible connection with epilepsy is discussed and a review presented of the literature on the subject.

2. Critical observations have been made on the technique of skin testing and a search instituted for the ideal method as applied to the present work.

3. Investigations have been conducted into the personal and family histories of seventy-two individuals in a search for allergic manifestations.

4. The case records of fourteen epileptics are presented in some detail, each of the series being skin tested, dermally and intradermally, and results tabulated.

5. The treatment of allergy is critically reviewed and a method adopted combining specific elimination and specific desensitization, while the Eosinophilic Index is suggested as a means of guiding dosage.

6. Six epileptics have been given a course of specific intramuscular injections controlled by eosinophilic readings, and a second six given a similar course but uncontrolled by such observations.

7. Two further series of skin tests have been carried out, one immediately following treatment and the other three months later.

8. Finally, results are assessed and conclusions inferred.

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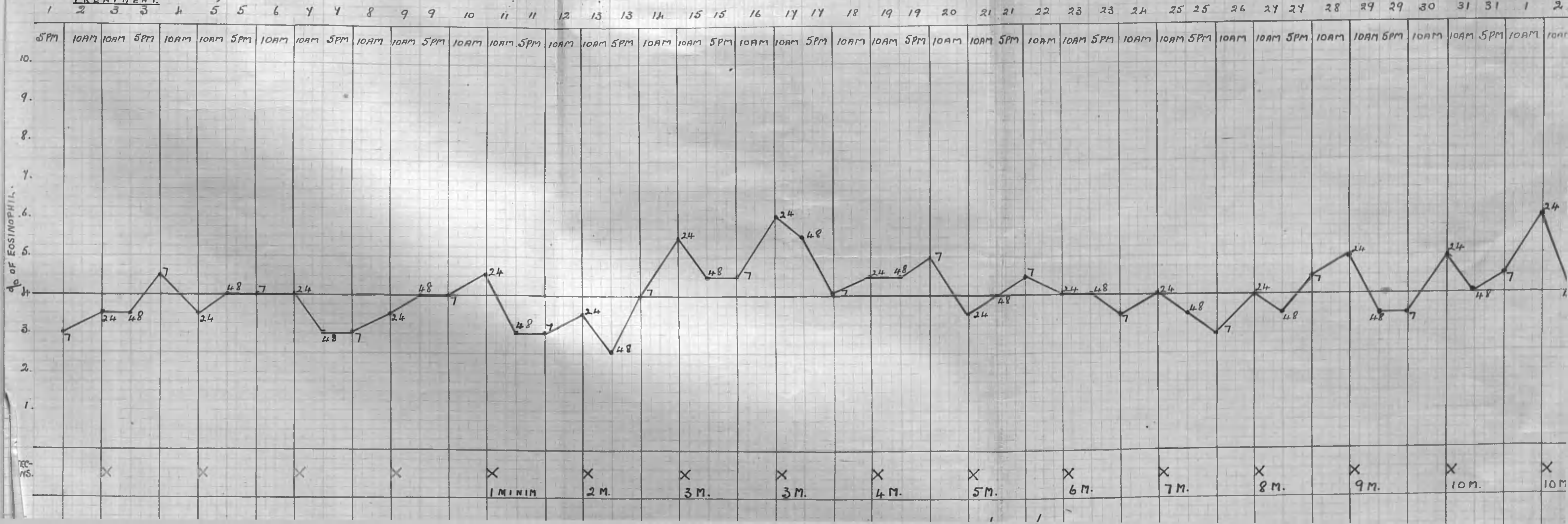
MEAN READING PRIOR TO TREATMENT } = 3·7%

MEAN OF TWENTY FOUR HOUR READINGS } = 5%

MEAN READING DURING TREATMENT } = 4·2%

EOSINOPHILIC INDEX.

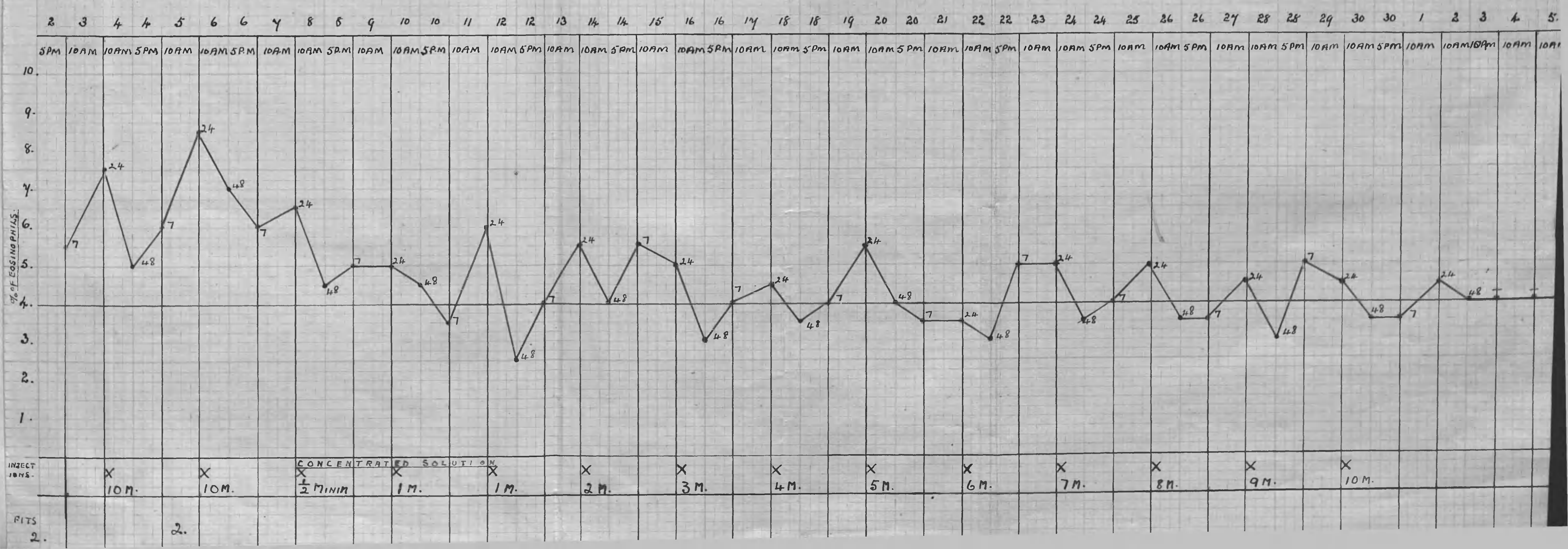
T. LAIRD: MARCH, 1910. CASE 1.



EOSINOPHILIC INDEX.

T. LAIRD.

APRIL 1940



CASE 2.

KELLY: MARCH, 1960.

EOSINOPHILIC INDEX.

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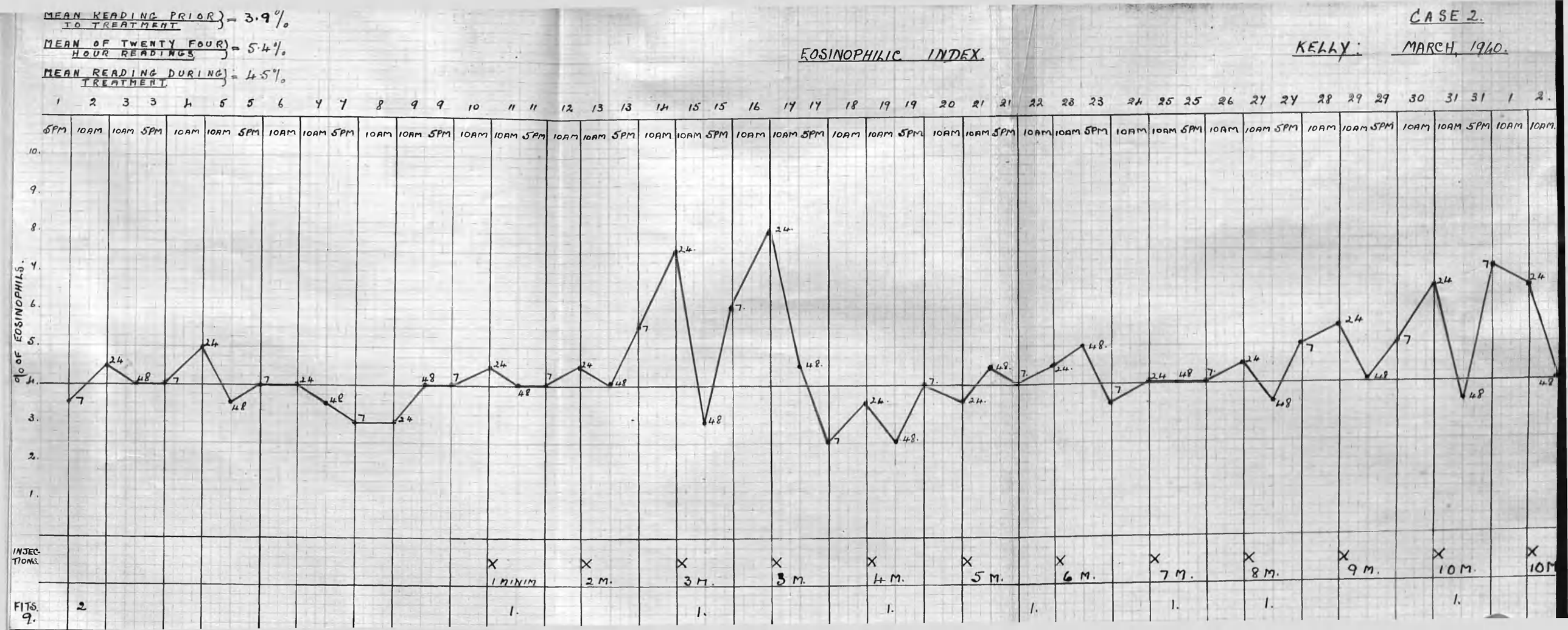
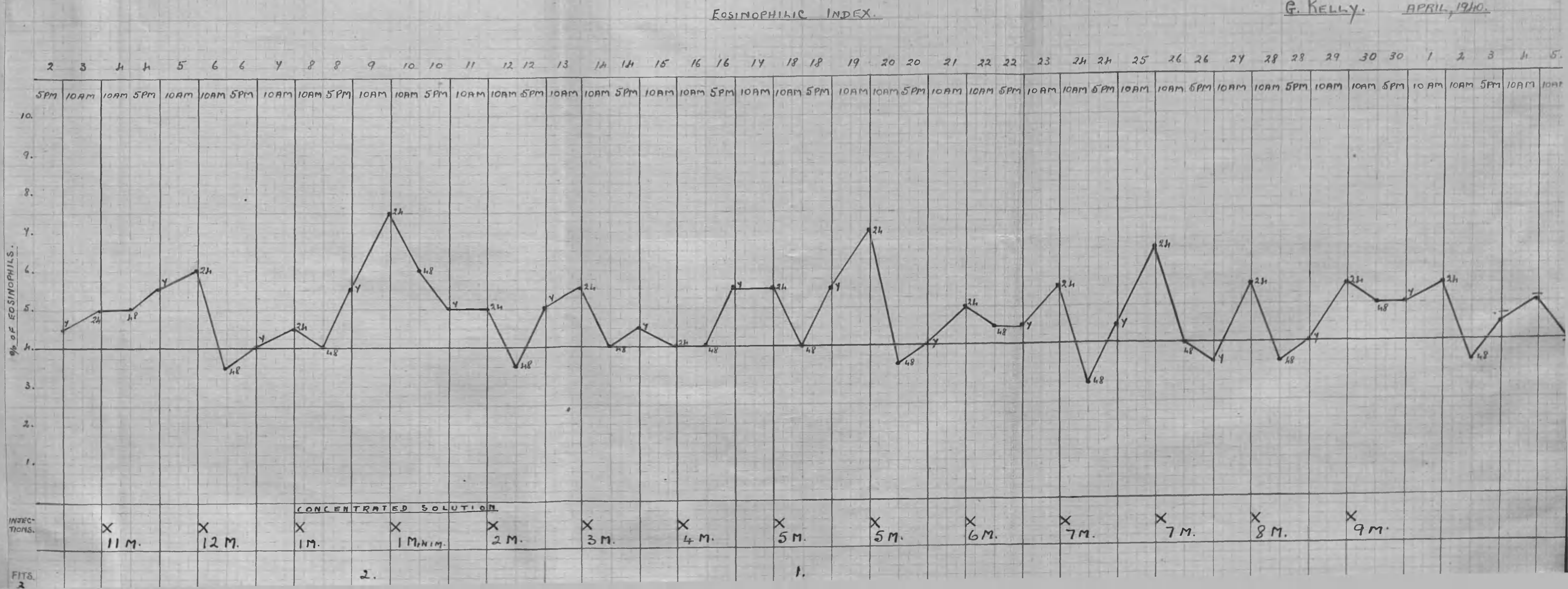
MEAN OF TWENTY FOUR HOUR READINGS = 5.4%

MEAN READING DURING TREATMENT = 4.5%





EOSINOPHILIC INDEX.
G. KELLY.
APRIL, 1910.
% OF EOSINOPHILS.
INJECTIONS.
CONCENTRATED SOLUTION
11 M.
12 M.
1 M.
1 Minim.
2 M.
3 M.
4 M.
5 M.
5 M.
6 M.
7 M.
7 M.
8 M.
9 M.
FITS.
2.
1.

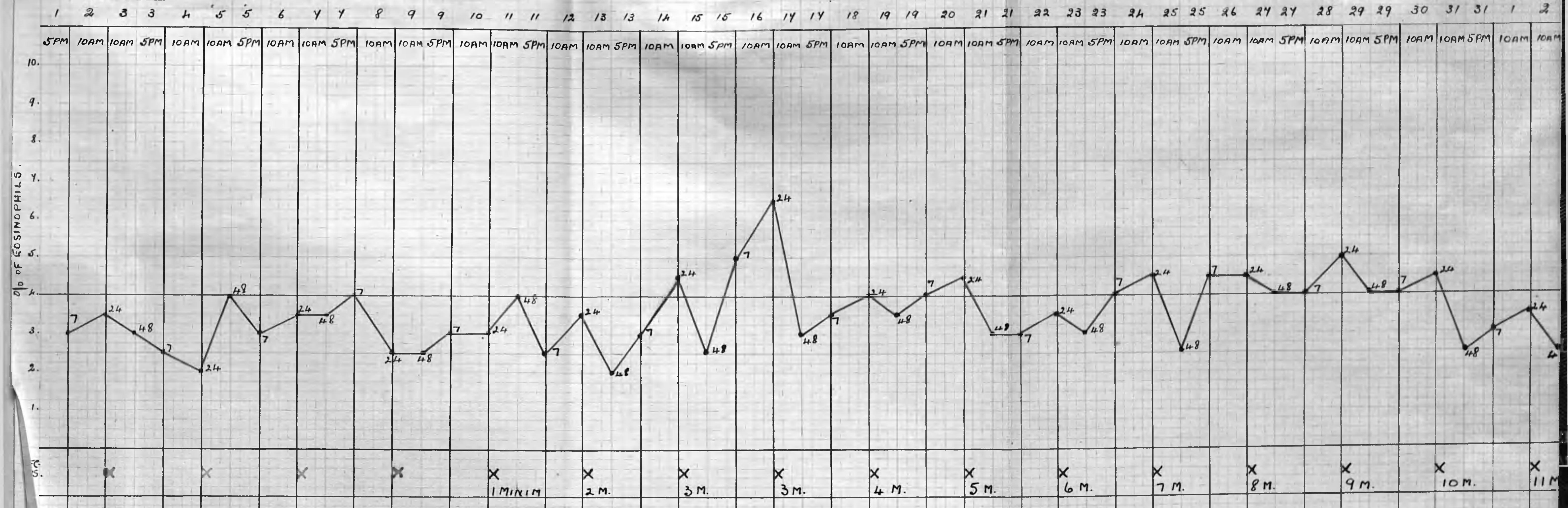
MEAN READING PRIOR TO TREATMENT. } = 3 %.

MEAN OF TWENTY FOUR HOUR READINGS } = 4·5 %.

MEAN READING DURING TREATMENT } = 3·8 %.

EOSINOPHILIC INDEX.

MRS. BRENNAN: MARCH, 1940. CASE 6.



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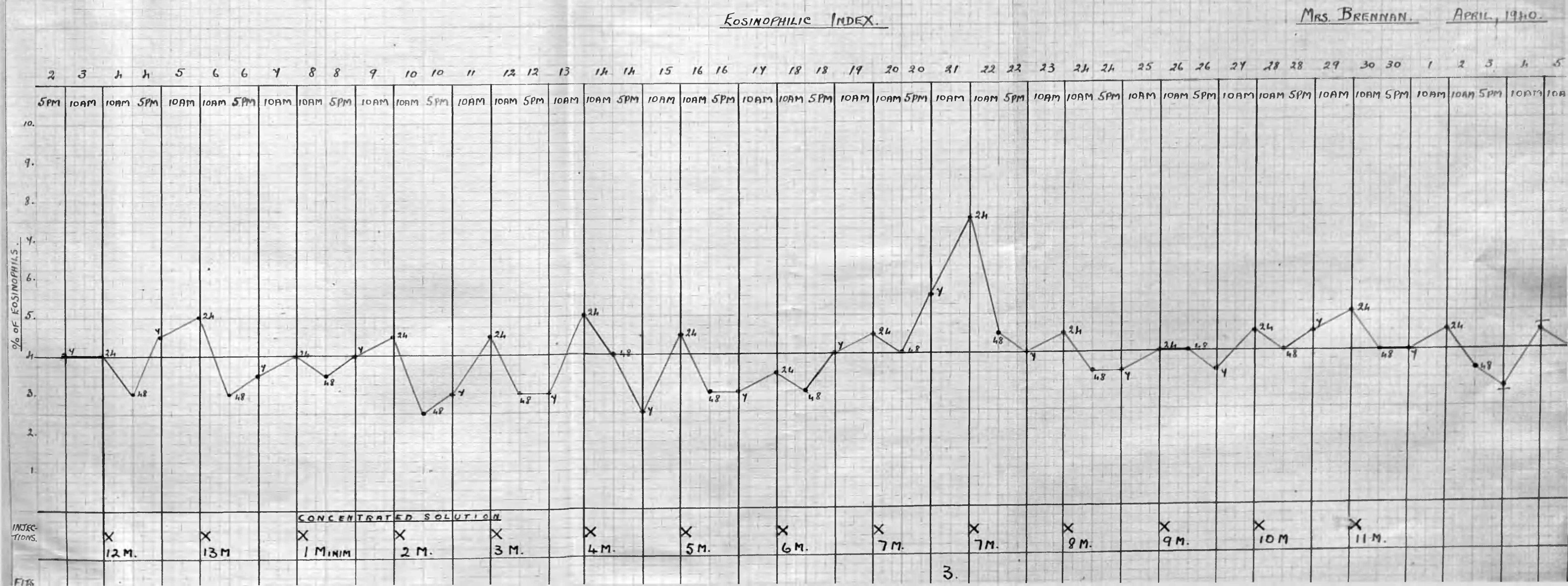
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MRS. BRENNAN.
APRIL, 1940.
% OF EOSINOPHILS.
INJECTIONS.
CONCENTRATED SOLUTION
12 M.
13 M
1 MINIM
2 M.
3 M.
4 M.
5 M.
6 M.
7 M.
7 M.
8 M.
9 M.
10 M
11 M.

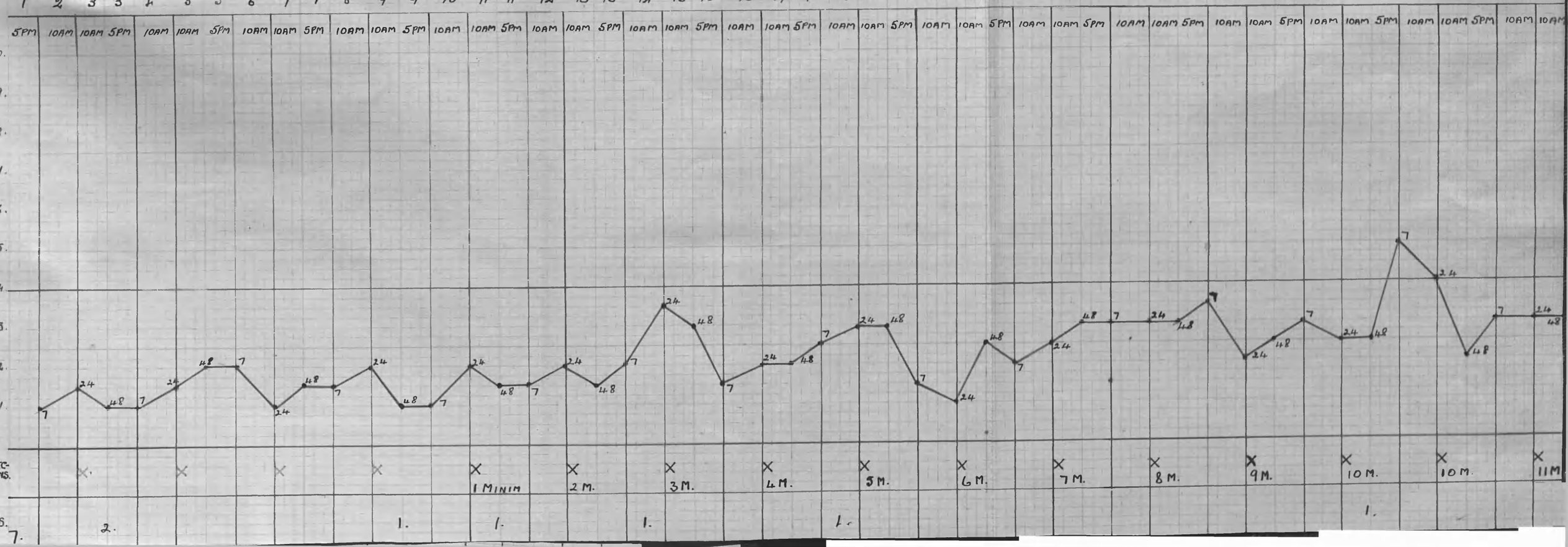
MEAN READING PRIOR TO TREATMENT = 1·4%

MEAN OF TWENTY FOUR HOUR READINGS = 3·1%

MEAN READING DURING TREATMENT = 2·8%

EOSINOPHILIC INDEX.

H. McALEESE. MARCH, 1940. CASE 10.



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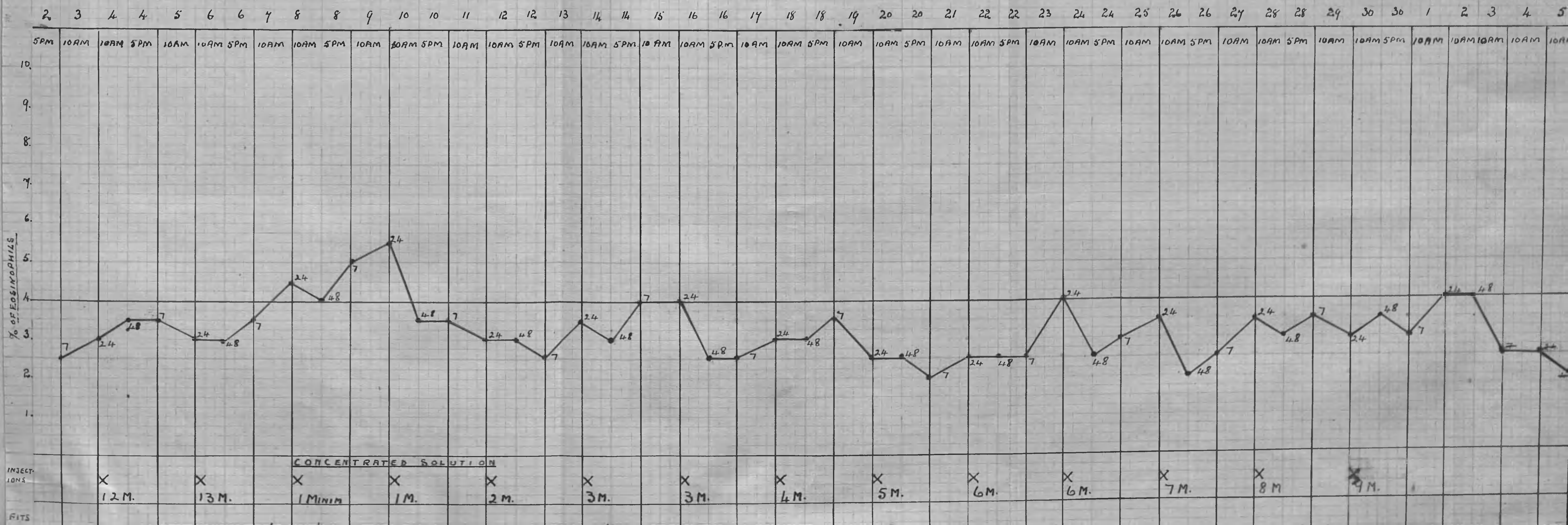

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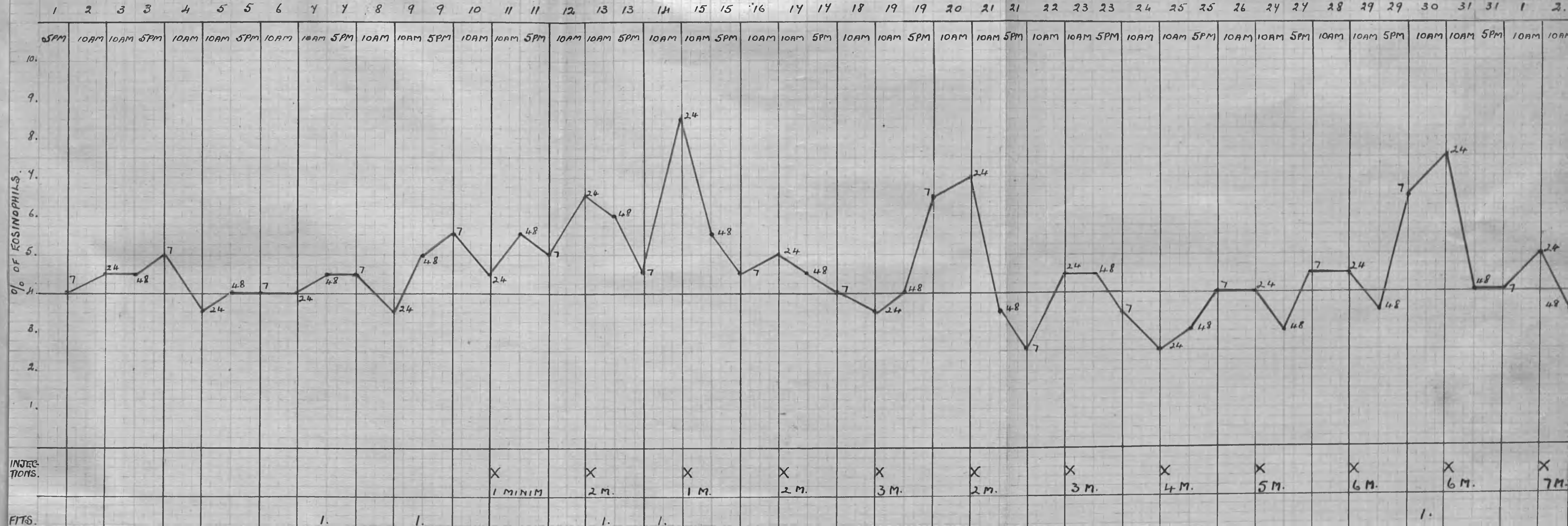

EOSINOPHILIC INDEX.

A. E. ELLIS. APRIL 1940.