EXAMINATION OF CERTAIN BIOCHEMICAL FACTORS IN IDIOPATHIC EPILEPSY

with special reference to the

BLOOD SUGAR LEVEL,

AND SUGGESTIONS ON THE POSSIBILITY OF TREATMENT BY SURGICAL INTERVENTION.

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1. THE SIGNIFICANCE OF URINARY "PROTEOSE."

2. BLOOD CALCIUM INVESTIGATION.

3. BLOOD SUGAR ESTIMATION.

INTRODUCTION.

There is probably no disease with a longer and more interesting history than Epilepsy.

The condition was well known to the ancients and the description of the disease given by Hippocrates is so complete that, in spite of the passage of over two thousand years, very little, if any improvement can be made upon it.

The condition is described in various parts of the Bible and accounts of Epileptic attacks are to be found throughout Roman literature.

Epilepsy is further remarkable in regards to the number of historical characters who are reputed to have been among its victims. Julius Caesar is stated to have suffered from epileptic seizures in infancy. St.Paul is supposed to have been subject to convulsions and Napoleon was at one time thought to have been an Epileptic, though of late it has been suggested that the attacks of unconsciousness and convulsions from which he suffered were due to cerebral anaemia arising from the marked bradycardia which he is known to have possessed.

The therapeutic measures recommended for the treatment of Epilepsy have been legion. In Roman times the freshly shed blood of gladiators was

considered a specific, but this and the host of more or less repulsive remedies used throughout mediaeval times had no influence on the condition, and it was not till Bromides were introduced in the middle of the eighteenth century by Duncan Gibbs, Sir Charles Locock, and Hughlings Jackson, that any real advance was made.

It was quickly realised that though Bromides controlled a certain large proportion of Epileptics the drug was far from being a specific. Toulouse[1] in 1904 pointed out that the Bromides could be made more effective by administration with a salt free diet and this was confirmed by Laudenheimer,[2] von Weiss and others.

It is only within the last two decades that the value of the barbitone derivatives in the controlling of epileptic fits has been realised, and luminal (Phenobarbital) has been shown to be the most effective. Even with this drug, however, Epilepsy remains a vast problem in general practice and is responsible for a high proportion of admittances to Mental Hospitals.

In view of these facts it was decided to carry out certain investigations on the Epileptic patients confined in the Gloucestershire County Mental Hospitals.

In the two hospitals there were a little over a hundred Epileptic patients, voluntary and certified.

The mentality of these showed variations from almost normal in the voluntary patients to all but complete dementia in certain of the certified who had been subject to fits for many years. All were subject to Grand Mal convulsions.

The investigations carried out were of three types:-

1. To discover the significance, if any, of Urinary Proteose in Epilepsy, and to find whether desensitization towards this substance would give clinical improvement in the condition.

2. To investigate the Blood Calcium level to discover whether Epileptic convulsions could be related to Spasmophilia and parathyroid Tetany.

3. To estimate Blood Sugar values and find whether Epilepsy was in any way associated with Hyperinsulinism.

The results obtained are shown in the three parts of the paper following.

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1. THE SIGNIFICANCE OF URINARY "PROTEOSE."

1. THE SIGNIFICANCE OF URINARY "PROTEOSE".

The most widely accepted hypothesis of the causation of epileptic fits is that which postulates the presence of some convulsant toxin in the circulating blood. Much experimental work has been done to demonstrate the plausibility of this, and fits closely resembling, if not identical with, those found in clinical epilepsy have been produced by the administration of various toxic substances. Magnan,[1] one of the earliest workers in this line of approach, produced fits, both in human beings and in dogs, by oral administration and intravenous injections of absinthe, while Rhoeber[2] and others produced similar results with picrotoxin. Purkinje succeeded in obtaining epileptiform fits in himself by taking appropriate doses of camphor, and Muskens[3] and others have carried out extensive experiments on the fits produced by camphor monobromide.

The conclusion reached by all the observers was that the fit was a direct response to the presence of the particular poison in the circulating blood. It was a normal physiological response, the result being to "discharge" the animal for the time being - probably by breaking down the toxic material to some innocuous substance. Thus Wiedemann[4] found that when recovery took place from the epileptiform fits produced by

camphor, all the camphor was excreted in the harmless form of uramido-camphoglycuronic acid and camphoglycuronic acid, and he considered that the fits themselves had caused this breakdown.

All this work, though of considerable value from the point of view of pure science, in the demonstration of the exact nature of myoclonic reflexes, threw no light on the actual causation of true epilepsy.

Periodically observers (particularly Pagniez, Mouzon, and Turpin[7]) have reported that they have withdrawn the blood from epileptics during fits and have injected this into normal people, producing in them convulsions. This seems to support the hypothesis of a circulating convulsant, but Goodall[5] and others, working at the Cardiff City Mental Hospital, report that they have been unable to demonstrate the toxicity of either the blood or cerebro-spinal fluid in epilepsy or in psychotic conditions. On the other hand, Loewe[6] has stated that he has been able to extract from the urine of epileptics an insoluble adialysate which, when injected intravenously, was capable of producing convulsions identical with those of epilepsy, though an adialysate similarly prepared from the urine of normal people proved non-toxic.

To explain the periodicity of epileptic fits and the production of an endogenous convulsant poison various views have been brought forward, and many

observers consider that the disease should be grouped with migraine and asthma as an allergic manifestation. In 1924 Collier[8] suggested that epilepsy was probably a metabolic dyscrasia, and cited reports of good results obtained by removing the blood from epileptics and attempting to desensitize the patients to their own serum - presumably on the assumption that it contained some fit-producing material (see above). On the other hand Worster-Drought[9] reported that, working on the idea of the supposed relationship between epilepsy and asthma, he had carried out a series of cutaneous reactions for protein sensitization with common food extracts on forty cases of idiopathic epilepsy, and had failed to obtain a single positive reaction.

INVESTIGATION.

In view of these conflicting results it was decided to carry out certain tests on the epileptics in this hospital.

Favourable results having been reported in the district on the treatment of cases of asthma and migraine by injection of "urinary proteose" as recommended by Oriel and Barber,[10, 11] it was decided as a preliminary to examine the urine of epileptics for the presence of these substances. Sixty-eight unselected cases were taken and all treatment temporarily stopped. The urine was tested, and in forty-eight cases (71 per cent.) "proteose" was found to be present; in 47 per

cent. of these it was found to be present in considerable amounts. It was decided that no useful purpose would be served at this stage in attempting to estimate the amount quantitatively. Urine specimens were next taken and actual specimens of the "proteose" extracted by the method recommended by Oriel.[12] The so-called "proteose" we found to be a greyish-white powder, insoluble in water or ethyl alcohol, but readily soluble in ether. Fresh specimens, it was found, dissolved rapidly in decinormal sodium hydroxide, though specimens that had been kept for two or three days dissolved less easily, probably indicating that they had undergone some chemical or physical change. Solutions were made in decinormal sodium hydroxide and subjected to various chemical tests. Consistently negative results were obtained with Millon's test, the biuret and xanthoproteic reactions, to which positive results were reported in all cases by Barber and Oriel in the urinary "proteose" of asthmatics.[11]

Ten epileptics were next taken and, all treatment having been stopped, urine specimens were collected and extracted, the resulting "proteose" being made up into sterile solutions at dilutions of 1 in 10, 1 in 100, and 1 in 1,000. Into the anterior aspect of the forearm of each case 0.1 c.cm. of a 1 in 1,000 solution of the patient's own "proteose" was injected

intradermally; while into the other arm a corresponding volume of similarly diluted caustic soda was injected as a control. The arms were examined every ten minutes for an hour, and then at half-hourly intervals for four hours. In all cases a slight area of erythema rapidly developed round the site of inoculation, but in no case was any characteristic wheal produced indicating hypersensitivity towards the injected material, and in no case was the erythema more marked in the "proteose" injected arm than in the control arm. The only interesting fact that emerged was that one of the injected patients developed a severe urticarial rash the next day, which, it was considered at the time, might be due to a sensitivity towards the injected "proteose."

A week later the same ten cases were taken and again injected, this time with a different "proteose." Five were injected intradermally with 0.1 c.cm. of a 1 in 1,000 solution of a "proteose" obtained from another epileptic, two were injected with a similar volume of a "proteose" obtained from the urine of an asthmatic, and three with a "proteose" from a case of migraine, the last solutions being kindly supplied by Dr.E.N.Davey, the pathologist to the Gloucestershire Royal Infirmary. At the same time three normal healthy persons were injected with a similar amount of epileptic "proteose." Again no reaction was produced in any of those injected.

At the end of another week a further series of injections were given, using a 1 in 100 solutions, but with these again no reaction indicating sensitivity was produced.

Attempts at Desensitization.

The above results were considered to have proved that cases of epilepsy possess no skin sensitiveness to "proteoses" from their own urine, or from the urine of asthmatic or other related diseases, but it was considered that it might be feasible to suppose that the "proteose" in the urine might be a specific cerebral irritant, and might even be identical with the adialysate described by Loewe[6] or the toxin present in the blood mentioned by Pagniez and others.[7] Working on this hypothesis it was decided to attempt to desensitize certain patients to "proteose."

Ten cases were again taken. Seven of these were treated with their own "proteose," two with "proteose" from other epileptics, and one with "proteose" from an asthmatic. In all the cases subcutaneous injections were given at weekly intervals, starting with 0.1 c.cm. of a 1 in 100 solution, the dose being doubled every week till, finally, 3.2 c.cm. were given. The following results were obtained. The two cases injected with other epileptics' "proteose" were unchanged and the patient injected with asthmatic "proteose" was unchanged. Of the seven cases injected with their own "proteose" four showed absolutely no

change in the number or force of the fits, or in their general mentality. At the end of the course of injections one patient who regularly had fits nearly every week went for three weeks with no fits, and for the time being showed an improvement in mental outlook. She has since relapsed, and has become worse than before. One patient who was previously having strong major fits, almost daily, has since had mostly minor fits, though the frequency has been unchanged and the typical epileptic mentality persists. The last patient, who always has a bout of four or five fits once a month followed by a week of marked mental confusion, went for two months with no fits, and although the fits have now returned, she is mentally almost normal and her fits are not followed by the semi-stuperose state.

DISCUSSION.

These results, though taken from far too small a number of cases to be conclusive, point to the fact that the "proteose" of the urine of epileptics is not of great fit-producing significance, and that it is unlikely to be the same substance as Loewe's adialysate.

Certain facts which we elicited, however, tend to point the other way, and might be looked upon as showing that the urinary "proteose" is of importance either as a convulsant toxin or is in some way related to the production of fits. Thus it was found in those

patients whose fits are controlled by luminal (phenyl barbitone) treatment, the "proteose" tends to vanish from the urine, but when the luminal is stopped and the fits return the "proteose" appears again in the urine. But in those cases where no benefit was derived from luminal administration it was found that the drug had no influence on the amount of "proteose" excreted. Another point of interest which came to light was that when an epileptic has a bout of fits, the urine is loaded with "proteose" at the commencement, but specimens withdrawn at intervals contain decreasing amounts, so that finally, at the end of the bout, when the fits stop, no "proteose" is discovered. This seems to fit in with the theory of Muskens and others that the fits "discharge" the subject by causing the body to destroy the circulating convulsant toxin, which, from the last observations, might well be the "proteose" or its precursor.

It is obvious from these contradictory results that no definite conclusion can be drawn, and it is yet to be proved or disproved that urinary "proteoses" are of significance in this type of case. It would probably be better, particularly as considerable doubt has of late been thrown on the specificity of "proteose" in other definitely allergic conditions,[13, 14] to await further reports from the Asthma Research Council before continuing work on these lines.

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2. BLOOD CALCIUM INVESTIGATION.

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In view of the recent suggestions, both in this country[1] and on the continent[2] that the convulsions of Epilepsy may be due to pathological variations in the Blood Calcium level, it was decided to investigate the Blood Calcium of a series of Epileptics in this hospital, and at the same time examine the evidence in recent literature that might throw light on the possibility of hypocalcaemia being an aeteological factor in this condition.

The close resemblance between the convulsions seen in spasmophilia and after parathyroidectomy in experimental animals, and that type of epileptic fits which Collier[3] and others have described as "myoclonic" is so obvious that it was natural that observations in the variations of Blood Calcium in Epilepsy should be made.

In favour of the hypothesis of a hypocalcaemic factor in fit causation was the known fact that bouts of fits are particularly common in females at the time of menstruation when it has been shown that there are marked variations in the Blood Calcium level (4, 5, 6,7). Pathological findings were also in favour of the Hypothesis for Schon and Susman[8] have reported abnormalities in the histological structure of the

parathyroids of epileptics, and areas of hypofunction associated with sclerosis have been noted by Schmiergeld.[9] From the experimental aspect support was also given to the hypothesis by the work of Brodski[10] who reported beneficial results in certain cases of Epilepsy from transplanting into them parathyroid gland tissue. While from the comparative aspect the work of Dryerre and Greig[11] in the convulsion of Milk Fever in Cattle, and Greig[12] in Lambing Sickness in Sheep, in both conditions in which a definite hypocalcaemia was demonstrated, naturally again suggested the possibility of a low Blood Calcium being of importance in the fits of Ideopathic Epilepsy. Though on the other hand the convulsions of Eclampsia[13] and in Beri-Beri[14] have been shown conclusively to be unassociated with a low concentration of Calcium in the Blood.

The largest series of Epileptics subjected to Calcium investigation were those reported by Lennox and Allen[15] who examined seventy-seven cases and found the Blood Calcium level to be normal, though the Calcium level in the Cerebro-Spinal Fluid was slightly low. Armstrong and Hood [16] reported normal blood figures, and normal figures in smaller numbers of cases have also been noted by Osanto, Killian, Garcia and Mattice,[17] Patterson,[18] Stewart and Percival[19] and Hepburn and Neibaum[20].

For the purpose of this investigation typical epileptic cases were taken and for the time being all medicinal and dietetic treatment was stopped. As certain observers have suggested that varying degrees of activity of the autonomic nervous system[21,22,23], and alterations in the Blood sugar level[24,25] have an influence on the Blood Calcium, all specimens were taken when the patients were under similar basic conditions, and the period chosen was that of fasting before breakfast. The Serum Calcium was estimated by the Pincussen and Schimmelpfing[26] modification of the method of Kramer and Tisdall, i.e. the serum calcium was precipitated by potassium oxalate, and allowed to stand for twenty-four hours instead of the thirty minutes originally recommended, the precipitate being then washed, dissolved in dilute sulphuric acid and titrated against standard Potassium Permanganate solution.

Fifty-four cases, - twenty-four female and thirty male - were examined. The values found were with the one exception noted below, within fairly definite limits though the variations were far greater than these noted by observers in normal subjects. Thus though the average value for the female cases was 10.6 mgs. Ca per 100 cc.serum the figures obtained varied between 9.6 and as high as 12.2. While the male average value of 10.5 mgs. per 100 cc. was

obtained from figures varying from 8.5 and 13.3 mgs. per 100 cc. Though the vast majority of the values certainly lay between 9.5 and 12.

The average figures found it will be noticed are slightly higher than these recorded in healthy subjects for, although Watehorn[27] gives 10. - 10.8 as the normal figures, most observers, using the method of Kramer and Tisdall give figures between 9.6 and 9.9. Di Foutsin [28] has, however, noticed that persons in bed for long periods tend to have a raised serum calcium, and it may be that the slightly high figure is due to this factor, for though the majority of the patients were not permanently in bed, they were all liable to long periods there, after a severe bout of fits.

As previously mentioned one case, a female, did not give values in the least normal. This patient was one of the few that gave definite warning of the onset of fits, the predromal symptom being that of twitching of all the muscles of the body. Blood withdrawn during this state showed a marked hypo-calcaemia, readings as low as 3.8 mgs. / 100 cc. being obtained on one occasion. When the twitching had stopped and the fit occurred the Blood Calcium was found to be normal. Attempts were made to collect specimens of blood from other patients immediately before and in the fits, but owing to the fact that the

moment of onset of the fit can never be known and that during the fit the convulsions make Venu-puncture impossible, only three specimens were obtained two of which gave normal readings and one the high figure of 13.1. Specimens of blood withdrawn from a case of Status Epilepticus in the twentieth fit, after the twenty-second fit and an hour after the fits had been stopped by injection of luminal, all gave normal readings. As one would expect from these figures an intravenous injection of 20 cc. of 10% Calcium Glucolate into one case during a short bout of fits gave no beneficial result. Similarly Klein and Forcrone[29] have reported that they obtained no benefit from Intravenous injection of Calcium Chloride.

As mentioned above it has been stated that alterations in Blood sugar level influence the Blood Calcium figure.[24,25]. So as blood sugar investigations were being undertaken in the hospital it was decided to withdraw Blood specimens at the same time for Calcium estimation. A fasting specimen was first withdrawn and then 50.gms. glucose given and further specimens withdrawn at half-hourly intervals. Twenty-eight cases were investigated in this manner. No regular curve was obtained corresponding to the rise and subsequent fall of the blood sugar, and although the calcium readings were not constant in individual cases, the values found were all within the limits of

normal physiological variation and experimental error.

In combination with other observations it was decided to examine the influence of variations on the tension of Autonomic Nervous System in the number of fits and the Blood Calcium levels.

In five Epileptics the parasympathetic nerves were paralysed by giving $\frac{1}{100}$ grain Atropina three times a day for a month. In all cases dilatation of the pupil occurred and towards the end of the month, when the patient was fully under the influence of the drug, blood specimens were withdrawn. No alteration in the number of fits occurred and no appreciable change in the blood calcium resulted. These results are in accordance with the finding of Lietes[21] who reports that division of the Vagi though giving a temporary fall in the Calcium level has no lasting effect.

A further series of five Epileptics were subjected to stimulation of the parasympathetic nerves by $\frac{1}{40}$ grain of Physostigmine Salicylate three times a day. In these cases also no improvement was noticed in the number of fits and blood analysis showed no alteration in the Calcium content.

In the last group of five the Sympathetic side was stimulated by giving $\frac{1}{2}$ grain Ephedrine hydrochloride three times daily. Again no improvement was

found in the number of fits, and the Blood Calcium remained approximately the same. This last finding was in accordance with these noted by Lamelas[30] who reports that section of Splanchnics and injection of adrenalin have no influence on the Blood Calcium of cats, but they do not correspond with the findings of Hetényi and von Gaal[23] who report a fall with stimulation of the sympathetic, or of Richter[22] who reports a rise.

C O N C L U S I O N S .

The Calcium content of the blood in Epilepsy is normal and thus the condition can not be related to the convulsions of Spasmophilia or Milk Fever. The Blood Calcium value is independent of the Blood Sugar level and neither the number of fits nor the Blood Calcium is influenced by alterations in the tension of the Autonomic Nervous System.

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3. BLOOD SUGAR ESTIMATION.

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In the whole realm of medicine there are few more easily recognisable clinical symptoms than those which have been grouped together under the generic term of Idiopathic Epilepsy and consequently it is not surprising that this condition was one of the first to give rise to scientific clinical investigation. As early as 1822 Marshall Hall[1] published a report of his investigation of experimental convulsions in animals, and Russmaul and Tenner[2] only a few years later gave accounts of similar experimental work.

Various unsuccessful attempts were made in the later part of the nineteenth century to localise a definite centre in the brain as responsible for epilepsy, while at the same time much work was done on the experimental fits produced by such drugs as Absinthe,[3,4] Carbolic acid,[5] and Camphor.[6,7].

Hughlings Jackson[8] considered Epileptic Fits to be due to localised instability of the Cerebral grey matter and thought that this instability might be due to abnormal nutrition of the affected part. Russell[9] held that all Epileptic fits were due to localised Cerebral Anaemia, and Shaw[10] working from an entirely different aspect came to the same conclusion. Similar views have been reported by Hodskins et-Al.[11] and

Tracey[12] who considered that the Anaemia was due to faulty vaso-motor control. Kennedy[13] from the surgical aspect supports this view and states that when a fit occurs during intra-cranial operations definite blanching of the exposed brain tissue can be observed. The fact that beneficial therapeutic results have been reported in Epilepsy by treatment with Caffein[14, 15, 16], and Luminal, might be said to give further to support this view, for both these drugs are stated to dilate the cerebral blood vessels and thus give an increased circulation to the brain.[17]

Many observers consider that Epilepsy may be due to an upset in the Endocrine balance, and the fact that fits are liable to start in infancy, in adolescence and at the menopause, is in favour of this view, for at these periods of life there is often a definite derangement in the Endocrine balance. A similar state of affairs exists in pregnancy as shown by Turnbull[18] and others, and may account for the sudden onset or equally sudden cessation of fits described by Collier[19] as occurring sometimes in pregnant women; similarly the milder Endocrine disharmony which occurs at the onset of menstruation may account for the excessive number of fits described by Turner,[20] as appearing at this period. There is no Endocrine which has not been implicated as being responsible for Epilepsy. Pituitary lesions have been reported by many observers, thus Zabriskie[21] reports acromegalic

tendencies in Epileptics, and Barros[22] states that Epilepsy is the most common mental symptom in this condition. Schon and Susman[23] and Vizioli[24] have reported that the pituitary gland of Epileptics is hypertrophied. On the other hand Tucker[25] reported hypopituitrism in 31 per cent. of the Epileptics he examined, and obtained improvement in their condition by feeding with extract of the whole gland. Cushing[26] described Epileptiform symptoms in undoubted cases of deficient pituitary secretion. Various observers have reported macroscopic and microscopic abnormalities in the parathyroid.[23,27]. The Adrenals have been stated to be abnormal; the Pancreas has been described as hypertrophied[28] and within the last five years Liver deficiency has been demonstrated by Widal[29,30] and Worster-Drought,[31] using the haemoclastic function test, and by Gosden and Fox[32] by the laevulose tolerance test, while Patterson and Weingrow[33] state that they found the general average of Liver weights to be below the accepted normal minimum. Thyroid lesions have been described, though Notkin[34] reported normal basal metabolic rates in Epileptics and Lennox and Wright[35] failed to find any gross abnormality in either direction in the basis metabolism of 130 cases they examined. Normal figures were also reported in 50 cases by Davis.[36] Twenty-four cases whose Basal Metabolic Rates were calculated here by Reid's formula[37] gave values within the normal limits.

Abnormalities in the Autonomic nervous system have from time to time been suggested as important aetiological factors in Epilepsy and this view has recently been revived by Tracey[38] and Loewy.[39] Attempts to stop the fits by removal of cervical sympathetic ganglia were made some years ago by Alexander in Edinburgh[40] and Jacobet in America[41] but both of these failed to obtain any beneficial results from their operations. More recently Santenoise et-Al.[42] have suggested that the condition of Epilepsy is associated with excessive vagotonia and support is given to this view by the good therapeutic results obtained by Damaye[43] by the administration of atropine.

Epileptiform fits are liable to occur in a number of varied conditions. They are seen in localised cerebral irritations in General Paralysis of the Insane in general toxaemias such as acute fevers, in diabetes, or uraemia, and when the blood supply of the brain is deficient as in Stokes-Adam's syndrome or advanced myocarditis or when potassium iodide solution is injected into the carotid arteries for radiographical purposes.[44] They may also be produced artificially by pressure on the carotids or slowing the heart artificially by vagal stimulation. The fits observed by Marshall Hall[45] and others after severe haemorrhage in warm-blooded animals were probably due

to the same cause, and also since Collier[19] states that fits can not be due to tissue irritation it is reasonable to suppose that the fits observed in over 30 per cent. of cases of cerebral tumours[46] are due to the increased intracranial pressure interfering with the circulation of the brain, and further in view of Sargent's[47] statement that traumatic Epilepsy is due to adhesions, it is more than likely that the convulsions in this condition are due to a local anaemia of the cerebral tissue.

The effect of an anaemia of the brain is to deprive the nerve cells both of oxygen and of nutriment in the form of glucose. Anoxaemia alone does not give rise to convulsions as has been shown by the work of Barcroft and Haldane, and the convulsions observed in asphyxia are only grossly exaggerated respiratory movements due to the rise of carbon dioxide pressure in the blood. The factor then which is responsible for the irritation of the brain in cerebral anaemia is probably the absence of blood glucose. That lack of a sufficient glucose supply to the brain can give rise by itself to Epileptiform symptoms is known from the work of Banting, Campbell, and Fletcher,[48] and many others[49,50,51] who all report symptoms indistinguishable from Petit and Grand Mal by hypoglycaemia from injections of Insulin.

In view of these last facts it was decided to

investigate the blood sugar value of series of Epileptics to find whether hypoglycaemia could not be the causative factor in Idiopathic Epilepsy. It seemed peculiar that although abnormalities in both directions of activity are known to exist in the Thyroid and Pituitary glands only hypo-function of the Islets of Langerhans has been described. From theoretical considerations a hyper-activity of the Islet tissue should produce identical symptoms as are seen in injections of Insulin into a healthy subject. As shown above the results produced can be indistinguishable from Idiopathic Epilepsy, the nervous instability, "Epileptic" cry, and the complete lack of memory of the fit on recovering, all being present. Further, John[52] has stated that hyper-insulinism gives rise to great hunger, one of the most marked characteristics in chronic Epileptics.

For the purpose of investigations all the Epileptics in the hospital were taken, irrespective of the number, severity, or duration of their fits. Attempts were made to collect specimens of blood immediately before the fit, in the fit, and directly after, but this was found to be impossible as none of the cases under examination had sufficiently long predromal symptoms and during fits the convulsions were too violent to permit withdrawal of blood. Specimens could have been obtained after the fit but these were

considered unnecessary as Olmstead and Logan[53] and others have shown that any convulsions raised the blood sugar, and Kersten[54,55] has shown that this occurs in Epilepsy, the mechanism being a stimulation of the Supra-renals by the muscular excitement with consequent outpouring of Adrenalin and mobilization of Liver glycogen.[56]

The first series of examinations consisted in estimating the fasting blood sugar levels of those Epileptics in the hospital who were under no medical or dietetic treatment and were still liable to fits. The blood specimens were withdrawn by venu-puncture and their glucose estimated by the method of E. G. B. Calvert.[57] The blood analysis was started as soon as possible after withdrawal to prevent there being loss of sugar from glycolysis, and throughout the investigations standard glucose solutions were estimated and normal blood specimens examined to exclude any experimental error.

The complete results obtained by 124 examinations on 80 patients are shown in Table 1.

TABLE I. /

TABLE I.

FASTING BLOOD SUGARS IN mg.% IN UNTREATED EPILEPTICS.

1.	99	34.	86	67.	78
2.	74	35.	84	68.	97
3.	104	36.	109	69.	106
4.	93	37.	85	70.	72
5.	86	38.	81	71.	78
6.	89	39.	90	72.	108
7.	73	40.	57	73.	103
8.	94	41.	86	74.	84
9.	91	42.	92	75.	80
10.	77	43.	98	76.	93
11.	78	44.	82	77.	79
12.	94	45.	91	78.	93
13.	67	46.	86	79.	74
14.	100	47.	68	80.	81
15.	79	48.	87		
16.	92	49.	84		
17.	73	50.	90		
18.	89	51.	83		
19.	102	52.	86		
20.	73	53.	72		
21.	82	54.	81		
22.	94	55.	81		
23.	82	56.	60		
24.	63	57.	81		
25.	77	58.	99		
26.	83	59.	68		
27.	90	60.	60		
28.	103	61.	76		
29.	105	62.	101		
30.	80	63.	87		
31.	87	64.	104		
32.	66	65.	79		
33.	91	66.	80		

The average fasting sugar value from these results is 84.9 mg. per cent. Different observers report varying values for the fasting blood sugar in healthy subjects, thus Beaumont and Dodds[58] give 100 mg. per cent. for the normal value. Wright[59] gives 80 to 100 mg. per cent. and others regard any figure lying between 80 and 120 mg. per cent. as being within the normal limits. In view of the low average value of 84.9 mg. per cent. obtained here and the fact that no less than 64 per cent. of the figures lie below 90 mg.%, and 26 per cent below 80 mg.%, and that no figure is over 110 mg.%, we are undoubtedly justified in stating that a degree of hypoglycaemia occurs in Epileptics, for Seale Harris [60] in the 1867 normal persons he examined only found fasting sugar below 79 mg.% in 4 per cent. of the cases.

The isolation of Insulin and its use in the treatment of Diabetes rapidly brought to light the fact that an over-dosage could give rise to a dangerous condition of hyperglycaemia in which Epileptiform fits were liable to occur. J.W.Mackay[61] was the first to suggest that these fits might be related in any way to clinical Epilepsy. At the present time a considerable number of reports on blood sugar values in Epilepsy exist. The larger number of cases published are those of Lennox, of O'Connor and Bellinger[62] who examined the fasting blood sugars of a series of 267 Epileptics. Their figures show an average value of

90 mg.% compared with 100 mg.% found by them at the same time in healthy subjects. The true value should probably be below this figure for unfortunately a certain proportion of their cases - they give no idea what proportion - were under treatment with Luminal (Phenobarbital); and Stein Steinnetzer and Swaboda[63] and Jacoby[64] have shown that any hypnotic raises the blood sugar, and Bang,[65] Underhill and Sprunt,[66] and S.Weiss[67] have demonstrated that this is particularly true of the barbitone group to which Luminal belongs. In a series of 140 blood sugar curves in Epileptics, Lennox and Bellinger[68] obtained a similar series of fasting blood sugar values, but it must be noted that 66 per cent. of the figures lay below 100 mg.%, and 34 per cent. below 90 mg.%. Unfortunately these figures are also useless for purposes of comparison as an unstated proportion of the cases were under treatment with Luminal.

In 1931 Mackay and Barbash[69] published a report of the blood sugar estimations in 66 Epileptics. The average fasting value in their cases was 81 mg.% (Folin and Wu[90]), only one case of the series having a fasting blood sugar over 100 mg.%. Gosden and Fox[32] in 17 cases found an average value of 82 mg.% (Folin and Wu). Wlandyczko[70] reported definite hypoglycaemia in 18 cases and obtained clinical improvements with a high carbohydrate diet. Shaw and Moriarty[71] obtained remarkably low figures in the blood sugar of

fasting Epileptic children and Patterson and Levi[72] report low sugar content in the cerebro spinal fluid. Goodall in the Maudsley lecture 1927[73] stated that Epileptic Fits could definitely not be due to hypo-glycaemia and gave as authority for this statement the work of Daly et-Al[74] who only examined four cases and then obtained low figures; of Drury and Farran-Ridge[75] who state that they found normal fasting sugars in 15 Epileptics but do not publish the figures they obtain, and Holmstrom[76] who reported that blood sugar values of 20 Epileptics examined were normal, but in view of the fact that a quarter of an hour before withdrawing the blood specimens he injected Adrenalin, it is not surprising that he obtained higher figures than other observers.

Examinations of the results which are of any value quoted above show that the fasting blood sugar of an Epileptic is generally a little over 80 mg.%, whatever method of analysis is employed. That is just within the lower limit of normality. It is a known fact that though the fasting blood sugar of a healthy subject is fairly constant it is liable to periodic minor variations upwards and downwards throughout the day.

Kersten,[77] Holmstrom,[76] and Vollmer[78] have demonstrated that this fluctuation is very well marked in Epileptic patients and they have also shown that

the fits occur at the lowest point in the sugar curve. Macleod[79] states that hypoglycaemic symptoms are liable to occur in human beings when the blood sugar lies between 80 to 70 mg.%, and Wright[59] reports that the fits may develop anywhere between the sugar values of 75 and 32 mg.%, depending on the individual. It can easily be seen that if the fasting level of an Epileptic is in the level of 80 or a little more he has a very small factor of safety for fluctuation, and consequently any relatively minor drop in the sugar level which would pass completely unnoticed in a normal individual would, in an Epileptic, give rise to symptoms of hypoglycaemia with a possibility of Petit Mal or Grand Mal convulsions. The result of these convulsions would be to stimulate the sympathetic and so cause a rise in blood sugar by calling on Liver glycogen, the convulsion being as Muskens[51] has said, a protective reflex. It is reasonable to suppose that some times a fit may occur when no glycogen is present in the Liver. If this were to occur recovery could not take place and one fit would run on into another, the condition of Status Epilepticus being produced.[51 & 56] In favour of this view we have the statement of Muskens[51] and Turner[20] that Status Epilepticus never occurs in a well nourished animal, and further the fatty degeneration of the Heart which has been reported from postmortem examinations on patients who have died in Status Epilepticus by Mott[80] and more recently

by Collier, and considered to be indicative of a severe toxaemia, might equally well be due to acute cardiac malnutrition due to hypoglycaemia coupled with the excessive work for the Heart owing to the labour of the prolonged convulsions.

Having shown that the degree of hypoglycaemia does exist in Epilepsy, further investigations were made in an attempt to discover the cause.

Glucose tolerance tests were carried out on patients who were still subject to fits and were under no medical treatment. A fasting specimen of blood was withdrawn by venu-puncture, 50 grs. of glucose administered, and further blood specimens taken at half-hourly intervals, the blood specimens being estimated as above by Calvert's method.[57] The curves obtained are shown in Table 2.

TABLE 2.

BLOOD SUGAR CURVES IN UNTREATED EPILEPTICS.

1.	89	137	119	99	86	
2.	96	90	80	79	79	
3.	66	103	87	-	-	
4.	79	116	84	73	72	
5.	80	142	65	78	59	
6.	68	92	122	59	67	
7.	82	113	88	71	90	
8.	81	115	89*	90	111	* Fit at this point.
9.	81	130	91	-	89	
10.	82	115	126	113	101	
11.	93	94	81	82		
12.	57	123	171	134		
13.	81	151	181	-		
14.	97	119	93	-		
15.	89	154	145	116		
16.	102	168	140	126		
17.	101	104	-	118		

TABLE 2. (Continued.)

18.	91	88	104	101	
19.	88	130	101	103	
20.	109	143	146	138	
21.	73	146	150	137	
22.	105	137	140	120	
23.	109	180	185	159	
24.	87	133	134	118	
25.	99	133	140	118	
26.	91	125	114	90	
27.	101	121	132	112	
28.	118	150	128	101	(Excited)
29.	89	115	102	72	
30.	57	97	96	90	
31.	64	129	-	86	
32.	79	96	82	80	
33.	80	93	83	-	
34.	97	117	123	98	
35.	84	114	115	109	
36.	87	119	128	101	
37.	90	97	93	94	
38.	82	93	108	77	
39.	84	118	114	92	
40.	93	123	123	128	
41.	90	91	88	92	
42.	92	102	70	63	
43.	83	116	104	81	
44.	109	114	96	101	
45.	91	97	105	109	
46.	98	112	115	95	
47.	106	169	124	108	
48.	93	140	98	90	
49.	93	146	142	88	
50.	99	169	132	90	
51.	103	128	107	92	
52.	104	186	146	119	
53.	108	115	104	101	
54.	78	103	102	80	
55.	100	135	105	101	
56.	87	150	106	82	
57.	105	137	118	99	
58.	83	106	98	95	
59.	67	131	127	192	
60.	89	132	99	81	
61.	79	120	96	96	
62.	74	82	99	-	
63.	72	72	80	89	
64.	78	110	93	63	
65.	80	146	111	71	
66.	86	137	91 *	67	* Fit mid-way between these two.

A previous series of glucose tolerance curves from 66 Epileptics have been reported by Mackay and Barbash,[69] and they have suggested the curves obtained should be classified under the following headings:-

I. Hyperglycaemia group in which the maximum sugar content in the curve exceeds 180 mg.%.

II. Normal group when the maximum blood sugar content lies between 150 and 180 mg.%.

III. Sub-normal group where the maximum sugar content is between 125 and 150 mg.%.

IV. Markedly sub-normal where the maximum sugar lies below 125 mg.%.

This classification is not really satisfactory for the shape of the curve is as important with regards to its normality as is the peak level; further the normal peak value is generally between 120 and 140 mg.%, and not over 150 as in this classification, though Trumper and Cantarow[99] state that 140 to 160 are general figures. Nevertheless for the sake of uniformity Mackay and Barbash's classification will be retained in this paper. Examination of the curves in Table 2 shows that 32, i.e. 48.5 per cent., fall in group IV; 25, i.e. 38 per cent. fall in group III; 9 per cent. fall in group II; and only 4.5 per cent. fall in group I. Mackay and Barbash have published a report on the glucose tolerance curves in 66 Epiletics but a private communication with Mackay shows that at least 6 of these were under Phenobarbital treatment.

The remaining 60 show only 8% in group I, 20% in group II, 22% in group III, and 50% in the markedly sub-normal group IV. As the complete curves obtained by Mackay and Barbash have never been published, those that are still available, which are unfortunately only those from male patients, are shown here in Table 3 by permission of Dr S.W.Mackay. The 140 curves obtained by Lennox and Bellenger are, as mentioned above, useless for purposes of comparison as an unspecified proportion were having Barbitones administered; in spite of this 26% of their curves are in group IV.

TABLE 3. /

TABLE 3.

GLUCOSE TOLERANCE CURVES IN EPILEPTICS

OBTAINED by G.W.J.MACKAY and H.BARBASH.

First Examination.						Second Examination.					
Case						Case					
1.	83	136	107	79	51	1.	88	115	160	93	79
2.	88	-	-	-	-	2.	-	-	-	-	-
3.	93	125	63	54	68	3.	79	107	100	88	75
4.	79	107	107	88	83	4.	-	-	-	-	-
5.	88	93	88	79	65	5.	75	93	62	68	71
6.	88	125	100	75	60	6.	-	-	-	-	-
7.	75	115	88	83	75	7.	-	-	-	-	-
8.	93	115	125	75	79	8.	83	125	88	83	79
9.	100	166	187	150	107	9.	100	166	187	150	107
10.	93	187	170	67	78	10.	-	-	-	-	-
11.	100	115	79	68	71	11.	78	107	75	55	68
12.	88	136	65	85	68	12.	88	136	65	85	68
13.	88	105	94	88	-	13.	100	125	107	83	107
14.	75	93	62	68	71	14.	-	-	- -	-	-
15.	79	115	125	96	93	15.	75	100	115	96	-
16.	83	100	107	88	93	16.	79	100	93	88	83
17.	107	125	100	83	93	17.	93	125	115	197	88
18.	83	150	88	63	57	18	79	125	71	88	75
19.	93	136	142	88	79	19.	70	88	100	83	-
20.	75	93	88	65	71	20.	-	-	-	-	-
21.	83	93	100	88	57	21.	-	--	-	-	-
22.	83	150	100	75	75	22.	-	-	-	-	-
23.	83	125	125	88	60	23.	79	125	100	83	68
24.	88	136	88	63	60	24.	-	-	-	-	-
25.	86	138	93	79	-	25.	-	-	-	-	-
26.	88	160	125	115	100	26.	-	-	-	-	-
27.	88	79	83	125	62	27.	-	-	-	-	-
28.	88	160	138	138	60	28.	-	-	-	-	-
29.	85	187	166	160	100	29.	-	-	-	-	-
30.	88	103	93	96	83	30.	-	-	-	-	-
31.	93	166	160	136	100	31.	83	115	107	75	71
32.	100	187	187	150	103	32.	-	-	-	-	-
33.	75	75	107	136	115	33.	-	-	-	-	-
34.	85	125	138	160	93	34.	75	136	83	60	55
35.	73	166	75	75	60	35.	75	125	93	88	60

The fact that such low peak values are found in the sugar curves of Epileptics, as indicated by the high proportion falling in Mackay and Barbash's group IV and III, coupled with the low fasting values, indicates a definite hypoglycaemia to be present in Epilepsy. Indirect evidence is given to this by Raimann[81] who noted increased sugar tolerance in this condition.

Hypoglycaemia occurs as a result of various endocrene disharmonies,[82,83] particularly hypopituitrism, in hypothyroidism, in suprarenal insufficiency, in hyperinsulinism, and in Liver deficiency.[84] Cammidge[83] states that it occurs in nervous conditions but it is reasonable to suppose that any nervous symptoms might be secondary to the low sugar rather than primary, for Greisheimer[85] found that in decerebrate dogs the nervous irritability was inversely proportional to the blood sugar level, and Hoxie and Lisherness[86] in a series of routine blood sugar examinations noted nervous and mental abnormalities in those persons that gave low sugar value. Further cases of mental symptoms and convulsions associated with low blood sugar have been described by Ramsbotham and Eastwood,[87] Guy-Laroche et-Al.[88] Moore, O'Farrell et-Al.[89] and many others.

From the examination of the shape of blood sugar curves it is impossible to state the cause of

the hypoglycaemia. The various reports on Basal Metabolic Rates[34,35,36] and our own finding excludes hypothyroidism. None of the classical symptoms of hypopituitism were shown by the patients under examination though Tucker[25] states that he found this function of this gland in a high proportion of his cases. Any abnormality of Adrenal function could not have been present in the cases in Tables 1 and 2 as the blood pressure and the Heart rate were within the normal limits. Private inquiry shows that the cases of Mackay and Barbash were similarly normal in this respect. Liver deficiency though stated to be present to some degree in Epilepsy[20,30,31,32,38] could not have been marked enough to give rise to such low sugar values without showing some other sign of impaired function. Further the sugar curves in Liver deficiency would be of a more peaked type. Hyperinsulinism with symptoms undistinguishable clinically from Epilepsy has been described in a number of cases recently in America. Howland et-Al.[91] described a case which was found to be due to carcinoma of the Islets, and similar cases have been described by Wilder et-Al[92]. Carr, et-Al.[93] described a case of Adenoma of the Islets, and McClenahan and Morris and Allan et-Al.[94] review a number of similar cases whose fits and the mental symptoms improved as a result of the rise in blood sugar produced by removing the neoplastic pancreatic tissue. Hypoglycaemia, where no

neoplasm was present and simple hypertrophy was suggested as a cause, was present in the case described by Finney and Finney.[96] A vast number of other cases of hyperinsulinism and dysinsulinism have been collected by Harris.[97]

In view of these reports and the absence of other localising signs hyperinsulinism is most probably the cause of Epileptic hypoglycaemia. Support is given to this statement by the fact that the blood sugar figure obtained in the last specimen in the glucose tolerance test, as can be seen in Tables 2 and 3, is considerably below the fasting value which Depisch and Nasonchre[98] state is an indication of Islet activity. Further support is given to this statement by the increased number of fits noticed in Epileptics at the menstrual period[20 &c.] at which time Vogt,[100] and Rothery and Rudolf[101] have shown that women are particularly sensitive to Insulin, due to the high folliculin content of the blood which activates the Insulin present.[102]

The therapeutic facts are also in favour of this statement. The Barbitones which are indisputably the most efficacious drugs in Epilepsy, it has been shown, raise the blood sugar.[65,66,67.] Further, Jackson[103] has shown that Sodium Barbital prevents two-thirds of the experimental fits obtained by Insulin injection, which is approximately the proportion of Epileptics which benefit from Luminal.

Chloral which Zabraskie[21] and others recommend in Epilepsy similarly raises the blood sugar.[104, 105]

Caffein, which has been described as relieving Epilepsy[14,15,16] has also been shown by Popper and Jahoda[106] to prevent the convulsions of Insulin intoxication.

TABLE 4.

	Gloucester curves.	Mackay & Barbash.	Lennox & Bellinger.
	%	%	%
Group I.	4.5	8	(20)
Group II.	9	20	(28)
Group III.	38	22	(26)
Group IV.	48.5	50	(26)

FURTHER INVESTIGATIONS.

1. Effect of Luminal (Phenobarbital).

All the Epileptics under treatment in the hospital with Luminal (Phenobarbital) were examined, fasting blood sugars being obtained from 14 cases and estimated by Calvert's Method.[57] The results are shown in Table 5.

The average value is 93 mg.%, 9 mg. higher than the fasting average in untreated cases. Unfortunately it was not possible to upset the routine treatment of this hospital and obtain specimens of blood from a number of patients, first without luminal and later under its influence. Two Epileptics, however who were admitted during the period of these investigations showed fasting blood sugars of 78 and 92 mg. respectively and values of 86 and 101 when under luminal, which corresponds with the findings that the barbitones raise the blood sugar.[65,66,67].

TABLE 5.

FASTING BLOOD SUGARS in mg.% in EPILEPTICS under treatment with Luminal (Phenobarbital).

1. 115	6. 106	11. 112
2. 82	7. 65	12. 76
3. 116	8. 90	13. 84
4. 98	9. 67	14. 101
5. 81	10. 86	

Average Value 93 mg.%.

Blood Sugar Curves obtained from 10 Epileptics under treatment with Luminal are shown in Table 6. Here again the general increase of the blood sugar level over that of untreated cases is apparent, and further the glucose content of the final specimen withdrawn tends to be higher than the fasting valuc which might be due to decreased activity of the Islets of Langerhans.[98]

TABLE 6.

GLUCOSE TOLERANCE CURVES of EPILEPTICS under treatment with Luminal (Phenobarbital).

Case					
1.	112	168	152	161	160
2.	115	106	101	103	
3.	90	129	116	89	
4.	83	116	104	81	
5.	82	138	106	100	
6.	98	154	129	104	
7.	106	118	109	95	
8.	65	112	226	168	
9.	81	133	-	102	
10.	67	131	127	102	
11.	74	104	61	79	
12.	101	164	153	134	

2. Glucose Tolerance during Post-Epileptic Confusion.

As pointed out previously specimens of blood for analysis were not withdrawn immediately after the fits as previous work has shown that high sugar value would be obtained.[53,54,55.]

A certain proportion of the Epileptics in the hospital it was noticed, however, became markedly confused after a bout of fits, and during this period they were not subject to convulsions. Glucose tolerance curves done during this period are shown in Table 7.

TABLE 7.

Post-Epileptic Confusion.

No.					
1.	108	128	125	137	
2.	110	128	136	146	
3.	108	172	118	130	
4.	106	172	118	130	
5.	86	101	180	142	
6.	93	148	126	99	
7.	112	168	152	161	Under Luminal treatment.
8.	106	134	94	71	

These figures show that in the period of Post-Epileptic confusion the glucose tolerance is considerably reduced and that far higher blood sugars are present. This fact is probably responsible for the immunity from fits during this period.

3. Influence of Autonomic Nervous System.

The Pancreas has been shown in recent years to receive a large nerve supply from the Vagus[107] and this nerve has been said to supply the Islets of Langerhans.[108,109] A considerable amount of work has been done to determine its influence on the Blood Sugar. Clarke[110] in 1925 reported that drugs which stimulate the parasympathetic nerves lower the blood sugar, but the same observer in 1931 stated that the Vagus carried inhibitory fibres to the Islets.[111] Sakurai[112,113] reports that stimulation of the Parasympathetic by pilocarpine lowers the blood sugar and that this can be prevented by paralysing the parasympathetic nerves by Atropine. Lange[114] found that by paralysing the parasympathetic by large doses of Atropine the blood sugar could be raised, though small doses had the opposite effect. Casangra[115] on the other hand, states that Atropine has no influence on the Blood Sugar level and does not affect the hypoglycaemic curve produced by insulin injection. Ramsbotham and Eastwood[87] found that it had no influence on a case of spontaneous hypoglycaemia. These conflicting results are probably in part due to the fact that the Islets of Langerhans are capable of producing insulin independent of any nerve supply.[107]

In view of the suggestion that Epilepsy might be due to an excessive Vagotonia,[2] and the various ideas of Autonomic upset,[38-41] a certain number of

patients were put under special treatment.

(a) Five cases were subjected to Parasympathetic stimulation by Physostigmine Salicylate 1/40 three times a day for a month. The results obtained are shown in Table 8.

TABLE 8.

Case	Normal No. of fits / month.	Normal Blood Sugar. mg.%	No. of fits under drug.	Blood Sugar /drug mg.%
1.	40	88	42	71
2.	1	82	2	81
3.	32	81	34	97
4.	2	81	7	65
5.	8	91	7	74
	Total 83	Average 83	Total 92	Average 78

Result: Slight increase in number of fits with fall in average fasting blood sugar level.

(b) Five cases had their Parasympathetic nerves paralysed for a month by Atropine Sulphate 1/100 grain three times a day. The results obtained are shown in Table 9.

TABLE 9.

Case.	Normal No. of fits / month.	Normal Blood Sugar. mg.%	No. of fits under drug.	Blood Sugar / drug. mg.%
1.	2	106	7	94
2.	2	74	0	89
3.	3	71	4	86
4.	3	73	2	77
5.	32	101	35	109
	Total 42	Average 85	Total 48	Average 91

Result: Slight increase in number of fits and in Blood sugar.

(c) Five cases were subjected to stimulation of the Sympathetic Nerves by means of Ephedrine Hydrochloride ½ grain three times a day for a month. The results obtained are shown in Table 10.

TABLE 10.

Case.	Normal No. of fits / month.	Normal Blood Sugar.	No. of fits under drug.	Blood Sugar / drug.
		mg.%		mg.%
1.	7	97	5	102
2.	15	72	13	111
3.	9	66	8	87
4.	1	80	2	97
5.	5	74	2	77
	Total 37	Average 78	Total 30	Average 95

Result: Slight decrease in the number of fits with slight rise in the blood sugar.

These three series are, of course, too small to permit any definite conclusion being made, but they do show that variations in the balance of the Autonomic Nervous System has only a very limited influence on the Blood Sugar concentration and the fit incidence. It would appear from Tables 8 and 10 that increase in the Sympathetic tone raises the fasting blood sugar and tends to decrease the number of fits, though the findings in Table 9 are not in accordance with this view.

4. Glucose Tolerance Curves in Epileptics no longer subject to fits.

In the hospital there were five patients who had previously been subject to severe Epileptic fits but had for a number of years been completely free from convulsions though the Epileptic mentality persisted. Glucose Tolerance curves from these patients are shown in Table 11.

TABLE 11.

Case					
1.	65	112	226	168	Under Luminal
2.	61	100	155	-	
3.	91	136	140	140	
4.	88	88	116	101	
5.	92	150	169	191	

These patients show very little difference in the fasting blood value from that which one finds in the normal untreated cases with frequent fits, but on the other hand the shape of the sugar curve is totally different, the general impression here being that of diabetes (hypoinsulinism) though this is counter-indicated by the low fasting sugar level. The impression given by these curves is that hyper-insulinism is present, but the other influences controlling blood sugar are keeping the fasting level at that figure, which was previously the patient's normal.

GENERAL DISCUSSION.

Having shown that Epilepsy is associated with an abnormally low fasting blood sugar, and that the drugs which are of most value in the control of Epileptic fits probably exert their influence, partly if not wholly, by raising the blood sugar level, it is necessary to consider whether this effect could not be brought about by simpler methods.

The obvious preventative for hypoglycaemia is to put patient on a high carbohydrate diet. The hypoglycaemia which has been found in the convulsions of pregnancy[116,117] has been prevented by this course[118], and further Allen[119] controlled the fits in a case of Carcinoma of the Islets by intravenous injection of glucose solution, and Heyn[120] prevented the fits of hyperinsulinism by a high carbohydrate diet. Unfortunately the problem is complicated by the fact that excess of carbohydrates stimulates the formation of Insulin, thus Gibson and Larimer[121] found that hypoglycaemia could be produced by intravenous injection of glucose solutions, and it is possible that the large number of cases of hyperinsulinism described by American observers may partly be due to the excessive carbohydrate diet in the United States.[122,123]

Waters[124] successfully treated three cases of marked hypoglycaemia with a low carbohydrate diet,

and Sexton[125] treated a case whose fasting blood sugar was only 60 mg.% with a Ketogenic Diet and obtained considerable improvement. These results are particularly interesting as marked diminution in the number of fits has been reported to take place in Epileptic children placed on a Ketogenic Diet.[126 &c.] The explanation probably is that just as a high carbohydrate diet stimulates the Islets, a low carbohydrate or Ketogenic diet tends to dull down their activity.

The factor of heredity in Epilepsy is still far from completely understood, though Davenport and Weeks and Lunborg[132] state that it is a Mendelian Recessive character. In view of this it is of interest to note that Cammidge and Howard[127] have recently shown that hypoglycaemia is inherited as a Mendelian Recessive in mice, and Dunn[128] states, from consideration of Cammidge and Howard's previous work,[129] that hypoglycaemia is recessive to the more prevalent hyperglycaemia. On the other hand there is evidence to show that hypoglycaemia may be a condition acquired in intra-uterine life, for Dubreuil and Anderodais[130] and Gray and Freemster[131] have described cases of foetal hyperinsulinism due to hypertrophy of the embryonic Islets to counteract maternal diabetes.

In these cases of Epilepsy which do not

respond satisfactorily to medical treatment, it would appear that operation and partial removal of the pancreas should be carried out. Finney and Finney[96] have shown that such a procedure is practical and beneficial results have been obtained in those cases of hypoglycaemia due to neoplasm of the Islets of Langerhans.[91,92,93,94,95].

S U M M A R Y /

S U M M A R Y .

1. Epilepsy is associated with a low fasting blood sugar.
2. The glucose tolerance curve in Epilepsy shows the Islets of Langerhans to be over-active.
3. Those drugs which are beneficial in Epilepsy raise the blood sugar.
4. In the post-convulsive phase of Epilepsy the immunity from fits is due to a raised blood sugar.
5. Variations in the balance of the Autonomic Nervous System have little influence on the incidence of fits.
6. Natural recovery from Epilepsy is associated with the onset of hypo-insulinism.

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