THE FACTOR OF HYPOGLYCÆMIA IN THE ÆTIOLOGY OF IDIOPATHIC EPILEPSY.*

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IN the whole realm of medicine there are few more easily recognizable clinical syndromes than those which have been grouped together under the generic term of "epilepsy" or "epileptiform convulsions"; nevertheless, in spite of a vast amount of research work, the causation of these conditions is still imperfectly understood.

The most widely accepted theory at present is that which supposes the condition to be due to a "metabolic dyscrasia" (Collier (1)). The literature bearing on this view was summarized in a previous paper (2).

Considerable support has been given in this country (3), and on the Continent (4), to the suggestion that fits might be related to spasmophilia and parathyroid tetany, but examination of the blood of epileptics has failed to demonstrate any abnormality in the level of the blood calcium (5, 6, 7).

Hughlings Jackson (8) considered epileptic fits to be due to localized 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 localized cerebral anæmia, 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 the anæmia to be due to faulty vaso-motor control. Kennedy (13), from the surgical aspect, supports this view, and states that when a fit occurs during intracranial 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 caffeine (14, 15, 16) and luminal might be said 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

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may account for the sudden onset or equally sudden cessation of fits described by Collier (1, 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 Zabreski (21) reports acromegalic tendencies in epileptics, and Barros (22) states that epilepsy is a common symptom in this condition. Schön and Susman (23) and Vizioli (24) have reported that the pituitary gland of epileptics is hypertrophied. On the other hand, Tucker (25) reported hypopituitarism in 31% 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 hæmoclastic function test, and by Gosden and Fox (32) by the lævulose 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 basal metabolism of 130 cases they examined. Normal figures were also reported in 50 cases by Davis (36). Twenty-four cases in which the 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 ætiological 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 localized cerebral irritations, in general paralysis of the insane, in general toxæmias, such as acute fevers, in diabetes, or uræmia, and when the blood-supply of the brain is deficient, as in Stokes-Adams'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 hæmorrhage in warm-blooded animals were probably due to the same cause, and also since Collier (1) states that fits cannot be due to tissue irritation, it is reasonable to suppose that the fits observed in over 30% 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 anæmia of the cerebral tissue.

The effect of an anæmia of the brain is to deprive the nerve-cells both of oxygen and of nutriment in the form of glucose. Anoxæmia 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 anæmia is probably the absence of blood glucose; for the fact 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 report that symptoms indistinguishable from *petit* and *grand mal* can occur in hypoglycæmia produced by insulin injection.

In view of these facts it was decided to investigate the blood-sugar values of a series of epileptics to find whether hypoglycæmia 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, until the last few years only hypofunction of the islets of Langerhans has been described. From theoretical considerations a hyper-activity of the islet tissues should produce identical symptoms as those seen when insulin is injected into a healthy subject. As shown above, the results produced can be indistinguishable from idiopathic epilepsy, the nervous instability, "epileptic" cry, and complete lack of memory for the occurrence of the fit, all being present. Further, John (52) has stated that hyperinsulinism gives rise to great hunger—which, in my experience, is a marked characteristic in chronic epileptics.

For the purpose of investigation, all the epileptics in the hospital were taken irrespective of the number, the severity, or the duration of their fits. An attempt was 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 prodromal symptoms to permit withdrawal of specimens before the fits, and during the 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 convulsions raise the blood-sugar, and

Kersten (54, 55) has shown that this occurs in epilepsy, the mechanism being a stimulation of the suprarenals by the muscular excitement, with consequent outpouring of adrenaline 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 veni-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 in 80 patients are shown in Table I.

The average fasting sugar value from these results is 84·9 mgrm. %. Different

TABLE I.—*Fasting Blood sugars in mgrm. % in Untreated Epileptics.*

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

authorities report varying values for the fasting blood sugar in healthy subjects; thus Beaumont and Dodds (58) give 100 mgrm. % for the normal value. Wright (59) gives 80 to 100 mgrm. %, and others regard any figure lying between 80 and 120 mgrm. % as being within the normal limits. In view of the low average value of 84·9 mgrm. % obtained here, and the fact that no less than 64% of the figures lie below 90 mgrm. % and 26% below 80 mgrm. %, and that no figure is over 110 mgrm. %, we are justified in stating that a degree of hypoglycæmia occurs in epileptics, for Seale Harris (60), in the 1,867 normal persons he examined, only found fasting sugar below 79 mgrm. % in 4% of the cases.

The isolation of insulin and its use in the treatment of diabetes rapidly brought to light the fact than an over-dosage could give rise to a dangerous condition of hypoglycæmia 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 largest number of cases published are those of Lennox, 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 mgrm. % compared with 100 mgrm. % 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); 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 Benninger (68) obtained a similar series of fasting blood sugar values, but it must be noted that 66% of the figures lay below 100 mgrm. % and 34% below 90 mgrm. %. 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 blood sugar findings in 66 epileptics. The average fasting value in their cases was 81 mgrm. % (estimated by the method of Folin and Wu (90)), only one of the series having a fasting blood sugar of over 100 mgrm. %. Gosden and Fox (32) in 17 cases found an average value of 82 mgrm. % (Folin and Wu). Wladyenzko (70) reported definite hypoglycæmia in 18 cases, and obtained clinical improvement with a high carbohydrate diet. Shaw and Moriarty (71) obtained remarkably low figures in the blood sugar values of fasting epileptic children, and Patterson and Levi (72) report low sugar contents in the cerebro-spinal fluid. Goodall, in the Maudsley Lecture, 1927 (73), stated that epileptic fits could definitely not be due to hypoglycæmia, and gave as authority for this statement the reports on the work of Daly *et al.* (74), who only examined 4 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 obtained, and Holstrom (76), who reported the blood sugar values of 20 epileptics examined to be normal, but in view of the fact that a quarter of an hour before withdrawing the blood he injected adrenaline, it is not surprising that he obtained higher figures than other observers. Examination of the results which are of any value shows that the fasting blood sugar of an epileptic is generally a little over 80 mgrm. % whatever method of estimation is employed. This figure is just within the lower limits 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 particularly well marked in epileptics, and they have also shown that the fits occur at the lowest point in the sugar curve. Macleod (79) states that hypoglycæmic symptoms are liable to occur in human beings when the blood sugar lies between 80 and 70 mgrm. %. Wauchope (133) gives similar figures, though Wright states that convulsions are not liable to occur till the blood sugar is below 75 mgrm. %. It can be seen that, if the fasting blood sugar of an epileptic is at 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 hypoglycæmia 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 the liver glycogen, the convulsions being, as Muskens (51) has said, a protective reflex. It is reasonable to suppose that sometimes 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 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 well-nourished animals, and further, the fatty degeneration of the heart which has been reported from *post-mortem* examinations of patients who have died in *status epilepticus* by Mott (80), and more recently by Collier (1), and considered to be indicative of a severe toxæmia, might equally well be due to acute cardiac malnutrition due to hypoglycæmia, coupled with the excessive work for the heart due to the labour of the prolonged convulsions.

Having shown that a degree of hypoglycæmia 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 veni-puncture, 50 grm. 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 II.

TABLE II.—*Glucose Tolerance in Untreated Epileptics (mgrm. %).*

	Fasting.	½ hour.	1 hour.	1½ hours.	2 hours.
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
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	..
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	..

* Fit at this point.

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Table II—*continued.*

	Fasting.	½ hour.	1 hour.	1½ hours.	2 hours.
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 midway between these two.

A previous series of glucose tolerance curves from 66 epileptics has been reported by Mackay and Barbash (69), and they have suggested that the curves obtained should be classified under the following headings:

(i) Hyperglycæmia group in which the maximum sugar content in the curve exceeds 180 mgrm. %.

(ii) Normal group where the maximum sugar content lies between 150 and 180 mgrm. %.

(iii) Subnormal group where the maximum sugar content is between 125 and 150 mgrm. %.

(iv) Markedly subnormal where the maximum sugar lies below 125 mgrm. %.

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This classification is not really satisfactory, for the shape of the curve is as important with regard to its normality as is the peak level ; further, the normal peak value is generally between 120 and 140 mgrm. %, 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 II shows that 32, *i.e.*, 48·5%, fall in Group IV, 25, *i.e.*, 38%, fall in Group III, 9% fall in Group II, and only 4·5% in Group I. Mackay and Barbash's report covers 66 epileptics, but from a private communication it appears 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 subnormal 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 III by permission of Dr. G. 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.

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 groups IV and III, coupled with the low fasting values, indicates that a definite hypoglycæmia is present in epilepsy. Indirect evidence is given to this by Raimann (81), who noted increased sugar tolerance in this condition.

Hypoglycæmia occurs as a result of various endocrine disharmonies (82, 83), particularly hypopituitarism, in hypothyroidism, in suprarenal insufficiency, in hyperinsulinism, and in liver deficiency (84). Cammidge (82) states that it occurs in nervous conditions, but it is reasonable to suppose that any nervous symptoms might be secondary to the hypoglycæmia rather than primary, for Greisheimer (85) found that in decerebrate dogs the nervous irritability was inversely proportional to the blood sugar level. Hoxie and Lisherness (86), in a series of routine blood examinations, noted mental and nervous abnormalities in those with low sugar values, and Cameron (134) describes how nervous instability in children can be alleviated by glucose. Further cases of mental symptoms and convulsions associated with a low blood sugar have been described by Ramsbotham and Eastwood (87), Guy-Larroche *et al.* (88), Moore, O'Farrel *et al.* (89), and many others.

From the examination of the shape of the blood sugar curves obtained, it is impossible to come to a definite conclusion as to the cause of the hypoglycæmia. The published figures of the basal metabolic rates in epilepsy (34 35, 36) and our own findings exclude hypothyroidism. None of the cases under examination showed any of the classical symptoms of hypopituitarism, though Tucker (25) states that he found dysfunction of this gland in a high proportion of his cases. Any marked abnormality of adrenal function could not have

TABLE III.—*Glucose Tolerance Curves in Epileptics obtained by G. W. J. Mackay and H. Barbash.*

	First examination.					Second examination.					
Case.	Fasting (mg. %).	½ hour (mg. %).	1 hour (mg. %).	1½ hours (mg. %).	2 hours (mg. %).	Case.	Fasting (mg. %).	½ hour (mg. %).	1 hour (mg. %).	1½ hours (mg. %).	2 hours (mg. %).
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

TABLE IV.

	Gloucester curves (%).	Mackay and Barbash (%).	Lennox and Bellinger (%).
Group I . .	4·5 .	8 .	(20)
Group II . .	9·0 .	20 .	(28)
Group III . .	38·0 .	22 .	(26)
Group IV . .	48·5 .	50 .	(26)

been present in the cases examined, as the blood-pressures and pulse-rates were all within normal limits. Private inquiry shows that the cases in Table III were also normal in this respect. Liver deficiency, though stated to be present to some degree in epileptics (29, 30, 31, 32, 33), could not have been marked

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enough to give rise to such low sugar values without showing some other sign of impaired function ; further sugar curves in liver deficiency would have been of a more peaked type. Hyperinsulinism with symptoms indistinguishable from clinical epilepsy have been described in a number of cases recently. 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) describe a case of adenoma of the islets, and McClenahan and Norris (94) and Allen *et al.* (95) review a number of similar cases in which both fits and mental symptoms improved as a result of the rise in blood-sugar produced by removing the neoplastic pancreatic tissue. Hypoglycæmia where no neoplasm was present and simple hypertrophy of the islets tissue was suggested as the cause has been described by Finney and Finney (96), and more recently by Griffiths and de Wesselow (135). A review of the published cases of hyperinsulinism has been made by Harris (97).

In view of these reports and the absence of other localizing signs, it is probable that hyperinsulinism is the cause of the low blood sugars found in the epileptics under examination. Support is given to this statement by the fact that the figure obtained in the last specimen in the glucose tolerance test in Tables II and III is often considerably below the fasting value, which Depisch and Hasenohrl (98) regard as a sign of islet activity. Further support is given to this view by the fact that an increased number of fits occurs in epileptics at the menstrual periods (20, etc.), at which time Vogt (100) and Rudolf and Rothery (101) have shown there is an increased sensitivity to insulin due to the high folliculin content of the blood activating the insulin present (102).

The therapeutic findings in epilepsy are also in favour of this hypothesis, for the barbitones, which are indisputably the most efficacious drugs, raise the blood sugar (65, 66, 67). Jackson (103) has shown that sodium barbital prevents two-thirds of the experimental fits obtained by insulin injection, and this is approximately the proportion of epileptics who benefit from luminal (phenobarbital). Chloral, which Zabreski (21) and others recommend in epilepsy, similarly raised the blood-sugar (104, 105), and caffeine, which has been described as relieving epileptic convulsions (14, 15, 16), has been shown by Popper and Jahoda (106) to prevent the convulsions of insulin intoxication.

Further Investigations.

1. *Effect of Luminal (Phenobarbital).*

All the epileptics under treatment 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 V.

The average value is 93 mgrm. %—9 mgrm. higher than the fasting average in untreated cases. It was not considered advisable 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 mgrm. % 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 V.—*Fasting Blood-Sugars in mgrm. % in Epileptics under Treatment with Luminal (Phenobarbital).*

1	.	115	6	.	106	11	. 112
2	.	82	7	.	65	12	. 76
3	.	136	8	.	90	13	. 84
4	.	98	9	.	67	14	. 101
5	.	81	10	.	86		

Average value 93 mgrm. %.

TABLE VI.—*Glucose Tolerance in mgrm. %, of Epileptics under Treatment with Luminal (Phenobarbital).*

Case.	Fasting.	½ hour.	1 hour.	1½ hours.	2 hours.
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	..

Blood sugar curves obtained from 12 epileptics under treatment with luminal are shown in Table VI. 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 value, which might be due to decreased activity of the islets of Langerhans (98).

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).

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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 VII.

TABLE VII.—*Glucose Tolerance during Post-Epileptic Confusion* (*mgrm.* %).

No.	Fasting.	½ hour.	1 hour.	1½ hours.
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*
8	106	134	94	71

* Under luminal treatment.

These figures show that in the period of post-epileptic confusion the glucose tolerance is considerably reduced and that far higher blood sugar levels 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 lowered 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. Casengra (115), on the other hand, states that atropine has no influence on the blood sugar level, and does not effect the hypoglycæmic curve produced by insulin injection. Ramsbotham and Eastwood (87) found that it had no influence on a case of spontaneous hypoglycæmia. 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 (42) or other types 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 $\frac{1}{40}$ gr. three times a day for a month. The results obtained are shown in Table VIII.

TABLE VIII.

Case.	Usual number of fits per month.	Normal blood sugar (mgrm. %).	Number of fits under drug.	Blood sugar/drug (mgrm. %).
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 84	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 $\frac{1}{100}$ gr. three times a day. The results obtained are shown in Table IX.

TABLE IX.

Case.	Usual number of fits per month.	Normal blood sugar (mgrm. %).	Number of fits under drug.	Blood sugar/drug (mgrm. %).
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 $\frac{1}{2}$ gr. three times a day for a month. The results obtained are shown in Table X.

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TABLE X.

Case.	Usual number of fits per month.	Normal blood sugar (mgrm. %).	Number of fits under drug.	Blood sugar/drug (mgrm. %).
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 of any definite conclusion being made, but they do show that variation 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 VIII and X that increase in the sympathetic tone raises the fasting blood sugar and tends to decrease the number of fits, though the findings in Table IX 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 several years been completely free from convulsions, though the epileptic mentality persisted. Glucose tolerance curves from these patients are shown in Table XI.

TABLE XI.

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

* Under luminal.

These patients show very little difference in the fasting blood value from what one finds in the normal untreated cases with frequent convulsions; but on the other hand, the shape of the curve is totally different, the general impression here being of diabetes (hypoinsulinism), though this is counter-indicated by the low fasting sugar level. The impression given by these curves is that hyperinsulinism has ceased to exist in these patients and that they are tending to become diabetics, but that at the same time the other

blood sugar controlling factors in the body are tending to keep the glucose fasting level in the blood at the figure which was previously normal for the patient.

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 preventive for hypoglycæmia is to put the patient on a high carbohydrate diet. The hypoglycæmia 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 Laurimer (121) found that hypoglycæmia 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 hypoglycæmia with a low carbohydrate diet, and Sexton (125) treated a case whose fasting blood-sugar was only 60 mgrm. % with a ketogenic diet and obtained considerable improvement. These results are particularly interesting since marked diminution in the number of fits has been reported to take place in epileptics, especially children, placed on a ketogenic diet (126, etc.). The explanation probably is that just as a high carbohydrate diet stimulates the islets, a low carbohydrate or ketogenic diet tends to diminish 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 hypoglycæmia is inherited as a Mendelian recessive in mice, and Dunn (128) states, from consideration of Cammidge and Howard's previous work (129), that hypoglycæmia is recessive to the more prevalent hyperglycæmia. On the other hand, there is evidence to show that hypoglycæmia may be a condition acquired in intra-uterine life, for Dubreuil and Anderodais (130), and Gray and Freemster (131), had described cases of fœtal hyperinsulinism due to hypertrophy of the embryonic islets to counteract maternal diabetes.

In those 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 practicable, and beneficial results have been obtained in those cases of hypoglycæmia due to neoplasm of the islets of Langerhans (91, 92, 93, 94, 95).

Summary.

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 level (except bromides, which reduce the irritability of the cerebral cortex).

4. In the post-convulsive phase of epilepsy the immunity from fits is associated with 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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