Epilepsy: A Metabolic Disease. By GUY P. U. PRIOR, M.R.C.S., L.R.C.P., Medical Superintendent; and S. EVAN JONES, M.B., Medical Officer, The Mental Hospital, Rydalmere, N.S.W.

GOWERS states that the morbid state causing epilepsy "consists in some trifling alteration in the chemical constitution of the grey matter of the brain on which the instability spoken of depends." (1)

Munson says: "I believe that the epileptogenous change affects the chemical structure of the cell. Function is the result of change in the chemical structure of the cell, brought about by the laws governing chemical action. Disease being a change or failure of normal function, it follows that disease is the result of interference with the normal chemical processes of the cell" (2).

We have for twelve months been making observations upon the more easily detected chemical changes in the blood and urine, to throw if possible some light upon the changes of which Gowers, Munson, and other authorities speak.

We first made records upon the calcium contents of the blood and urine, in a number of epileptic patients. This we did by the methods taught by Dr. Blair Bell, (3), and it is due to a chance reference to his work that we have been able to undertake and develop these investigations. We found marked changes from the normal, and had some successes in treating patients with salts of calcium. We published these earlier observations in the *Australian Medical Journal* of March 4th, 1916. Since then we have extended our investigations and made observations upon the alkalinity, coagulability, and leucocytes of the blood; upon the changes in the amount of phosphates and chlorides excreted in the urine, and also upon the blood-pressure of epileptics. We have treated a number of patients with calcium and with the extracts of various ductless glands.

It is upon the records of the last six months of our work that we now write. At first we took weekly observations upon a number of patients, but have found since then that to be of any value the observations must be made daily, as such changes as are shown before or after a fit can only with certainty be obtained this way.

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First, with regard to the calcium excreted in the urine. In our paper before referred to, we pointed out that epileptics, as compared with others, excreted in the urine less calcium (7).

Since then we have made 730 records of the calcium excretion of nineteen patients, and of these 395 showed less than half the normal amount, 165 were from half of to below normal; fifty-one were normal; eighty were between normal and twice normal; and on twenty-nine occasions the excretion was more than twice the normal amount. The amount excreted varies greatly with the individual patient, some patients seldom excreting more than a trace, others excreting as a rule a normal amount or more. We have found changes in the excretion both before and after a fit or series of fits. In the case of eight patients daily observations were made extending from thirty to 112 days.

Average Daily Excretion in Grams Per Cent.

Case.	Grams per cent.	Period in days.	Fits.
34	·0014	30	5
33	·004	38	5
11	·009	80	29
29	·01	30	6
3	·011	112	197
8	·018	80	22
6	·016	112	40
26	·026	30	22

Taking the normal average percentage excretion of calcium as 0·2 grm., the above table shows that with the exception of one case the excretion was low, and in the Cases 33 and 34, markedly so. The amount of calcium excreted does not appear to bear any relationship to the number of fits.

During the period under review the patients had thirty serial attacks, besides occasional isolated convulsions.

In twenty-six instances there was an increased calcium excretion preceding the onset of the convulsions.

In twenty-seven instances there was a diminution following the increase. In twenty-six cases the diminution was followed by a secondary rise. The preliminary rise occurred from the fifth day to the day immediately preceding the series. The rise varied considerably, averaging 1·6 of the normal. In cases which had been showing a continued low excretion the rise did not always exceed the normal; but was nevertheless high for the particular case.

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A rise is often seen in the calcium excretion without a fit occurring; associated with those observations changes in the calcium blood index and coagulability that we have noticed to precede a fit have not taken place. After a series there is a fall in the excretion, which during a series lasting several days usually remains high.

Table showing Relationship of Preliminary Rise to Commencement of Series.

No. of days before series	5	4	3	2	1	
No. of instances in which rise was noted	3	6	10	6	1	(total 26).

The preliminary fall was observed as shown by the following table:

No. of days before series	3	2	1	1st day of series.
No of cases	2	12	9	4

The average excretion during this phase was 0·23 of normal, *i.e.* 0·0046 grm. *per cent.*

The secondary rise occurred thus:

Days before series	2	1	1st	2nd	3rd day of series.
No. of instances	2	10	8	6	1

The average secondary rise was 1·1 of normal, *i.e.* 0·022 grm. *per cent.*

The Phosphorus Excretion.

It was thought that changes which occurred in the calcium excretion might influence the output of phosphorus in the urine. Accordingly daily examinations were made on several patients over periods from one to three months.

The results of our observations showed a distinct contrast between the male and female patients.

In four women, whose urine was examined in each case daily for one month, the excretion of phosphorus was found to be remarkably uniform, being in all of them below normal, and with very little variation, and showing no relationship to epileptic attacks.

The males, however, all showed an irregular excretion with a wide range. One of these had numerous fits daily, so we were unable to draw any conclusions, but three patients were

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subject to serial outbreaks, and they all presented similar variations in the phosphorus excretion.

During the period under consideration these three men had twenty-one serial attacks. On fifteen occasions the phosphorus excretion fell to a minimum on the second and first day before the commencement of a series, and in a similar number of instances there was a rise succeeding the series.

We observed also that an injection of calcium iodide was followed by, in many cases, a great output of phosphorus. There appears then to be ground for thinking that coincident with the increased excretion of calcium before a series, there is a retention of phosphorus.

Chlorine.

The excretion of chlorine was found to be irregular in the men, but less variable in the women. Beyond an occasional fall preceding a series we were unable to detect any special relationship to the epileptic attacks.

Calcium Blood Index.

We have examined the calcium blood index also, according to the directions given by Dr. Blair Bell (3 *and* 4). By his method blood is prepared, and the calcium crystals counted on a hæmocytometer; he impresses the fact that there are diurnal variations, and advises that the blood be taken at the same time every day. He gives the normal as being from 0·8 to 1·0 crystal per square. During the time under review we have had estimations of the calcium blood index of eighteen patients, whose urine was also examined. We have grouped the results as follows:

Calcium blood	·4 and lower	·4 to ·6	·6 to 8	·8 and higher.
	40	178	119	70

It will be seen that the index in most cases is subnormal, *viz.* 337 times out of 407.

Whereas in the matter of calcium excretion each patient tends to have his individual peculiarity as to high or low amount daily excreted, this is not to the same extent noticeable in the blood index, but the variations of each patient are greater. There is apparently no constant change in the calcium blood index before a fit. The amount sometimes is

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high, but usually there is more variation in the count at the time a fit is going to take place than at other times, and more often than not there is from a few hours to two or three days before a fit a high blood-index together with a high excretion, accompanied with changes in the alkalinity and coagulability of which we will speak later. Towards the end of, and immediately subsequent to a series, there is always a high though variable calcium blood-index, which falls a day or two after its termination. In conditions of status epilepticus a high blood-index is found reaching from 1 to 1·5. We have not found the blood-index to have any constant relationship to the urinary excretion, to the alkalinity, or the coagulability, though often the index has been found to be highest when the coagulation-time was shortest, but to this there are many exceptions, though often before a series, and always during status, both are high together.

Coagulation.

We have examined the coagulation-time of the blood by means of drawing some into a capillary tube, transferring it to a glass slide and noting the time it takes to draw out fibrin threads, and using our own blood as a control.

Turner says that in epilepsy there is an increased tendency for the blood to clot, that this is more marked before and during a fit, and that after a fit the time may be lengthened (5). Besta found diminished coagulation-time in 37 cases out of 45, and that the diminution was in proportion to the number of fits. Perugia found in 36 cases all to be of lowered coagulability, which could be rendered normal by giving calcium salts (5). We have made 464 examinations as to the coagulability of the blood; 416 of these were made upon 18 of the patients on whom we were making daily or weekly observations; 48 were made upon other epileptics. These and all our examinations have been made about the same time each day; the relationship of an examination to a fit or a series of fits is by chance. Of the casual 48, the coagulation of 35 was shortened, of 7 normal, and of 6 lengthened. We find that as a rule before a fit, and more markedly so before a series, there is a shortening in the coagulation-time; if the patient's coagulation is usually short this becomes shorter. During a series the coagulation-time is short, but after a series approaches

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the normal, and often becomes lengthened. We have also noticed, in some cases, that during those months when the fits have been fewest, the coagulation-time has been longest.

In Case 29, upon whom observations were made for 5 months, only in 1 month did she show any lengthening of the coagulation time. This she did in 3 examinations out of 4; the fourth was approaching the normal. In this month she only had one fit, whilst in the other 4 months the fits were from 5 to 13. During these months 33 examinations were made, 6 times the coagulation-time was normal, and 28 times shortened.

Case 34, on whom 23 observations were made in 1 month, showed only twice a lengthening of the coagulation-time; one of these occasions was about 2 hours after having a fit. In the same patient an observation was obtained about 2 hours before a fit, when the coagulation-time was only $\frac{1}{3}$ of normal.

Case 18, upon whom 54 examinations were made in $2\frac{1}{2}$ months, shows less tendency to shortening of coagulation-time than most epileptics, it having been short or normal 24 times out of the 54 examinations. Two days before the commencement of a series his coagulation time shortens, remains short until the end of a series, then rises, and remains normal for 16 days, during which time he is free from fits, when again the diminution of the coagulation-time, with an increase in the calcium urinary excretion and a fall in the alkalinity of the blood, indicate the probability of another series occurring. After this next series of 6 fits in 4 days the coagulation-time remains subnormal for 4 days, when he has 3 more fits, and the coagulation-time again becomes plus.

In case 36, 17 observations were made in 4 months. In the 4 months when she was receiving pituitary gland, her coagulation-time was decidedly lengthened in 3 examinations out of 4; during the month in which this happened she had but 1 fit. During the other 3 months she received no treatment, and had 10, 6, and 4 fits respectively. In these months the coagulation-time was shortened in 10 examinations out of 13. In the month in which the 10 fits occurred the coagulation-time was decidedly shortened in all four examinations.

In all cases of status epilepticus we have found the coagulation-time more markedly shortened than at other times.

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Alkalinity.

We have examined the alkalinity of the blood by Boycott and Chisolm's method. To do this a series of small tubes are prepared containing quantities of N/1,000 sulphuric acid, rising by 0·1 c.c. from 0·0 to 1·2 c.c.; the volume in each being made up to 2 c.c. with distilled water. About 0·02 c.c. of blood is then added to each tube, the contents well mixed, and the tubes placed in a water bath for one hour. With normal human blood, a coarse flocculent precipitate makes its appearance, when the tubes containing 0·7 to 0·9 of acid are reached. The appearance of this precipitate is considered to indicate the neutralisation point (8).

Charon and Brich have studied the relationship of epileptic convulsions to the normal variations in the alkalinity of the blood. They found the seizures to stand in inverse relation to the degree, and that the minimum frequency of the attacks corresponded with the maximum blood alkalinity (5). Pugh reports interparoxysmal alkalinity lower than the average, a sudden fall immediately before a fit, and a further fall after. He ascribes this as being due to acid toxines, absorbed from the intestinal tract (5).

We have made 290 examinations as to the alkalinity of the blood, and all but 32 of these have been on the same 18 patients as the other observations. Of these 290 examinations made on 50 patients, only 15 times have we met with a degree equal to what Boycott and Chisolm give as normal; and of these 15, 13 were made on different occasions with the blood of the same patient, making only 3 patients that gave a normal degree of alkalinity. The rest were subnormal, many giving a very low degree of alkalinity. With slight variations, many patients seem to run their own degree of alkalinity, which makes larger variations at the time of epileptic attacks. We have found that, as a rule, there is a fall of blood alkalinity before a fit, and after an attack, a rise, to what might be called the patient's own normal, or above. This rise we have observed a few hours after a fit; the pre-fit fall may take place a few hours before, or there may be an irregular and falling alkalinity some days before the fit occurs. During a series the alkalinity continues to fall or remains low.

In case 32 nine observations on the alkalinity were made

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in two months, the neutralising point varying from 0·4 to 0·6; being, on two occasions, 0·6, shortly after a fit had occurred.

Case 6 had 10 fits in two series. Before the first series alkalinity fell from 4·5 to 4, remained low, and at the end of the series reached 3, then rose, and fell again before the next series.

Leucocytes.

In the case of the same patients as those on whom we have made the other observations we have made 395 leucocyte counts, and in 183 of these we have made differential counts.

Turner states that the leucocytes in epileptics are 20 *per cent.* below, and under bromides they approach the normal. Lewis Bruce has observed a hyperleucocytosis after a serial outburst or attacks of status (5).

We have found that Blair Bell's (3) method of preparing blood for calcium crystals is also an excellent way of showing leucocytes, and that we could easily make a differential count on the same slide as we counted the blood crystals. We have divided the results into four classes, those

Below 7,000.	Between 7,000 and 10,000.	Between 10,000 and 16,000.	Over 16,000.
88	108	132	42

We have found that patients have their own peculiarities as to leucocytes, some seldom giving counts above 5,000 or 6,000, others seldom below 12,000 or 14,000, and one patient has shown an individual peculiarity in his differential count, having small lymphocytes increased out of proportion to the polymorphonuclear leucocytes.

We have found that as a rule before a series, and at times before an isolated fit, there is a fall in the number of leucocytes often to as low as 4,000 or 5,000, and that during a series the number will gradually rise, and that after a series the count will often be 19,000, or 20,000 or more.

In one case of status, on a day in which the patient had 77 fits, two days before her death the leucocyte count totalled over 70,000. During an hysterical attack which in one of our patients often replaces a fit, we have noted a leucocytosis of over 20,000. In several cases in which the leucocytes have for one month been consistently higher than during another, we have observed that during the month of high count

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there have been fewer fits, also that during a free interval the leucocyte count is higher than at the time of taking fits. As to the differential count we have found, with the exception already mentioned, the relationship between the large, small, and polymorphonuclear to be about normal, and that in the post-epileptic rise, the increase in number is almost entirely in the polymorphonuclear leucocytes, when of necessity they become increased out of proportion to the others.

Blood-Pressure.

We have made 258 examinations on the systolic blood-pressure by means of Tycos' sphygmomanometer. Of these examinations 134 have been made on 64 male patients and 124 on 51 female patients. The pressure has been taken both in the recumbent and standing positions on each examination. The patients are of all ages from 20 to 70 years, the majority being between 30 and 50 years of age.

The results are as follows:

	Below 100 mm. Hg.	100–120	120–130	130–150	150–170	Over 170 mm. Hg.
Male patients:						
Standing:	7	56	35	24	11	1
Recumbent:	7	45	37	32	8	4
Female patients:						
Standing:	32	51	18	9	10	4
Recumbent:	23	59	15	18	7	2

Of the male patients, on 62 occasions the pressure in the lying position exceeded that in the standing position. On 22 examinations the pressure when standing and lying was equal. Of the female patients on 56 occasions the recumbent pressure exceeded that of the standing, and on 17 examinations the pressure in the two positions was equal.

The significance of the fact that more than half the blood-pressures taken by us were equal or higher in the recumbent position than when standing we do not understand. Ludlum and Carson White in an instructive article mention this variation of blood-pressure as occurring in some cases of dementia

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præcox, giving certain Abderhalden reactions, and the results they obtained by giving the underactive gland (16).

Calcium.

Calcium salts have for some time been considered of use in the treatment of epilepsy, and many cases have from time to time been reported that have greatly improved on calcium; others have reported that no good but harm results from its use. As far as we are aware no concise account of the use of this drug in epilepsy has been written, nor any clear reasons for or against it advanced. The best summary of its employment we have seen is contained in an Editorial Review of Epilepsia. Here it states: "Sabbatani concluded that calcium in the cortex exercises inhibitory influence, and that its diminution may bring about convulsive phenomena" (6). The same review quotes Donath's conclusions: "That calcium plays no important part in epilepsy or tetany." These conclusions he bases on 9 cases treated for 124 days. Sir J. Barr says that in epilepsy all soluble calcium salts do good, and advises that decalcifying agents such as acids and fruits be avoided (9). Blair Bell states that hystero-epilepsy is due to depletion of lime salts from the tissues, and that calcium lactate may cure this condition (10).

We have for the last twelve months treated 20 male and 10 female cases with calcium, either alone or combined with bromides, and during the last six months have added one or more extracts of the ductless glands. All except two of our patients are insane epileptics of many years standing; the class of case of which Turner says—"that in confirmed epileptics, with frequently recurring fits, little if any benefit is to be derived from treatment, whether medical or dietetic" (5).

Of these 30 cases none were any the worse for receiving calcium. Donath records that he had to stop treatment in one of his cases on account of increasing fits (6). Five of our cases, all male, are neither better nor worse. Thirteen have had their average number of fits reduced by half or more than half, the other twelve have shown a lesser reduction. In several in whom the fits are not much reduced in number they are less severe, and the after-effects are much less; many are mentally brighter and are capable of more work. Two who had not

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worked for years have taken to doing so since being treated with calcium. Their outlook is brighter, and they have more interest in life.

Glands.

Having had some success with treating these patients with calcium we then added to the treatment the extracts of various ductless glands, doing so in the first instance because of their influence upon calcium metabolism. We have used extracts from the thymus, thyroid, parathyroid, suprarenal, and pituitary glands. All these have appeared to be of use in some cases; all with the exception of thymus have apparently done harm in other cases. The indications for any special gland extract in any given case are at present vague and indefinite. The influence which the secretion of these glands have upon calcium metabolism is said to be as follows:

Thymus—removal of this gland increases the calcium excretion (11). It is said to be engaged in hindering the formation and neutralising the excess of acids in the organism; its enucleation leads to acid excess. A puppy without a thymus lacks intelligence (12).

Suprarenals—removal leads to retention of lime in blood and tissues and prevents excretion of calcium (9).

Pituitary extract causes increase of calcium in the blood (13). Thyroid and ovarian diminish the free and fixed lime in the blood and tissues and thus lessen viscosity. If the thyroid is removed the calcium index rises.

Parathyroids control the distribution of calcium; if the secretion is deficient the tissues lose calcium (14).

If the thyroid and parathyroid are removed in cats the animals have convulsions (11).

Of these glands we have found the thymus to be of most use and the only one from which harm may not occasionally result. We used thymus as it is the gland that undergoes definite change at the time that the commencement of epilepsy is commonest. We looked upon the hypertrophy and persistence of this gland, which is often found in epileptics, as a compensatory one, and thought that its secretion might be needed more in these patients than in normal people. The blood of epileptics is less alkaline than that of others, and the thymus is credited with neutralising acid excess (12). Myers

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states that in acid intoxication the calcium content of the blood is increased, probably at the cost of the tissues. He also says that oxalic acid poisoning is relieved by calcium, owing to its replacing the calcium withdrawn by the oxalic acid (15).

We have been partly guided by the blood-pressure as to which gland to give (16).

Turner says that epilepsy commences most commonly during the time of the greatest activity of the thymus, and that thymus given to epileptics aggravates the disease (5).

The female patients have on the whole made more improvement on the calcium treatment than the men. Some have been more regular in their menstrual periods while on this drug than they were formerly. Blair Bell says that menstruation is dependent upon a certain supply of calcium, and if this is deficient the function will not take place. He also says that if a patient suffering from amenorrhea due to debility be given calcium the function will become reestablished (11). We have treated two cases of primary dementia, both of whom had amenorrhea for over three years, as he advises. The first case menstruated within a month of the commencement of the treatment, and has now done so regularly for over twelve months. The physical improvement in this patient was beyond expectations, she having put on two stones in weight and maintained it. The other case did not respond so readily, but after taking calcium for three months, and when also taking pituitary gland, the menses reappeared. We suggest, therefore, that the irregularity of the katamenia which occurs in epileptics, may be another expression of the same disturbance of the calcium metabolism which is responsible for the epileptic phenomena.

Injections of Calcium Iodide.

We have used intramuscular injections in cases of serial epilepsy. It has been pointed out that calcium is a nervine sedative, and that it lowers the excitability of the cortex to faradic stimulation. It has also been shown by Ringer that calcium salts control the excitability of muscle, which points to the fact that muscle and nerve are less irritable when plentifully supplied with calcium. Although at the time of a serial attack the coagulation time is shortened, and the calcium blood index

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is generally raised, we have thought that this may have resulted from depriving the nerve tissue of calcium, rendering it more irritable, and that by adding calcium to the system this irritability might be lessened. We have treated 60 serial attacks in 13 different patients with the following results:

One injection:

No. of fits after injection	0	1	2	3
Times	21	14	2	4

Twice a second injection was given, the patient not having responded to the first; each time there were two fits after this second injection. Twelve times there was apparently no improvement, the series being as long or longer than the patient's usual average. These injections were given to patients who habitually have their fits in series. Of course it is impossible to say that some of these patients might have had no more fits, without receiving an injection; it is certain from their former habits that the majority would have had. One patient who becomes extremely dull and is only semi-conscious after a few fits, becomes quite conscious and almost bright within half an hour of receiving calcium in this way. The calcium iodide is prepared according to the directions given by Sir J. Barr, *i.e.* it is made up in a solution of glucose in salt solution (17).

We inject as much as 10 gr.; no harmful effect has resulted, except that in two cases abscesses have occurred. We were then using solutions of 4 gr. to the c.c., which is probably too strong. Before and since we have used solutions of half this strength.

Cases Illustrating the Treatment.

A lad, æt. 21, had convulsions at the first dentition; from the age of 2 to 11 years he had about one fit yearly. From the age of 15 he had been getting worse. For six months before admission he averaged 77 fits a month. Most of these attacks were not ordinary convulsive attacks, but he would lose consciousness, run round in a circle from right to left, micturate, and then lie down. He was given a mixture of bromide and calcium every four hours. For the next nine months he averaged less than one fit a month, these being all of the ordinary major type. He then left the Hospital, and is

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now, three years after admission, reported to have about one fit in three months.

CASE 3.—Before comingunder our care, he had for many months averaged 120 fits a month, although being treated with bromides. He is a man, æt. 26, and has been an epileptic since the age of 20. Most of his attacks were what his friends aptly describe as "squealing fits." He would lose consciousness for a few seconds, would scream loudly, and if not held would fall. We have treated this patient for six months. For the first month he was given calcium chloride four-hourly, and thymus gland 5 gr. every morning, and the number of attacks dropped to 90. For the second month he was given in addition potassium bromide, 30 gr., every four hours; in this month the fits increased to 118. For the last four months suprarenal gland has replaced the thymus and 10 gr. of bromide been added to each dose. The number of fits during these four months has been 21, 4, 2, and 0 respectively. In spite of the large dose of bromide that he has been taking, he has put on weight, is lively and good-natured, and works daily on the farm. Before treatment his coagulation-time was on most examinations lengthened.

CASE 4.—A lad, æt. 20, has been treated by us for eight months. Before admission he is stated by his father to have averaged one fit every night. This we did not verify, but commenced treating him shortly after admission. He was given thymus gland, 10 gr., and a mixture of bromide and calcium. During the next seven months he had no fit; during the eighth he had 9, which followed upon the reduction of his bromide from 15 gr. to 10 gr. per dose.

Thymus in this case seems to have undoubtedly done good. It was given as the fits commenced about puberty.

CASE 2.—A man of little intelligence and an eater of all sorts of rubbish, with an especial liking for grass. For six months before treatment he averaged 41 fits a month, with a maximum of 64 and a minimum of 25. All this time he was receiving bromides. For eight months he was given calcium and bromide; the fits during these months ranged from 18 to 6, giving an average of 13. For one month he had in addition suprarenal gland, 5 gr., every morning; this month he had 10 attacks. For another two months thymus replaced the suprarenal; during these two months he averaged 19 fits a

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month. In the course of twelve months treatment he has not in any month reached half his former average.

CASE 25.—A dull imbecile, an epileptic since infancy, for six months previous to treatment averaged 10 fits a month. For ten months she received calcium lactate, 10 gr., and potass. bromide, 15 gr., every four hours. In three of these ten months she had no fits (which had never been recorded of her previously) the monthly average for the whole period being 3·8. Having a low blood-pressure, she was for three months given pituitary gland, 2½ gr. daily, in addition to the calcium and bromide. For these months she averaged 6 fits a month, the pituitary gland seemingly having increased the number of fits. This patient has made considerable mental improvement. She formerly was too dull to converse or to have any interests; she is now a working patient and fairly bright.

CASE 28, æt. 35, an epileptic since 12 years of age. She was dull and lethargic, and her fits are associated with a periodic cyanotic condition of her fingers and toes. For the six months previous to treatment her attacks averaged 18 monthly, ranging from 16 to 21. For two months she was given calcium lactate alone, for which months her fits averaged 12. For two months bromide, 15 gr., was added to each dose of calcium, for which time the monthly average of fits rose to 15. As she on all examinations had a moderately high blood-pressure, she was for three months given thymus gland daily, as well as the calcium and bromide, the resulting average of fits being seven a month. For four months she received thyroid gland three days alternately with the thymus, the monthly average of fits rising to 10. Since taking thymus and calcium the attacks of cyanosis, which formerly were very frequent, have almost disappeared. This patient improved with calcium alone, but made a more decided improvement when taking thymus in addition. There was a slight increase in the number of fits with thyroid gland, but when taking this gland she becomes mentally much brighter.

CASE 23.—A woman, æt. 66, an epileptic since the age of 54 years. This is a case of alcoholic origin, and arose at the time she ceased to menstruate. For six months previous to treatment she had averaged 21 fits a month, with a range of from 13 to 29. For four months she received calcium and suprarenal gland, with a resulting average of 13 fits a month,

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showing a maximum of 17 and a minimum of 5. For one month 5 gr. thyroid replaced the suprarenal, with the result that this month she had 34 fits, the most ever credited to her in any one month. This patient improved with calcium and suprarenal gland and without bromide. Thyroid gland with her increased the number of fits.

CASE 31.—A boy, æt. 19, an epileptic since infancy. For the twelve months previous to treatment he averaged 6 fits a month, ranging from 1 to 8. His epileptic attacks are associated with sexual instability, as before a fit he practises onanism freely. For three months he has taken thymus, 5 gr. daily. During the first month of treatment he had no fit, in the second 4, and in the third 1. The patient states that since taking thymus his genital organs have caused him less temptation, and to this he attributes the diminution in the number of fits.

Pathogenesis of Epilepsy.

Various writers have assigned numerous causes for the recurrent explosive attacks which characterise epilepsy. These may be classified as

(1) Toxic.
(2) Vascular.
(3) Infective.

The supporters of the toxic theory do not agree as to the nature of the toxin. Krainsky says ammonium carbammate, Haig uric acid, whilst others support a non-specific intoxication due to some failure of the digestive functions.

Experiment in our hands failed to justify the supposition that there is a specific toxin in epilepsy. Krainsky by subcutaneous injections into rabbits of blood taken from epileptic patients in conditions of status produced convulsions and death of the animal in 4 or 5 days. His results are quoted by many authors, but as far as we have been able to ascertain have not been repeated. We have injected 3 guinea-pigs with 2 c.c. of blood, aud 3 with 2 c.c. of cerebro-spinal fluid, taken from three patients suffering from status epilepticus, and beyond a slight malaise the animals showed no ill-effects.

That the agent responsible for the convulsions is a non-specific toxin hardly needs refuting. There are too many

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cases of intestinal toxæmia which do not exhibit symptoms of epilepsy. Russell's vasomotor explanation (18) has not been supported by pressure records made by Munson (22).

J. Turner (5) has observed intravascular coagula in the central nervous system, and offers them as the cause of the attack, postulating, however, as do many supporters of the toxic theory, a brain hereditarily and structurally predisposed to irritability and convulsions, which seems to be begging the question.

Bra, and more recently an American writer, have claimed to have isolated specific organisms from the blood of epileptics. The trend of modern opinion, however, is in favour of the biochemical theory, as expressed in the quotations at the head of the article.

The analogy of reflex action may usefully be applied to reactions of the organism of a higher order. It may be stated that motor actions occur in response to conditions which arise in the environment, using the term to include endogenous as well as exogenous states. It follows then that every motor action is preceded by an afferent impulse, which in the case of voluntary action may enter consciousness, whilst in the case of the vascular and intestinal musculature the reaction is outside the field of consciousness. The environmental condition may not be immediate in point of time but may remain, or rather the conception of it, as a motive to action. Ordinarily, then, a motor action is elicited by the excitation of appropriate cortical motor cells by some higher centre, and the action is adequate to the purpose. This adequacy depends on inhibitory and possibly facilitatory mechanisms in the cortex which confine the impulse to its proper channel. The complex and intimate nature of the interrelations of the cortical cells by association paths explains the importance of the inhibitory functions, which have been attributed to cells of the second and third layers.

In epilepsy degenerative changes have been described in these layers, and Southard has advanced an explanation of the epileptogenous discharges, suggesting that removal of inhibitory control permits an uninterrupted excitation of the motor cells (19). Whether or not inhibitory functions are localised in these cells, it seems certain that their activities are manifested at the synapses.

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The Epileptogenous Discharge.

The outstanding features of the epileptic crises, the disturbance of consciousness and convulsive attacks, indicate that we must look to the central nervous system for the rationale of their causation.

The convulsions mean simultaneous activity of the cortical motor cells, and necessarily an abeyance of inhibition. We suggest that the fundamental pathological change is an alteration of the chemical or physical state of the synapses depriving them of selective or inhibitory activities. In this connection it is instructive to consider certain diseases in which there are specific nerve toxins, *e. g.*, rabies, tetanus, and strychnine poisoning. In these a sensory stimulus precipitates a convulsive attack.

"Reflex epilepsy," and cases exhibiting epileptogenous zones, are analogous to these, and the relation between a sensory stimulus and the occurrence of an epileptic seizure is well known. In one of our cases the first convulsive attack followed a fright from an alarum clock; in another, a patient æt. 33, the first fit occurred while having a cold shower. A third patient, to whom we were giving injections of calcium iodide, always became extremely suspicious and irritable after a fit, and resisted strongly when an injection was being given, with the result that he invariably had another fit. In the first two cases there was a sensory impression, in the last an emotional state, which normally produce physiological reactions, *i. e.*, movement expressing fear or surprise, shivering and movement of resistance respectively, by excitation of appropriate cortical motor cells. The exciting stimulus in these patients was, however, distributed widely through the motor areas, with the result that convulsions occurred.

The disturbance of consciousness is explicable on the same supposition that the originating stimulus is uncontrolled by the inhibitory mechanism. Lugaro states, "the fundamental character of the phenomenon of consciousness is distinction" (20), *i. e.*, clearness of consciousness is proportional to the restriction of its field.

The "Law of Avalanche" of Ramon y Cajal is an expression of the complexity of neuronic associations in afferent paths (20). We suggest, therefore, that consciousness is

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swamped by an overflow of the ascending impulse to numerous cortical areas, the process being comparable to the loss of consciousness that may occur with the reception of a severe sensory impression.

Evidence of Metabolic Disturbance in Epilepsy.

Munson (2) has reviewed the evidence of disturbance of metabolism in epilepsy, and finds the results of different authors somewhat discordant. Much work has been done on the urinary constituents, particularly after convulsive seizures, when one might expect the results to be invalidated by the presence of katabolic products. A reduced alkalinity of the blood has been established, as also a shortened coagulation-time.

We carried our observations over long periods, and were enabled to follow the daily changes.

Our conclusions may be summarised thus:

Calcium: The calcium index of the blood is low in epileptics, with tendency to rise after a serial attack.

The excretion of calcium in the urine is low, but shows a a rise some days before a series.

The coagulation-time is shortened, with a further shortening before a series, and a lengthening after.

The alkalinity of the blood is low in epileptics, and there is a fall before a fit.

Phosphorus excretion we have observed in some cases to be low before a series.

The Importance of Calcium in Metabolism.

In recent years the importance of calcium in the economy of the body has been fully recognised. Its presence is necessary for the coagulation of the blood and muscle, for the action of rennin, and Ringer demonstrated its influence on the contractility of cardiac muscle.

Sabbatani showed that calcium salts lowered, while sodium oxalate enhanced, the excitability of the cortex (6), and Roncorini demonstrated the inhibitory influence of calcium salts, and opposite influence of neutral sodium phosphate (6).

The association of the menstrual period and the puerperium with increase in the number and severity of epileptic seizures is well known. In this connection it is interesting to note that

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Blair Bell found the menstrual fluid to contain a considerable amount of calcium. The onset of lactation involves a drain by way of the milk. Good results have been obtained in the treatment of epileptics with calcium. We have been able to cut short serial attacks by subcutaneous injections of calcium iodide and by intravenous injections of calcium chloride. Ballantyne has treated cases of eclampsia with intravenous and rectal injections of calcium chloride with good results (23). There is reason to suppose, as indicated by experiments referred to above, that between calcium and sodium salts there is a physiological antagonism; if this is so, the beneficial results of salt-free diet and calcium treatment in epileptics are explicable by a substitution of calcium for sodium, with the effect of reducing cortical irritability.

The organs responsible for the disturbance of calcium metabolism may possibly be found in the ductless glands. Marked changes do occur in these tissues, the most frequent being persistence and enlargement of the thymus, the significance of which we think has been underestimated.

Sir W. Gowers says that more than 25 per cent. of epileptics have their fits between the ages of 12 and 16 years (21), the period of puberty, when retrograde changes occur in the thymus.

We think that the periodic crises of epilepsy represent an exaggerated psychomotor reaction, there being an afferent impulse which excites a wide area of the cortex and causes unconsciousness and an uninhibited motor excitation, the abeyance of inhibition being the consequence of deficient resistance or refractivity at the synapses, and due probably to disordered calcium metabolism.

References.

(1) *Allbutt's Medicine*, vol. viii.

(2) Munson, J. F.—"Is Epilepsy a Disease of Metabolism?" *Epilepsy and Epileptics*, 1906.

(3) Bell, W. Blair.—"Estimation of Calcium Metabolism," *Brit. Med. Journ.*, vol. ii, 1912, p. 698.

(4) Bell, W. Blair.—"General Calcium Metabolism," *Brit. Med. Journ.*, vol. i, 1909, p. 517.

(5) Turner, W. A.—*Epilepsy*, 1907.

(6) "Editorial Review of Epilepsia," *Brit. Med. Journ.*, vol. i, 1910, p. 281.

(7) *The Medical Journal of Australia*, March, 1916.

https://doi.org/10.1192/bjp.63.260.36 Published online by Cambridge University Press

(8) Martindale and Westcott.—*Extra Pharmacopœia*, vol. ii, 1915.
(9) Barr, Sir. J.—"Lime Salts in Health and Disease," *Brit. Med Journ.*, vol. ii, 1910, p. 829.
(10) Bell, W. Blair and Hick.—"Observations in Physiology of Female Genital Organs," *Brit. Med. Journ.*, vol. i, 1909, p. 517.
(11) Bell, W. Blair.—"General Functions of Ductless Glands in the Female," *Lancet*, April, 1911.
(12) Thursfield, H.—"Status Lymphaticus," *Clin. Journ.*, June 16th, 1916.
(13) Bell, W. Blair.—"Use of Hermones in Obstetrics," *The Practitioner*, February, 1915.
(14) Herty, A. F.—"The Parathyroid Glands," *The Practitioner*, February, 1915.
(15) Meyer, Hans.—"Action of Lime Salts," *Brit. Med. Journ.*, vol. ii, 1910, p. 1594.
(16) Ludlum and Carson White.—"Thymus and Pituitary in Dementia Præcox," *Am. Journ. Insan.*, April, 1915.
(17) Barr, Sir J.—"Rôle of Lime Salts as Therapeutic Agents," *Brit. Med. Journ.*, vol. ii, 1912, p. 695.
(18) Russell, A. E.—"The Ætiology of Epilepsy," *Epilepsy and Epileptics*, 1906.
(19) Southard.—"Histopathology of Epilepsy," *Epilepsy and Epileptics*, vol, v.
(20) Lugaro.—*Modern Problems in Psychiatry*, p. 103.
(21) Gowers, Sir W.—*Epilepsy*.
(22) Munson, J. F.—"Heart's Action Preceding Epileptic Seizures," *Epilepsy*, 1907.
(23) Ballantyne, J. W.—*Brit. Med. Journ.*, vol. ii, 1912, p. 1122.

The Origin of Mental Power. By CASPER L. REDFIELD, Chicago.

THE ordinary biological teaching is to the effect that the inheritance of the child is not affected by the education of the parent. That dictum is not based upon a direct investigation of the matter itself, nor is it based upon an investigation of anything which is related to human intelligence. The dictum is nothing but an unwarranted deduction from observations on the colours of animals, and some experiments on amputating the tails of mice.

Men have been educated more or less regularly in our schools for several generations; horses have been educated on the race track; and hunting dogs have been educated in the field. The education in these cases has been both mental and physical, and an investigation of the thing itself tells a very different story from that told by the biologists. That story

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