Part I.—Original Articles.

THE SIXTEENTH MAUDSLEY LECTURE: PHYSICAL SYMPTOMS IN ACUTE CONFUSIONAL INSANITY.

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I am fully aware of the honour and responsibility conferred on anyone who is asked to deliver a Maudsley Lecture. That great physician realized that the knowledge of medicine advances by devious paths. I have availed myself of his broadmindedness to lay before you to-day some of the physical symptoms associated with a group of mental cases labelled "acute confusional insanity". I will lay before you facts which support the belief that in all these cases the departure from health affects the functions of the whole body, the heat-regulating centre, the cellular and serum defences, the renal functions, the carbohydrate metabolism, and the effect of the injection of insulin on low blood sugar.

The main question which should always be before us when considering the problem of mental diseases is, What are the causes of these disorders? It is so obvious that it is impossible to treat a disease without the knowledge of the cause or causes, that it looks almost foolish to make such a statement. It is a fact that the hospital environments of our patients have improved in the last forty years out of all recognition, and that the nursing in mental hospitals is intelligent and excellently trained. Patients, many of them admitted in a deplorable condition of malnutrition and neglect, respond to their new environment in a marked manner. That is as it should be, but we must admit that the incidence of mental diseases has not been reduced, nor has the recovery-rate of these illnesses been raised. The physician in charge of such hospitals who is to reduce the incidence of these diseases and raise the recovery-rate must know more about causation than we know now. We talk of early cases, but we do not even know what early cases are; it is highly probable that a sudden onset of confusion or mania or delirium may be merely an incident in the course of a long-continued insidious disease; impairments or underminings and premonitions of such present no external evidence and are not readily assessable.

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There is one factor in causation which we are all more or less agreed upon, and that is the hereditary predisposition to insanity. Hereditary predisposition exists in at least 40% of the cases we have to treat. But there are cases where no trace of heredity can be obtained, and it is reasonable to suppose that a predisposition to any bodily weakness must be gradually evolved in a family, from a period when no such predisposition existed.

My observations on acute confusional insanity must be preceded by a definition. It is a group of diseases of adolescence and middle age; it is not at all common in the climacteric or old age. There is a prodromal period of mild confusion, incapacity for connected thought with sleeplessness. This is followed, often quite suddenly, by complete lack of knowledge of time and place, with vivid and often terrifying hallucinations of hearing and sight, great motor restlessness and rapid heart action. Delirium, more or less severe, is always present in first attacks. The patient looks very ill; there are sordes on the teeth and lips, the tongue is dry, foul and cracked, the habits are untidy, the lumbar centres discharging their functions reflexly. Common sensibility is greatly reduced. With nursing and care, 90% of these cases recover. First attacks almost always recover, though they may last for two or three years. The mental symptoms gradually subside, sleep returns, but at first the sleep is disturbed as if a condition of delirium existed during the state of sleep. When recovery is complete, the patients often put on a great deal of bodily weight—a fact also noticed as common in patients recovering from some bacterial infections. To judge by the records of the cases I know, 40% of these confusional recoveries relapse. The patients who suffer from prolonged original attacks, taking two, three and even five years before sanity is restored, make excellent recoveries, and, so far as my records go, never relapse. The patients whose initial attacks are short are the cases that relapse. The first relapse may repeat the symptoms of the original attack, but third and later attacks show an alteration in the mental symptoms. Confusion is less marked; noise, restlessness and sleeplessness are all there, but the typical delirium of the first attack is not in evidence. Hallucinations persist and become chronic, and delusions based on these sensory disturbances are frequently expressed. The attacks now may even resemble manic-depressive excitement, and require a history to assist in the true diagnosis.

We admit many patients into our mental hospitals who, without any history of an acute onset, present all the symptoms of these chronic confusional cases. They are undoubtedly cases of chronic toxæmia, and some of the histories show insidious long-continued onsets. I merely mention these chronic cases to point out that, if the causation of the acute conditions can be discovered, many of these so-called chronic cases can be treated with good hope of recovery. I have seen many of them recover.

All of us who have seen a typical acute confusional case, without any obvious cause, in what one might call the typhoid state, must have been struck with the

fact that though the patient looks very ill, the bodily temperature of the vast majority of them shows so little disturbance; 100° F. is not seen very often, and disorder of the heat-regulating centres is very transient, lasting one or two days at most. Let us say that the acute confusional patient develops an acute intercurrent disease, such as erysipelas, particularly erysipelas of the head and face, the temperature runs up to 104° and 105° F. In 99 cases out of 100 the mental symptoms clear up at once, the disease is cut short and recovery may follow, or the febrile attack may originate from the undiagnosed local focus of toxæmia. I saw a case some years ago of a somewhat over-nourished gentleman who suddenly developed a condition of confusion and delirium. The only physical symptoms were gastric disorder and a rapid pulse of 100 per minute. A week later he developed a temperature of 103° F., the mental symptoms cleared up, and an acute cholecystitis was diagnosed. He refused surgical treatment, and he has had two subsequent attacks, both of which terminated suddenly with the onset of a febrile attack. Compare these cases with cases of apical pneumonia, sometimes certified as cases of confusion and delirium. They have temperatures of 103° and 104° F., and their mental symptoms are so typically those of acute confusion that to the casual observer the thermometer is the only certain test to indicate that your patient is suffering from an acute infection. Take a case of acute puerperal mania with foul lochial discharges; you have again a patient with all the mental symptoms of acute confusion and delirium, with temperatures of 104° F. and higher, and yet the high fever in these cases does not assist mental recovery; rather the reverse. So we seem to have two types of confusion with delirium, one without fever, the other with fever. In the first class, if an intercurrent disease supervenes accompanied by raised temperature, the patient will certainly improve and even recover. In the second class, with accompanying fever, that symptom may have to be controlled, to assist recovery and save the life of the patient. But they have a factor common to both—the complication of the mental symptoms. We all see cases of chronic toxæmias, pneumonias —apical and otherwise—puerperal cases with foul lochia and high temperature without a trace of mental symptoms. Why should these cases every now and then become mental cases? Are they as individuals hypersensitive to some particular group of poisons, or are they inadequately supplied with the defences which are common to mankind in general? Or are the mental centres unstable?

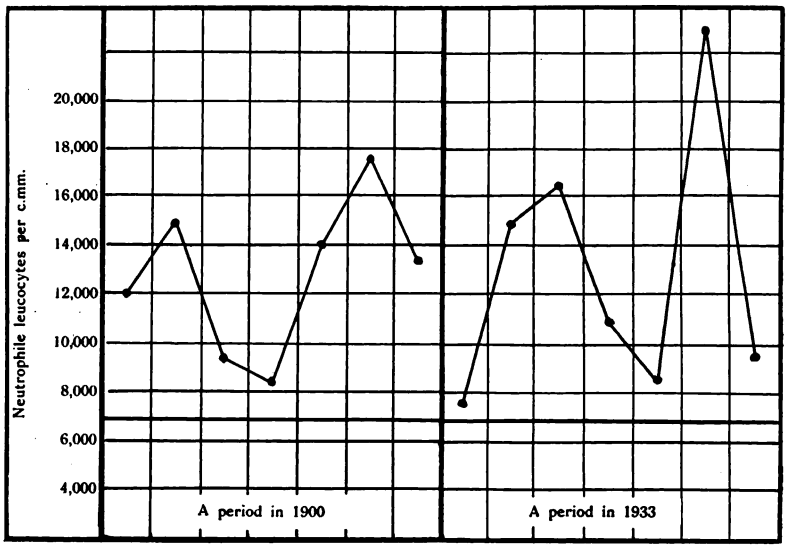
Many alienists have noticed these beneficial results of febrile attacks and attempted to simulate them. My experience, in pyretotherapy—started long before the method of induced malaria gave such successful results in the treatment of general paralysis—is as follows: Intravenous injections of streptococcus vaccines, two hundred million to the c.c., gave no febrile reaction whatsoever. Polyvalent staphylococci vaccines gave a delayed and very mild reaction 48 hours after injection. Some of the patients treated with

staphylococcus vaccines improved. Injections of typhoid and paratyphoid A and B and *Bacillus coli* vaccine gave marked pyretic reaction, but no beneficent results followed. Malaria was tried in one case of some five years' standing and was followed by a rapid recovery, but it has been tried repeatedly since without a single success.

My opinion is that intercurrent illnesses, plus fever, associated with streptococcal infections are those which produce the beneficial effect in confusional cases which have become chronic. All my recoveries were accidental infections with erysipelas, in addition to two cases that recovered after attacks of scarlet fever.

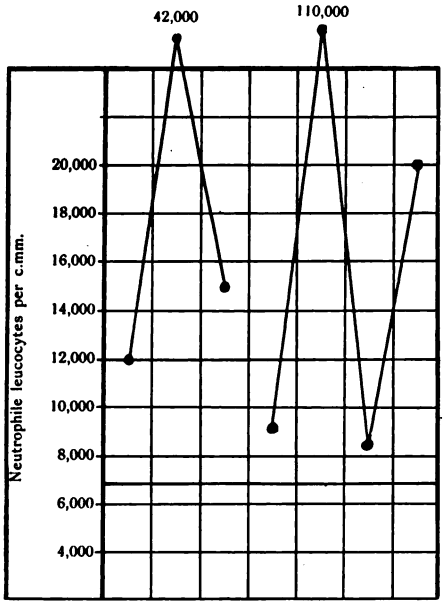
Many years ago, in my Morison Lectures for 1908, I drew attention to the fact that in confusional insanity there was a marked leucocytosis in the acute stages of the disease, and the increase was in the neutrophile cells—cells which, among other causes, are increased in certain bacterial toxæmias. In the majority of confusional cases which recover, the leucocytosis actually increases and remains above the average of health during the period following recovery, to fall again on relapse, and rise again on a second recovery. It was then my practice to assist the recovery of such cases by raising the leucocytosis by oral administration of nucleinic acid, subcutaneous injections of various bacterial vaccines, terebine (30% in sterile olive oil), and injections of sterile distilled water. I am now against bacterial vaccines used in ignorance of the causation of the disease, for they may load the dice against the patient. Terebine injections are painful, and liable to produce abscess. Subcutaneous injections of distilled water 1 c.c. to 5 c.c. per day are sometimes very efficacious, and there is no risk of danger. Whatever the treatment we adopt which leads to apparent success, remember we are only temporarily raising the resistive power of the patient; the toxæmia persists. Such recovered patients live for ever sitting on a volcano. Under stress or strain, physical or mental, the toxæmia will overmaster the defences and an attack of confusion with delirium and hallucinations may follow. I show you a neutrophile leucocyte chart which extends over a period of thirty-three years (Chart 1). The patient was admitted to the hospital, a young woman, suffering from a very acute first attack. She recovered and relapsed twice in the hospital and then went home. For fourteen years she had repeated threatenings of attack. I saw her at least three or four times a year, and every time I saw her I made a blood examination. On no occasion was the leucocytosis down to that usually regarded as occurring in health. She was treated on general lines, nerve tonics, rest, changes of scene, and no acute attack actually developed. During the war years she was lost sight of, but after the war she came in as a voluntary patient. She was certainly mentally impaired, but not demented. The chart shows a period in 1900 and a period in 1933. During these thirty-three years she suffered from a toxæmia of unknown origin, which undoubtedly impaired her mental health without her ever exhibiting an actual attack of confusion

CHART 1.



NEUTROPHILE LEUCOCYTE CHART.
Case of confusional insanity extending over a period of 33 years.

CHART 2.



NEUTROPHILE LEUCOCYTE CHART.
First rise following injection of urinary proteose; second rise intravenous injection T.A.B. vaccine.

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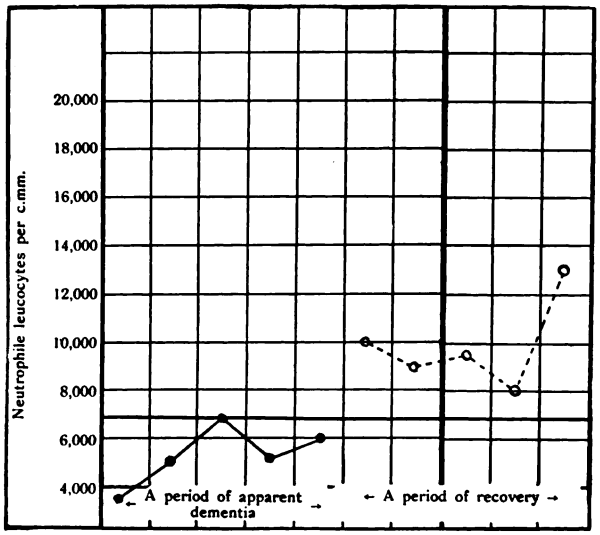
and delirium between 1901 and 1933. One must look upon these leucocytoses as protective conditions. They are certainly not there without a cause. There are people with leucocytosis discharging the duties of life with energy and efficiency and showing no symptoms, mental or physical. One has only to examine controls to satisfy oneself on that point.

So many of these cases during the period of convalescence from acute attacks develop an eosinophilia, a form of leucocytosis which, among other causes, occurs during convalescence from bacterial infection, that I have come to regard an eosinophilia in these confusional cases as a sign of recovery. In

CHART 3.



NEUTROPHILE LEUCOCYTE CHART.

later years I have seen good recoveries result without the presence of an eosinophilia. I always regarded a leucocytosis—whether natural or induced—in the acute stages as a good symptom, denoting a strong resistive power, and a corresponding improvement temporarily at least, but I can show you a chart which upset all these beliefs (Chart 2). This patient had on two occasions an induced neutrophile leucocytosis of 42,000 and 110,000 without the slightest apparent benefit. Yet twelve months later she made a most excellent and unexpected recovery after an illness lasting, in all, over two years. The only facts which I can advance regarding the symptom of leucocytosis are these. Firstly, I have never seen a recovery without a leucocytosis, and, secondly, when dementia sets in, leucocytosis falls. It does not follow, however, that because a leucocytosis is low, with a low neutrophile percentage, the patient will not recover. I show you a chart of a patient with an acute onset, who appeared to sink into dementia, but who finally made a good recovery (Chart 3).

If the disease is directly or indirectly complicated by bacterial toxæmia, the toxins should be excreted by the urine. There are pathological changes in the kidneys of the chronic insane which indicate some toxic irritant, but they are the results of a long condition of chronicity, and not necessarily a symptom of the acute onset(1). The toxin I hoped to obtain was beyond my knowledge, but with the assistance and advice of my friend, the late Dr. James Ritchie, who was then Director of the Laboratory of the Royal College of Physicians, Edinburgh, a substance which certainly deviated complement when mixed with various doses of the serum obtained from confusional cases was obtained. That work and the records of that work were, however, lost during the period of the war. It was not until 1930, when Oriel and Barber (2) recorded their work on urinary proteoses in allergic conditions, that I was reminded of the theory of toxin in the urine. Following the methods of extraction described by these workers, I extracted the urinary proteoses in eight acute and recent cases. In every case the skin reaction was tested with the extracted proteose, and in every case the reaction was negative. There are, however, two facts worth recording: when 0·1 c.c. of a 1 : 1,000,000 dilution was given by an intradermal or subcutaneous injection the patient's mental symptoms were much exaggerated; when a slightly larger dose was given subcutaneously the leucocytosis increased out of all proportion to the dose of proteose administered.

My more recent records of urine examinations show that in acute confusional cases 60% present albumen in the urine and 40% bacteria in the urine, chiefly streptococci and *Bacillus coli communis*. The centrifuged deposits show a marked increase of leucocytes and false tube-casts. These symptoms of renal disturbance are in most cases transient, lasting for perhaps two or three days, but they are liable to return if the patient relapses. Vaccines produced from these streptococci were used as treatment; as before stated, I have discarded them, but the positive skin reaction obtained from these organisms led me to examine the skin reaction in a series of 52 recent acute admissions.

Each patient was tested (1) to streptococci by means of a polyvalent filtrate in a dilution of 1 in 100 (3); (2) to staphylococci by means of a polyvalent vaccine; (3) to tubercle by a mixture of equal parts of human and bovine bacillary emulsions; (4) to *Bacillus coli* by means of a standard vaccine. The results are shown on the accompanying chart (Chart 4). It is surely more than a coincidence that positive skin reactions to streptococci filtrate occurred in 14 out of the 20 cases of confusional insanity.

When working at specimens of urine in the laboratory, I had noticed that the urine of acute confusional cases quite frequently reduced Fehling's solution, but as Fehling's solution is reduced by albumen, which is so frequently present in these cases, and the specific gravity was never high, it never occurred to me that this chemical change was of moment; but when three years ago I made a blood sugar test in an acute case which showed an unusual reading, I started blood sugar observation in every acute case. In the earlier cases Fehling's

CHART 4.

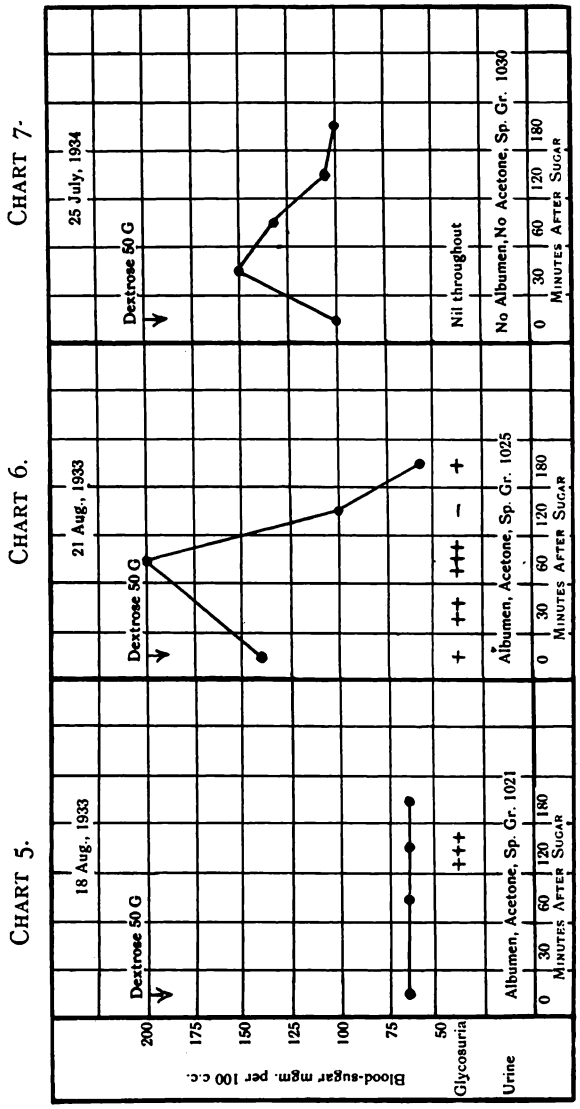
	Cases.	Positive Reactions to Strep.	Staph.	T.B.	*Bac. coli.*
Confusional	20	14	5	1	0
Manic-depressive	22	4	3	8	0
General paralysis	1	0	0	0	0
Schizophrenia	7	1	1	1	0
Enceph. lethargica	2	0	2	0	0
Total cases	52	19	11	10	0

solution was used to test the glycosuria and some of the results were obviously false. I have discarded these results. In the latter cases, which number only fourteen, Benedict's solution was employed. I know that fourteen cases are too few to support an observation, but the results are so interesting that I include them for what they are worth, and possibly some later worker may find them of value. Take, for instance, the chart of an extremely acute case (Chart 5). At the hour 0, on an empty stomach and after a sleepless night, the blood sugar was only 65 mgrm. per 100 c.c. ; 50 grm. of dextrose were given at that hour ; 60 minutes later the blood sugar was the same, 65 mgrm. per 100 c.c., and it was at the same figure three hours after taking the 50 grm. of dextrose at hour 0. Glycosuria was present at hour 3. Albumen and acetone were both present. The specific gravity was 1021. Take a chart of the same case after a good night's rest, the result of a sleeping-draught of chloral and bromide (Chart 6). At hour 0, 50 grm. of dextrose were given ; the blood sugar was 138 mgrm ; at 60 minutes the blood sugar was 200 mgrm. ; at 120 minutes it was 100 mgrm., and at 180 minutes it had fallen to 56 mgrm. The delirium and restlessness were very acute throughout. Sugar was present in every specimen of urine obtained. Specific gravity was 1025 ; albumen and acetone were present. Chart 7 is that of the same patient, who made an excellent recovery. Hour 0 gave a blood sugar of 100 mgrm. per 100 c.c. ; ½ hour later it was 150 mgrm., at 60 minutes 140 mgrm., and it fell to 100 mgrm. at 180 minutes. There was no glycosuria throughout, no acetone, albumen or bacteria present.

Of the fourteen cases examined, all gave abnormal blood sugar : 12 showed glycosuria during the acute stage of their illness ; in the other two cases no urine could be obtained.

Of the seven cases who recovered, glycosuria and albumen completely disappeared in six cases. The blood sugars came within the limits of health, possibly on the low side. One of these recovered cases has already relapsed with the usual symptoms—low blood sugar, glycosuria, albumen and tube-casts. Chart 8 is of a case of confusion complicated by asthma. The two conditions did not exist together. This patient, a young male, was admitted

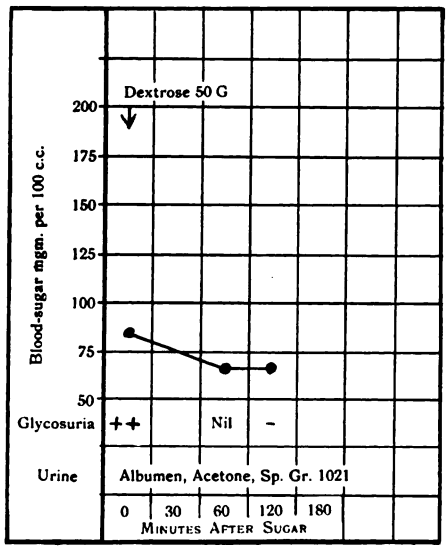
in a state of acute delirium with complete confusion. He was prepared for a blood sugar observation the morning following his admission. When I took the first blood at 9 o'clock the patient was suffering from asthma, and the



delirium and confusion had vanished. His blood sugar then was 85 mgrm. per 100 c.c. He took readily at that hour 50 grm. of dextrose. After 60 minutes the blood sugar had fallen to 65 mgrm. At 120 minutes the blood sugar was still 65 mgrm. He was then greatly distressed, so the observation

was stopped and ephedrine administered. The ephedrine relieved the condition. The patient then vomited, the vomited matter was the supper he had eaten the previous evening at 6 o'clock, and showing no signs of any digestive action whatsoever. Arrest of digestive power is known to exist in the acute stages of confusional insanity, and from the blood sugar chart it is possible that the solution of dextrose taken at 9 a.m. was not absorbed. The only specimens of urine obtained were, first, that obtained at 9 o'clock, hour 0 on the chart, and which reduced Benedict's solution, and secondly, that obtained at 10 o'clock, 60 minutes after taking 60 grm. of dextrose, which did

CHART 8.



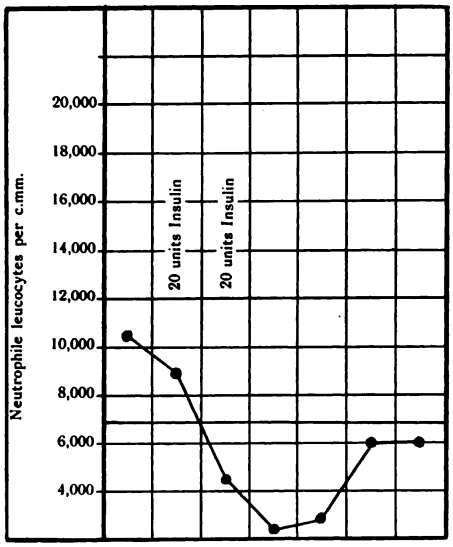
not reduce Benedict's solution. I have examined the blood sugar of 4 cases of asthma not associated with confusional insanity. The blood sugar varied greatly during these asthmatic attacks, and glycosuria was always present. When the patient was free from asthma, the glycosuria disappeared.

Having noticed that the blood sugar in these confusional conditions is low, I tried as treatment insulin injections, 10 units night and morning with 1 oz. of syrup of glucose before each injection (each ounce of syrup contained 13·6 grm. of glucose), plus a dietary rich in carbohydrates. Two cases were selected because they were in poor physical condition. The results of these insulin injections was an exacerbation of acute delirium in both cases, so acute that it was impossible to carry out a blood sugar observation. The only reading I could obtain in one case was so low—35 mgrm. per 100 c.c.—that I doubt its accuracy. In both cases leucocyte counts could be made, and

both showed a low neutrophile percentage (Chart 9). Injections of insulin given in ordinary conditions of diabetes raise the leucocyte count. Discontinuing the insulin and doubling the glucose ration in these cases cut short these attacks.

Taking these blood sugar charts as a group, the blood sugar is below that of health; in conditions of confusion and delirium the low blood sugar might be attributed to exhaustion, but in cases of acute confusion with vivid hallucinations but no motor restlessness the blood sugar is still low. Chart 10 is from a young man, æt. 30, in his second attack. At hour 0 the blood sugar was

CHART 9.



NEUTROPHILE LEUCOCYTE CHART.
Showing fall following insulin injections with acute delirium.

60 mgrm. per 100 c.c. At 60 minutes after the administration of dextrose the blood sugar was 140 mgrm., but it fell one hour later to 75 mgrm., and an hour after that to 65 mgrm. Glycosuria was present throughout. The specific gravity of the urine was 1024 at hour 0, and 1027 at hour 1. There was no albumen, but *Bacillus coli* was present.

In all these cases with more or less extensive glycosuria, even with so low a renal threshold as 65 mgrm. to the 100 c.c., none presented symptoms of diabetes. All were certainly badly nourished, and when they recovered, their body-weight and general physical conditions were much improved. In conditions of non-diabetic glycosuria the causes advanced are (1) defective storage, (2) hyperthyroidism, (3) sepsis, which may disturb carbohydrate metabolism, (4) dyspituitarism.

CHART 10.

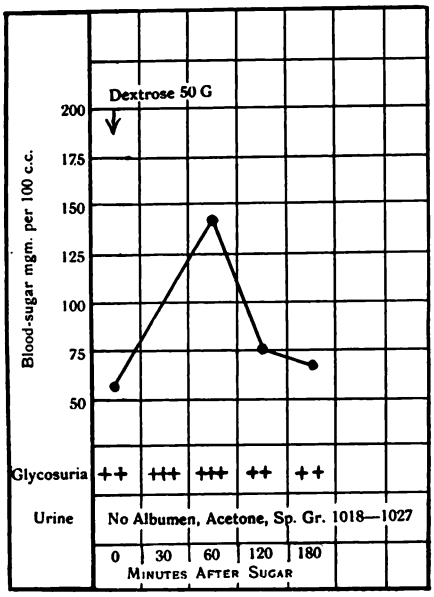


CHART 11.

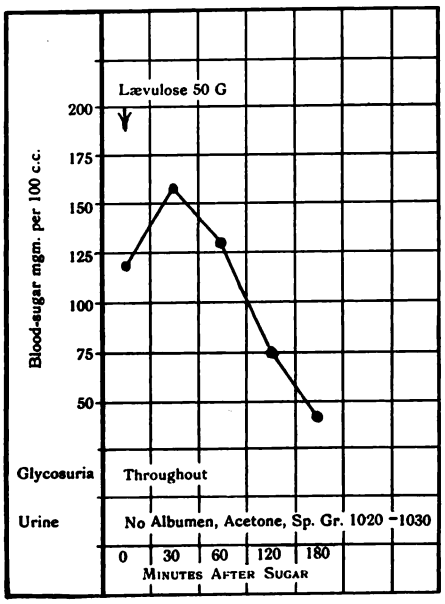


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CHART 12.

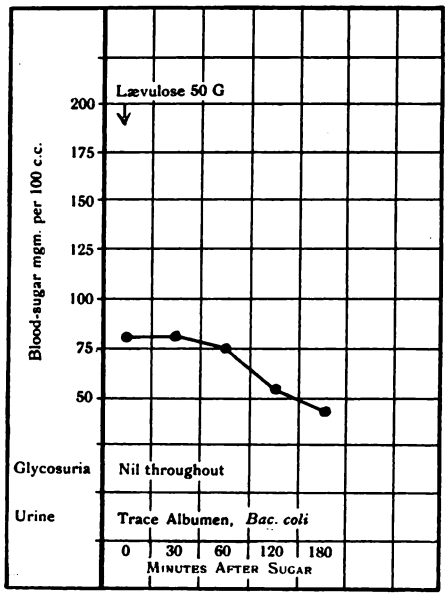
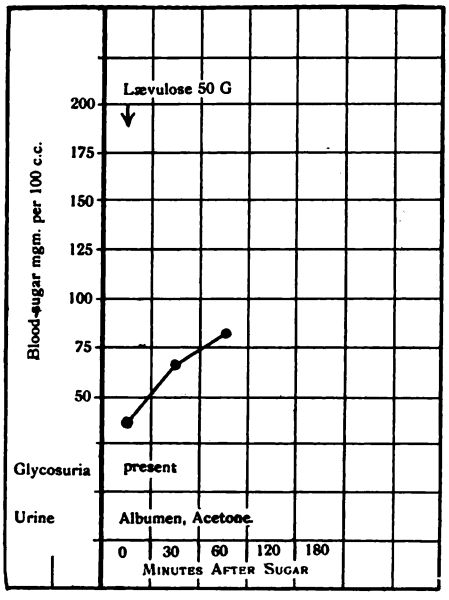


CHART 13.



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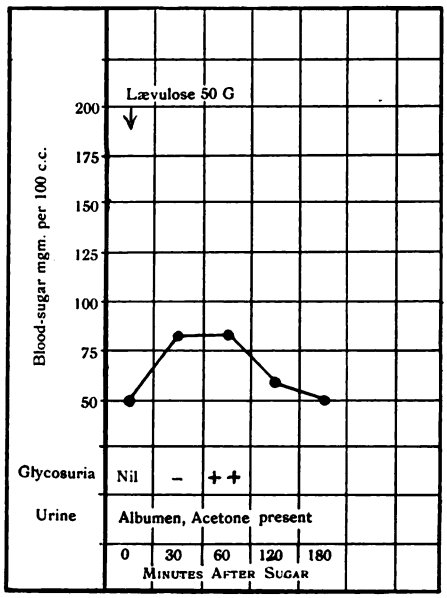
Blood sugar tests conducted with lævulose instead of dextrose are employed to test the part the liver plays in sugar metabolism. In the ordinary condition of health a dose of 50 grm. of lævulose shows no rise in the sugar curve. I show you the blood sugar chart of four acute recent cases. Chart 11 is that of a young male very confused and hallucinated. The blood sugar curve rises from 120 to 160 mgrm. in half an hour, and does not fall to 75 until 120 minutes later. Chart 12, a young girl, confused, hallucinated and with great motor restlessness, 30 minutes after taking 50 grm. of lævulose the blood sugar rose from 50 to 80 mgrm., and did not fall until 120 minutes after the taking

CHART 14.



of the sugar. Chart 13, a very acute puerperal case. At hour 0 the blood sugar was on 38 mgrm.; 30 minutes later it had risen to 70 mgrm., and 60 minutes later to 80 mgrm. per 100 c.c. Chart 14, that of a puerperal case recovering rapidly. There is no rise in the blood sugar and there is no glycosuria. Albumen was still present in the urine. So far as I can observe there is no difference between puerperal cases and the confusional cases of unknown origin, excepting that the temperatures in the early acute puerperal cases are high.

I trust I have laid before you evidence which proves that in these conditions which are labelled as mental there is a widespread departure from health in the functions of the body which must be explained. During thirty-five years I have endeavoured to search for causes in all these confusional cases. In over 200 attempts to isolate bacteria from the blood I can only point to two cases in which their presence in the culture fluid was not a contamination; one was

a case of confusion and one a case of manic-depressive insanity. For the rest, causations which I believe to have been genuine and capable of treatment, and where treatment was successful, could be counted on the fingers of one hand.

The day of the solitary worker is done. Medicine has made such advances that one brain is no longer capable of grasping the problem. What we want for research work alone is a ward attached to some great general hospital where the physician in charge with a thorough knowledge of mental diseases can call upon the expert knowledge of a team—bacteriologists, biologists, gynæcologists, pathologists, etc. I do not wish to remove the interests of medicine from mental hospitals. My special ward attached to a general hospital would contain ten beds at most, and there the specialized knowledge of the general hospital staff would be available to assist in elucidating one type of mental disease at a time, such as conditions of confusional insanity—a mental departure from health which is most closely akin to the disorders found in general medicine.

References.—(1) Shera, *Journ. Ment. Sci.*, July, 1931, p. 573.—(2) Oriel and Barber, *Lancet*, August 2, 1930, p. 231.—(3) Kindly given me by Dr. O'Brien of the Wellcome Research Institute.