

not in the finding of the causal organism in the fæces of the ordinary case ; in fact his laboratory " boy " did it regularly. The difficulty was that the carrier gave no signs. A woman patient had dysentery recently, of which she died in three weeks ; and when he made the *post-mortem*, he found she must have had it three years, during which time she gave no signs, but went about her work in the ordinary way. If a pathological test could be established for these cases, that would settle the whole question ; for when once the carriers were eliminated, epidemics would be abolished in a few years ; certainly the disease would no longer be a scourge.

(¹) *Journ. Ment. Sci.*, October, 1913, p. 605.

The Clinical Value and Significance of Leucocytosis in Mental Disease(¹). By D. J. JACKSON, B.A., M.D., Ch.B., Assistant Medical Officer, Cardiff City Mental Hospital, late Assistant Medical Officer, County Asylum, Chester.

THE problem of leucocytosis has been the subject of much discussion in recent years. Amongst the earlier workers on the subject Virchow stands prominent, and he first gave the name of leucocytosis to a temporary increase in the number of leucocytes in the blood, this occurring both in physiological and pathological conditions. During the past twenty years special attention has been paid to this phenomenon, bringing to light some very important information. Amongst later workers Metchnikoff has done more to enlighten us as to the problem than any other worker. To briefly recapitulate his doctrine. The leucocytes protect the organism against harmful germs by catching them up in their pseudopods, by investing them, and thus robbing them of the possibility of exerting their deleterious action externally. The termination of an infective process would therefore depend alone on whether leucocytes possessing this function are present in the blood in sufficient numbers to overcome the invasion of the germs. The doctrine of Metchnikoff has been modified and also extended by other workers, notably Denys, Löwy, and Richter, who have proved that the value of the leucocytes does not depend on their pseudopods, but that their chemical products yield the strongest

protection to the organism. The leucocytes are able by means of the bactericidal or antitoxic substances which they give off to paralyse the toxins produced by the bacteria, and in this way render the microbes harmless by depriving them of the weapons of attack, even if they cannot destroy them.

Much has been written of recent years regarding the clinical significance of leucocytosis. In practically all the acute infectious diseases, and in all disease of bacterial origin in which toxins play an important part, there is generally found during the course of the disease a leucocytosis, *e.g.*, pneumonia, erysipelas, and septic conditions of various origin.

Perhaps the one most carefully studied in this respect is pneumonia, and it can be said that the occurrence of leucocytosis is a constant phenomenon during the typical course of this disease.

Pneumonia is believed by some observers to be a local manifestation of a general disease, and whatever type of lesion the pneumococcus produces, one thing is always observed—the intense stimulation of leucocytic action, both immediately and afterwards during the progress of the lesion. In the infection of the meninges, lungs, or pleuræ, pathological examination shows the lymph-spaces to be filled with leucocytes. Clinically it is recognised that a large white count in pneumonia is of good prognostic significance. From these and other facts it would seem that the leucocyte plays an important part in the resistance to pneumococcal infections. The cases which suffer from a very severe toxæmia, or which are atypical in their course, often show a leucopænia, and it has been shown by several observers (Löwy and Richter, Jacob) that an artificial hyperleucocytosis influences the course of an infective process favourably, at all events in experimental animals.

As a rule the infectious diseases begin with a leucocytosis in which the greatest increase is seen in the neutrophile cells, and it is mainly with these that we are concerned.

Applying the phenomenon of leucocytosis to acute attacks of insanity it is necessary to have a general view as to the probable origin and exciting cause of the attack. The insane person is generally one who starts life with an hereditary taint or neuropathic predisposition, and as he advances to manhood he becomes subject to the action of various toxins arising from different poisons, such as alcohol, syphilis, influenza, etc. In

a normal individual these poisons exert a very deleterious action, in many cases breaking down the strongest constitutions, but in the case of those with an heredity of insanity, crime, tubercle, etc., the toxins of the above microbes are able to work with greater vigour on soil already prepared.

Asylum statistics show how large a proportion of insanity has for its exciting cause such poisons as alcohol, syphilis, tubercle and influenza. Although these may not be directly attributable causes for the attack, yet by lowering the general vitality of the subject they render him liable to other infections which thus precipitate the attack. The typical case of confusional insanity which is daily admitted into the asylums of this country resembles that of a man suffering from an acute toxæmic condition, *e.g.*, we generally find the following picture on admission :—

Patient poorly nourished ; for a considerable period has not been taking his food and sleeping badly ; restless, agitated, and generally confused ; tongue furred, mouth septic ; breath foul, with sordes on the lips ; pulse rapid, feeble, and probably irregular ; bowels constipated ; urine high-coloured, with traces of albumen ; temperature varying from half to two degrees above normal. Examination of the intestinal flora of such a patient shows that it is abnormal, and often septic organisms may be isolated from the genito-urinary tract—the patient apparently suffering from a general toxæmic condition.

In such cases as this, systematic observations on the white cells of the blood are most useful from the view of diagnosis, prognosis, and treatment.

In the following typical cases the method I adopted was as follows : The blood specimens were taken each day about the same time, and preferably not sooner than three hours after a meal in order to prevent the occurrence of physiological leucocytosis due to the digestion of proteids. Blood-count taken by the ordinary Thoma-Zeiss hæmocytometer, and at least two slides taken for the differential count. I generally counted 400 cells in order to avoid sources of error, and by multiplying the number of leucocytes in each c.mm. of blood by the percentage of polymorphs, and dividing the result by 100, the number of polymorphic cells in each c.mm. of blood was computed, and as these are the main fighting cells with which we are concerned, on their number the following charts have been

drawn up. The slides for differential count were generally stained with Louis Jenner or Leishmann, though the May-Grunewald was also occasionally used.

The different types of case examined include the following : Acute mania, acute melancholia, and acute manic-depressive insanity, general paralysis, dementia præcox, and epilepsy. Many of these observations were continued over several months until the patients had either recovered or had come to be regarded as irrecoverable.

CASE 1 : *Confusional insanity*.—E. B—, female (admitted February 20th, 1911), æt. 37. Supposed cause : hereditary factors. Duration : six weeks. History : She had been nursing her baby for some time previous to her admission. She had also a lot of domestic worry and had allowed herself to get into a low state of bodily health.

State on admission.—She was excited, restless, and at times noisy. She talked in a disconnected and almost incoherent manner. Occasionally she had disorientation of place, talking, shouting, and imagining she was on the sea-shore. Said her husband was in the room opposite. She apparently had hallucinations of hearing. She would bury her head in the pillows, talking incoherently about the children, saying she wanted to plough, sow, and reap, made grimaces, ground her teeth, clutching a towel, and was generally excited.

Physically.—She was very anæmic and in a bad bodily condition generally. Her tongue was furred, breath foul, and bowels constipated. Appetite poor. Her heart-sounds were weak and action irregular.

Lungs.—Nothing abnormal could be found.

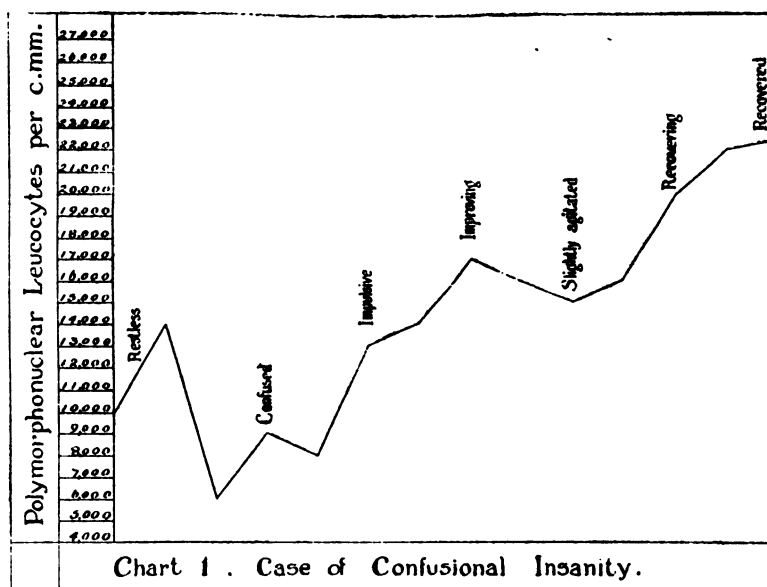
Kidneys.—Ditto.

A leucocytic count on admission showed variations from ten to seventeen thousand leucocytes per c.mm. For several weeks after admission her leucocytic count oscillated, and during this period she continued restless, confused, and at times resistive, noisy, and impulsive, having to be confined to a padded room. She showed a great tendency to constipation, and she was well dosed with Epsom salts, and kept principally on a milk diet, with beef-tea and gruel.

About a month after this treatment was commenced she began to show some improvement ; she became quieter, showed an appreciation of her surroundings, and recognised the fact that she had been ill. She slept much better and began to eat her food. As her mental condition improved her leucocytic count showed a corresponding increase, rising steadily up to

20,000 leucocytes per c.mm. A differential count showed that the greatest increase was to be found in the polymorphonuclear cells, whilst there was a diminution in the mononuclears. Her mental condition continued to improve for about six weeks when she had a relapse, again becoming restless, uneasy, and generally excitable. She again showed a tendency to constipation, and lost all desire for food.

Correspondingly her blood-count fell down to 5-7,000, the polymorphic cells registering only from 57-62 per cent. Careful



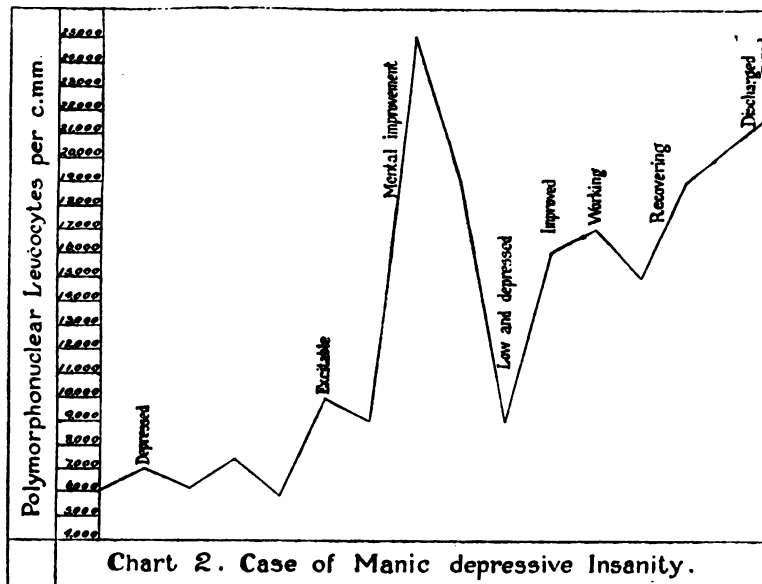
regulation of her diet and bowels resulted in a general improvement of her condition. She again recognised the fact that she had been unwell, and from this onwards she continued to show a decided mental improvement, and was allowed to work in the kitchens, where she evidently felt more at home. After three months' residence in the asylum she was discharged as recovered. During her period of convalescence her leucocytic count, taken daily, showed about 27,000 leucocytes per c.mm., with a high percentage of polymorphic cells, showing that her resistive powers to the toxæmia from which she had been suffering were much increased. On discharge she had increased a stone in weight. A report from her husband a few months

after her discharge showed that her mental improvement was well maintained.

CASE 2: *Manic-depressive insanity*.—J. M. B—, female (admitted December 7th, 1910), æt. 24. Duration: two months. History: No hereditary history or neurosis could be traced. She had neglected herself, and got into a low state of bodily health—lived principally on tea and white bread; had allowed her bowels to remain constipated for a week at a time.

State when leucocyte observations were commenced:

Physical.—Tongue furred and dry. Teeth defective; breath foul;



anæmic and sallow. Temperature was 98·2° F.; pulse, 95. Lungs: her respiratory note was generally weak, but no organic changes could be detected. Heart-sounds almost inaudible, and the apex-beat was displaced downwards and outwards. Her bowels were very resistive to treatment, and it was only by a combination of enemata and Epsom salts that the bowels could be kept open.

Nervous system.—Tongue was slightly tremulous. Knee-jerks diminished. No "Babinski." Eyes reacted sluggishly to light and accommodation.

Mental.—She was dull, and her consciousness to her surroundings was very much clouded. She did not know where she came from or where she was. Her answers to questions were chiefly restricted to "Yes" or "No." She was inclined to refuse her food, and took absolutely no interest in her surroundings. Occasionally she would get out of bed and try to climb through the window.

Her leucocytic count varied from 5,000–10,000 leucocytes per c.mm., with a low percentage of polymorphic cells. Under proper dieting she became more rational in her behaviour, and began to take a slight interest in her surroundings.

Her blood-count rose steadily to 30,000 leucocytes per c.mm., and during this time she continued to show decided mental improvement. She continued to improve for two months when she had several relapses (*vide* Chart II), but in a short time she again started to recover, and from this time onwards the progress of the case was uneventful. She was discharged after six months' residence. During the above remissions her blood-chart synchronised with her mental condition—an increase in the leucocytes going hand in hand with an improved mental condition. It should be noted that for several months before her discharge her leucocytic count remained pretty constant between 23,000–27,000 per c.mm.

Her subsequent history after discharge was good, and she has not had any more attacks.

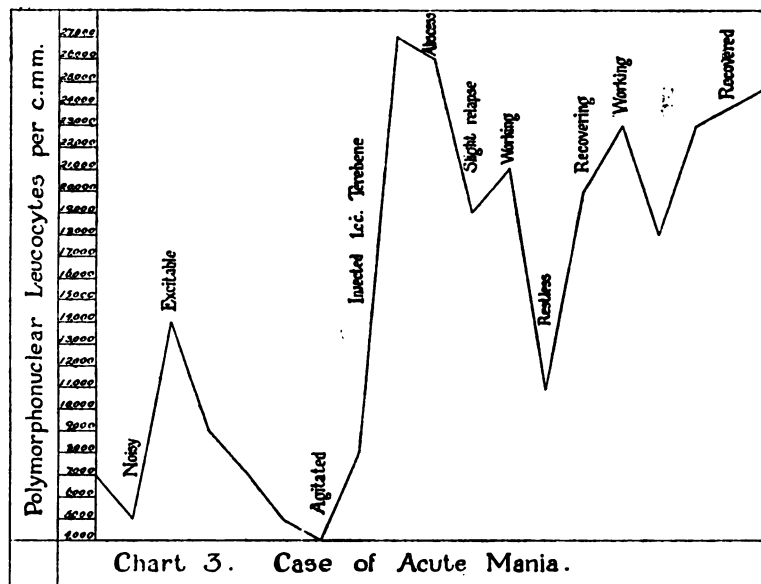
CASE 3 : *Acute mania*.—E. H—, female (admitted February 10th, 1911), æt. 29. Duration : three weeks.

State on admission.—She was very excitable and restless, and it was with difficulty she could be kept quiet. She roamed restlessly round the ward, moved her arms and body into all kinds of positions, and was quite irrational in her behaviour. On being questioned she laughed in a foolish manner and made grimaces, then commenced to chatter to herself in a silly way. She had hallucinations of sight, and used to imagine that her room was filled with people. She was dirty in her habits. Physically: Her tongue was furred, her breath foul, and her bowels were constipated. There were sordes on her lips, and her appetite was poor. There was a slight systolic murmur in her mitral area, but her heart was not enlarged. Normal vesicular breathing was heard over the chest. Her urine contained a slight trace of albumen. Her knee-jerks were diminished. No "Babinski" or ankle clonus present. Her pupils were more widely dilated than normal, and both reacted sluggishly to light and accommodation.

After admission she was given calomel gr. iij, followed afterwards by a saline purge, this being repeated every alternate day. She still continued restless and noisy, so a series of hot baths were given her. These helped to give her sleep and made her much quieter.

Her leucocytic count varied between 7–10,000 per c.mm.

and her percentage of polymorphic cells was about 52-58. After three weeks of treatment she was somewhat quieter, although still foolish and irrational in her conduct. As her leucocytic count did not show any considerable increase, I injected 1 c.c. of terebene into her flank. In a few days an abscess arose at the site of the injection, and as she was rather restless she managed to pull off the dressing, and so got a secondary infection. Concurrently her leucocytic count commenced to rise to a level of almost 30,000 per c.mm., and



mentally she became much more coherent in her conversation and commenced to show an appreciation of her surroundings. By the time her abscess had healed up, she had shown a decided mental improvement, and commenced to take an interest in the work of the ward, although at times she became rather restless.

Her blood-count, taken daily, showed a hyperleucocytosis of about 27,000 per c.mm. with a high percentage of polymorphic cells, a decrease in the mononuclears, evidently showing that she was reacting to the toxæmia from which she had been suffering.

Her mental condition with occasional relapses continued to

improve. She was allowed to work in the laundry, and she gradually resumed her normal mental balance again.

On discharge two months later, recovered, her blood showed a leucocytosis between 23–30,000, the polymorphic cells averaging about 70–78 per cent.

CASE 4: *Mania, with suicidal tendencies.*—C. E—, female (admitted October 10th, 1910), æt. 38. Duration: two weeks.

State on admission.—She was very noisy and troublesome and tore all her clothes off. She would scream and shout for hours at a time,

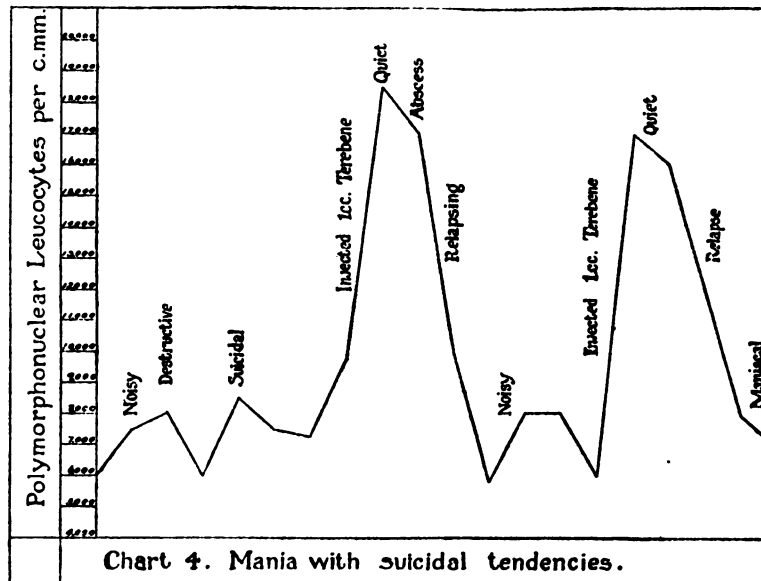
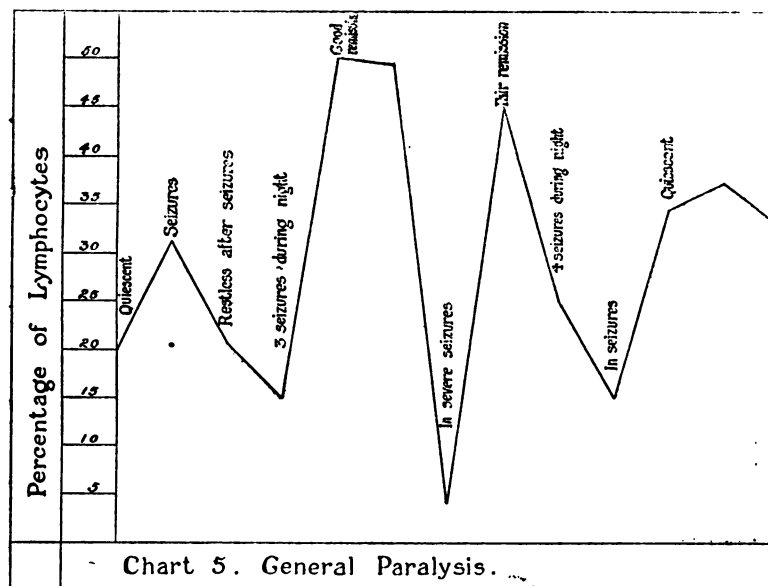


Chart 4. Mania with suicidal tendencies.

until exhaustion caused her to stop. On being questioned she disregarded everything that was said to her and would only answer in some blasphemous words. She several times attempted to commit suicide by tearing strips from the rugs and tying them round her neck.

The usual course of treatment was adopted, sedatives, baths, purges, etc., but she still continued as noisy as ever. For a day at a time she would keep quiet, but she would then have an outburst that lasted a week. Seeing that no treatment seemed to have any avail, I sent her to bed and injected 1 c.c. terebene into her flank, and in about a week's time she developed an abscess. Mentally she seemed much improved and became much quieter. Her blood-count showed a marked

hyperleucocytosis ; it had formerly been below normal. Her mental improvement was maintained until the abscess had healed up, when she became as noisy as ever and showed a recurrence of all her symptoms. Her blood-count fell to the low level it was at previously. In about another week's time I gave her an abscess in the other flank by injecting 1 c.c. terebene and she again became much quieter in her conduct and more rational in her conversation. This condition remained as long as her abscess was still in an active state, and during this



period she exhibited a well-marked leucocytosis. Unfortunately as soon as the abscess had healed she again relapsed into her former noisy state, and on several occasions tried to commit suicide. Her leucocytic count remained low, *viz.*, 7-10,000 per c.mm., and she still remains in the asylum, being as noisy and troublesome as ever, with no indication pointing towards a recovery.

Cases of general paralysis were next examined. For the purpose of accurate information ten cases were chosen, most of them at different stages of the disease. Their temperatures were taken at morning, noon, and evening ; any variations from the normal were immediately reported, so that the cause, if any,

could be investigated. Special attention was also paid to any change in their mental state, as undue excitement, depression, etc., so that blood specimens might be taken under all possible conditions. These observations have been carried on for a period of nine months.

During the remission period (*vide* Chart 5) each case without exception showed a well-marked lymphocytosis, but as soon as seizures commenced the blood picture was changed; a polynucleocytosis ensued whilst the lymphocytes fell down to a lower level than the recognised physiological mean. Marked changes in temperature, *e.g.*, a rise of 2° F. with undue mental excitement, though seizures were absent, also showed a corresponding change in the leucocytic formula resembling that found in seizures, *viz.*, a polynucleosis, but the change was not so pronounced.

A typical case (Chart 5) selected from one of the ten will illustrate these changes.

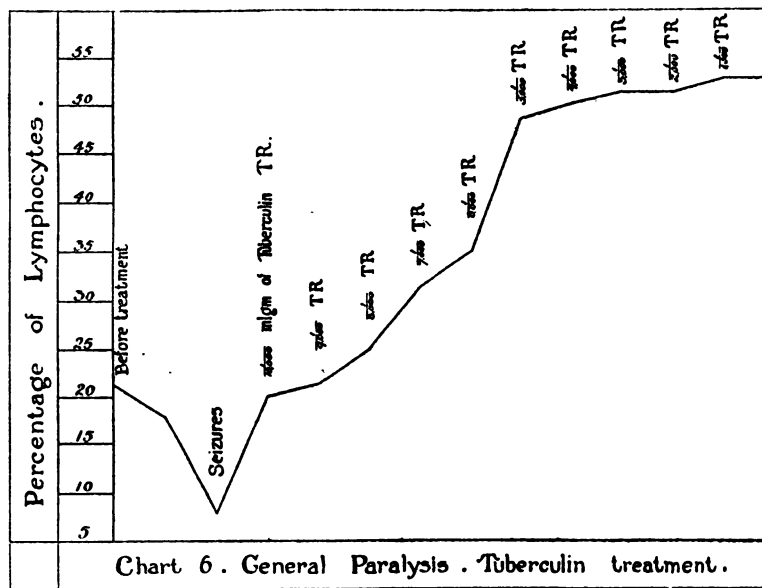
CASE 5 : *General paralysis*.—D. L—, male (admitted September 26th, 1913), æt. 39. Duration : nine months. History of previous syphilitic infection. A few of the observations taken during the course of his case are as follows. (Eosinophiles and basophiles are not included, for the sake of clearness.)

Date.	Total count.	Percentage of polymorphs.	Percentage of lymphocytes.	Remarks.
27 : 12 : '12	17,000	79·5	19·0	In seizures.
19 : 2 : '13	12,000	80·5	16·5	After seizures.
11 : 4 : '13	21,000	84·0	16·0	Seizures during the night, with marked tremors still present.
23 : 5 : '13	8,000	52·5	47·5	Good remission, working.
24 : 6 : '13	23,000	92·0	7·0	In seizures.
25 : 7 : '13	12,200	60·0	39·0	Fair remission.
31 : 7 : '13	18,000	85·0	15·0	In seizures.
29 : 8 : '13	9,200	65·0	34·0	Quiescent, but somewhat restless.

He had several seizures towards the end of September, and died on October 1st, 1913.

The other cases showed similar variations, a polynucleosis being present with seizures, and a remission state being characterised by a lymphocytosis.

Analysis of the recurrence of polynucleosis with seizures would point to the fact that the seizures were directly connected with a recurring toxic process or infection. During the remission period, when many general paralytics are able to be up and doing some ward work, the blood picture changes, and a marked diminution in the number of polymorphic cells is seen with a large relative increase in the number of lymphocytes. From this it will be seen that lymphocytosis is characteristic



of the remission period of the disease, and polynucleosis is a constant of the period when seizures occur.

Arguing on the above lines that lymphocytosis is a constant always found in remission states, anything that tends to encourage or promote lymphocytosis will also tend to promote a state of remission, a series of cases was taken, and having made a few preliminary observations on their blood, a series of tuberculin injections were commenced. Two of the cases received injections of T.B. emulsion, and the other two received tuberculin T.R. The dosage started was 1000 mgrm. in each case, and no striking changes were noticed in the blood until 2000 mgrm. was reached, when a fall in the polymorphs was noticed, and this continued until the dosage in each case

reached $\frac{1}{1000}$ mgrm., when a well-marked and continuous lymphocytosis was seen present (Chart 6).

Since then I have tried two fresh cases with tuberculin T.R., starting with the following dosage: $\frac{1}{1000}$ to $\frac{1}{500}$, etc., and so on, until a dose of $\frac{1}{100}$ mgrm. T.R. was reached. No more marked increase in the number of lymphocytes was noticed than in the case of those with the lower dosage, and clinically an increase of temperature up to 102° F. was recorded by those patients who received these large doses. The cases that exhibited the desideratum, *viz.*, a lymphocytosis, without rise of temperature, were those who received series of doses ranging from $\frac{1}{5000}$ to $\frac{1}{1000}$ mgrm. T.R., and during the period over which the injections were spread no seizures occurred, and a marked lymphocytosis was a constant feature of their blood examination.

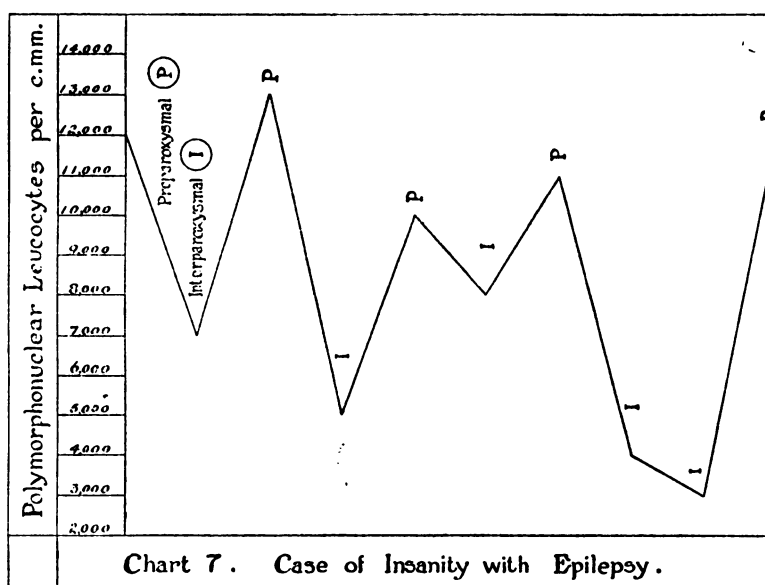
The next series of cases examined were epileptics. For the purpose of clinical observation each case, when the blood examination was carried out, was regarded either as being in a pre-paroxysmal or an inter-paroxysmal condition. Considerable difficulty was encountered in examining the blood of the patients in their pre-paroxysmal condition in order to obtain it sufficiently near the time of the fit to be of any clinical value, as many of the patients showed no indications of a seizure until a few moments before the fit, and thus rendering it impossible to obtain a blood specimen. However, a considerable number of cases were examined in the pre-paroxysmal period, where a fit followed in periods varying from a half to one and a half hours afterwards. The cases as a whole did not show a marked uniformity in their corresponding changes, as seen in their leucocytic picture. This may have been due to the unequal periods that elapsed in some of the cases between the taking of the blood specimen and the appearance of the fit. It was generally found, however, that a polynucleosis was present in the pre-paroxysmal period, whilst a marked fall was evident in the polymorphs during the inter-paroxysmal period. The case which exhibited the most constant change in the different states is shown in Chart 7. Examination of the chart shows a rise in the polymorphic curve in each of the pre-paroxysmal states, whilst there is a marked fall in the curve during the interparoxysmal periods.

A number of cases of dementia præcox examined exhibited

varying degrees of leucocytosis, with a tendency towards hypo-eosinophilia, but no marked similarity in the blood picture could be found amongst the cases. Many of them showed a similarity to the leucocytic type of manic-depressive cases, particularly when they were in a noisy or maniacal state.

All the cases of pure delusional insanity examined exhibited no variation from the usual leucocytic formula; this was also seen in cases of terminal dementia.

Examinations of the blood in mental cases may therefore be



considered from two points of view—namely, as to whether they have a diagnostic and prognostic value, and whether they throw any light on the nature of the pathogenic agents causing the mental disturbance.

In regard to the first point it would seem from the researches of Sandri and Psanna-Salaris, and also from my own cases, that there is a clinically distinct form—acute confusional psychosis—which presents a constant and characteristic type of deviation from the normal leucocytic formula. They claim that this is so characteristic that this type of blood formula can be of importance in differentiating acute confusional psychoses from other psychoses, such as stuporose melancholia, or a confusional

episode initiating a psychosis of chronic character, *e.g.*, dementia præcox. My observations do not lead me to support this view in its entirety. It is true that all cases of acute confusional psychosis I examined presented an intense polynucleosis, diminution of lymphocytes, and an eosinophilia, and it is claimed that this is the characteristic formula of this disease. In many cases, however, of dementia præcox and manic-depressive insanity at the beginning of the disease, or when the morbid phase manifests itself, there exist alterations in the leucocytic formula, which, though smaller in degree, yet resemble closely that found in acute confusional insanity, so that all cases exhibiting a resemblance to the above formula must not necessarily be classified as belonging to the form of acute confusional insanity. From the diagnostic point of view, therefore, due caution and attention must be used in the correct interpretation of the leucocytic formula which each individual case may present.

From the prognostic point of view, those cases which present a fairly well-marked and continuous polynucleosis with an eosinophilia may be regarded as favourable, while the cases that present a long-continued low polymorphic count with a hypo-eosinophilia may be regarded as unfavourable, and point towards chronicity.

As was pointed out in the early part of this paper, stimulation of the leucocytes by injections of substances like terebene tends to produce a leucocytosis and hasten the termination of the attack. It is a recognised fact that many intercurrent diseases which occur in the course of different psychoses have a favourable influence on the mental attack by their action in stimulating leucocytosis. Although terebene injections do certainly produce leucocytic stimulation, yet the reaction is not sufficiently strong, or the kind of leucocyte that has been called forth in response to the stimulus is not the one that may be "characteristic" for the disease in question. In many cases, however, due stimulation of the leucocytes by injections of terebene, etc., may prove of considerable value.

Hæmatological knowledge in the field of general clinical work and in experimental pathology leads to the conclusion that in mental disease also the leucocytic disequilibrium found is an expression of a toxic infection, or of an acute or subacute intoxication. It is difficult to establish the nature of this

infective or toxic agent, its importance, and its mode of action in determining the causation of mental disease, and the relationship between the blood change and mental state on one hand, and the nature of the infection on the other.

Sandri suggests that in the case of confusional psychoses the pyogenic micro-organisms normally inhabiting the intestine produce in particular morbid conditions abnormal quantities of toxins, which by invading the organism may be the cause of the attack, and give rise to the hæmatological changes which have been described. But to understand how this pyogenetic intoxication, in many cases, runs its course without any psychic disturbance, while in others it gives rise to severe mental crises, it is necessary to suppose, as is pointed out in the earlier part of this paper, the concurrence of a complex of morbigenic conditions that have prepared the ground—in fact all those commonly regarded as ætiological factors.

Pardøe considers that the exacerbations of manic-depressive psychoses are caused by crises of intestinal auto-intoxication.

Since the blood reaction in the sense of leucocytosis and polynucleosis is common to a great number of toxic infections and intoxications, it would not be illogical to suppose that the true and essential cause of the psychoses also produces the disequilibrium of the blood.

All these points lead to the supposition that mental disorder is only a mode of manifestation of cerebral disturbance consequent upon a general morbid alteration of the organism. This supposition, as Graziani points out, does not suffice of itself to clear up the various points of this complex and obscure problem, for the solution of which further researches in the chemico-biological properties of blood would be of assistance, especially if they were conducted simultaneously with a general study of metabolism.

Conclusions.

- (1) That cases of acute confusional insanity present a fairly well marked picture, namely, a polynucleosis and eosinophilia.
- (2) That cases of manic-depressive insanity and dementia præcox show variations in the leucocytic formula resembling (1), but not so well marked nor so constant.
- (3) That a continuous polynucleosis and eosinophilia point

towards recovery, and absence of polynucleosis and hypoeosinophilia point towards chronicity.

(4) That recovery may be hastened by stimulation of the leucocytes by terebene, etc.

(5) That the remission stages of general paralysis are characterised by lymphocytosis, and seizures by polynucleosis.

(6) That remissions in general paralysis may be prolonged by suitable doses of tuberculin.

(7) That cases of delusional insanity and terminal dementia do not exhibit a leucocytosis.

(8) That epileptics show a polynucleosis in their pre-paroxysmal condition, and a diminution in the leucocytes in their inter-paroxysmal state.

I am indebted to Dr. Grills, Medical Superintendent, County Asylum, Chester, for permission to include a number of the cases which I investigated whilst there, and also for information regarding the progress of these cases since.

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(¹) A paper read at the Autumn Meeting of the South-Western Division held at the Devon County Asylum, Exminster, on October 24th, 1913.