(27) Reichlin, C.—*Riv. Speriment di Fren.*, 1908.
(28) Bunge.—*Phy. and Path. Chem.*, translated by Wooldridge, 1890.
(29) Köster.—*Neurol. Centralb.*, December, 1903.
(30) Bonhöffer.—*Allg. Ztschr. f. Psych.*, 1904.
(31) Tansi.—*Text-book of Mental Disorders*, translated by Ford Robertson and Mackenzie, London, 1909.

EXPLANATION OF PHOTO-MICROGRAPHS.

FIG. 1.—Nerve-cells in the upper part of the third (pyramidal) layer from frontal convolution, in a state of fatty degeneration. × 600. Notice also the breaking up of the myeline fibres into a beaded condition. The section from which this photo-micrograph was taken was from a case of acute delirium not of alcoholic origin, but precisely similar appearances are met with in alcoholic cases.

FIG. 2.—Large pyramidal cells from the ascending frontal convolution in a case of alcoholic insanity. To show the marked increase of satellite cells around the nerve-cells (× 400). Many, if not all, these bodies represent mesoglia cells, and by special methods their cell-body and branches can be shown, the latter to a large extent embracing the body of the nerve-cells.

FIG. 3.—Longitudinal section of the right posterior tibial nerve in a case of alcoholic insanity, showing recent degeneration of the myeline, which is darkly stained and broken up into beads (× 100).

FIG. 4.—Transverse section of posterior tibial nerve in a case of advanced general paralysis, showing a fairly healthy condition (× 100) in contrast with—

FIG. 5.—Transverse section of posterior tibial nerve from a case of alcoholic insanity, showing marked neuritic change characterised by disappearance of myeline fibres (× 100).

The Systematic Estimation of the Leucocytosis in Certain Cases of Insanity: with Special Reference to the Toxæmic Theory.[1]

By S. CARLISLE HOWARD, M.D., Assistant Medical Officer, London County Asylum, Horton, Epsom; formerly Assistant Medical Officer, District Asylum, Murthly, Perth.

SURVEYING insanity as a whole, one recognises as a fundamental fact that insane persons belong to a class who start life with a "deficient grade of organisation" of the nervous system called "hereditary predisposition." Some authorities hold that this is the *sine quâ non* of insanity, but such a view, I consider, is not strictly accurate. It is certainly not borne out by statistics. All observers, using even indifferent discrimination, must have noticed cases in which no hereditary factor could be traced, but in which much self-abuse had occurred—either in the form of alcoholic, sexual, and other excesses—or where

syphilis or other powerful toxæmic conditions had been contracted. Such conditions, I argue, may themselves break down the most hardy constitution and leave it a prey to secondary infections or intoxications, which may manifest themselves as insanity. Assuming that the insane, prior to their attack of mental disease, suffer from either some hereditary weakness, or some acquired constitutional degeneration, it is most probable that such defects act a dual part, weakening not only the nervous system, so that it is more susceptible to the actions of toxins and environments, but also weakening the natural defences of the body. The nervous system of these people is thus laid open to more severe and frequent attacks from poisonous substances, whether of bacterial, metabolic, or other sources, than is the nervous system of a more normally organised individual. In support of this statement I would mention that Dr. L. C. Bruce (1) has pointed out that over 60 *per cent.* of maniacal patients were deficient in the normal protective agglutinin to certain strains of *Staphylococcus aureus*. This agglutinin is always present in healthy sera. Further, Dr. C. J. Shaw (2) has ably demonstrated that the reason tubercular diseases account for so large a proportion of the deaths in asylums lies, not in any faulty hygienic precautions, but in the fact that the resistive power of the insane to tubercular infection is below par. Assuming that this hypothesis is true, we can more readily understand why the various insanities so frequently resist our efforts to cure them.

Besides this hereditary or acquired weakness of the nervous system and general defences, some secondary or combination of secondary influences is usually necessary to tilt the mental balance of these people towards insanity.

These secondary influences have been very broadly divided by Dr. L. C. Bruce (3) into two main divisions, namely, the "toxic" and "non-toxic" causes of insanity. It is with the toxic division—or, more strictly speaking, with that subdivision which Dr. Bruce has called "the toxins of bacterial origin"—that I shall deal. Reviewing the toxæmic theory of insanity, one finds that Macpherson (4 and 5), more than ten years ago, compared the pathology of the histological changes occurring in puerperal and certain of the confusional insanities. He believed that puerperal insanity was frequently of toxic origin, and, reasoning by analogy, he classified confusional

insanities as also toxic. It is now universally admitted that the majority of puerperal cases are of undoubted bacterial origin. Further, he states, "the basis of all forms of insanity is a presumption for which there is a fairly good foundation, but no direct proof. . . . There is, however, every reason to believe that the field of toxic nerve-disease is one of the most extensive in morbid psychology, and that it is because we are still on the threshold of inquiry that its recognition is not more general."

Following closely in the path suggested by Macpherson, we have Dr. Ford Robertson (6), who, with microscope and highly trained histological technique, corroborates and augments Macpherson's observations. Later, we find Dr. Thomas Claye Shaw (7) saying, "It would indeed have been strange if the advent of bacteriology, and the study of toxins and vaccines, had not influenced our opinions and treatment of mental disease. There has indeed been a revolution in our estimation of causes and pathological processes since the study of micro-organisms was seriously undertaken, and it is clear now that many of our old postulates will have to be re-written."

Further, we have on the Continent Bianchi and Piccinino (8) examining the blood and meninges of the insane bacteriologically, and discovering, in certain delirious cases, a bacillus, for which reason they have termed the condition "acute bacillary delirium." A little later we find D'Abundo and Agostini (9) formulating hypotheses as to the part taken by intoxications and infections in the causations of nervous and mental diseases. They regard these agents as the most frequent, conspicuous, and active elements in the pathogenesis of nervous diseases in general. They further consider that infective toxic agents can manifest their action in any part of the nervous system "leading to peripheral or central, systemic or disseminate localisation, and resulting in acute or chronic neuropsychosis." At the present day Dr. L. C. Bruce is prominent and active among the pioneers of the toxic theory. He champions this theory with much vigour from a general and exhaustive clinical point of view, paying particular attention to hæmatological and bacteriological observations. Armed with a thorough appreciation of the advances made in general medicine by the improved methods in clinical technique, he has gleaned much of that positive knowledge the absence of which Macpherson so much deplored.

A *resumé* of Dr. Bruce's findings and methods of investigation will not be out of place here. His field of research lay in three principal divisions, *viz.*:

(1) The estimation of the leucocytosis.

(2) The bacteriology of the urine, fæces, and blood.

(3) The estimation of the excretion of urea and chlorides.

I shall review the first two divisions, and omit the last one as it does not come within the scope of this article.

Dr. Bruce's leucocyte count consisted of an estimation of the total leucocytosis by means of the Thoma-Zeiss apparatus and a differential count from blood-films stained with Jenner's eosin methylene blue. In this way Dr. Bruce examined a large number of cases of confusional mania, *folie circulaire*, katatonia, hebephrenia, and excited melancholia, in all of which he found a fluctuating hyper-leucocytosis which bore a definite relationship to the course of the disease. Such observations include thirty-six cases of mania of the *folie circulaire* type, and thirty-one cases of the confusional type—in every case a varying degree of hyper-leucocytosis was observed.

Bacteriologically, Dr. Bruce's initial case was one of mania with confusion in the typhoid state. From the blood of this case he isolated a short streptococcus. The serum of the patient agglutinated this coccus in a dilution of 1 in 30 within half an hour. Two control sera failed to give a reaction after twelve hours. After this case Dr. Bruce and his assistants made numerous bacteriological examinations of the insane, not only of the blood but also of the urine and fæces. The last source ultimately proved the most fruitful. The agglutination was the test by which the invading organism was identified. Briefly, if an organism isolated from any of the above mentioned sources was agglutinated by the serum of the patient, and not by the serum of the controls, that organism was considered as a causal toxic agent.

I have followed on the lines indicated by Dr. Bruce, and I hope to demonstrate the high importance of systematic blood examination.

(1) As a possible means of diagnosis.

(2) As an indication to treatment.

(3) As an aid to the forming of a prognosis.

In the first instance I intend to review briefly the condition

of the leucocytosis in well known and well understood infective and infectious cases. By so doing the strong light of analogy will assist us in reading a possible solution where certain links in the chain of positive information are at present wanting. In certain well-recognised infective conditions such as appendicular abscess, furuncle, carbuncle, empyema, superficial abscess, etc., the symptom of hyper-leucocytosis is practically never absent, and may rise higher than 20,000 per c.mm. (10) of blood. In the same way, in general infections such as diphtheria, pneumonia, rheumatic fever, etc., a more or less decided leucocytosis is regularly seen. This rise of the leucocytes in strength of numbers is regarded as an effort of the human organism to rid itself of the inimical and irritating invading factor. In short, it is a protective reaction, a mobilising of the body's first line of defence for its self-preservation.

The knowledge of this functional characteristic or defensive action of the leucocytes is rapidly becoming universally disseminated, and in consequence we hear more and more frequently of the artificial stimulation of a leucocytosis for prophylactic purposes, particularly before surgical operations. It is also often used in the initial stages of various diseases.

From this short survey it will be observed that in a large number of diseases, admittedly of a bacterial origin, a hyper-leucocytosis is a common and regular feature. Further, it should be noted that this leucocytosis is regarded as Nature's method of removing, or attempting to remove, the causal disease from the body. From this I think I may with good reason argue conversely that where there is a hyper-leucocytosis one may expect to disclose some focus of irritation, most probably of a bacterial nature. Unfortunately, such foci are often obscurely placed, and only discovered after very careful search, and frequently escape one even in spite of every effort to locate them.

Again, if such a hyper-leucocytosis occurs, as a common feature, in a series of cases all presenting the same train of symptoms, and therefore deserving to be classed under a common diagnostic term, such as cases of confusional mania, it may be reasonably deduced that such a hyper-leucocytosis very strongly suggests that that class of disease is of bacterial origin, or that a bacterial invasion is intimately connected with it.

There are considerable differences of opinion as to the exact meaning to be read from leucocytic reactions. Ehrlich, Cabot, and other authorities on the subject, hold that in conditions of an inflammatory nature the number of leucocytes per c.mm. of blood varies directly with the intensity and extent of the infection. Dr. McCuen Smith, of Philadelphia, at the meeting of the British Medical Association at Toronto in 1906, stated that the number of leucocytes per c.mm. of blood is an indication of the amount of the body resistance, while the percentage number of polymorphonuclear leucocytes indicates the intensity and extent of the infection. Still another method of interpreting the leucocytosis is to estimate the polymorphonuclear leucocytosis per c.mm. This is done as follows :

Total number of leucocytes per c.mm. × Percentage of polymorphs to other forms of leucocytes = Total number of polymorphs per c.mm.

For example, in a given case we may have a leucocytosis of 15,000 per c.mm., and a polymorphonuclear count of *70 per cent.*, the actual number of polymorphs per c.mm. is therefore 10,500. By this means we know how many of the fighting variety of leucocytes are in each c.mm. This is the method I have adopted. The accompanying charts indicate the polymorphonuclear leucocytosis per c.mm. of blood.

In making these systematic observations of the changes occurring in the relative and absolute number of the white blood-corpuscles, I estimated the leucocytosis by means of the Thoma-Zeiss apparatus, after the method advocated by Coles (11). In the differential count the film was stained by Jenner's eosin methylene blue, and an oil-immersion lens was used. I never counted less than 200 cells, and in doubtful cases I counted 400. Moreover, care was taken to obtain the blood at a regular hour on each occasion. The hour selected was just before the mid-day meal ; by this precaution the error of the presence of a lymphocytosis excited by food was avoided.

These observations include cases of mania and melancholia of the *folie circulaire* type, *i.e.*, the manic-depressive variety of Kraepelin, mania with confusion, and so-called alcoholic insanity. The observations were made either every day or every second day, and were continued for at least one month, and, in some cases, for as long as from three to six months. It will be

noticed that the leucocyte reactions stand in bold relation to the remissions of such conditions, and in certain cases to their subsequent relapse.

Case of D. McA—.—Male, æt. 21, admitted September, 1906, suffering from excitement without confusion of fourteen days' duration.

History.—His uncle on his mother's side had suffered from insanity. The patient was a youth of steady habits, he was a total abstainer, and smoked in moderation. He had been losing weight for some two months previous to admission. Otherwise he had always been healthy.

Physical condition.—He was tall and well developed, but anæmic, ill-nourished, and run down. His tongue was coated, his breath was foul, and his bowels constipated. He had very little desire for food. Previous to admission he had slept badly and dreamt a great deal. His temperature was 99° F., pulse 72–84, and leucocytosis 6000 per c.mm.

Nervous system.—He had no tremors, either of hands, tongue, or facial muscles. His pupils acted equally to light and accommodation. His superficial reflexes were exaggerated, his deep reflexes were nearly absent. No ankle clonus was present. Mentally, though restraining himself with an effort, he was facetious and childish in his behaviour. His special senses were hyperacute, and in consequence his attention was unsteady. Any little sound or movement in the wards immediately attracted him. He was not confused, and had neither hallucinations nor delusions. During the first fortnight of his stay in the hospital he restrained himself fairly well. Occasionally he became restless and impulsive, and in explanation of such conduct he said, " I could not help it; I just lost control of myself." At first he slept very badly, and later he became restless, excited, talkative, and at times maniacal. During the more acute period his face was flushed, his tongue and lips were dry and covered with sordes, and his breath was foul. His leucocytosis was very irregular, but had never risen above 18,000 per c.mm. At this period I injected him in the flank with 1 c.c. of terebine; three days later his polymorphonuclear leucocytosis rose to 21,000, his temperature to 100° F., and his pulse-rate to 100 per minute. Mentally he became much quieter and more obedient. Ten days later he had another attack, when his leucocytosis fell to 5,000 per c.mm. At the

end of the twelfth day, however, they rose again to 22,000 and he again became quieter. This second rise of his leucocytosis I regarded as being due to the irritation to which he had subjected the abscess in his flank during his restless period. A week later he had another slight maniacal attack, during which his leucocytosis rose to 23,000 per c.mm. On this occasion, instead of falling and remaining low for several days, it continued to swing for nearly a month between normal and 13,000

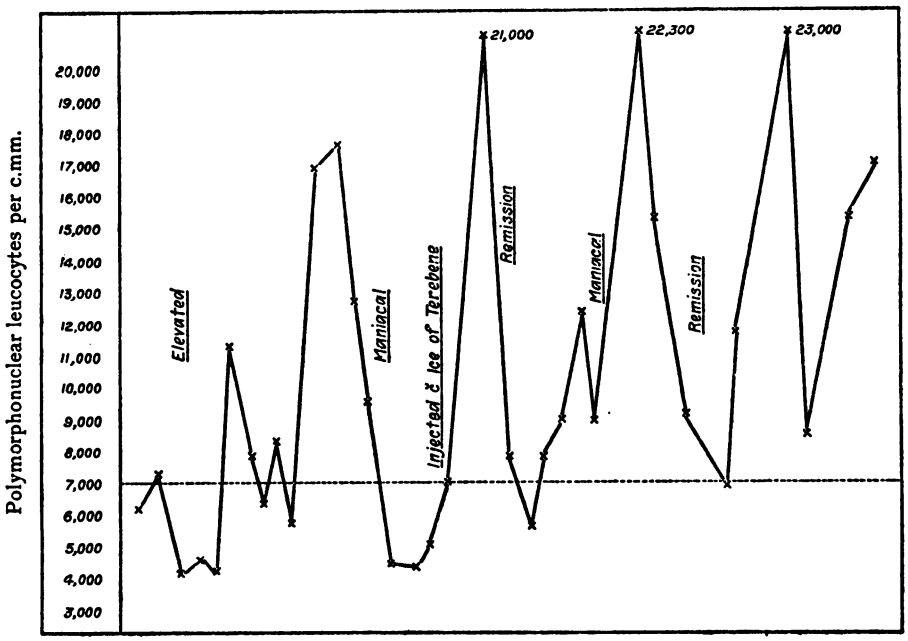

CHART 1.—Case of mania (manic-depressive).

per c.mm. Thereafter it gradually fell to normal. After this last leucocytic rise his mental symptoms improved and he put on weight rapidly ; he increased from 9 st. 2 lb. to 10st. 12 lb. in two and a half months. I isolated from the fæces and urine of this case a short streptococcus, which his serum agglutinated in a dilution of 1–40 in twenty minutes. Control sera did not affect it in twenty-four hours.

For the leucocytosis of this case see Chart 1.

He was discharged recovered in June, 1907, and has continued well ever since.

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Case of W. B—.—Male, æt. 16, admitted September, 1907, suffering from acute excitement and impulsiveness of about one week's duration.

History.—No hereditary insanity or neurosis could be traced. His father and mother were both dead; I was unable to discover the cause. One month prior to admission he had been incarcerated in the Perth Penitentiary for theft, and had since been somewhat depressed and moody. He neither smoked nor drank and he seemed a very respectable lad.

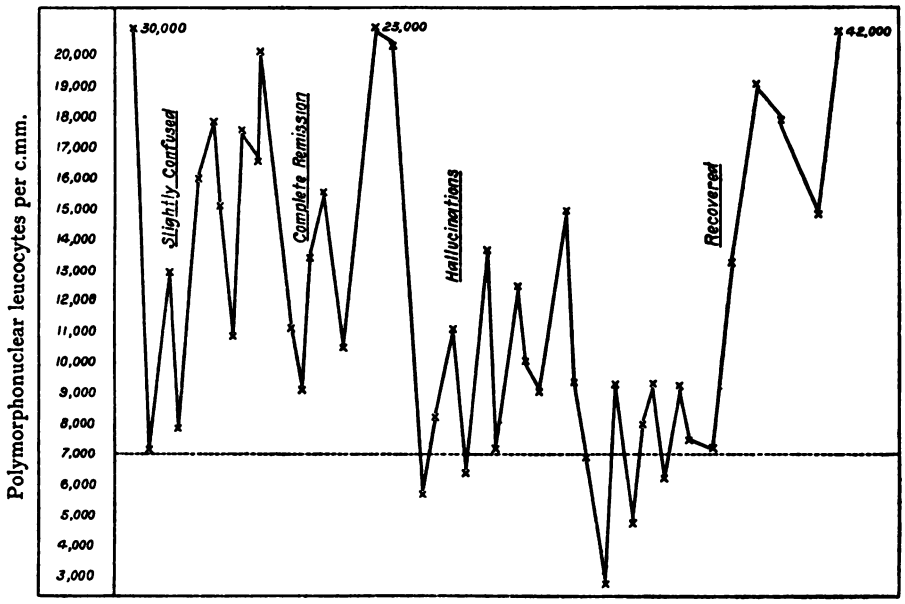

CHART 2.—Case of mania (confusional).

Physical condition.—He was fairly well developed, indifferently nourished, and very anæmic. His tongue was coated, his breath was foul, and in spite of large doses of saline aperients and extract of cascara sagrada his bowels had not moved for a week. His temperature was 97·8° F., pulse 85–93 per minute, full, regular, and of high tension. His lungs and heart were normal. His leucocytosis was not taken until he had been injected with 1 c.c. of terebine—a week after admission. His leucocytosis then registered 30,000 polymorphonuclear leucocytes per c.mm. of blood (*vide* Chart 2).

Nervous system.—His tongue was very tremulous. His

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superficial reflexes were exaggerated and his deep reflexes were deficient. There was no ankle clonus. His pupils reacted to light and accommodation.

Mentally.—On the day of admission he was very excited, noisy, and somewhat confused. The following day he had hallucinations of hearing, delusions of identity, and was dejected. He thought I was God, and sought forgiveness of his sins. He was constantly moaning or shouting, and refused to take food. He remained more or less in this state for four days, taking very little more than a glass of milk a day, and that only when poured into his mouth. At night he frequently required one to two drachms of paraldehyde before he could sleep. On the fifth day after admission I injected him in the flank with 1 c.c. of terebene. The following day he was mentally much clearer; he sat up, took his food voluntarily, and at night slept eight hours. This improvement synchronised with a high polymorphonuclear leucocytosis of 30,000 per c.mm. He continued well for three weeks and then had a return of his hallucinations. Under the treatment of a large saline enema and a dose of calomel this attack passed off in a couple of days. From that date he progressed steadily, and was discharged recovered two months after admission.

Case of Mrs. McN—.—Æt. 36, admitted November, 1906.

On admission she was restless, excited, and at times maniacal. She talked incessantly and incoherently, but was not in any way confused.

History.—Five years before admission to this asylum she suffered from puerperal mania, for which she was under treatment in one of the Glasgow asylums for about six months. In October, 1905, she became slightly elevated, but was then successfully treated at home.

Physical condition.—She was well developed and well nourished, although somewhat anæmic and run down. She had been in bad health for about one month prior to admission. Her stomach was out of order, her bowels were constipated, and she had no desire for food. She had been menstruating irregularly. She had an aortic systolic murmur. Her temperature was 98·6° F., her pulse was 77 per minute, full, of fairly high tension, and somewhat irregular. Occasionally it quickened in the morning to 80 and 86 beats per minute.

Nervous system.—She had tremors of hands, tongue, and

facial muscles. Her pupils reacted equally, though sluggishly, to light and accommodation. Both her superficial and deep reflexes were deficient. *Mentally* her special senses were hyper-acute, and she remained for about ten weeks in a restless, noisy, and talkative condition. She had no delusions, but she occasionally showed evidence of hallucinations of hearing. At the end of these ten weeks she became quieter and commenced to put on weight. Three weeks later she showed well-marked signs of depression, which lasted for nearly three months,

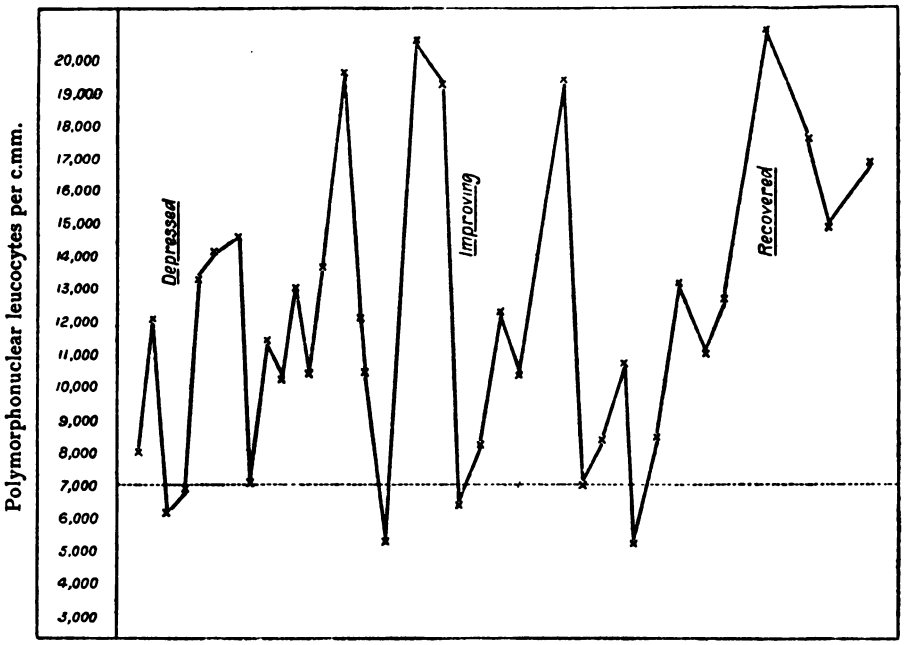

CHART 3.—Case of melancholia (manic-depressive).

during which period I kept a record of her leucocytosis, and her body reaction was fairly good (*vide* Chart 3).

After eight months' treatment she was discharged recovered but she was readmitted about three months later suffering again from melancholia. On this last occasion she remained under treatment for about seven months, and was subsequently discharged recovered.

The following three cases are particularly interesting, throwing as they do a side-light upon the question of alcoholism as a cause of insanity:

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Case of J. Cyn—.—Male, æt. 34, was admitted suffering from maniacal excitement with considerable confusion.

History.—He had a long history of excessive alcoholic and nicotine indulgence; he usually smoked from four to six ounces of strong black tobacco per week. He was a "chronic soaker" rather than of the dipsomaniac type. A few weeks prior to admission he had taken rather more alcohol than usual, and, owing to irregular employment, had been underfeeding himself.

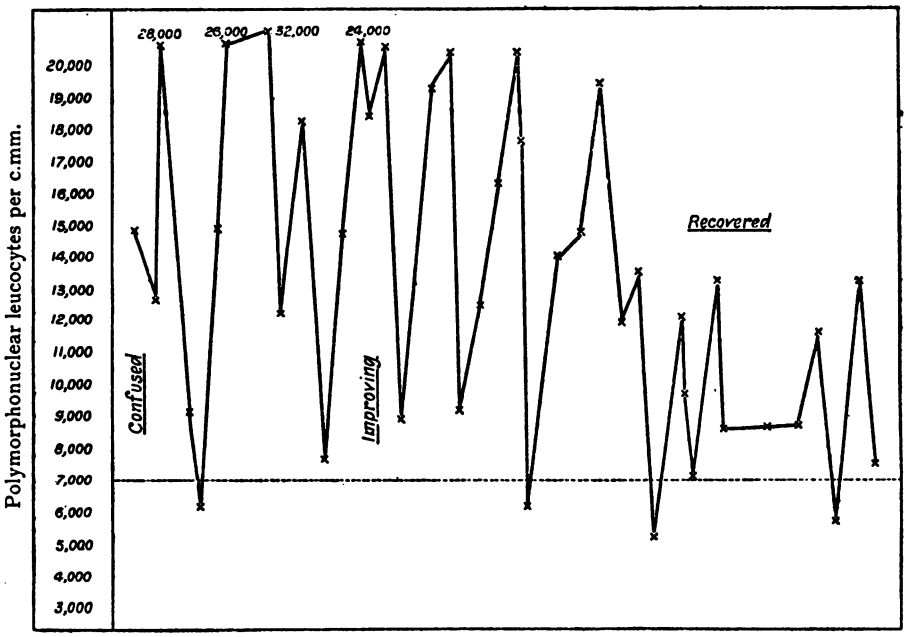

CHART 4.—Case of mania with confusion.

Physical condition.—On admission he presented all the symptoms of a chronic toxæmia. He was ill-nourished, ill-developed, and anæmic; his tongue was coated with a thick fur, his breath was very offensive, and his bowels stubbornly constipated. His skin was dry and sallow. His temperature was 98·6° F., with a tendency to be irregularly subnormal; pulse was 98 and feeble.

Nervous system.—His reflexes, both superficial and deep, were deficient. It was impossible, owing to his confusion, to

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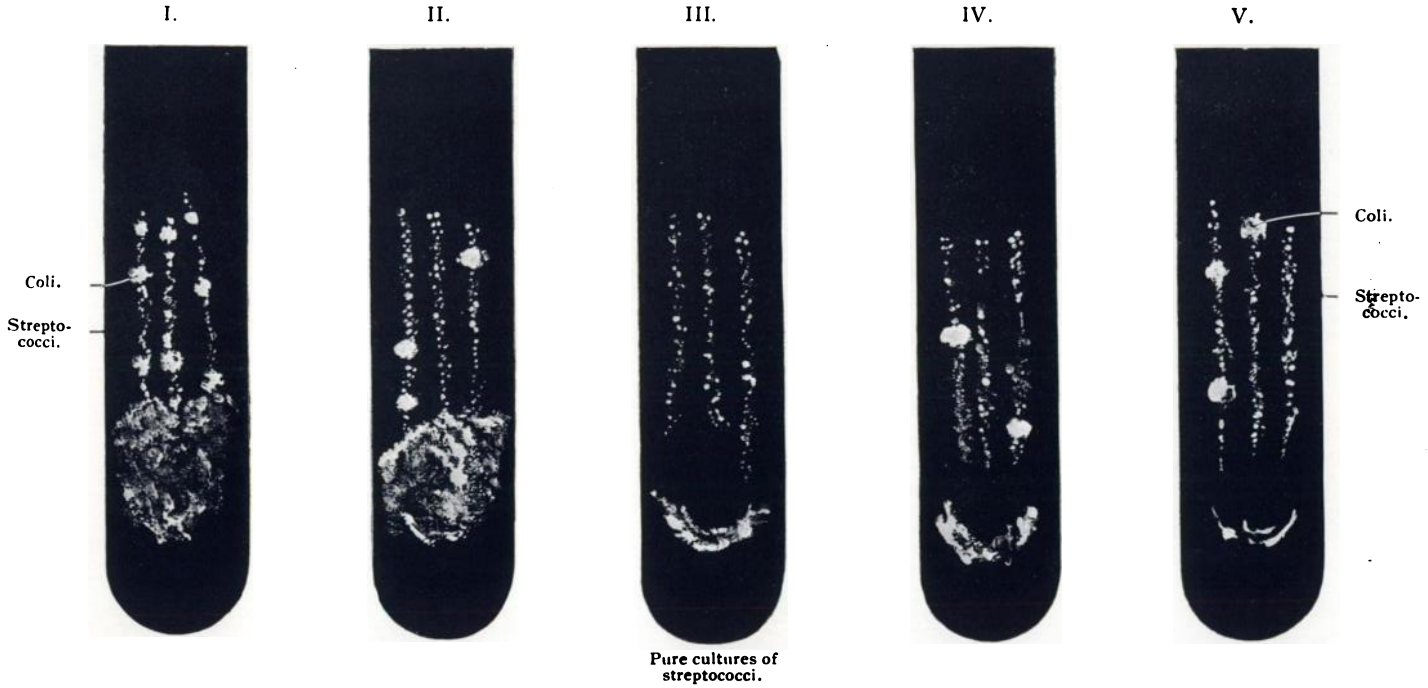
CHART IVA.



Culture from fæces in a case of mania (confusional).

To illustrate Dr. S. Carlisle Howard's paper.

Adlard & Son, Impr.

test his recognition of pain, temperature, or sensation. He had fine tremors of the muscles of the hands and tongue.

Mentally, he was incoherent, restless, and impulsive. He had hallucinations of sight, and delusions that he was going to die " to save the world."

I examined his leucocytosis three days after admission, and found his polymorphonuclear leucocyte count per c.mm. of blood to be 14,946. I observed it regularly every second day from that date until he was discharged recovered four months later. It was found to fluctuate from 5,000 to 32,600, the majority of the counts being well above the normal line (*vide* Chart 4).

Shortly after his admission I isolated from his urine a short streptococcus, which his serum agglutinated in twenty minutes in a dilution of 1 to 40. Two control sera did not affect it in twenty-four hours. A short time later I examined his fæces bacteriologically. The technique employed was as follows: A sample of his fæces was placed in a sterile Petrie's dish, and from it a sterile platinum needle was charged; three strokes were then made on each of seven sloped agar tubes, the same surface of the needle, as near as possible, being used to make each stroke. The tubes were then incubated for forty-eight hours, when cultures were found of almost pure streptococci colonies. There were only six colonies of *Bacillus coli*, the remaining growth being streptococci (*vide* Chart 4A). Testing these cocci to the various sugars, as recommended by Houston, I found that they were the same as those isolated from his urine.

Case of J. C—d.—Male, æt. 27, admitted suffering from confusion and excitement.

History.—There was again a history of alcoholism and loose living. He had recently been in prison. He was confused, restless, and impulsive. During his confinement in this asylum he made one or two indifferent attempts at suicide. On one occasion he swallowed an open safety-pin, and on another occasion he tied a sheet round his neck. He had neither hallucinations nor delusions, but was a physical and mental degenerate. He presented an irregular polymorphonuclear leucocytosis, varying from 2,000 to 13,400 (*vide* Chart 5).

It is interesting to note that in this case the leucocyte

reaction was very indifferent, and that, although under treatment for nine months, he did not recover. He was discharged to the care of his friends "relieved."

Case of Alex. C—.—Male, æt. 25, admitted suffering from acute excitement.

History.—He was an Army pensioner, and while in the service he lived for several years abroad. During his sojourns he suffered from dysentery, malaria, and finally heart disease, for which he was invalided home. For a few weeks prior to admission he indulged in alcohol to great excess, and in consequence he became delirious and delusional. He was treated at home for a week and then sent to this asylum.

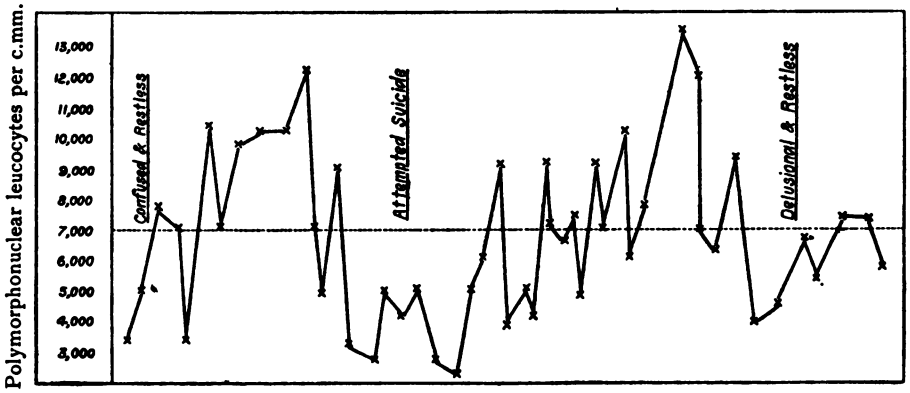


CHART 5.—Case of mania with confusion.

On admission he was sleepless, restless, and disinclined to take food. He had delusions that his stomach had been removed, and that he was to be cut to pieces and thrown into the river Tay. His leucocyte reaction was subnormal, being 3,240 per c.mm., and during the six weeks he was in the asylum it never rose above 8,768 per c.mm. (*vide* Chart 6). Under the treatment of bromides, milk diet, and rest in bed, he made a rapid recovery.

On reviewing these three cases there can be no doubt that the last-mentioned was one of uncomplicated alcoholism. The poison having been withdrawn, and the general system placed in the most favourable circumstances for its rapid restoration to health, the patient naturally made a speedy recovery.

In the first two cases, however, there is an additional condition to contend with as evidenced by the polymorphonuclear

hyperleucocytosis. The nature of the complication, arguing on the lines previously mentioned, I judged to be a bacterial one. This conclusion was later strongly supported by the isolation of a streptococcus from both the urine and fæces of the first case, which organism was agglutinated by the patient's serum, and was not in the least affected by the sera of two control cases. It naturally follows that although the alcohol, which may be considered as the "last straw," is withdrawn, yet the body must overcome or suppress the complicating source of toxæmia before recovery can take place. In the first case we saw that recovery took place within four months. In the

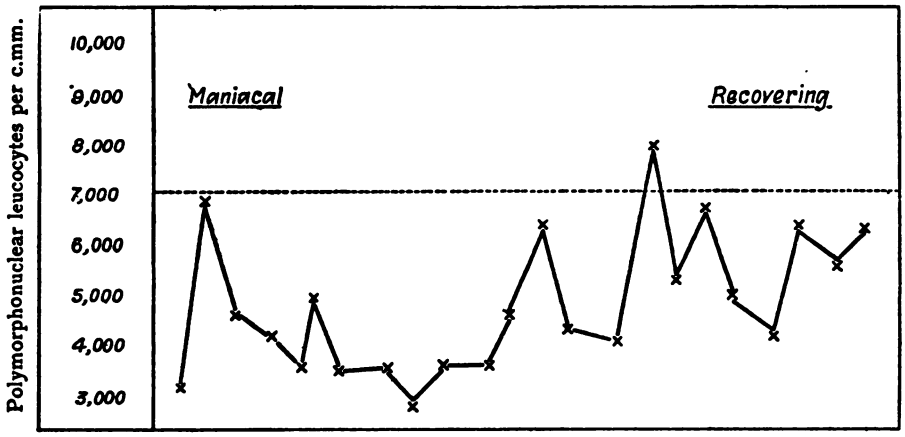


CHART 6.—Case of mania (delirium tremens).

second case the body was incapable of overcoming the toxæmia even within nine months. The possible explanation of this I shall discuss later when drawing a comparison between the acute and chronic cases.

Case of Mrs. R—.—Æt. 40; admitted January, 1907, suffering from hallucinations of sight and hearing, with acute excitement.

Physical condition.—She was very anæmic and ill-nourished. Her tongue was covered with a white fur; her breath was foul and bowels constipated. Her temperature was 98·9° F., pulse 85, full, irregular in rhythm and of high tension. She had little desire for food, and occasionally had to be hand-fed. She slept irregularly, and frequently required paraldehyde.

Nervous system.—Her pupils reacted equally to light and

accommodation. She had fine tremors of the fingers and tongue. Her sense of touch was deficient, but that of pain was normal. Her plantar reflexes were deficient, and there was a tendency to dorsiflexion of the foot. Her knee reflexes were markedly deficient. She had no ankle clonus. Her organic reflexes were under control.

Mentally, she was elevated, noisy, and restless. Her special senses were hyperacute. She was constantly chattering incoherently, but she always remained conscious of her surroundings. She had vivid hallucinations of sight and hearing. Occasionally she barricaded her bed with pillows, bed-clothes, or anything movable she could get hold of, in order " to keep away evil spirits." Her attention was readily attracted, but she

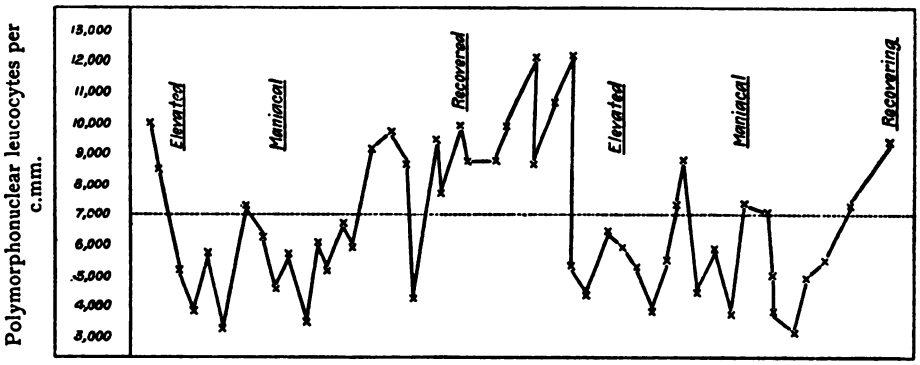


CHART 7.—Case of recurrent mania (manic-depressive).

lacked the power of concentration. During her quiescent periods she always remembered and could relate what had occurred during the time of her excitement.

The initial attack of mania for which she was admitted into this asylum lasted for five months. Since that time she has had recurrent attacks, each one lasting about fourteen days, and I was thus enabled to obtain records of her leucocytic reactions which corresponded with the alternating phases of her mental condition (*vide* Chart 7).

Case of Mrs. M—.—Æt. 66; admitted in May, 1907, suffering from acute excitement with confusion.

History.—Up to about three months prior to admission she was healthy and active. She then began to grow thin, look pale, and lose interest in her work. She had severe headaches during the day, and at night she suffered from insomnia.

Physical condition.—She was anæmic and ill-nourished. Her complexion was sallow and unhealthy; her skin was greasy. Her tongue was coated with a white fur, breath was foul, and she was very constipated. Her pulse-beat was from 82 to 94 per minute, hard and incompressible; temperature normal. She had reduplication of the second sound, heard at the apex and the aortic area. She had varicose veins of the legs.

Nervous system.—Her pupils reacted equally but sluggishly to light and accommodation. Her hearing was very good. Her motor functions were deficient and senile. Her plantar reflex was delayed and abnormal; there was slight dorsiflexion, with considerable abduction of the foot. Her knee reflexes

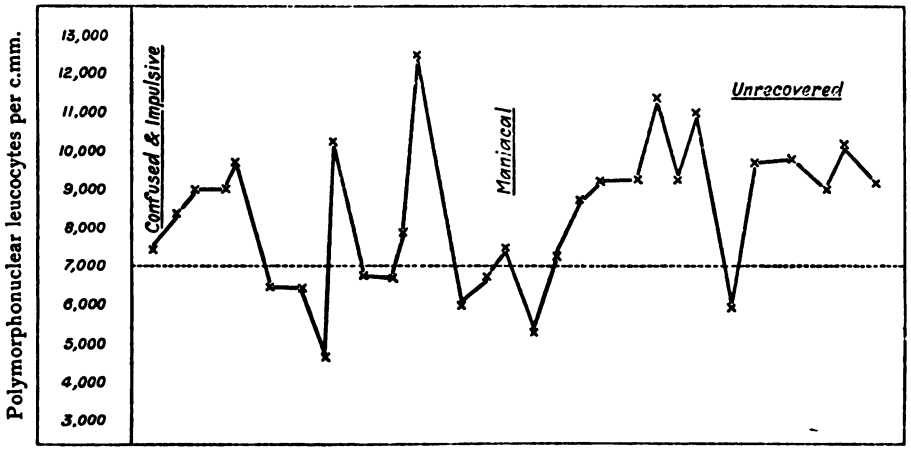


CHART 8.—Case of mania (confusional).

were practically absent. She had fine tremors of the muscles of the hands and tongue. Her organic reflexes were under control, although during severe attacks of confusion with torpor she passed her motions in bed.

Mentally she was confused, restless, noisy, and at times impulsive and dangerous. She had the delusion that she was blind and said she was haunted by dreams.

The leucocytosis shows that the power of her body to react to the toxæmia is very poor and unsatisfactory. She has now been under treatment in this asylum for about a year, and she shows no tendency towards mental improvement (*vide* Chart 8).

In considering the foregoing charts and cases, a most striking difference will be noticed between those which recover and

those which do not. In the curable cases the body reaction, as registered by the polymorphonuclear leucocytosis, is high and powerful. Such cases usually run a fairly definite and favourable course. In the unrecovered cases, judging by the leucocytosis, the course and the relapsing character of the case, the body is apparently incapable of reacting to the bacterial invasion. In consequence the toxæmia continues to assert its destructive action, and attack follows attack in quick succession till, finally, organic brain changes occur, and with them come fixed delusions and dementia.

The reason why one person is capable of reacting to and of resisting such a bacterial invasion while another person is incapable of offering anything but a weak resistance (and, in consequence, mentally and intellectually succumbs) is probably but part of the, at present, impenetrable mystery of hereditary predisposition. This theory is supported by the observations of Drs. Bruce and Shaw. The former discovered in the insane as a class an absence of normal agglutinins to certain strains of *Staphylococcus aureus*, while the latter observed a deficiency in the resistive power of the insane to the tubercle bacillus. This deficiency, he holds, accounts for the high mortality among that section of the community from tubercular diseases.

From such a comparison of the curable and incurable cases it will be seen that an estimation of the polymorphonuclear leucocytosis may be a valuable means of forming a prognosis. This is particularly so in cases of mania, which class of disease forms at least 50 *per cent.* of the admissions into most asylums.

In those cases in which the leucocytosis fails to react in anything but a small degree, and in which the mental symptoms are prolonged over many months—as exemplified in Charts 5, 7, and 8—a bad prognosis may with confidence be given. Such leucocyte reactions can but mean one of two things; either a very severe toxæmia, causing a leucopænia, or a deficiency in the activity of the leucocyte-producing tissues. In either case the ultimate result will be the same. Since the body is not in a condition to offer satisfactory resistance to the causal toxic agent, the nervous system will continue to be poisoned till its higher centres are eventually destroyed by the ever-present toxin.

Again, if the leucocyte reaction is such as is demonstrated

in Charts 1, 2, 3 and 4, and the patient's environment and age are favourable, a good prognosis may be readily given. In such cases the leucocytosis would register the resistance offered by the body, and by a judicious stimulation, either by a terebine abscess or otherwise, the body may be made to react more powerfully and over a longer period than it would do were the disease merely allowed to run its course. In the wise and special use of such means there is an encouraging possibility of suppressing and even eradicating the seat of infection before permanent brain damage has occurred.

In the three so-called alcoholic cases previously discussed, I stated on the evidence of a polymorphonuclear leucocytosis that I considered two of these cases to be suffering from a toxæmia (of a streptococcal character) complicated with alcoholism. The third case I considered was one of uncomplicated alcoholism. The course and termination of these cases justified and corroborated the diagnosis made. In the uncomplicated case, once the patient was placed in a more healthy environment, his supply of alcohol stopped, and his daily habits regulated, the recovery was rapid. In the other two cases, however, this treatment was not sufficient to obtain a quick return of the mental balance. The cause of this retardation was without doubt the action of that more subtle toxæmia, the presence of which was indicated by the hyperleucocytosis and bacterial agglutinins in the blood. From these observations it will be apparent that the systematic estimation of the leucocytosis may be of much diagnostic value. By its means a case of simple alcoholism may be readily differentiated from more serious conditions. It is stated by Cabot that alcoholism is occasionally associated with a hyperleucocytosis. The fact that a hyperleucocytosis is only sometimes found would seem to indicate that some complicating source of toxæmia is occasionally associated with this condition. This can be readily understood when the state of the alimentary canal is kept in mind.

These observations are the result of repeated and continuous estimation of the leucocytosis. An examination of the accompanying charts very clearly shows that a single estimation, or even half-a-dozen counts, may coincide with a temporary leucopænia, and the result of such observations would be entirely misleading and deceptive.

In regard to treatment, I mentioned that, in the cases of McA— and Wm. B—, terebene abscesses were made in the flank, and that in consequence the polymorphonuclear leucocytosis rose as high as 21,000 per c.mm. of blood in the former case, and 30,000 per c.mm. in the latter. As a result—or at least synchronously with this rise in the polymorphs—there was an abatement of the acute symptoms and a rapid improvement in the general tone and character of the physical condition. The question arises—were these changes in the patient's condition and demeanour a mere coincidence, or were they vitally connected with the leucocytosis which had been artificially induced by the injection of terebine? The literature of psychiatry contains many instances in which, after an intercurrent attack of one of the exanthemata, of carbuncles, erysipelas, or some other severe inflammatory state, unexpected recoveries have been recorded. Unfortunately such intercurrent conditions which are followed by a favourable turn in the mental symptoms are of exceptional rather than common occurrence. A striking example came under my notice about twelve months ago. A female patient was admitted into this asylum suffering from melancholia of the manic-depressive type. She had previously been under treatment here. Two days prior to admission she set fire to her nightdress, sustaining a severe and extensive burn over the left thigh and lower part of the abdomen; she also received a number of smaller burns on the fingers of both hands and upon the right thigh. I only estimated her leucocytosis on two occasions, when it registered 31,040 polymorphonuclear leucocytes per c.mm. on the first day, and 30,600 per c.mm. on the second day. She remained under treatment in the asylum for about three months, and during that time she showed no mental symptoms beyond slight irritability and a tendency to be emotional, yet she had been depressed for five weeks prior to admission, and her previous attack treated in this asylum lasted for six months. Dr. Clouston, in his *Clinical Lectures on Mental Diseases*, says, "I think we shall some day be able to inoculate a septic poison and get a manageable counter-irritant and fever, and so get the alterative effect of such things, and the reaction and stimulus to nutrition that follows febrile attacks."

The "alterative" effect referred to by Dr. Clouston is what we need to study with the greatest care in order that we

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may understand what produces the effect and the manner in which it obtains its result.

In examining the leucocytosis of the intercurrent diseases which are reported in literature as being followed by a remission of the mental symptoms, it will be found that they are diseases which are very frequently associated with the phenomenon of hyperleucocytosis. I have already mentioned that this increase in the number of the leucocytes is Nature's method of repelling, or attempting to repel, the invading and irritating factors productive of the disease. This rise of the leucocytosis in these secondary conditions is, I consider, the cause of the "alterative" effect commented upon by Dr. Clouston. If in a condition such as mania, which is accompanied by a hyperleucocytosis, an intercurrent disease of an inflammatory nature occurs, *e.g.*, erysipelas, the leucocytosis, providing the leucocyte-producing powers of the individual are fairly normal, will, owing to the extra stimulus, be greatly increased. This addition to the defensive forces is obviously bound to have a very definite action upon the course of the primary disease, *i.e.*, the mania, as well as upon the intercurrent condition. By a study of such accidental cures we see dimly into Nature's methods and get a hint of a means we might profitably adopt. To test the efficacy of this method it remains but to imitate Nature. This I have done by injecting 1 c.c. of terebene in two of the cases here quoted, and in doing so I have been able to corroborate similar results obtained by Dr. Bruce. In some of Dr. Bruce's cases the best results followed upon the accidental contamination of the abscess cavity by *Staphylococcus aureus* and other organisms. Such a contamination led to a well-sustained leucocytosis, and none of the patients presented disagreeable physical symptoms. In fact they steadily gained weight and made excellent recoveries.

In all the foregoing cases it will have been noticed that the general physical symptoms were very much alike. I will now review these symptoms and also supplement them from other cases which have come under my observation.

In such toxic cases the patient is usually anæmic and ill-nourished. These symptoms almost invariably come on a month or two before any mental symptoms are noticed. The temperature is irregular and usually subnormal. It frequently rises a point or two above normal at the beginning or during

an acute attack. The pulse is irregular in rhythm and tension, and it increases in both characters at the beginning and during an acute attack. This observation is valuable in the case of impulsive patients. It is usually the first sign noticeable, and when present is distinctly indicative of an impending attack. The tongue is frequently covered with a dirty white fur, the breath is foul, and bowels severely constipated. In the course of an acute attack of mania the teeth and tongue may be covered with sordes. The appetite is usually poor and variable, the desire for food is often absent or perverted. The skin may be dry, or unnaturally moist and greasy. Under these latter conditions the odour is always offensive, and, in spite of frequent bathing, usually remains so until convalescence. Headaches and neuralgic pains are frequently present, and in women menstruation is often suppressed. The reflexes, both superficial and deep, are irregularly abnormal.

Such symptoms occur very frequently in the initial stages of various conditions of disease, and are to be met with in every-day practice. In them there is nothing very striking. They are the signs of malaise which may precede many acute conditions or accompany many chronic ones. In states of insanity, however, they are alike interesting and suggestive, especially when observed with a hyperleucocytosis and the presence of specific agglutinins in the blood. Symptoms such as these suggest that insanity is not merely a mental aberration, arising *de novo* in some part of the central nervous system, but also a very serious disturbance of the normal physiological balance. Some authorities hold that such an upsetting of the physical health is entirely secondary to the mental disease. Such a statement is incompatible with the mental improvement which accompanies the return to physical health in those cases which recover. Further, it cannot be said that the physical improvement is due to the mental regeneration, for we very frequently find patients who grow stronger and healthier in body while not in mind ; in fact the prognosis in such cases in usually very bad. Again, the condition of the intestinal flora of these forms of insanity is considerably changed. Normally, in agar stroke cultures of the fæces of the human subject, the growth of the *Bacillus coli communis* is so abundant that all other organisms are obliterated. In the insane the growth is stunted and abnormal, and colonies

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of cocci are frequently seen between the colonies of *coli*. In some cases the *coli* are very scanty and occasionally almost absent. A sketch of the growth taken from the fæces of a case of alcoholic mania is given opposite page 74. In it the *Bacillus coli* is almost absent and colonies of cocci are very numerous.

Resumé.

The points deserving notice are:

(1) That the insane as a class possess an inferior grade of organisation of the nervous system, which may be due to hereditary factors or may be the result of devitalisation by toxins—such as accompany syphilis, influenza, and other allied diseases.

(2) That the balance of this inferiorly organised system may be readily overthrown by numerous secondary conditions, one set of which is broadly termed a "toxæmia."

(3) That in this country and abroad toxins of some description or other, whether of intra- or extra-corporeal origin, are widely credited as the active cause of the majority of psychopathic conditions.

(4) That that class of the insane falling under the category of mania presents a very definite and persistent clinical picture, a most noteworthy and important feature of which is the hyperleucocytosis. Moreover, that the general physical symptoms are similar to those found in the more common toxic conditions. This fact, taken in conjunction with the hyperleucocytosis, the abnormal condition of the bacterial flora of the intestine, and the presence of specific agglutinins in the blood-serum, strongly support the theory of the toxic origin of these conditions of insanity.

(5) That maniacal patients as a class form at least 50 *per cent.* of the admissions in most asylums, and that therefore anything which aids in their diagnosis, prognosis, or treatment is a step of great value.

(6) That for purposes of diagnosis the estimation of the polymorphonuclear leucocytosis may be of use to differentiate simple alcoholism from more serious conditions in which alcoholic excess has merely precipitated an attack although it receives the credit of being the exciting cause.

(7) That the systematic observation of the leucocytosis is of

value in prognosis. It has been shown that in those cases in which the leucocytic reaction is not marked there is a strong tendency to chronicity, terminating in fixed delusions and dementia; and conversely, that those in whom the leucocyte reaction is high most frequently recover.

(8) That with regard to treatment by the artificial stimulation of the leucocytosis, the mental illness is often considerably shortened, and that an impending attack may be aborted.

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The Histological Evidence that Toxins reach the Spinal Cord via the Spinal Roots; with Special Reference to Plasma-Cells.

By DAVID ORR, M.D., and R. G. ROWS, M.D.

IN May, 1907, we published the results of our first series of experiments dealing with the question of toxic absorption along the lymphatic paths of nerves and the effects upon the spinal cord, medulla, and pons.

The experiment consisted in placing a celloidin capsule containing a broth culture of an organism underneath the sciatic nerve or under the skin of the cheek of rabbits and dogs, and we held from the microscopical examination of the

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