That in adults it is safer to do the operation without general anæsthesia.

That aspiration is disappointing as a curative agent, but is useful in some cases temporarily.

That incision and drainage with antiseptic precautions may be trusted to cure all cases of curable empyema.

That irrigation is unnecessary and dangerous.

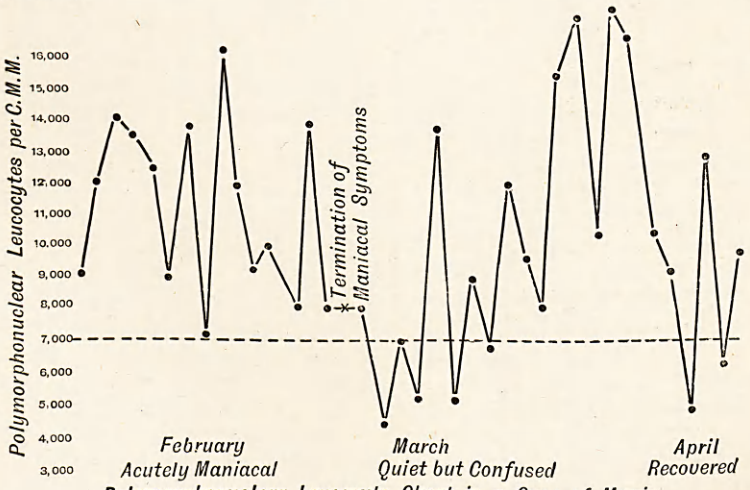
That rib resection is needful in some neglected cases, but in the generality of cases it is meddlesome surgery.

THE SYMPTOMS AND ETIOLOGY OF MANIA.

By Lewis C. Bruce, M.D., F.R.C.P.Ed., *Medical Superintendent, Perth District Asylum, Murthly.*

(*Continued from p.* 120.)

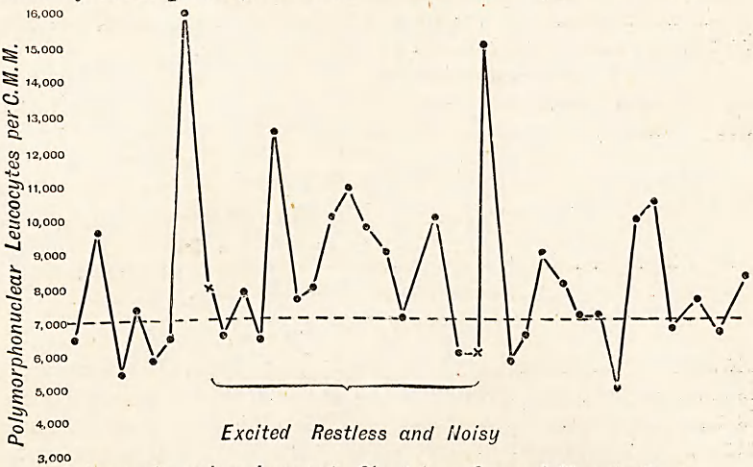
In cases of recent mania of the confusional type, the leucocytosis is always high, and the higher the leucocytosis the more hopeful is the prognosis. In a patient who suffers from a short sharp attack of mania and makes a rapid recovery, the polymorpho-nuclear leucocytosis is uniformly high, even after recovery is complete. And this hyper-leucocytosis persists apparently indefinitely. In one female adolescent patient whose blood I have had opportunities of examining at intervals during the last three years, during which she has enjoyed sound mental health, I have always found a polymorpho-nuclear hyper-leucocytosis present.



Polymorphonuclear Leucocyte Chart in a Case of Mania (Confusional Type)

Chart 3.

In cases of confusional mania who convalesce more slowly, the polymorpho-nuclear cells are at first greatly increased in number, then they subside somewhat, only to increase again as complete recovery takes place (Chart 3).



Polymorphonuclear Leucocyte Chart in a Case of Chronic Mania (Confusional Type)

This is a continuous daily record for thirty-six days.

CHART 4.

In patients who do not recover, one of two things happens. Either the patient suffers from chronic mania with recurrent exacerbations of excitement, or the patient becomes demented.

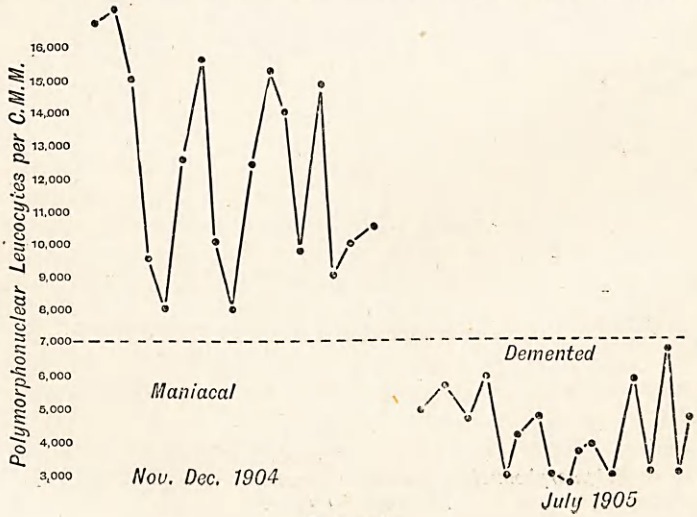
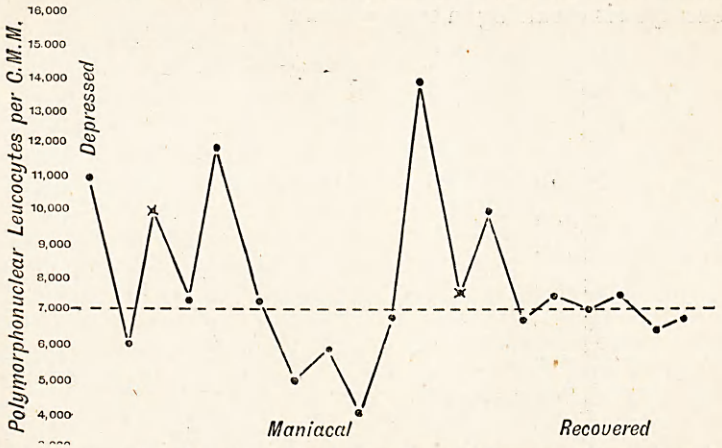


CHART 5.

If the disease takes the form of chronicity with recurrent exacerbations, the polymorpho-nuclear leucocytosis varies considerably, but presents distinct waves corresponding to the recurrent attacks of excitement (Chart 4). If the patient becomes demented, then the polymorpho-nuclear leucocytosis falls below the normal as if to indicate that the patient was exhausted and unable to cope further with the toxæmia (Chart 5). I have seen a few of such cases recover, however, if their leucocytosis was accidentally or artificially stimulated (Charts 6 and 7).

In cases of mania of the manic-depressive type, the symptom of hyper-leucocytosis is often present, and corresponds to the period of excitement; thereafter it falls to normal, and with the exception of an occasional rise remains at normal until another attack of excitement or an attack of depression sets in (Chart 8).



Polymorphonuclear Leucocyte Chart in a Case of Recurrent Mania (manic-depressive), showing the leucocytosis throughout the course of an attack

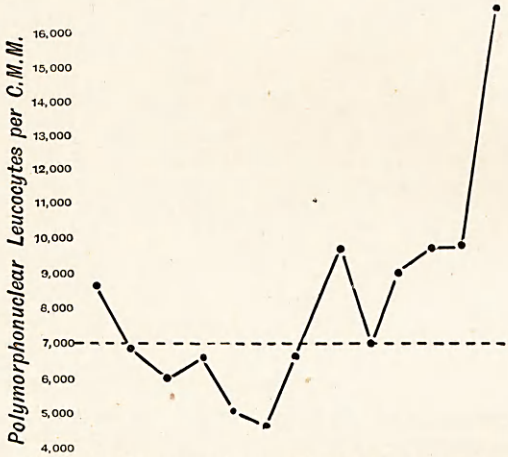
CHART 9.

In many of these cases of manic-depressive insanity, however, there is a regular sequence of events in the leucocyte curve which I am only able to show you in chart form in patients who suffered from short attacks. The period of excitement in many of these cases of manic-depressive insanity is so prolonged, lasting perhaps three and four months, that it is impossible to represent the leucocytosis in a lantern chart (Chart 9).

Chart 9.—The patient, a male, æt. 50, had suffered from short recurrent attacks of the manic-depressive insanity since adolescence. The attack, the leucocytosis of which is represented in the chart, commenced with depression, which lasted for a little more than a day, and the polymorpho-nuclear leucocytosis was 11,000 per c.mm. The following day it had fallen to 6000, and the patient complained of pains in the joints, which he ascribed

to rheumatism. On the third day he was maniacal, and the polymorpho-nuclear leucocytosis had risen to 10,000 per c.mm. For the next nine days he was in a state of great elevation and excitement. It will be noticed that at the commencement and termination of the maniacal attack there were marked rises in the polymorpho-nuclear leucocytes, but that at the very height of the attack the polymorpho-nuclear leucocytes fall below 7000 per c.mm. Recovery followed the last rise, and the leucocytosis at once returned to about 7000 per c.mm. Subsequent attacks in this patient always presented the same sequence of symptoms and the same leucocyte curve, and similar records have been obtained in other cases where the attacks were so short as to facilitate continous examination.

As interesting comparisons I show you two charts of hyper-leucocytosis occurring in sane persons.



Polymorphonuclear Leucocyte Chart in a Case of Fissure of the Tongue

CHART 11.

Chart 10.—A. R. is a case of rheumatic arthritis. The leucocytosis is shown for a period of fourteen days, when the patient was suffering from a recurrent attack of pain in the joints, together with general malaise.

Chart 11.—K. D. is a member of the nursing staff who volunteered to act as a control to certain observations which we were making on the tuberculo-opsonic index. It was noticed that her polymorpho-nuclear leucocytosis became high, the pulse was a little fast, but otherwise the subject appeared to be in excellent health. There was no disturbance of temperature. Her serum strongly agglutinated the washed red blood corpuscles of a healthy person. It was only accidentally that we discovered that this

control volunteer was suffering from a fissure of the tongue—a lesion only ½ in. long and ⅛ in. deep, and yet the resulting bacterial toxæmia as indicated by the leucocytosis is most marked.

In many cases the results obtained from leucocyte observations are of value in indicating the disease process when practically no diagnosis can be made from the mental symptoms alone.

Chart 12 shows the leucocytosis in a case of peculiar interest. The patient, a married woman, æt. 34, was admitted suffering from delusions of suspicion. She was thin and poorly nourished, and the husband stated that he had observed a gradual change coming over her. She became irritable, changed in character, and at times exhibited violent temper on little or no apparent provocation. Then she suffered from hallucinations of hearing, which led her to suspect the presence of other people in the house, and finally she became suspicious of her husband, believing that he was trying to poison her. On admission she simulated a case of delusional insanity. She was apparently quite clear and sensible, answered questions and expressed her delusions freely. On physical examination nothing could be detected beyond the fact that there was a hyper-leucocytosis, which is not as a rule a symptom of delusional insanity. Further questions elicited the fact that she had been delivered of a child some two years prior to admission, and that since then she had occasionally suffered from a vaginal discharge. Upon examination she was found to be suffering from a fissure of the cervix about ½ in. deep and ¾ in. long. The discharge from the fissure when inoculated upon agar gave a rich growth of streptococci. Her blood serum strongly agglutinated a streptococcus obtained from a case of confusional mania. The local lesion was treated and healed in two months, and the patient made a perfect recovery. She remembered everything that had happened prior to and since her admission, but she stated that the period of her existence corresponding to her illness seemed to her to be like a dream. It was quite evident, therefore, that there had been a considerable amount of mental confusion, and I regard this case as one of confusional mania in whom the symptom of maniacal excitement had been suppressed.

Chart 13 is a very similar case occurring in a married woman, æt. 50. For several years she had been irritable, delusional, and morbidly suspicious of her husband. She searched his clothes, read his letters, and had all his movements secretly watched, because upon one occasion she had discovered a hair upon his topcoat which was certainly not her own. She was sent to me as a case of chronic delusional insanity.

On admission, the only symptom which we could detect was a hyper-leucocytosis, and she looked thin, pinched, and badly nourished.

The nurse reported, however, that the patient had a vaginal

discharge, and upon examination she was found to have an intra-uterine fibroid. The discharge from the uterus was swarming with organisms, chiefly streptococci. Her blood serum contained agglutinins to a streptococcus isolated from an undoubted case of confusional mania. In this case, as in the previous one, we demonstrated the presence of a bacterial toxæmia with the probable local lesion. The patient was removed by her friends.

Chart 14 throws some light upon the vexed question as to whether alcoholism is a cause or a symptom of insanity.

The patient, a male, æt. 34, was admitted suffering from hallucinations of sight and hearing and also delusions. His history was that for years he had been drinking heavily, was arrested by the police, found to be insane, and transferred from the prison to the asylum.

Polymorphonuclear Leucocytes in a Case of so-called Alcoholic Insanity

CHART 14.

On admission he appeared well nourished and healthy. He had undoubtedly vivid hallucinations of sight and hearing, and he was dangerously impulsive. Upon two occasions he made sudden unprovoked attacks upon the night attendants who were in charge of the dormitory in which he slept. Such attacks are very typical of alcoholism. He presented a very marked hyperleucocytosis, but no temperature. From his urine my assistant, Dr. Howard, isolated a streptococcus which was agglutinated by the patient's serum in a dilution of 1 in 20 within an hour, while the sera of control persons gave no reaction. The bacterial examination of the fæces gave an almost pure growth of streptococci, the *B. coli* being practically absent.

He recovered after a residence of four months, but during the

whole period of his stay in the asylum he presented this symptom of hyper-leucocytosis.

Chart 15 shows the leucocytosis in a similar case occurring in a male æt. 20. The patient was of the degenerate type. He had been three times discharged from the army for drunkenness. He was admitted suffering from hallucinations of hearing and sight. Beyond general tremulousness of the muscular system, he presented no symptoms except a hyper-leucocytosis. His serum contained agglutinins to several strains of streptococci isolated from cases of undoubted confusional mania. During his residence in the asylum he suffered from several slight attacks of restlessness associated with a return of the hallucinations of hearing. He was eventually transferred to a neighbouring asylum.

Both these patients were undoubtedly cases of alcoholism, but the fact that they presented definite symptoms of bacterial toxæmia suggests that the alcoholism was a symptom rather than a cause of their mental state. Since these observations were made three additional cases of chronic alcoholism have been examined, and they all presented the same physical symptoms.

Chart 16 shows the leucocytosis in a female, æt. 26. The girl was sent to the asylum because she was unmanageable at home.

On admission, the patient showed the very common symptom in adolescent cases of arrested development, but no mental or physical symptoms of disease could be detected. Her blood was regularly examined, and very shortly after admission a hyper-leucocytosis was noted, together with a quick pulse of over 100 per minute. She became irritable and quarrelsome, sometimes refused food, and behaved like a petulant child. This condition lasted for about a week or ten days and then passed off, the leucocytosis falling to about 7000 per c.mm. and the pulse rate to between 60 and 70 per minute. Her serum showed agglutinins similar to the cases already cited. Several similar attacks have occurred with similar physical symptoms. If no observations had been made upon the leucocytosis and serum reaction, these periodic attacks would have been ascribed to fits of bad temper, whereas all the symptoms point to the patient as being a masked case of confusional mania.

The consistency of the results shown by these blood observations alone are in my opinion suggestive. They suggest bacterial invasion, and that the victims of confusional mania suffer from a chronic insidious toxæmia not only during the maniacal attack but for a subsequent indefinite period. The mania, in fact, may be only an accidental symptom of the disease; while the manic-depressive cases suffer from recurrent attacks of toxæmia. But whatever the significance of this symptom may be, these observations are facts not fiction, which future workers may relegate to their proper sphere when the great problem of the causation of mania is solved.

Doubts have been thrown upon the accuracy of these records, but I know of no observer who has conducted similar observations, dividing the various forms of mania from one another, or made continuous observations extending over weeks and months. There is also this additional fact, that six different workers in the Murthly Laboratory, several of whom were sceptical, have corroborated these results, and further, our collective observations upon the leucocytosis of healthy persons tally with those of accepted published records.

Summary of Lecture II.—The blood serum in health contains protective agglutinins to certain strains of staphylococcal and streptococcal organisms. These protective agglutinins cannot be demonstrated in the blood serum of over 60 per cent. of maniacal patients.

In addition to these agglutinins, which we may call normal agglutinins, the blood serum may contain agglutinins directly the result of disease, an example of which is the typhoid agglutinin which appears in the blood serum as the result of an attack of typhoid fever. Such agglutinins are known as specific agglutinins because they act only upon the infecting organism.

In the blood serum of patients suffering from mania, specific agglutinins to certain organisms of the streptococcal group can be demonstrated to exist, and similar agglutinins are rarely present in the blood serum of apparently sane and healthy people. The streptococcal organism with which these observations were made were isolated from the blood, urine, and fæces of maniacal patients.

The leucocytosis, or the number of white blood corpuscles in the blood of maniacal patients, is greatly increased, and this increase is largely due to an actual and relative increase in the polymorpho-nuclear leucocytes. A hyper-leucocytosis of the polymorpho-nuclear leucocytes is generally regarded as an evidence of bacterial toxæmia.

Continuous blood observations in cases of confusional mania reveal the further fact that after recovery from the maniacal attack the patients present this symptom of hyper-leucocytosis, and it is reasonable to suppose that this evidence of toxæmia was also present before the maniacal attack. In other words, in the type of mania which I call confusional, the disease is a chronic, insidious toxæmia, of which the maniacal attack is only an incidental complication.

Lecture III.

In the first lecture I dealt with the physical symptoms which occur in cases of mania. I drew attention to the commonly accepted belief that maniacal states are conditions of brain

poisoning. It was shown that the blood serum in over 90 per cent. of maniacal patients contained an agglutinin which agglutinated the red blood corpuscles of healthy persons. This agglutinin can also be demonstrated in the serum of over 50 per cent. of persons who are sane and apparently healthy, and can be artificially produced in the lower animals by infecting them with coccal organisms. The presence of such an agglutinin in the blood serum was therefore taken to indicate some form of coccal invasion, but as the sane as well as the insane present this symptom, some further factor must assist in the production of maniacal states, and this further factor was stated to be an inherited or acquired instability of the nervous system which would render it peculiarly liable to disorder from states of toxæmia.

The evidences of general failure of nutrition, the disorders of the alimentary tract, and the character of the nitrogenous excretion by the urine, are all such as would lead one to expect that maniacal states are closely allied to the diseases known as infective.

In the second lecture I mentioned the fact that the blood serum of healthy persons contains protective agglutinins to certain strains of coccal organisms, and that these protective agglutinins cannot be demonstrated in the blood of over 60 per cent. of patients suffering from mania. In addition to these normal agglutinins, the serum of maniacal patients was shown to contain specific agglutinins to certain strains of streptococci isolated from the blood, urine, and fæces of such patients.

The hyper-leucocytosis found in patients suffering from mania was described, and it was pointed out that the increase of the polymorpho-nuclear leucocytes was strong evidence of bacterial toxæmia.

I divided cases of mania into two great classes—mania of the confusional type and mania of the folie circulaire type or manic-depressive insanity. In this lecture I merge all manias into one great group.

If, as indicated in my first two lectures, the diseases known as mania are due to bacterial toxæmias, then the natural question arises, what organism or class of organisms produce the toxæmia, and how do they attack the patient? To answer these questions it is necessary to describe in detail the various observations undertaken to discover the organism.

My first observations were conducted as follows. I argued that if the organism was circulating in the tissues it might be possible to obtain it in pure culture from a sterile necrotic area. I knew that the subcutaneous injection of certain irritants produced a hyper-leucocytosis which frequently improved the condition of the patient, and I combined this method of treatment

with bacterial investigation. I injected therefore with aseptic precautions from 0·5 to 1 c.c. of terebine subcutaneously. In the course of a week an abscess formed and from 1 to 2 c.c. of the abscess contents were then withdrawn hypodermically with a needle attached to a syringe. The pus so obtained was mixed with nutrient broth and incubated at 37° C. for twenty-four hours. The whole operation was conducted painlessly with local anæsthesia. Out of fifteen such abscesses I isolated a short diplo-bacillus in seven cases. The remaining abscesses were sterile. I merely mention this work to dismiss it, because after working with this organism for some six months I came to the conclusion that it had nothing to do with the disease, and was possibly an accidental contamination.

I next directed my attention to the blood, and by means of a 10 c.c. glass syringe attached to a needle, 10 c.c. of blood was withdrawn from any prominent vein in the forearm and transferred to two flasks, each containing 250 c.c. of sterile bouillon. In some instances these flasks were immediately placed in the incubator at 37° C., in others twenty-four hours were allowed to elapse prior to incubation to allow the leucocytes to die and so inhibit their phagocytic action. The blood was examined in this manner in fifteen cases of mania, all acute recent cases. In twelve of the observations the flasks were sterile at the end of seventy-two hours, two were accidentally contaminated, and only one yielded a short streptococcus, which was eventually proved to be in some way connected with the disease process. As mentioned in the previous lecture, it was found that the blood serum of the patient from whom this organism was obtained agglutinated the organism in dilutions up to 1 in 100, and that similar agglutinins were found in over 70 per cent. of all the cases of mania subsequently examined, while control persons and insane patients who were not suffering from mania only gave agglutination in a proportion of 15·8 per cent. This single successful blood observation was of immense service in stimulating further research, but it was obvious that blood observations alone would not yield satisfactory results.

With the help of my assistants I therefore turned my attention to the bacterial examination of the urine. In the male cases the urine was passed directly into sterile urine glasses, and in the women urine was drawn by means of a sterilised catheter. By neither of these methods can sterile urine be obtained, because the urethra invariably contains organisms which are either washed out by the urine or infect the catheter employed. I trust to the fact, however, that if we obtained an infecting organism the blood serum of the patient would agglutinate it, and this was the test which we employed in every case to separate the infecting from the non-infecting organisms. Control serums were, of course, used in every case.

The first fact which we noted in the urine observations was that the urine of patients suffering from mania contains, when examined microscopically, a very large number of various forms of organisms. To control this observation, we examined the urine of healthy males and compared the results with those obtained from the examination of the urine of male patients suffering from mania. The method of examination was conducted as follows. The urine, immediately after being passed, was taken to the laboratory. Thirty c.c. were divided equally between two sterile centrifuge glasses and subjected to centrifugation for ten minutes. The supernatant fluid was then pipetted off, leaving 1 c.c. in each glass. A sample was taken from each glass and examined microscopically, and the remainder was then distributed equally between two agar plates, allowed to solidify, and placed in the incubator at 37° C. to incubate for twenty-four hours. The urine of the maniacal male patients was found to present microscopically great numbers of bacteria, chiefly coccal organisms, while the urine of five control males showed only a very small proportion of organisms. In spite of the fact that the urine of the maniacal patients when examined under the microscope presented a large number of organisms, in several instances the number which actually grew upon the agar plates was very small in proportion. On the other hand, the urine of the control males when incubated on agar plates presented often as many as 300 colonies in each plate. It is inferred from this that a large percentage of the organisms in the urine of the maniacal patients were dead, and had probably been excreted by the kidneys, while the organisms in the control urines were living and had probably been washed out of the urethra. Counting both male and female cases, the urine was bacterially examined in twenty cases, and from the organisms so obtained only two were agglutinated by the blood serum of the patient yielding the organism. Control sera failed to agglutinate either of these organisms. Both organisms were short streptococci. In none of these patients was the urine offensive, nor did we suspect bacillurea until microscopic examination was made. According to the researches of Adami, the presence of organisms in the urine may be explained as follows. Adami found that if the livers and kidneys of apparently healthy animals were removed with antiseptic precautions and placed in agar and incubated, organismal growth was obtained in nearly every case. He believes that under ordinary conditions the leucocytes pass out through the mucosa on to the free surface of, more especially the alimentary tract, some of these cells there undergoing destruction, while others, now laden with various foreign matters, including bacteria, pass back into the submucosa and find their way into either the lymphatic channels or into the portal venules. Such isolated bacteria which may have escaped leucocytal destruction or removal by the lymphatic glands, or

by the endothelium of the portal system, may pass either through the thoracic duct, or through the liver, and enter the systemic circulation, from which they are eliminated chiefly by the kidneys. Such a condition is known as "latent infection" or "latent microbism," and is compatible with perfect health.

The intestinal tracts of patients suffering from mania present, post-mortem, catarrhal areas. Dr. Ford Robertson, the pathologist of the Scottish asylums, examined such a condition in the ileum of a very acute case of mania of the confusional type who died in the typhoid state. His report is as follows: "In the ileum the mucosa was narrowed, the villi were diminished in number, fibroid and atrophied. There was great increase of interglandular fibrous tissue, and the bases of many of the glands were in consequence widely separated from one another, while the submucosa showed fibrous thickening." In his opinion the condition was one of severe chronic atrophic catarrh. There were also in this case fatty changes in the epithelial cells of the liver. I have noticed similar changes in the small intestines of nearly every case of mania examined post-mortem. The presence of such lesions may possibly explain the presence of such numbers of organisms in the urine, as a catarrhal condition of the intestine would naturally favour the presence of leucocytes which would be attracted to the area by chemiotaxis.

The fifteen blood and twenty urine bacterial observations had so far, therefore, yielded only three organisms which were agglutinated by the blood serum of the patients from whom the organisms were obtained; but beyond the fact that they all belonged to the streptococci group, they differed somewhat from one another in their growth characteristics and in their agglutinating sensibility when tested with the serum of various cases of mania. The researches of Adami, however, naturally suggested the intestinal tract as a field for bacterial investigation. We therefore made cultures from the fæces of cases of mania. The technique was as follows. A small portion of the fæces was taken immediately after being passed. A straight platinum needle, sterilised by flame, was charged once from the centre of the mass, and successive stroke cultures were then made on a series of six agar tubes, three strokes being made upon each tube. These tubes were then placed in the incubator and incubated at a temperature of 37° C. for a period of twenty-four hours. Twenty-seven observations were made on twenty-seven different cases, and it was noted that colonies of cocci were very numerous in the bacterial flora of fifteen of these maniacal patients (Chart 1). Upon examination it was found that these colonies of cocci were in almost every case streptococci. Control observations made upon the fæces of healthy persons and cases of insanity other than the subjects of mania very rarely yielded more than one or two colonies of streptococci, whereas in some of the maniacal patients the

streptococci were by far the most numerous organisms present. Houston, in examining the bacteriology of the fæces in twenty healthy persons, found streptococci in excess in one case. Sub-cultures were made from these colonies of streptococci obtained from the fæces, and each individual patient's serum was tested to broth cultures of these organisms to ascertain if specific agglutinins were present. Control sera for healthy persons were used in every case to check the agglutinating experiments. Organisms, to which such agglutinins could be demonstrated to exist in the patient's serum and to be absent from the sera of control persons, were found in six of the maniacal patients. In one case the same organism was isolated both from the urine and the intestinal tract. The mere presence of large numbers of streptococci in the intestinal flora was no indication that specific agglutinins would be found in the blood serum of the patient. For instance, in one patient ten different colonies of streptococci were isolated from the fæces, but the patient's serum agglutinated only one of them. In another case fourteen colonies of streptococci were examined, but none of them was agglutinated by the patient's blood serum. In many instances the streptococci obtained were agglutinated both by the patient's serum and the control sera, while in other cases the control sera produced rapid agglutination, but the organism was not affected by the patient's serum.

The characteristics of these eight organisms obtained from the blood, urine, or fæces are as follows:—

Microscopically they appear as short chains of four, five, six, seven, and eight cocci, or just as frequently as diplos. They stain readily with all aniline dyes, and they hold Gram's stain. They all grow at the ordinary atmospheric temperatures except No. 1, obtained from the blood, which, when first grown on artificial media, showed no capacity for growth at the room temperature, but was capable of long life under such conditions, as an inoculated agar tube, after being kept for a month at room temperature, upon being incubated for twenty-four hours at 37° C., produced a characteristic growth. After passing through several subcultures, this organism was found to have acquired the power of growing at ordinary temperatures. In broth they all form a uniform turbidity in less than twenty-four hours, and they turn the media acid. Stab cultures in gelatin grown at 22° C. show as a pale clear streak, which in all eventually becomes feathery along the edges. There is little surface growth. No. 1, after being sub-cultured for two years, was found to liquify gelatin, a characteristic which it did not possess when first obtained. Stroke- and smear-cultures on sloped nutrient agar tubes grow as thin bluish-white streaks or smears, which under magnification are seen to consist of numerous small translucent colonies. The size and opacity of these colonies differed considerably in some of the

organisms when first obtained, but after several subcultures had been made they all tended to one type of growth. All grew in litmus milk, which was curdled by four of the eight organisms, while the blue litmus was changed to red by seven.

When tested on animals, their action was obscure. Intravenously in rabbits in doses ranging from 0·1 c.c. to 2 c.c., they produced a slight febrile reaction. Intraperitoneally in rabbits in doses ranging from 0·5 to 5 c.c., they produced no outward result, but young rabbits so infected almost invariably developed paralysis of the hind-quarters in from one to two months from the date of infection. Several of these infected animals died, but no lesion could be demonstrated post-mortem. In one, however, a pure culture of a streptococcus was isolated from the heart blood, which in appearance, growth characteristics, and to a slighter degree in its agglutinating properties, resembled the infecting organism.

Subcutaneous injections of doses ranging from 0·1 to 2 c.c. produced no suppuration, but repeated injections produced rapid loss of body weight, although the animal continued to take food well and did not appear to be ill. The fact that these organisms are not pus producers separates them from the pyogenic streptococci and allies them to the *Micrococcus rheumaticus*. Attempts were made to immunise two goats with the view of obtaining an antiserum, but both animals rapidly lost weight, and the injections were discontinued. Neither appeared to be ill, they took food greedily, and were active and energetic. Both died some months after the injections had been discontinued, apparently of some intercurrent disease the nature of which I did not understand.

A sheep which was immunised by weekly injections of doses commencing at 1 c.c. of mixed broth cultures of four of the organisms, the dose being gradually increased to 4 c.c. at the end of six weeks, very rapidly lost weight, but was otherwise apparently healthy. Serum was taken from both the goats and the sheep and tested in the laboratory, and also used in the treatment of cases of mania. In the laboratory no immune body could be demonstrated *in vitro*, and when injected into cases of mania in doses ranging from 10 to 20 c.c., the only result noticed was a fall in the pulse rate. Although these attempts to produce antiserums were unsuccessful, I still believe that there is a field for the use of antiserums in such cases. According to Ehrlich's theory, in a condition of toxæmia the patient's blood contains toxin molecules which gradually stimulate the cells of the body to throw out antitoxin molecules, which by combining with the toxin molecules render them inert. When one immunises an animal against toxins, these antitoxin molecules are in excess in the blood serum of the immunised animal, and it is probable that the injection of a large dose of such antitoxic molecules into a

patient suffering from mania would produce a temporary remission sufficiently prolonged to allow of the natural defensive processes of the body to come into play. A polyvant serum would, of course, be a necessity, as the streptococci found in connection with these disease processes are not identical.

Having failed to obtain an efficient antiserum, it occurred to me that the patients might form their own immune bodies if dead cultures of the organisms which they agglutinated were injected subcutaneously. The earliest of these observations were made before Wright published his researches on opsonins, and pointed out the necessity for the exhibition of small doses. The initial doses of vaccine used at Murthly were all too large. It was found that the injection of a 0·5 c.c. dose of a broth culture of these organisms when injected subcutaneously into a maniacal patient produced an exacerbation of the mental symptoms, corresponding to Wright's negative phase. This was followed by a temporary improvement corresponding to Wright's positive phase, but the results were very transitory, and in several patients, after a period of treatment extending over six weeks, no immune body could be demonstrated to exist in the blood serum when tested *in vitro*. During and corresponding to the positive phase, the polymorpho-nuclear leucocytes were always increased. After Wright published the results of his researches upon the opsonic indices in tubercle and *Staphyloccus aureus*, we examined the opsonic power of the blood serum in our maniacal patients, using as the testing organism the variety of streptococcus which each particular patient agglutinated. These observations were continuous in each case, and in some instances we were fortunate enough to obtain records throughout the whole period of short attacks of manic-depressive insanity and of confusional mania.

With the help of my assistant, Dr. C. J. Shaw, I made control observations on members of the asylum staff.

I am also able to show you opsonic index charts in the case of chronic rheumatic arthritis, and the control who suffered from a fissure of the tongue. The testing organism used in the case of rheumatic arthritis was the *Micrococcus rheumaticus*, a culture of which was kindly given to me by Dr. Dowson of the Wellcome Research Laboratory. And the testing organism used in the case of tongue fissure was a variety of streptococcus which the patient's serum partially agglutinated.

In estimating the opsonic index, we followed the technique introduced and described by Wright. An emulsion was made from a twenty-four hours' agar culture of the organism, which when necessary was shaken up with sterilised glass beads to insure subdivision of the cocci. Blood corpuscles, usually taken from a control person, were washed in 1 per cent. citrate of soda solution and then in normal saline. A sufficient quantity of serum was obtained from the patient and also from a control

subject. It is certainly more accurate to mix two or three control sera, but we were not able to do this frequently, but we tested our control sera every now and then against one another, and found them fairly steady in their reaction.

Equal quantities of emulsion, blood corpuscles, and serum were then mixed, drawn into a capillary tube, and incubated for fifteen minutes at 37° C. The contents of the capillary tubes were then blown on to slides, made into a film, dried and stained. The films were then examined under a microscope, the oil-immersion lens being employed, and the number of organisms, ingested by thirty, forty, fifty, or sixty polymorpho-nuclear leucocytes, were counted in both the patient's and the control films. The number of organisms ingested by the polymorpho-nuclear leucocytes in the patient's film were divided by the number of organisms ingested by an equal number of polymorpho-nuclear leucocytes in the control's film—the result being the opsonic index of that patient to the particular organism used in the observation.

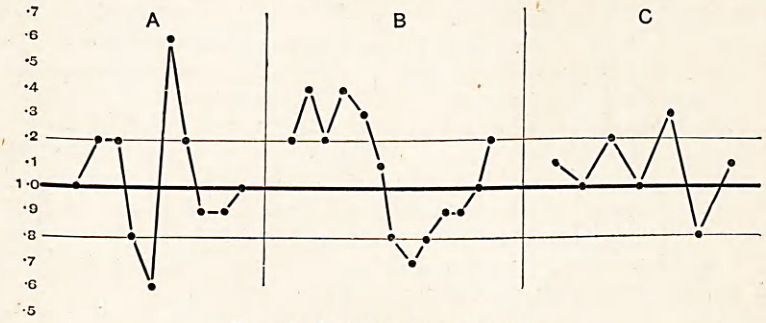
The average opsonic index of health as found by Wright and other observers to tubercule and staphylocci varies between 0·8 and 1·2, and in the charts which I will show you I have adopted these limits as the limits of the opsonic index in health to these streptococci, as to the best of my knowledge no data exist as to the average index in health to any of the organisms of the streptococci group.

Chart 2 shows the opsonic indices of members of the asylum staff to one of the streptococci isolated from a case of confusional mania. The sera of Cases A and B both agglutinated the red blood corpuscles of healthy persons, which reaction, as stated in an earlier lecture, is presumptive evidence in favour of some form of coccal toxæmia, although both were apparently in perfect health. The serum in Cases C did not agglutinate the red blood corpuscles in healthy persons. It will be noticed that the variations in the opsonic indices of these control persons are marked, much more so than in the case of tubercule, but when one comes to compare these charts with the charts of cases suffering from mania, the fluctuations in the indices of the maniacal patients are more marked than in the control persons.

Chart 3 shows the opsonic index in the case of a female adolescent suffering from acute mania of the confusional type. The patient was admitted in a state of wild delirious excitement, and a culture made from the fæces gave a rich growth of strepto-cocci, one colony of which the patient's serum agglutinated in dilutions up to 1 in 50. This organism was used in estimating the opsonic power of the patient's serum.

For the first four days the patient was maniacal and delirious, and the index was low. On the fifth day the index rose to 1·6, and on the sixth day to 2. On that, the sixth, day the patient

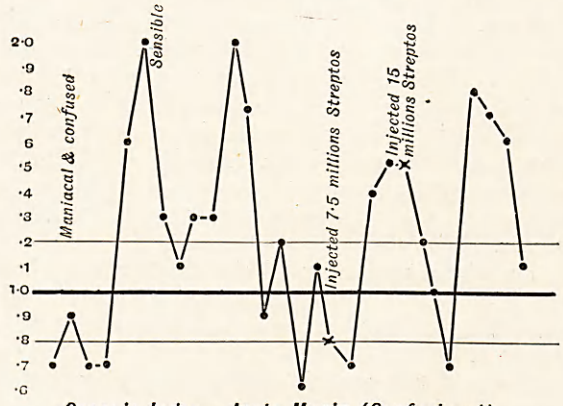
became conscious of her surroundings. Two days later the index had fallen to normal, and this was again followed by a marked rise or positive phase and a subsequent fall. During the whole of this period the patient was sensible, quiet, sleeping well, and



Opsonic Indices in Control Cases

CHART 2.

progressing favourably. On the seventeenth day I injected 7½ millions of dead streptococci killed by heat. The following day the index fell to 0·7, and the patient was slightly dull and apprehensive. This was followed by a marked positive phase,



Opsonic Index. Acute Mania (Confusional)

CHART 3.

which lasted for three days, during which the patient was in good mental health. I then injected 15 millions dead streptococci, and this dose was followed by a prolonged negative phase lasting for three days, during which the patient was dull and confused. This was succeeded by a marked positive phase associated with mental clearness. The patient made an excellent recovery

without suffering from any relapses, which are extremely common in adolescent cases, but whether in spite of or because of the treatment it is impossible to say.

Chart 4 shows the index in a very acute case of delirious mania in a young male epileptic. For the first seven days the index was never above 1, and on two occasions as low as 0·4. Then a sudden rise to 2 occurred, with some mental improvement. On the eleventh day I injected 7½ millions streptococci, and this injection was followed by a fall or negative phase which lasted for two days, and this was succeeded by a positive phase lasting for two days. On the sixteenth day another injection of 7½ millions dead streptococci was given, and was followed by a marked fall or negative phase with exacerbation of the mental symptoms, and this was succeeded by a marked rise or positive phase reaching 2·4, accompanied by decided mental improvement.

Chart 5 shows the opsonic index in a case of chronic mania of the confusional type, occurring in an adult woman who had been ill for more than two years. The organism used in this case was the streptococcus obtained from the blood of the case of acute confusional mania. It will be noticed that the positive and negative phases follow one another with great regularity, and whenever the index fell below normal, a marked exacerbation occurred in the mental symptoms. Such a chart, interpreted according to our present knowledge of the opsonic index, would read as follows. The chart commences with a positive phase succeeded by a mild auto-intoxication which stimulated another positive phase. Then follows a more marked auto-intoxication, producing a decided negative phase, accompanied by excitement and noise. This is again succeeded by a positive phase with comparative mental improvement. Lastly, a still more marked auto-intoxication producing a negative phase lasting for four days, and again a reaction of the body to the toxins represented by a positive phase.

It will have been noticed in all the charts which I have shown, that the positive phases are extremely short, whether they occur as the result of auto-intoxication or as the result of the injection of dead bacteria.

Chart 6 shows the opsonic index throughout an attack of maniac-depressive insanity. The patient, a woman æt. 55, suffered from repeated attacks every three or four months. Each attack was short, rarely lasting for more than two or three weeks. The index throughout two separate attacks was observed, and it was practically identical on both occasions. On the first day the mental symptoms were those of depression with an index of 0·7, then follows a marked rise to 2, followed by a fall to 0·5. The patient became maniacal on that, the third day of her illness, and with the exception of a rise of the index to 1·6 on the fourth day, the index was low for eight days, during which the maniacal symptoms were

most acute. This period was followed by a sudden rise to 2 with marked mental improvement, and a subsequent index which closely approached the normal line associated with a rapid convalescence and recovery. This chart reads as follows:—Auto-intoxication with a negative phase and a subsequent positive phase. A further auto-intoxication with an abortive attempt at a positive reaction followed by a long negative phase lasting seven days. A mastering of the toxins shown by the return of the positive phase with a subsequent persistence of high opsonic power associated with recovery.

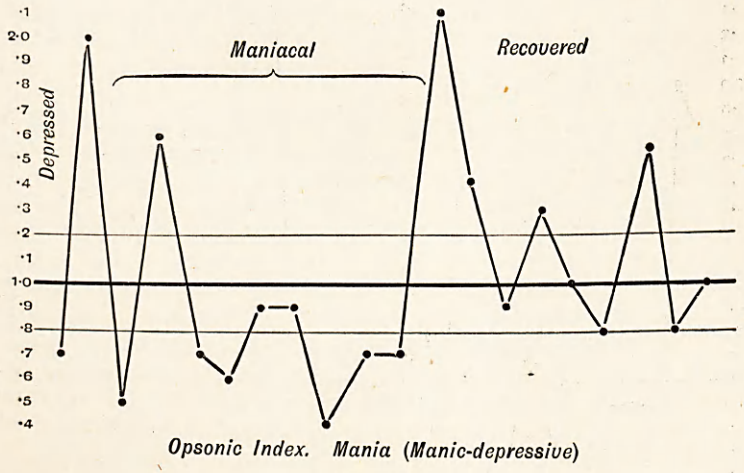


CHART 6.

Chart 7.—As an interesting comparison I show the opsonic index in the control case suffering from fissure of the tongue. The subject, a member of the asylum staff, volunteered to act as a control in some observations which were being made on the tubercule opsonic index, and at the same time the opsonic power of the blood serum was tested to one of the streptococci isolated from a case of confusional mania. The leucocyte chart, which was shown during the previous lecture, indicated that there was some source of toxæmia unknown to us, and we subsequently discovered that the lesion was a fissure of the tongue. It will be noticed that the index in this control upon two occasions rose much above the limits of health. The subject was apparently in excellent health, but the blood serum agglutinated the red blood corpuscles of a healthy person.

Chart 8 is also an interesting comparison with those of maniacal patients, as being the index of a sane person suffering from chronic rheumatic arthritis to the *Micrococcus rheumaticus*, who was also injected with vaccines of the organisms. The chart

starts with a marked positive phase, succeeded by a prolonged negative one, during which the patient suffered from nausea, intestinal disorder, and acute pain and swelling in the joints. The chart restarts with a positive phase, and on the fourth day an injection of $7\frac{1}{2}$ millions of dead *Micrococcus rheumaticus* was given. This was followed by a decided negative phase during which the patient suffered from a rheumatic attack, and this was followed by a positive phase with a return to comparative comfort. Next day another injection of $7\frac{1}{2}$ millions of *Micrococcus rheumaticus* was

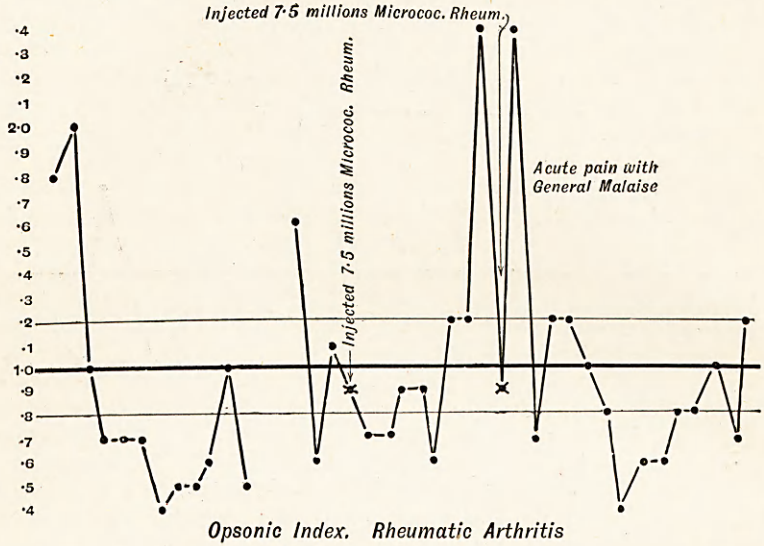


CHART 8.

given, which was followed by first a rise and then a prolonged fall of the index, and again the patient suffered from malaise and rheumatism.

When one compares such a chart made in the case of a person suffering from a disease which is almost certainly bacterial in origin with those made in the subjects of mania, there is a very marked similarity between them, both in the extreme variations of the index and the associations of the rheumatic and maniacal symptoms with the periods of the negative phases.

SUMMARY OF LECTURE III.—As the result of bacterial observations on the blood of fifteen patients suffering from mania, a streptococcus was isolated from the blood of one case of confusional mania. The blood serum of this patient agglutinated the organism in a dilution of 1 in 100, while the serum of few control persons gave agglutination. The blood of the remaining fourteen cases

of mania was sterile. It may be surmised, therefore, that organisms are not frequently present in the blood of maniacal patients.

As the result of bacterial observations upon the urine of twenty patients suffering from mania, it was noted that the urine of these cases when centrifuged and examined microscopically presented a large number of organisms, chiefly cocci. The urine of five control males when centrifuged and examined microscopically presented very few organisms. Cultures made from the centrifuged urine of the maniacal patients presented comparatively few colonies of organismal growth, considering the number of organisms seen microscopically. On the other hand, the urine of the five control males when inoculated on agar plates and incubated for twenty-four hours at 37° C. showed a large number of organismal colonies. It is inferred from this that the organisms in the urine of the maniacal patients were largely dead, and had been probably excreted through the kidneys, while the organisms in the urines of the five control males were living and had probably been washed out of the urethra. The excretion of organisms in the urine of maniacal patients may be explained from the fact that the small intestines of these patients when examined post-mortem present evidences of atrophic catarrh, which would favour phagocytic action by the leucocytes. Two streptococcal organisms were isolated from the urines of the maniacal patients. These streptococci were agglutinated by the blood serum of the patients yielding the organisms, while the blood sera of control persons gave no agglutination.

A bacterial examination of the fæces in twenty-seven patients suffering from mania demonstrated the fact that in 59 per cent. of these cases streptococci were very numerous, so numerous that in two instances no *Bacillus coli* were present. Houston in examining the bacteriology of the fæces in healthy persons found an excess of streptococci in one case out of twenty examined.

Six streptococci, which were agglutinated by the blood serum of the patients yielding the organisms but not by the sera of control persons, were isolated from the fæces of the twenty-seven maniacal patients examined.

As the result of animal inoculations with these various streptococci isolated from the blood, urine, and fæces of maniacal patients, it was found that these organisms were not pus producers, which separates them from the pyogenic streptococci and allies them to the *Micrococcus rheumaticus*.

Attempts to produce antiserums to these organisms by inoculating two goats and a sheep failed.

Attempts were made to immunise the patients by injections of vaccines made from these organisms. It was found that large doses produced an exacerbation of the mental symptoms. Several patients were treated for periods of six weeks with weekly injec-

tions, but when, at the end of that period, their blood serum was examined, no immune body could be demonstrated *in vitro*.

The opsonic indices of several maniacal patients, when tested against some of the streptococci above mentioned, are very suggestive of a bacterial toxæmia, particularly the negative phase which follows the injection of vaccines made from these streptococcal organisms.

As the result of these observations, I believe that the diseases known as mania are conditions of brain poisoning, the poison or toxin in every case being a bacterial one. The bacteria causing these toxæmias are probably streptococci, and the point of attack is almost certainly the intestinal tract.

My explanation of the disease process is as follows:—Owing to some lowering of the bacterial defences, certain strains of cocci become unduly increased in the intestinal tract. These cocci do not actually enter the blood stream, but they form toxins in the intestine which are absorbed by the blood vessels and lympatics in such quantities as to escape destruction in the liver and lymphatic glands, and they thus pass into the general circulation. These toxins have a selective affinity for the most highly developed nerve structures of the brain, to which they are carried by the blood stream. When the toxin molecules are present in the blood stream in sufficient quantity to produce an acute brain intoxication, then an acute attack of mania is the outward result. When the poisoning is more gradual, then there is a gradual deterioration of the brain tissues, showing itself in eccentricities and changed character, which may lead finally to a chronic delusional state. The presence of toxin molecules, however, in the blood stream inevitably leads to the formation of antitoxin. The toxin molecules stimulate the cells of the body to throw out antitoxin molecules, which by combining with the toxin molecules render them inert. When a maniacal patient makes an apparent recovery, the antitoxin molecules have for the time being neutralised the toxin molecules, and so we have a cessation of the symptoms. On the other hand, a lowering of the general bodily health or a failure on the part of the cells to form a sufficient number of antitoxin molecules, immediately allows of the toxin molecules again to go free, further poisoning takes place, and another attack of mania is the result. The cause of the whole process, the streptococci in the intestinal tract, remain a source of danger, as they are unaffected by the formation of antitoxins, which cannot reach them in the intestine. This is not a mere hypothesis, because on examining the bacterial flora of the intestine in the cases of two patients who had recovered from confusional mania, I still found streptococci in almost as great numbers as when the patients were acutely maniacal.

It has been urged as an argument against the bacterial origin

of mania, that such a disease as pneumonia will sometimes cause a condition of delirious mania, and sometimes arrest an attack of mania. This is perfectly true, but one must remember that pneumonias are not always due to the action of one organism. The only case of pneumonia causing mania which I have been able to observe died, and post-mortem a pure culture of a streptococcus was isolated from the pneumonic patches in the lung. This organism was not the pneumococcus, but a short streptococcus closely allied to the group which I have isolated from cases of mania. It was not fatal to rabbits by intravenous, intraperitoneal, or intrapulmonary injection. A small quantity of the blood serum obtained from the patient the day prior to death rapidly agglutinated this organism in dilutions up to 1 in 100. The intestinal tract in this patient presented the same appearances of chronic catarrh similar to those observed in cases of uncomplicated mania dying from exhaustion. This was evidently a case in which the pneumonia was the last straw in precipitating the manical attack. The pneumonia and mania were in short only the terminal stages of a prolonged intestinal toxæmia. The cases of pneumonia which promote recovery in states of mania are always in my experience associated with high fever and hyper-leucocytosis, and were probably caused by the pneumococcus or some allied pyogenic organism.

In spite of all that has been said to the contrary, acute inflammatory conditions undoubtedly cut short attacks of mania, but these inflammatory conditions are always associated with high temperature and hyper-leucocytosis. The high temperature alone has some bactericidal action, of which we are at present only dimly conscious. Aurebach noted that a temperature of 108° F. rendered alkaline culture media bactericidal, and he argues that in acute infections the pyrexia, although it diminishes the alkalinity of the blood, at the same time may be beneficial in that it also increases its bactericidal power. A genuine inflammatory or infective leucocytosis, plus fever, is a much more potent defensive agent than a leucocytosis excited artificially with which there is no fever. I have undoubtedly cut short attacks of mania by injections of vaccines made from virulent cultures of *Streptococcus pyogenes*, turpentine, and similar agents, which promote recovery by the hyper-leucocytosis which they induce; but such injections often fail, and they fail, I believe, because one does not produce the temperature and leucocyte reaction of a true inflammatory process.