In her case the pulse of late years has become extremely slow, and she has presented some symptoms of myxœdema. It is remarkable that in this case the amyl class of drugs are useless, whilst strychnine gives speedy relief both to epileptic and cardiac phenomena.

"CARDIAC HESITATION."

Cases of cardiac hesitation with pulse of uneven rhythm, not amounting to intermittency and presenting occasional attacks of fainting, are not very infrequent amongst children, young boys especially, between six and puberty. They are easily tired, and are generally anæmic. It is quite exceptional to find them addicted to any secret vice. There is nothing abnormal beyond altered rhythm and vacillating force to be found in the heart. The distinction between this form of heart failure and *petit mal* is often difficult, and I am strongly inclined to regard the two conditions as allied. Removal from all mental pressure, an outdoor life and arsenical tonics generally result in gradual recovery.

I have endeavoured in this address rather to suggest lines of thought than methods of treatment, feeling that you are as competent as I to give a practical therapeutic interpretation to whatever of my suggestions may meet with your acceptance.

REFERENCES.

¹ *Health at School*, 1894, p. 331. ² *Die Altersdisposition*, 1879, p. 94. ³ *Loc. cit.*, pp. 6, 7. ⁴ Lumléan Lectures, On Treatment in Diseases and Disorders of the Heart. Lecture III.

CLINICAL AND EXPERIMENTAL OBSERVATIONS UPON GENERAL PARALYSIS

By LEWIS C. BRUCE, M.D., F.R.C.P.E.,

Physician-Superintendent, Perth District Asylum, Murthly, N.B.

In this paper I cannot enter into full details descriptive of the disease known as general paralysis of the insane. It is necessary, however, to define general paralysis as a disease marked by progressive degeneration of all the bodily and mental functions, commencing first with those most highly developed and recently acquired, and ending with complete wreckage of mind and body. The course of the disease varies greatly according to individual resistance. Some patients show mental symptoms, becoming maniacal or melancholic, before motor symptoms become prominent, while others present motor symptoms sometimes for years before any mental peculiarities develop. The disease is regarded as incurable; but remissions, often of such completeness as to simulate recovery, are by no means uncommon. The typical disease is further peculiar in having several stages. The first stage, in which the patient is often acutely ill, in which febrile temperature, loss of body weight, restlessness, excitement, and sleeplessness are the outstanding symptoms; the second stage, in which the patient becomes fat, facile, lazy, and liable to congestive seizures; the third stage, when the patient again loses weight, becomes mentally demented and physically paralysed.

The causes of general paralysis are very variously stated, but the opinion that syphilis, if not the only cause, is certainly one of the chief causes is at present gaining ground both in this country and abroad.

The following observations were made upon patients suffering from undoubted general paralysis. I would divide these observations into:

I. Those observations made upon patients in whom the disease was steadily progressive.

II. Those observations made upon patients in a state of remission.

III. Those concerned in an attempt to produce remission.

I.—PATIENTS IN WHOM THE DISEASE WAS PROGRESSIVE.

The system which I believe to be invariably affected throughout the whole course of general paralysis is the alimentary system. I have never yet seen a case of early general paralysis in which one did not meet with intestinal and gastric disorders—obstinate constipation, biliousness, capricious appetite, gastric crises, failure of digestive and assimilative power are the commonest symptoms. In the second stage bulæmia may be and generally is added to the symptoms of the first stage, while in the third and last stage constipation alternating with diarrhoea is the rule. These symptoms have

been commented upon by innumerable writers but their significance has not been appreciated, nor do I think any observer has ever realised that they run from beginning to end of the disease, as they are so frequently masked by mental symptoms. When you have heard from Dr. Ford Robertson the pathology of the alimentary tract in general paralysis you will agree that the alimentary symptoms as a group are very important symptoms.

Frequent observations have been made upon the temperatures of cases of general paralysis. Savage believes that there is nothing characteristic about the temperature in general paralysis. Clouston believes the febrile attacks so common in the course of the disease are maniacal temperatures. Mickle in an exhaustive treatise, draws many conclusions from the temperatures he observed, which for want of space I cannot repeat here. I have observed the temperatures of cases of general paralysis for several years, making continuous charts of four, five, and six months' duration. I admit there are some grounds for the diverse statements made regarding the temperatures in this disease. Some few cases, though steadily progressive, never have a temperature above 98.4° during the first and second stages of the disease; in others the temperature is an irregular one, febrile attacks occurring at long intervals. These peculiarities are explainable on the grounds that individual resistance to disease varies, and remissions in the course of the disease are very common. As the result of my observations I strongly endorse Macpherson's opinion that the most characteristic temperature in general paralysis is a recurrent febrile attack every one or two weeks. I have endeavoured to represent what I believe to be the characteristic temperature of the disease in the accompanying chart.

Upon admission there is probably mania with a febrile temperature of about a week's duration, then there is a remission for, say three weeks, and again a febrile attack, with or without mental symptoms, followed again by a period of remission which may be months in duration and take the patient well into the second stage. When the second stage is established the febrile attacks become more frequent and the remissions shorter, and this may continue for months. As the second stage gradually passes into the third stage the temperature tends to become subnormal, the febrile attacks of the second stage being represented by a gradual rise from subnormal to normal, but 99° F. is not often reached, the explanation being that the patient is becoming exhausted and does not react so vigorously to the disease as previously. When the third stage is fairly entered the temperature becomes very irregular—to-day slightly febrile, to-morrow subnormal, and so on, the outstanding feature being the irregularity. I have purposely omitted the febrile reactions to congestive seizures and apoplectic attacks, as these only complicate the main issue, and must be regarded as accidents in the course of the disease. Regarding such a temperature chart as a whole, the conviction is forced upon one that such recurrent febrile attacks can only be regarded as due to some recurrent cause, and that cause is a toxic one. Each febrile attack represents the resistive reaction of the body to some toxic substance, and each inter-febrile period an intermission when the resistive powers of the patient have subdued the action of the toxin. Kanthack considers it a rule "that previous to recovery from bacterial products an increase in the number of leucocytes takes place." It is hardly necessary to say that many workers have examined the blood in general paralysis; but such observations were single ones, made upon different patients, and gave the most irregular results. I therefore counted the leucocytes and took the temperatures daily, or every second day, of some 6 cases of general paralysis for three or four months continuously, and a glance at the dotted line on the chart will show that to every rise of the thermometer there was a corresponding rise of leucocytes. In the first stage the hyperleucocytosis was often very high, sometimes 20,000 to 30,000 per c.mm., and the higher and longer continued the leucocytosis the longer was the remission that followed the attack. In the second and early third stage the leucocytes still rose with each rise of temperature, but the reaction was not so vigorous, and between the attacks the leucocytes tended to fall lower than in the first stage. The remissions were also shorter. In the later period of the third

Chart 1.—First stage. Patient excited, restless, suffering from vivid hallucinations of sight and hearing, sleepless, physically thin, wasted, cachectic; bowels obstinately constipated; temperature shows two febrile attacks with hyperleucocytosis; the period of remission following febrile attack No. 2 was prolonged into the second stage.

Chart 2.—Second stage. Patient facile but irritable, physically fat and bloated; appetite capricious but as a rule abnormally large, had several attacks of gastric crises; temperature shows a recurrent febrile attack every three or four weeks with a corresponding hyperleucocytosis; the periods of remission are short.

stage the leucocytosis resembled the temperature in being very irregular, but did not necessarily coincide with the irregularities of temperature. There were practically no periods of remission. Those progressive cases of the disease in whom there was no recurrent febrile temperature nevertheless presented every now and then a hyperleucocytosis. These periods of hyperleucocytosis coincided with periods in which there was advance in the disease, and following upon these periods of hyperleucocytosis there were remissions just as in those cases with distinct febrile symptoms. Each examination of the blood was made at the same hour every day and upon an empty stomach. During the period when these observations were being made, we admitted into Murthly Asylum an acute early case of general paralysis. I was examining a fresh specimen of this man's blood one morning, and noticed a motile bacillus. A film specimen stained with methylene blue showed what looked like streptococci. Film specimens were sent to Dr. Ford Robertson, of the Scottish Asylums Pathological Laboratory, for examination, and he confirmed my observations. This patient also developed hæmaturia. Once ounce of his urine obtained with antiseptic precautions was centrifugalised, and in the deposit so obtained we found the same motile organism I had at first noticed in the blood, but no streptococci. Before I could obtain nutrient media, the streptococci and bacilli disappeared from the blood and urine. This is the only case of general paralysis in which I have actually found living organisms in the blood. I regard it as an accidental occurrence, but it may be an accident which occurs much oftener than is supposed if the condition is looked for.

Dr. Ford Robertson at this time drew my attention to the fact that the intestinal mucus in cases of general paralysis swarms with bacteria, chiefly the bacillus coli. The same fact was recorded by Cowan in 1895. As the motile bacillus observed in the blood and urine of the acute case of general paralysis above mentioned resembled the bacillus coli, I tested the blood serums of my general paralytic patients in various conditions of the disease, to see if they had the power of agglutinating bacillus coli. Dr. Welsh, Pathologist to the

Chart 3.—Third stage. Patient demented and physically weak; frequent attacks of diarrhoea; temperature irregular; leucocytosis irregular; no periods of remission.

Royal Infirmary, Edinburgh, kindly tested some of the serums for me, and supplied me with pure cultures of the bacillus coli, from which I made subcultures in nutrient broth. Dr. McRae, Assistant Physician to the Royal Edinburgh Asylum, was also good enough to send me many specimens of the blood of cases of general paralysis. The serums of 10 progressive cases of the disease were tested as to their agglutinative power on bacillus coli in dilutions varying from 1 to 5 to 1 to 20, and no reaction was obtained.

II.—PATIENTS IN A STATE OF REMISSION.

I would divide remissions in the course of general paralysis into two classes:

1. Remissions which follow upon Acute Attacks of Intercurrent Disease.

I have seen remissions occur after acute erysipelas of the scalp, pneumonias, severe carbuncles, etc. Such remissions are preceded by a high and long-continued hyperleucocytosis, but I have unfortunately not been able to make further observations upon such cases.

2. Remissions which occur Naturally and without Obvious Cause during the Course of the Disease.

In such cases it is extremely hard to say when a patient,

suffering from general paralysis, is in a state of remission, because, as I have pointed out, many cases, on account of individual resistive power, although they never show any marked progressive symptoms, are still, if observed for months, steadily progressive. I therefore record only such cases as I have observed actually to improve mentally and physically in the course of the disease, and not those who merely remained stationary. I found in those cases that the powers of the alimentary system improved. The temperature was never febrile, but the outstanding feature was the fact that the number of leucocytes in the early stage of the remission rose higher than they are in ordinary health, varying between 9,000 to 12,000 per c.mm. of blood.

As the remission became fairly established the leucocytosis gradually fell to that of ordinary health, that is, between 6,000 and 8,000 per c.mm., when the subject is fasting. The blood serum also of such cases contains some antitoxic substance which is not present in patients in whom the disease is progressive nor in the serum of healthy persons. The power of the blood serum to agglutinate *B. coli* in dilutions varying from 1 in 5 to 1 in 20 was tested in 10 cases in states of remission; 7 gave a definite agglutinative action. Nature then appears to check the disease and produce remissions by first producing a hyperleucocytosis, the leucocytes in their turn producing some substance of the nature of an antitoxin in the blood which protects the patient for a limited time at least against further doses of toxin.

III.—ATTEMPTS TO PRODUCE REMISSION.

My observations led me to believe that the majority of cases of general paralysis were due to toxic poisoning, the toxins being bacterial toxins absorbed through the stomach or intestines. I believed that each febrile attack represented the actual entrance of bacteria or the toxins of bacteria into the blood or tissues of the patients, and that during periods of remission the blood must possess some antitoxic substance. I tested the truth of these observations in the following way.

A case of general paralysis in the second stage of the disease, during a well-marked remission, had an attack of lumbago. I wet-cupped this patient with antiseptic precautions, and defibrinated the blood so obtained. I then placed two earlier and progressive cases of general paralysis in bed and injected subcutaneously into each of these patients 2 c.cm. of this defibrinated blood daily for three weeks. Patient No. 1 was in the early first stage. Patient No. 2 was in the early period of the second stage. This experimental treatment was conducted nearly two years ago.

Patient No. 1 became so far recovered that his friends insisted upon his discharge, and he accordingly left the asylum in February of this year. He called to see me last month. I found that he still presented some motor symptoms of general paralysis, and mentally he was impaired. Still he has supported himself by his own efforts in his trade as a saddler since his discharge.

Case No. 2 has shown physical improvement but no mental change, and I think his brain is permanently damaged. The progress of the disease, however, in his case has been definitely arrested for nearly two years.

Four other cases of general paralysis, contemporaries of these two so treated patients, are now all dead and it is a suggestive fact that these two men should have given the reaction they have done to treatment.

As it is obviously impossible to continue treatment on these lines, I believe, from the fact that the blood of patients in conditions of remission can agglutinate the bacillus coli, that small subcutaneous injections of blood serum of a horse immunised to *B. coli*, continued for three weeks or a month, may produce artificial remission in the disease, and I am giving this treatment a trial.

CONCLUSIONS.

My conclusions drawn from these observations and experiments are that:

1. General paralysis is a disease directly due to poisoning by the toxins of bacteria whose point of attack is through the gastric and intestinal mucous membrane.

2. The poisoning is probably a mixed poisoning, but the bacillus coli is apparently one of the noxious organisms.

3. The result of treatment with serum taken from a case of general paralysis in a condition of remission and injected subcutaneously into an early progressive case points strongly to the fact that some form of serum treatment is the proper treatment for this as yet incurable disease.

APPENDIX.

Observations made upon the Agglutinative Power of the Blood Serum of General Paralytics upon the Bacillus Coli.

Method of Investigation.—In every case a twenty-four hours' culture of the bacilli in broth media incubated at 98.5° F. was used. These cultures were made from a stroke culture on gelatine kept at ordinary room temperature. In every observation controls were used. The results were as follows:

1. The highest dilution in which as a rule agglutination occurred was 1 in 10, and even in this dilution agglutination was sometimes delayed for four or five hours. In one case only was the serum so potent as to agglutinate in a dilution of 1 in 100, but this was only a temporary condition.

2. Out of 18 control bloods, 3 (16.6 per cent.) produced a very slight degree of agglutination.

3. Agglutinative power was always absent from the serum of those cases in which the disease was progressive. The exception to this rule is that the blood of patients in congestive seizures agglutinates *B. coli*.

4. Agglutinative action was present in 70 per cent. of the serums of patients during periods of remission. When the remission was of long standing the serum was found in the same patient to vary in agglutinative power from day to day.

5. Agglutinative action was never a complete action. There always were between the clumps of bacilli motile bacilli apparently unaffected by the serum action.

6. A transitory agglutinative power was present in the serum of 60 per cent. of cases which were non-progressive, but which could not be said to be in a state of remission. This transitory agglutinative power was associated with conditions of hyperleucocytosis. The permanent agglutinative power of the serum of patients in a condition of remission was not necessarily associated with hyperleucocytosis, but is probably due to some antitoxic substance present in the blood. I do not regard this serum reaction as in any way diagnostic of the disease, but merely another link in the chain of evidence that general paralysis is caused by the toxins of intestinal bacteria, and that one of these noxious organisms is the *B. coli communis*.

OBSERVATIONS BEARING UPON THE QUESTION OF THE PATHOGENESIS OF GENERAL PARALYSIS OF THE INSANE.

By W. FORD ROBERTSON, M.D.,
Pathologist to the Scottish Asylums.

THEORIES OF THE PATHOGENESIS.

ALTHOUGH the various views that have been advanced in explanation of the pathogenesis of general paralysis of the insane are almost as numerous as the individuals who have written upon the subject, those that can at present be regarded as occupying a place in the field of controversy permit, I think, of being grouped into two main opposing theories. There is now practically no dispute as to the fact of the toxic origin of the disease. Nearly all authorities recognise that antecedent syphilitic infection is the essential cause in a very large proportion of cases. Some, indeed, go so far as to maintain that without syphilis there can be no general paralysis, but there is still a large consensus of opinion in favour of the view that other toxic agents, more especially alcohol, lead salts, and highly nitrogenous foods, may, independently of syphilitic infection, determine the occurrence of the same morbid process. The great point of controversy is really the mode of action of the toxins. Owing to the long interval that commonly elapses between the date of the syphilitic infection and the onset of the cerebral disease, most authorities have felt a difficulty in admitting that there is a direct action of the syphilitic poison upon the brain. An endeavour has therefore been made to discover some indirect relationship between the original toxic agent and the morbid process that occurs in the nervous system. Out of this endeavour the two opposing theories to which I have referred have arisen. On the one hand it is asserted that the syphilitic poison produces upon the most highly developed nerve cells of the cerebral cortex a certain impression, in consequence of which these cells after some years become exhausted of their trophic energy; and thus undergo premature involution. On the other hand, it is contended that there is a toxæmia of general paralysis which is in some way brought about in certain individuals by antecedent syphilitic infection, and also, it would seem, by certain other pathogenetic factors of a different nature. According to some this toxic action is exerted directly upon the cortical nerve cells; according to others it induces in the vessels of the central nervous system certain structural alterations in consequence of which the nutrition of the adjacent nervous elements is interfered with.

The theory of the premature involution of the cortical