cases disappointing. Hofmeister, for instance, having made from rice meal a preparation which certainly contained vitamin B in relatively large amount, obtained from it a crystalline base, but nothing else which gave evidence of purity. The base proved quite inactive. The much earlier attempts of Casimir Funk ended in a similar way, and so twelve years ago did endeavours of my own. The pursuit of pure chemistry has never involved analytical problems of such complexity, and there exists no classical technique for their solution. Maybe we shall have to replace the familiar use of selective solvents and precipitants by some new technique. Some have felt that there may be hope in the adoption of physical methods such as electrical transport, or in the use of selective adsorbents, on the lines of Willstätter's current endeavours to isolate enzymes. Vitamins would seem to be considerably more stable than enzymes, and the work done in attempts to purify them has encouraged at any rate a faith that the problem will be solved. I have already ventured an opinion that we shall not have to wait very long before the constitution of one or other of them is known.

Much current work is being done in the endeavour to decide how vitamins produce their effect in the body. It has from the first been clear that the influence of each is exerted on specific lines. The clear differences in function demonstrated by differences in the effects of deprivation have indeed constituted the main evidence for our belief in their diversity. In studies of metabolism, however, it is well to remember that chemical events in the organism, though they may often be more or less isolated experimentally, form an organized whole. No one process in the body can be rendered abnormal without ultimate effects upon other processes. Since there is a harmonious concurrence of events in normal metabolism, and since vitamins individually affect different aspects of metabolism, it is not unlikely that an optimum supply in the food would be one in which—apart from the absolute amounts—a definite proportionality obtains among them. Some unpublished experiments of my own seem to show that within certain limits this is the case. Vitamin A and B were supplied to rats on a synthetic dietary. In one experiment each was supplied in very small quantity, but the amount of the one bore a definite ratio to the amount of the other; growth was maintained, but was subnormal. In a second experiment the absolute amounts were increased, but the ratio was undisturbed; growth was normal. Next both vitamins were given in relatively very large amounts, but with the ratio still the same; growth was again normal and the animal's health was undisturbed. When, however, in another case, animals received A in the small amount employed in the first experiment and at the same time took B in the large amount of the third experiment, they showed little or no growth and failed to flourish, though there were no acute symptoms to suggest a direct deleterious effect from the large dose of A. These experiments require extension. If the results are confirmed they will show in respect of vitamins the importance of that balance among factors which has been demonstrated by others in the case of the mineral constituents of diets, and which E. Mellanby has recently insisted upon in the case of still other constituents.

In the hope of discovering the seat and mode of action of individual vitamins some have studied the effects upon functions, and others the nature of the anatomical or histological changes in the organs, which result when the animal is deprived of one or another of these substances. The remarkably specific lesions in the cornea seen in animals which have lacked a supply of vitamin A have been very fully studied (Stevenson and Clark, Mori). The latest view is that the immediate effect is upon the lacrymal glands and the entire secretory apparatus of the eye. The failure of secretion leads to xerosis of the conjunctiva and eyeball, to which the destructive lesions in the cornea are secondary. Whether this be so or not there is no doubt that in avitaminosis the glandular organs are especially prone to suffer and the changes in them differ in kind and sequence from what is seen in actual starvation. McCarrison, several years ago, showed that in pigeons deprived of vitamin B, while most organs lose

weight the adrenals increase to two or three times the weight of those of control birds. This I find occurs also in the rat. Certain secretions have been said to fail when vitamin B is absent, but causal relations here have not been fully established. Hess, Abderhalden, and others have found that the oxidizing capacity of the tissues is diminished in animals which have been deprived of vitamin B, and Funk has brought forward evidence that the functions of this vitamin have some special concern with carbohydrate metabolism. In estimating the present outlook it is well to remember that studies of the kind just indicated are continuously going on. They have not yet told us what precisely is the function or mode of action of any one vitamin, but they are making to that end. The results reported by various workers seem to be reproducible and are therefore real.

There is one suggestion sometimes made in criticism of observations such as those I have been discussing which those concerned have a right to resent. I mean the suggestion that we are not exploring the properties of nutrients unrecognized before, but are carelessly engaged in removing or supplying familiar necessities—a due supply of iron, for instance, or other minerals. This implies that those devoted to vitamin studies lack common sense. An unbiased and close consideration of the technique employed will show how essentially baseless the suggestion has been, even though here and there insufficient attention may have been given to a general balance in the experimental dietaries employed.

One important aspect of the whole matter calls for final reference. Some few, while accepting the results obtained from animal experiments, feel that it is easy to exaggerate their importance in human nutrition. There is, however, nothing more characteristic of recent studies than their tendency to emphasize this importance. Species differ in the details of metabolism, and different species differ in their response to lack of vitamins; but the differences shown are superficial. They comprise variations in the actual severity of particular symptoms and in the sequence of their occurrence. Fundamentally the events are the same. We now possess actual experimental data, quite apart from the more general evidence from deficiency diseases, which link the behaviour of the rat suffering from vitamin deficiency through that of higher animals to that of human subjects. Although it be true, as is so repeatedly said, that a civilized adult community suffers no danger from any lack of vitamins it is different (this too has been frequently said) with the children in that community. If the conception of vitamins were a myth, instead of an important corrective to older views concerning nutrition, its advent would yet, in my opinion, have served a useful purpose. The discussion which it has called forth during the last ten years has assisted in directing special attention to the importance of all that comes under the head of "quality," as distinct from quantity, in the food of children, and this, in my opinion, has already greatly benefited the community.

THE REGULATING AND REFLEX PROCESS.*

BY

P. T. HERRING, M.D.,

PROFESSOR OF PHYSIOLOGY, ST. ANDREWS UNIVERSITY, AND
PHYSIOLOGIST TO THE ST. ANDREWS INSTITUTE FOR
CLINICAL RESEARCH.

PART III.—THE IMPORTANCE OF THE SYNAPSE IN THE REFLEX OR REGULATING PROCESS.

THE nerve impulse is practically invariable in strength, it being the property of the neurone to give a maximal response to any stimulus which is capable of setting it into activity. In the isolated nerve the strength of a nerve impulse can be cut down or even extinguished by subjecting the nerve to the vapour of certain anaesthetics, but it is doubtful if the strength of the anaesthetic required to do this can be attained in the body. Death would ensue much earlier from the effect of the anaesthetic

* The expense of this research was in part met by a contribution from the Medical Research Council.

upon other structures which are more susceptible to its action than the neurones. But we know that the end-result of a reflex, or any other form of nervous activity, is manifested in various degrees of strength, so that there must be some method of graduating the response of the effector organ. The individual nerve impulse is invariable, but the number and frequency of the nerve impulses in the neurone may vary within certain limits, as can also the number of neurones set into activity. The latter factor is probably the most important one in bringing about the graded response.

It is only seldom that the full activity of any organ or tissue of the body is required, and in some of them there is evidence that the active units are constantly varying. The phenomenon of fluctuation or variable activity can be demonstrated in the capillaries where changes are constantly occurring in the amount of circulation going on in any one capillary field. It is probable, though not certain, that the same phenomenon takes place in the nervous system. In the production of a minimal response in any effector only a few neurones suffice to carry the nerve impulses necessary, and it is likely that the ones actually employed are continually varying, there being active phases and resting phases for each individual neurone or groups of neurones. Such distribution of function is possible where there is a large reserve of units, and provides the body with a system which is capable of nicely graduated response to the widely different conditions it has to meet, and at the same time avoids the occurrence of fatigue in those parts of the nerve pathway, the synapses and receptive substances, which are susceptible to its incidence.

The first analysis of stimuli takes place in the receptors, which are so fashioned that normally they respond only to certain forms of energy. Light is the only stimulus which is normally capable of exciting the receptors of the retina, and is ineffective elsewhere. Similarly heat, cold, tactile impressions, and other stimuli, can only excite nerve impulses if they meet with receptors which they are capable of stimulating. If suitable receptors are not present in a tissue the stimulus is incapable of exciting nerve impulses unless it is so gross as to be a direct excitant of the neurone itself. The tissue is therefore incapable of sensation and of reflex response to such stimuli. On the other hand, forms of energy which can excite the receptors present set up nerve impulses which are carried by afferent neurones into the central nervous system. The individual nerve impulse is the same, no matter what its origin may be, so that its end-result must be finally determined by the nature of the response of the organ to which it is carried. In its passage through the central nervous system the nerve impulse has a number of potential pathways opened up to it by the branching of the neurones over which it travels, and is therefore capable of passing by different routes and so giving rise to a variety of end-results. The pathways are not, however, equally open. The synapses between the neurones interpose different degrees of resistance to the passage of the nerve impulse. The synapses, therefore, are structures which regulate the number of neurones engaged. The factors which alter their resistance will be discussed at a later stage.

If the nerve impulse is to give rise to sensation it must be carried to some part of the higher level of the central nervous system which is associated with the reception and interpretation of that particular form of sensation. If it is to bring about a reflex it must be conveyed by efferent neurones to some effector organ. The separation of the impulses giving rise to sensation and reflexes can take place at various levels in the nervous system.

While the end-results of the nerve impulse in any neurone is mainly determined by the anatomical connexions of that neurone, it is also dependent upon the nature of the synapses or receptive substance the nerve impulse meets with at the ending of the neurone. The final efferent neurones of involuntary muscle carry nerve impulses which excite the contraction or inhibit the activity of the muscle according as the intermediate substance between the neurone and the muscle—the "receptive substance" of Langley, or "myoneural junction" of Elliott—is of an excitatory or inhibitory character. In the case of voluntary muscle the

final efferent neurone ends only in excitatory material in the muscle, and the nerve impulses conducted to it always produce contraction of the muscle.

Voluntary muscle, however, is capable of being inhibited just as involuntary muscle is, and the process by which this is effected is similar in character though different in the site of its operation. In the case of voluntary muscle inhibition is exercised upon neurones in the lower level of the central nervous system, and the actual site appears to be in the synapse which intervenes between the last efferent neurone and the one immediately before it. Instead of the muscle being directly acted upon the inhibition is exercised upon the efferent neurone which supplies the muscle; in other words, the inhibitory substance is not in the muscle but in a synapse in the lower level of the central nervous system.

THE SYNAPSE.

We do not know the nature of the process which goes on in the synapse or even its exact anatomical structure, but many facts have been ascertained about the results it produces, and all point to its extreme importance. The synapse is irreciprocal and only allows the nerve impulse to pass through it in a forward direction. It does not conduct the nerve impulse as rapidly as does the neurone, and the passage of the impulse is always delayed there. The synapse interposes resistance, and a resistance which is capable of great variations in degree. A single stimulus of an afferent nerve sets up a nerve impulse which may fail to pass the synapse or synapses interposed on a reflex arc, even in a spinal animal, and it is only by repetition that the synapse becomes penetrable. The resistance of the synapse can be altered by a variety of circumstances. The repeated passage of a nerve impulse over it results in a lessened resistance, and the impulse then passes more readily. Repetition facilitates the passage of the nerve impulse over the synapses in any chain of neurones, and the effects may be more than temporary, so that one gets what is sometimes spoken of as "canalization." This implies that a path has become so "grooved" or deeply worn by frequent use that nerve impulses entering it tend to run in the same channels and produce the same end-results. As far as we know, such grooving of paths in the central nervous system is one, not of the neurones, but of the synapses which lie between them. The lowering of resistance occasioned by repetition of the nerve impulses through the synapses is of great importance. It is part of the normal process of education, and habits and skilled movements are thus acquired. Bad habits and abnormal ones may also be established by repetition, and the more frequently the nerve impulses pass through the same synapses the more difficult it becomes to re-educate the synapses, and to direct the nerve impulses into other pathways. This is true not only of the synapses on the pathways of nerve impulses bringing about reflexes, but also of those which carry nerve impulses giving rise to some forms of sensation. Conditions of hyperaesthesia and of hyperalgesia may be due to several causes. The receptors may undergo changes in adaptation and become more sensitive to stimulation, or the synapses may become less resistant in some part of the afferent paths, thus allowing the nerve impulses to pass more readily to the cerebral cortex. In conditions in which there is an increased irritability of the central nervous system the increased reaction appears to be due to a lessening of resistance in certain synapses; the response of the neurones is not altered in amount or in character but is more easily elicited.

The synapses may undergo alterations which modify not only their resistance but may completely change the nature of the influence the nerve impulse is capable of exerting upon the following neurone. Just as the receptive substance of muscle may be excitatory or inhibitory so the synapse may be excitatory or inhibitory. The synapse, however, differs from the receptive substance in that it can apparently alternate between the two phases and be excitatory or inhibitory as required. The inhibitory action exerted by the synapse appears to be more than a mere block to the passage of a nerve impulse, because it may prevent the neurone which it inhibits from being set into activity by other neurones. The nature of the alteration

taking place in the synapse is unknown. It appears to be brought into action automatically both by nerve impulses carried into the nervous system by afferent nerves, whether concerned with the production of reflexes or sensation, and by efferent impulses coming from the cerebral cortex and other higher levels. Possibly the refractory interval after each impulse may be the operating factor. However produced its effect may be compared with that of a system of water pipes in which there are numerous taps capable of being turned off or on so that the direction of the flow is regulated. The nerve impulse arriving by certain channels automatically controls the pathways taken so that the end-results are of a definite character. The pathways are more or less stable in the decerebrate animal, but in the intact nervous system can be altered by the control exercised by the higher levels. The pathway in the "unconditioned" reflex is accurately adjusted and is less liable to be interfered with by impulses from the higher levels, whereas the pathway for the conditioned reflex is readily changed by any of the numerous reactions to which the higher levels are subject. The power of inhibition is pre-eminently a function of the cerebral cortex, but its voluntary employment is limited to the inhibition of the efferent neurones which supply the voluntary muscles with nerve impulses causing their excitation. There is some evidence that the reception of nerve impulses which normally give rise to sensations, particularly of pain, can be interfered with in certain conditions, of which hysteria is an example. The explanation is probably to be found in an alteration in synapses somewhere along the chain of neurones which conveys the nerve impulses to the higher levels of the nervous system. The reflexes of involuntary muscle and of glandular secretions cannot be altered by volition, but may be increased or inhibited by emotional conditions. Tears, blushing, pallor, increased heart rate, and other visceral reflexes are examples of the kind.

The Action of Drugs and Toxins on the Synapses.

The synapse is readily affected by drugs and is far more susceptible to them than are the neurones. We expect, therefore, that when a drug is of sufficient strength in the body to alter the reactions of the nervous system it will do so by acting upon the synapse long before it can directly affect the neurone. There is evidence that the toxins produced by some micro-organisms also first exert their influence upon the synapse. Strychnine converts many of the synapses which should be inhibitory into excitatory ones; tetanus toxin has a similar effect. Under the influence of either of these poisons co-ordination of muscular movement becomes impossible because nerve impulses entering the lower level of the nervous system spread to all the efferent neurones of voluntary muscle and general convulsions follow. The toxin of hydrophobia also converts inhibition into excitation by its action upon certain synapses. In this condition a voluntary effort to open the mouth, instead of inhibiting the muscles which close the lower jaw, excites their contraction, and the more the patient tries to open the mouth the more firmly it is closed.

Chloroform converts the excitatory phase of the synapse into an inhibitory one; ether and alcohol have similar though less powerful effects. These drugs show a selective action upon the central nervous system and pick out the synapses of different levels in a definite order. The synapses in the highest level are the first affected, and confusion of thought and judgement is manifested. Other synapses in the lower levels become involved with disturbance of the co-ordination of muscles, especially at first of those concerned with the finer movements such as facial expression and skilled actions. The reflex arcs of postural activity and locomotion are affected, and last of all the reflex arcs which have to do with the vital processes of respiration and cardiac action. Other drugs may affect the same synapses in different order, or may act upon the receptive substances which are analogous to the synapse. Atropine paralyses certain of the receptive substances at the endings of efferent neurones in the heart and in some glands. A small dose abolishes the conductivity of the receptive substance between the vagus nerve endings and the sino-auricular node, and the heart freed from the in-

hibitory action of the vagus, beats more rapidly. A similar action is exerted by atropine upon many glands, which as a result fail to receive excitatory impulses and cease to secrete. Larger doses of atropine impair the vasomotor control of the blood vessels, and delirium may result from the involvement of the synapses in the higher levels of the nervous system.

Nicotine is another poison which has a selective action in the first place upon certain synapses, and its local application to the ganglia on the autonomic nervous system has provided a valuable experimental method of ascertaining the sites of the synapses between the pre-ganglionic and post-ganglionic fibres. After painting the ganglion with a weak solution of nicotine the synapses are rendered incapable of conduction, whereas the neurones are unaffected. Nicotine, when injected into the blood vessels, stimulates the receptive substance of muscle so that the muscles go into a state of contraction. Curare has the reverse effect and paralyses the receptive substance of voluntary muscle so that the nerve impulse can no longer pass from the neurone into the muscle. Adrenaline, one of the autacoids of the body, exerts its action upon the receptive substance which lies between the endings of the sympathetic neurones and the organs they innervate. When injected into the blood vessels it stimulates these receptive substances, and the result depends upon the character of the receptive substance. If excitatory, as in the case of the vasomotor nerves of the blood vessels, the muscles contract and the arterioles are constricted and the blood pressure in the arteries rises. If inhibitory, as in the sympathetic supply to the greater part of the muscles of the alimentary canal, the muscles of the gut are relaxed and cease to contract while under its influence. Adrenaline furnishes an example of a chemical material which exerts a selective influence upon certain portions only of the nervous system. It picks out the receptive substances at the ends of the efferent sympathetic neurones, and affects no others than the sympathetic. Several substances of a like chemical nature to adrenaline have a similar action, and these drugs have been called by Dale "sympathomimetic," because on injection into the blood they bring about effects which resemble those produced by stimulation of the sympathetic nerves.

There is therefore abundant evidence that the action of drugs upon the nervous system is one which is exerted upon the synapses or upon the receptive substances between the endings of the efferent neurones and the organs they innervate. We know also that fatigue is brought about by the action of waste products formed during activity upon the same structures. There is also evidence that certain toxins have a like action. Different substances pick out the synapses of different parts of the nervous system, and spread to others in definite manner. The action may be first manifested upon the synapses in the highest level of the nervous system, as in the case of chloroform, and gradually spread to the lower level involving the synapses upon the pathways of the vital reflexes last of all; or it may begin in the receptive substances and cause death from paralysis of the muscles of respiration, as happens in poisoning by curare. It may gradually spread to the higher levels, as in atropine poisoning or in the continued use of overdoses of digitalis. We suggest that many of the manifestations of ill health are due to toxins acting upon different parts of the nervous system. The symptoms of botulism are explainable in this way, and their serious nature is due to the fact that the toxin involves the synapses upon the reflex arcs of the vital processes at an early stage. Other and more common conditions are the results of toxins acting upon less vital processes. Forms of exhaustion, nausea, lack of appetite, changes in temperature, cardiac, vasomotor and visceral disturbances may sometimes be ascribable to the action of toxins upon the synapses of the pathways which are concerned in regulating normal processes. Disturbances of the normal processes are to be recognized by the sensations experienced by the patient and by the alterations that take place in the reflexes, especially those of the viscera, cardiac, vascular, respiratory or alimentary.

It is imperative, therefore, that these effects, whether

subjective or objective, should be carefully recorded and analysed. Many of them appear to be common to a number of different conditions, but it is hoped that they will eventually be capable of classification, and thus provide the material for an early diagnosis of the conditions producing them.

THE TREATMENT OF GENERAL PARALYSIS BY INFECTION WITH MALARIA.

BY

W. McALISTER, M.A., M.B., CH.B.,

DEPUTY PHYSICIAN SUPERINTENDENT, ROYAL HOSPITAL AT MORNINGSIDESIDE.

THIS paper is intended to give a preliminary account of an experiment in the treatment of general paralysis of the insane which has now been in progress for several months in the Royal Hospital at Morningside under the supervision of Professor George M. Robertson. Despite the fact that the etiology and the pathology of the disease—at least in their more significant details—have been successfully worked out, treatment has lagged far behind. Indeed, for the time being an impasse has been reached in the approach to the problem along the accustomed lines, and resort is being had to more empirical modes of treatment. Not that these are to be despised—if their fruits justify them, few will be found to cavil at their use.

In this latter category of reputed remedies one must place the treatment of general paralysis by inoculation with the plasmodium of malaria. The method has been used for a few years by Wagner von Jauregg in Vienna and by Weygandt in Hamburg, with results which, if confirmed, can hardly fail to arrest attention. It is claimed, for example, that out of a large number of patients treated in the course of twelve months no fewer than 41 per cent. can be regarded as completely cured; 20 per cent. sufficiently recovered to be able to resume their occupation though still retaining minor disabilities; and 10 per cent. as improved but not sufficiently so to warrant their discharge. The remainder failed to respond adequately to the treatment. The difference in the response to treatment seems to vary with the length of time the disease has been in progress before inoculation with malaria is resorted to. Thus, among the "cures" the duration was never more than two and a half years; among the "improved" the period was three and a half years; while in the case of the others the disease was of old standing. In practically every case, however, some improvement followed the treatment. In the most successful cases the physical signs of the disorder are said to have disappeared completely, though the laboratory findings—for example, the Wassermann reaction in the blood and cerebro-spinal fluid and the cell count and globulin content of the latter—remained unchanged. On the mental side there is reported a corresponding improvement. In other cases, though the results have been less satisfactory, there has apparently been some alleviation of the severity of the symptoms and a retardation of the rate of deterioration so characteristic of the disease. Such claims, confirmed as they were by the testimony of visitors to Wagner von Jauregg's clinic, seemed eminently worthy of practical investigation, and so the experiment was set in train.

Mode of Inoculation.

The first difficulty encountered at Morningside, when the experiment was resolved upon, was to procure a suitable supply of the virus. The help of the local health authorities was enlisted, but an exhaustive inquiry elicited the surprising fact that there was not at that time within the Edinburgh area an uncomplicated case of benign tertian malaria. The London School of Tropical Medicine was then approached, but even had a supply of the organism been available from that source, the practical difficulty of transporting it alive to Edinburgh was deemed insuperable. Just then there was admitted to Craig House from Burmah a young man whose mental breakdown was attributed to recurrent severe attacks of malaria, though no accurate information as to the type could be gathered. In due course this patient had a bout of fever which on clinical grounds

appeared to be benign tertian malaria, and this was confirmed in the laboratory. As an additional precaution Colonel Marshall, Lecturer in Tropical Diseases in the University of Edinburgh, was called in consultation and confirmed the laboratory findings. But for this fortunate coincidence the initiation of the experiment might have been indefinitely postponed.

On March 29th of this year the patient referred to had a paroxysm, at the height of which venipuncture was performed and sufficient blood withdrawn in an ordinary syringe to inoculate twelve cases of general paralysis. Each of these received a subcutaneous injection of approximately 2 c.cm. of infected blood. The site of the injection was the loose skin just below the angle of the scapula. When the needle was inserted the subcutaneous tissues were probed in all directions to a distance of about $1\frac{1}{2}$ inches so as to diffuse the plasmodium and promote absorption as rapidly as possible. A simple dressing of sterile gauze was affixed to the puncture by means of collodion, and any swelling resulting from the injection gently massaged. The patients immediately resumed their normal mode of life, but careful records were kept of their temperatures.

On reflection it would appear more prudent, in view of the difficulty of obtaining supplies of the virus, to substitute individual inoculation for the mass inoculation practised in this instance. In this way the virus can be kept alive for a long period of time by the inoculation of one patient from another in series. The one drawback would be that results would take longer to accumulate.

Incubation Period.

In every case the infection "took," though there were considerable variations in the length of the incubation period. The earliest cases had their first definite attack after eight days; a group followed the next day, and the others were spread out at irregular intervals till the sixteenth day. One case did not react till twenty-eight days had elapsed; while in another the interval was thirty-two days. Whenever a case was reported as having developed malaria a microscopic examination of the blood was made to confirm the diagnosis.

Subsequent Treatment.

The infection was allowed to run its course unimpeded for any number of paroxysms up to twelve—the average number being ten. During this time sponging was resorted to when required, but nothing more was done so long as the patient tolerated the condition well. In only two cases was it considered advisable to kill off the infection before the regulation number of paroxysms had occurred. In one of these an intercurrent affection occurred two days after the inoculation (and in no way dependent on it) and ended fatally, while in the other the decrepit condition of the patient before inoculation held out little hope that he would successfully carry the additional burden of a series of severe malarial attacks. He was therefore allowed to have only three paroxysms. To arrest the infection quinine hydrochloride was given in doses of 10 grains four-hourly for three days, and thereafter 5 grains thrice daily for fourteen days. In every case the temperature began to subside immediately after the administration of quinine was commenced, and by the fourth day was as a rule stabilized. In none of the cases has there been to date any recurrence of the malady.

The manifestations of malaria were in no way modified by its occurrence in cases already suffering from general paralysis, except that its discomfort was as a rule borne with forbearance which was as praiseworthy as it was unusual. On the fourth day after the subsidence of the temperature an intravenous injection of 0.3 gram novarsenobillon was given. This was repeated at weekly intervals for six weeks. There was generally a well marked degree of secondary anaemia after the infection had run its course, treatment for which was given simultaneously with the antispasmodic remedy.

Following is a brief account of the twelve cases treated:

CASE I.

An advanced case of general paralysis lasting for two and a half years. The patient died of peritonitis three days after inoculation.