due to local weakening of the vessel wall. It is also possible to tell that the walls of an artery have become more rigid; but it is impossible to tell clinically whether such an increased rigidity is due to increase of the muscular tissues of the media or to fibrosis of the media or to proliferation of the intima, or to functional increased action of the tissues of the middle coat—that is, the spasm of the muscle fibres. It is possible also to guess that the walls of the arteries may have become rigid from calcareous deposits in the middle coat, and this observation can be confirmed by x-ray examination. It is possible, finally, to tell that pulsation has ceased to take place in an artery; but it may be difficult to say whether such absence of pulsation in the smaller arteries is due to occlusion locally or at a spot nearer the heart unless it is possible also to demonstrate a tender swelling indicating the lodgement of an embolus. In larger arteries, however, it is quite possible to find that the loss of pulsation is directly due to local thrombosis; as is the thrombo-angitis obliterans of Buerger. It is possible by direct and indirect observation to detect that an artery is becoming occluded, as in intermittent claudication and in angina pectoris.

There does not appear to be any justification for bunching together all the above changes in the arteries under the title of "arterio-sclerosis," or "arterio-capillary fibrosis," which, strictly speaking, is not a clinical term, but a permissible pathological one to be used to describe particular conditions in which fibrosis affects the walls of an artery *in toto*, or only in part.

So valuable is the presence of hyperpiesis as a distinctive feature accompanying evidence of functional renal inadequacy that, during the war, persons showing albumin and hyperpiesis were looked upon as being much less fit to return to any form of military duty than were those in whom renal insufficiency was unaccompanied by hyperpiesis; this knowledge has been made use of by insurance companies, who are not disposed to accept at all cases of hyperpiesis and albuminuria, whereas cases of albuminuria without hyperpiesis are accepted with a load. Recent work has shown also that cases of albuminuria and dropsy without hyperpiesis are less likely to be accompanied by hyperuraemia than are cases of less marked albuminuria and dropsy accompanied by hyperpiesis.

In the same way tortuous and hardened arteries may be present in some cases without hyperpiesis and in others with this change; the outlook in the two sets of cases is quite different: in the former the tortuosity may be simply due to muscular effort, which, oft repeated, has led to temporary oft-repeated rise of blood pressure; whereas in the other the blood pressure is constantly raised and is dependent upon the circulation of pressor agencies—in fact, is due to hyperpiesia. It is not to be wondered at that with increasing age, especially in manual workers, the arteries are tortuous and thickened, but the prognosis is much more favourable than in hyperpiesia. The changes met with histologically in the arteries of the last two groups of cases may be strictly limited to the media which in the early stages show a true hypertrophy of the muscle fibres of the middle coat, and in late stages show an increase of fibrous tissue as well—a conservative process which *per se* is no menace to the individual, indeed is an insurance against rupture.

But arteries may appear to be tortuous and yet not feel thickened, and if hyperpiesis, temporary or permanent, is absent, such tortuosity may be referred to weakening of the middle, and even internal, coat of the artery. In such cases rupture is possible. It is almost certain that such cases are due to infection, as has been proved in the case of syphilis and typhoid infection; but such weakening has been demonstrated to be the result also of other infections, such as streptococci and other pyogenic infections, in which even the inflammatory arterial change may be acute (rarely) or chronic (frequently).

So far, two forms of arterial disease which may be recognized clinically have been discussed: (a) hyperpiesic and occupational tortuosity and hardening due to hypertrophy of the media, and (b) tortuosity and maybe hardening independent of hyperpiesia and occupation, but due to infection which causes formative inflammation of the coats

of the artery, as shown by cellular proliferation and by cellular exudation.

There remain other forms of arterial changes which may defy clinical detection—these are arterial degeneration affecting the intima (atheroma) and degeneration affecting the media. There can be little doubt that such degenerations are toxic in character, maybe from lead, but in many other cases the toxic material is, judging by analogy, due to bacterial infection, which instead of being formative and protective is destructive and menacing.

It is not to be wondered at that, in certain cases, histological examination may prove that arteries which show hypertrophy resulting from rise of blood pressure within the vessels—permanently as in hyperpiesia, or occasionally only as in manual workers—also show evidence of inflammation with new formation or degeneration; but these latter changes are not due to the hyperpiesis but to bacterial infection acting directly on the walls of the arteries, or indirectly through their toxins. The outlook in such cases is very grave, for the presence of the hyperpiesis is a menace, as Sir Clifford Allbutt says, to decadent structures, and rupture of arteries is very possible if they are degenerated.

It is thus clear, I hope, that as clinicians we can get on quite well without the use of the term "arterio-sclerosis"; arterio-sclerosis is not the cause of the hyperpiesis of hyperpiesia. Hyperpiesis causes hypertrophy of the media, and infection causes the new formations and degenerations of the media and of the intima. We do not know how calcification of the media is caused, but the only other infiltrations of arteries—namely, lardaceous and hyaline—are almost certainly micro-organismal in origin.

Thus I hope that in trying to make you familiar with a new conception—hyperpiesia—I have also helped you to other views of the significance of arterial changes, and to the relegation of arterio-sclerosis to the background, so that it need no longer cause difficulties.

THE TREATMENT OF GENERAL PARALYSIS.

BY

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THE action of the Board of Control in issuing the circular letter to which attention was called in the *BRITISH MEDICAL JOURNAL* of March 15th (p. 479) and the rules there printed in full will be welcomed by all medical practitioners who have to deal with this particularly tragic class of mental case. The moment seems, therefore, appropriate to call attention to one or two additional points which have become evident to me during the course of observations on this method of treatment during the past few years.

The beneficial effects of intercurrent fevers, such as erysipelas or enteric fever, in patients suffering from general paralysis have long been recognized. They have led to the introduction, for therapeutical purposes, of innocuous artificial pyrexia. This has been achieved by various methods, notably by injections of tuberculin, of sodium nucleinate, etc. Malarial inoculation, introduced by von Jauregg in 1917, seems rather more convenient, because not only is pyrexia induced by a single inoculation, but a whole series of resulting febrile reactions can be allowed to recur for days or weeks and then terminated by the exhibition of quinine. As a result of such pyrexial treatment remissions in the course of general paralysis have been obtained, sometimes lasting months or years, and in many recorded cases the mental symptoms have cleared up, so that the individual has been able, for a time at least, to resume his normal occupation. It is especially noteworthy, however, that in no case treated by von Jauregg or by any of his followers is it stated that the cerebro-spinal fluid has returned to normal. On the contrary, its characteristic pleocytosis and positive Wassermann reaction are observed to persist, practically unchanged, despite the improvement in the clinical symptoms. So long as this is so, it is evident that the patient is not really cured of his disease,

but is liable to further relapses. The aim of the physician must be to obtain a serological as well as a clinical cure. Is this possible?

A consideration of the pathology of paralytic dementia makes it obvious that the success of treatment is likely to vary with the promptitude with which the disease is recognized. It is now well established as a fundamental fact in cerebral pathology that nerve cells and nerve fibres within the central nervous system (unlike those in the peripheral nervous system), once they have undergone degeneration, are incapable of regeneration. The earlier the diagnosis is established, the brighter will be the prospects of improvement. The most hopeful cases are those early ones in which the nerve cells of the psychical centres are not yet actually destroyed by irreparable organic degeneration, but are only poisoned by the syphilitic toxin and still capable of disintoxication. The first point of importance, therefore, is to recognize paralytic dementia as early as possible, at a stage when its clinical features, physical and mental, are so slight as to be evident only to the expert observer. It is to be remembered that, in addition to changes in the personality and behaviour of the patient, the earliest and most constant physical signs are to be found in the cerebro-spinal fluid—namely, marked pleocytosis and a positive Wassermann reaction. To secure the maximum benefit in general paralysis, no matter what treatment be employed, the diseased neurones should be attacked in the early toxic stage, before organic degeneration has set in. If treatment be not begun until a later stage, organic degenerative changes with a more profound degree of dementia are already present, so that even though the disease be brought to a standstill permanent and irreparable damage has already been done.

Another maxim in connexion with the treatment of paralytic dementia—and one to which, in my opinion, sufficient attention has not been paid—is that the disease is essentially syphilitic, and that mere pyrexial treatment, whether by inoculation or otherwise, is not really attacking the cause of the malady. How, then, does malarial inoculation produce its beneficial effects? It does so mainly by the pyrexial reaction with its accompanying tissue changes—by a burning up, as it were, of some of the toxins affecting the cerebral cells, a sort of cleansing fire. But that the actual cause of the disease—the syphilitic encephalitis—is still uncured is demonstrated by the fact, repeatedly noted by von Jauregg and many other observers, that after malarial treatment, even when reinforced by energetic mercurial and salvarsan treatment, although the mental symptoms may clear up to a remarkable degree, the cerebro-spinal fluid retains its pleocytosis and its positive Wassermann reaction. This is a fact of supreme significance, for so long as the cerebro-spinal fluid shows syphilitic reactions it is obvious that the patient is still suffering from cerebro-spinal syphilis, and that his cerebral symptoms may recur.

Some physicians have grasped this fact and have therefore followed up the malarial treatment by assiduous anti-syphilitic treatment, by means of salvarsan, mercury, etc. But in no recorded case, so far as I can discover, has the cerebro-spinal fluid ever been restored by these methods to anything like its normal conditions. As a matter of experience, it has been found that the most energetic anti-syphilitic treatment, whether alone or in combination with malarial inoculation, has hitherto failed to make any serious impression on this most refractory variety of cerebro-spinal syphilis.

My object is to call attention to an important modification of the malarial treatment, which I have carried out during the past year or two, whereby not only is a general paralytic patient freed from his mental symptoms, but his cerebro-spinal fluid is restored to a normal condition, so that the pleocytosis disappears, and even the Wassermann reaction, most obstinate of all, may become negative. These results, it is submitted, are superior to those hitherto achieved by other methods.

Having selected for treatment patients in the earliest possible stage of general paralysis, in whom signs of profound dementia have not yet supervened, and who nevertheless show the usual changes in the cerebro-spinal fluid,

an intravenous inoculation of benign tertian malaria is given according to von Jauregg's method. After a short incubation period, varying from a day or two upwards, the resulting malarial pyrexia comes on and is allowed to run its course, until the patient has had seven, ten, or perhaps even twelve successive bouts of benign tertian fever, depending on his general physical condition. Quinine treatment is then employed to cut short the malarial infection. Thereafter the patient is given a weekly intravenous injection of salvarsan, neosalvarsan, or, perhaps best of all, silver-salvarsan. At each alternate salvarsan treatment—that is, once a fortnight—the patient's blood is withdrawn by venepuncture. From this an autogenous salvarsanized serum is prepared and injected into the patient's subarachnoid space, after withdrawal of a corresponding amount of cerebro-spinal fluid for purposes of control.

Intra-cisternal Injection of Salvarsanized Serum.

Hitherto it has been the custom, following the well known technique of Swift and Ellis, to inject salvarsanized serum into the lumbar theca through a lumbar puncture needle. It is evident that only a small proportion of serum thus introduced finds its way upwards into the cranial cavity and cerebral cortex, which is the region desired to be reached in cerebral syphilis. Some physicians have endeavoured to facilitate upward diffusion by lowering the patient's head and elevating the lower part of his trunk for several hours after a lumbar injection, and encouraging results have been recorded by this method.

The improved plan I have adopted to supplement malarial inoculation is to introduce the salvarsanized serum directly into the cisterna magna and roof of the fourth ventricle by means of a suboccipital or cistern puncture, according to the technique of Wegeforth, Ayer, and Essick. Serum introduced in this situation flows forwards with the current of cerebro-spinal fluid to the basal cistern and thence upwards to the cortical subarachnoid space, directly reaching the diseased cortical areas. I need not here recapitulate the technique of the operation of cistern puncture, for which only three requisites are necessary—a knowledge of anatomy, a steady hand, and a stout heart. One of my critics, Dr. Farquhar Buzzard, at a meeting in which this procedure was discussed, humorously remarked that the stout heart is required by the patient as much as by the physician! But, as a matter of clinical experience, I have performed this operation many scores of times without the slightest inconvenience or ill effects to the patient. In fact the discomfort is usually considerably less than that which follows a lumbar puncture.

Weekly intravenous injections of salvarsan, with fortnightly intracisternal injections of salvarsanized serum, are carried out systematically as above described. Daily mercurial treatment by the mouth is also given throughout. The cerebro-spinal fluid and blood are examined at every injection, and the treatment is continued not only until the clinical symptoms, physical and mental, have cleared up, but until the cerebro-spinal fluid becomes normal, as evidenced by the disappearance of pleocytosis and by a negative Wassermann reaction. That this result can be achieved is shown by the following examples:

CASE I.

A man, aged 51, was first seen by me in July, 1923. He had had an adventurous career in England and abroad. He acquired syphilis at a date which could not be accurately determined, but was treated for syphilitic symptoms some seven or eight years ago. Six months ago he became mentally peculiar, and a week ago he became acutely excited, burnt his wife's marriage settlement, and wrote a long incoherent birthday letter to his brother, most of which was taken up with instructions for making a fruit salad. He was quarrelsome and full of unreasonable and exalted religious obsessions. On physical examination I found him voluble and exalted. There were no facial or lingual tremors; the optic discs, pupils, and cranial nerves were normal, and the sensory, motor, and reflex functions were all normal, save for feebleness of the right ankle-jerk. The cerebro-spinal fluid showed marked syphilitic changes, containing 157.2 lymphocytes per cubic millimetre, and giving a strongly positive (+++) Wassermann reaction, as determined by Dr. Arthur Davies. The Wassermann reaction in the blood was negative (---).

Within a week the patient developed delusions of suspicion and thought he was being followed by a band of detectives. His excitement increased, so that he had to be certified and admitted for treatment at Camberwell House private mental hospital, where the diagnosis of early general paralysis of the insane was confirmed by the superintendent, Dr. F. H. Edwards, and by Dr. H. J. Norman and Dr. R. N. Nuthall, members of the medical staff of that institution.

On July 25th his mental exaltation still persisted. On that date I inoculated him intravenously with 5 c.cm. of blood obtained from another patient suffering from benign tertian malaria. Next day pyrexia appeared and he was allowed to have five successive typical attacks of tertian malarial fever. This latter was then cut short by quinine, and for four weeks the temperature remained normal; he then had a mild pyrexia of between 99° and 100° for nearly three weeks, but by the time I saw him again, on September 22nd, the temperature had been normal again for a week. Three weeks after his malarial inoculation his mental condition began to improve and within a week he became apparently normal. When I re-examined him, on September 22nd, he was quiet, coherent, and free from delusions of any sort. By this time he had had two intravenous injections of neosalvarsan, each of 30 cg., at intervals of a week, the last of which had been given the day before my examination.

So far, then, the medical condition having cleared up, he might have been regarded by an incautious observer as an example of cure by malarial inoculation. But examination of the cerebro-spinal fluid on September 22nd showed that the condition was still serious. The lymphocytes numbered 168.6 per cubic millimetre, and the Wassermann reaction was still strongly positive (+++).

A series of fortnightly treatments by salvarsanized serum intra-cisternally was accordingly undertaken, whilst in the intervals green iodide of mercury was given regularly by the mouth, with the following results on the blood and cerebro-spinal fluid:

Date.	Blood Wassermann.	Treatment Intravenous.	Cerebro-spinal Fluid.		Treatment Intra-cisternal.
			Cells.	Wassermann.	
1923.					
July 7...	---		157.2	+++	
Sept. 14 ...	---	N.A.B. 30 cg.			
Sept. 21-22 ...	---	N.A.B. 30 cg.	168.6	+++	Salvarsanized serum 40 c.c.
Sept. 28 ...	---	N.A.B. 30 cg.			
Oct. 5-6 ...	---	N.A.B. 45 cg.	57.4	+++	Salvarsanized serum 40 c.c.
Oct. 12 ...	---	N.A.B. 30 cg.			
Oct. 19-20 ...	---	N.A.B. 45 cg.	21.3	---	Salvarsanized serum 40 c.c.
Nov. 2-3 ...	---	N.A.B. 45 cg.	6.3	---	Do. do.
Nov. 16-17 ...	---	N.A.B. 45 cg.	6.2	---	Do. do.
1924.					
Feb. 6-7 ...	---	N.A.B. 45 cg.	2.8	---	Do. do.

CASE II.

A man, aged 53, who had led a strenuous social and political life, came under my observation in 1920, in conjunction with Sir Bruce Bruce-Porter, suffering from a *forme fruste* of tabes, evidenced by loss of pupillary reaction to light, lightning pains, absence of the ankle-jerks, and well marked syphilitic changes in the cerebro-spinal fluid. This contained 27 lymphocytes per cubic millimetre and gave a strongly positive (+++) Wassermann reaction, as determined by Dr. Braxton Hicks. The blood at this time gave a negative Wassermann reaction. Under treatment by intravenous salvarsan, together with intrathecal salvarsanized serum, administered by lumbar injections, he steadily improved, and after a couple of months the ankle-jerks had returned and the Wassermann reaction in the cerebro-spinal fluid had become negative. On repeated occasions in 1920 and 1921 he was seen by Sir Bruce and by myself and the improvement was maintained.

In May, 1922, the pupils were of Argyll Robertson type as before; the left ankle-jerk was now absent and he was noticed to have slight dysarthria, attributed at that time to alcoholism, as there were no facial or lingual tremors, nor were there any definite mental symptoms. The Wassermann reaction in the blood was now strongly positive. Accordingly he was given another assiduous course of salvarsan intravenously, with mercury by the mouth. In September, 1922, his mental condition had deteriorated. He was emotional, excitable, drinking alcohol in excess, and frequently drowsy.

In April, 1923, his mental condition further deteriorated. He became emotionally more excitable, talking incessantly for hours

at a stretch, becoming very angry if anyone ventured to interpose a sentence. He developed numerous delusions—for example, that he was a qualified medical man with five diplomas, that he knew every existing disease, that people were trying to burn his house down, that he had been living in a South American jungle as a wild man with a Zulu [*sic*] as his sole companion, and so on. He walked about the grounds of his villa armed with a loaded shot-gun and a large hunting-knife. This latter he pulled out frequently, explaining how he performed surgical operations with it. There was now slight dysarthria and a few facial tremors. He was seen in consultation several times by Dr. J. Chambers, who concurred in the diagnosis of early paralytic dementia.

In view of his mental condition the patient had to be certified and placed under careful control. Alcohol was at once withdrawn and suitable hypnotics were given. The exaltation, delusions of persecution, and dysarthria, however, persisted as before. The cerebro-spinal fluid was re-examined and found to contain 40 lymphocytes per cubic millimetre and to give a positive (++) Wassermann reaction. Intra-cisternal treatment by salvarsanized serum was then undertaken, as follows:

Date.	Blood Wassermann.	Treatment Intravenous.	Cerebro-spinal Fluid.		Treatment Intra-cisternal.
			Cells.	Wassermann.	
1923.					
May 31 ...	---		40	+++	
June 12-13 ...	---	N.A.B. 45 cg.	28	+++	Salvarsanized serum 40 per cent., 40 c.c.
June 26-27 ...	+++	N.A.B. 45 cg.	15	+++	Ditto 50 per cent., 40 c.c.
July 10-11 ...	+++	N.A.B. 45 cg.	8	+++	Ditto 50 per cent., 40 c.c.
July 24-25 ...	+++	N.A.B. 45 cg.	12	+++	Ditto 75 per cent., 40 c.c.
Aug. 7-8 ...	++-	N.A.B. 45 cg.	10	+++	Ditto 100 per cent., 40 c.c.
Sept. 27 ...	---				

Daily mercurial inunctions were also carried out in the intervals between the intra-cisternal injections. The delusional condition continued between June and July. Early in August he lost his delusions, and began to have lucid days in which he wrote coherent letters and was able to read the daily newspapers, but tended to relapse occasionally into a state of mild mental confusion.

It was accordingly decided to supplement the intra-cisternal treatment by malarial inoculation, and on August 15th 4 c.cm. of blood was transfused intravenously from another patient suffering from benign tertian malaria. Five days later the usual pyrexia appeared and quickly assumed a "double tertian" type of fever, and ten successive daily attacks were allowed to occur until they were cut short by quinine, the temperature thereafter remaining normal. By August 29th his mental condition had markedly improved, so that on August 30th he was able to be transferred to his own home on leave, continuing for a short time with moderate doses of quinine, and with intramuscular injection of sulfarsenol twice a week. The facial and lingual tremors were now absent, whilst the pupils remained of Argyll Robertson type and the ankle-jerks were absent as before. In the middle of September all certificates were withdrawn.

The subsequent progress of the case was excellent. Sulfarsenol was continued twice a week by intramuscular injections for six weeks. On September 28th the blood was re-examined, found free from malarial parasites, and giving a negative Wassermann reaction. In October he had for a day slight pyrexia, which promptly subsided after two $\frac{1}{4}$ -grain doses of quinine. Since then his improvement has been maintained. He leads his ordinary social life, directs his own business affairs, and has given up his former tendency to alcoholism. When last examined at the end of January, 1924, his mental condition was apparently normal, his memory was excellent, he was calm, coherent, and alert, and the only abnormal physical signs were those of the old tabetic lesion, consisting of Argyll Robertson pupils and absence of the ankle-jerks.

I submit that the results of the foregoing combination of malarial inoculation with intra-cisternal injections of salvarsanized serum are obviously superior to those induced by either method separately. In view of the desperate character of the disease, every additional therapeutic weapon which is proved to be efficient is worthy of trial. The technique of intra-cisternal injection is admittedly difficult at first, but it is well worth acquiring, for by this means we are enabled to introduce remedies into the cerebral subarachnoid space and to reach the diseased cerebral cortex in a direct manner.