vary only in degree. We can hardly doubt that the explanation of these differences is to be found in biochemical variations at present imperfectly understood.

Hereditary disposition may be explained on similar lines. These considerations illustrate the importance of the part played by the soil in which the germ of tuberculosis is planted. This fact had not escaped the acute observation of Villemin, who insisted on the interdependence of two factors in tuberculosis—the virus and the "*milieu organique*."

A further study of the soil or "*milieu organique*" is the most pressing need for the better understanding of the pathology of tuberculous infection. This inquiry is intimately connected with the explanation of immunity, a subject bristling with difficulties. In recent controversies concerning the relative importance of phagocytosis and chemical action of the body fluids we seem to witness a renewal of the old contest between the cellular and humoral pathologists. But in spite of the immense amount of research devoted to the study of immunity no general conclusion has yet been reached. This need not surprise us in view of the complexity of the problems involved.

When the infectious nature of the disease had been finally established by Koch, great results were anticipated from the application of this knowledge to the prevention of tuberculosis. But, so far, the results have been disappointing.

The death-rate from phthisis had been steadily falling for a number of years before the discovery of the tubercle bacillus, and no accelerated reduction has taken place in recent years. Furthermore, since the Great War began in 1914, there has been a steady rise in the phthisis death-rate, the causes of which have yet to be worked out. A recent paper by Brownlee on the epidemiology of phthisis pulmonalis, based on statistical tables of the death-rates at different ages in different districts, raises points of great interest. His conclusion is that there are at least two types of phthisis: one especially affecting young adults, and one middle age. The type affecting middle age seems to have been the chief type in London for more than 200 years. Sydenham's statement that the usual age at which death from phthisis occurs is between 15 and 30 is taken directly from Hippocrates.

When Morton, who gives the actual ages of phthisis deaths, is consulted, it is found that a very large proportion of cases are over the age of 30. Further, investigation has shown that the young adult type, which is the prevailing one in Ireland and Shetland, spreads independently of environment, being as common in the more healthy parts of a district as in the unhealthy, while the amount of middle age phthisis is correlated to the unhealthiness of a district.

The explanation suggested is that phthisis is not one disease, but a mixture of at least two allied diseases, an explanation to which the recent discoveries regarding typhoid fever furnish an analogy. In one form of phthisis the chief death-rate occurs between the ages of 20 and 30 years, in a second form the maximum death-rate occurs between the ages of 45 and 50 years. This hypothesis does not, in the present form, explain the occurrence of phthisis at high ages observed in Wales and Cornwall. It is possible that the senile form is due to the same organisms as that which causes the young adult type. It is well known clinically that many persons develop phthisical lesions in their youth which apparently heal, while later in life a recurrence of the disease or a new infection leads quickly to a fatal issue. No district by itself gave any clue to the meaning of the phenomenon of phthisis at the later age observed in Wales and Cornwall. Light on this type was obtained from the statistics showing the susceptibility to phthisis in different occupations. It was found from these data that a very marked susceptibility to phthisis at later ages was shown by coal miners, though the total amount of phthisis occurring among them was very small.

A study of the phthisis death-rate in England generally during the last sixty years shows a great reduction at all ages. This is most marked at the age period 20 to 25 years. At the middle and later ages the fall has not been nearly so marked. The result has been to raise the mean age at which death from phthisis occurs. No completely satisfactory explanation of this fact is possible at present. The figures available suggest that an epidemic of "young adult" phthisis culminated about the middle of last

century, since which date that form of the disease has markedly diminished. It is to be hoped that further investigations on these lines will enable Brownlee to clear up some of the questions raised in his valuable paper.

If we look back and review the progress of knowledge we see how Laënnec's great generalization was foreshadowed by the work of Richard Morton. For Morton was the first to point out that consumption is in all cases associated with the presence of tubercles in the lungs. Thomas Willis had previously broken away from the Hippocratic tradition that phthisis and ulceration of the lung are convertible terms.

Sylvius, their great contemporary, whose influence must have powerfully affected both Willis and Morton, had not taken up such a definite position himself, though, as already shown, he had made important contributions to the pathology of consumption. His views on the fluctuating activity of the humours or secretions of the body, and their relation to consumption, find their counterpart, at the present time, in the temporary immunity which Koch discerns in the course of many cases of tuberculosis. The mutual relations of the different humours or secretions advocated by Sylvius, and the modern development of the doctrine of the endocrine glands, provide another illustration of the well known fact that no great discovery is made without some previous preparatory work. Again, though the conception of tuberculosis as an infection first took definite shape in consequence of the experimental work of Villemin, we know that a belief in the contagiousness of consumption can be traced back as far as the time of Galen and Aristotle.

Let us not forget the debt we owe to the ancients. "Vixere fortes ante Agamemnona multi." How true was Elijah's outburst—"I am not better than my fathers."

THE ADVANTAGES OF INTRAMUSCULAR INJECTIONS OF SOLUBLE CINCHONINE SALTS IN SEVERE MALARIAL INFECTIONS.

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MEDICAL MEN practising in highly malarious countries find that severe plasmodial infections constitute an important cause of death, but one which is entirely preventable by early recognition and active treatment. In the most severe infections quinine by the mouth may be powerless to avert a fatal issue, as in cases reported by me last year in this JOURNAL¹ in a paper on the suitability of soluble salts of quinine and cinchonine for intravenous injection. I have for long advocated the prompt intravenous injection of soluble quinine salts in such dangerous cases, and in the paper referred to I advised the acid hydrobromide as the least toxic salt for this purpose. Captain R. Knowles, I.M.S., has since confirmed my conclusions, and reported prompt and favourable results from its use in the severe and dangerous bilious remittent malaria met with in Assam, in some of which quinine by the mouth could not be retained, and the patients' lives were in danger.²

The disadvantages of the intravenous method, especially in tropical countries with few highly trained medical men, are, first, that many doctors are insufficiently acquainted with the simple technique of giving intravenous injections, so the measure is liable to be postponed until too late; and secondly, unless the injections are given very slowly, it is possible to cause sudden death of the patient by the full doses of 10 to 15 grains of the drug required in the severe infections under consideration. The latter danger can be averted by injecting very slowly, or by dividing the dose into two equal parts with an hour or more between the two injections.

In my former paper I pointed out that cinchonine bi-hydrochloride and cinchonine acid hydrobromide intravenously in rabbits are very slightly less toxic than the corresponding quinine salts, while they are even more soluble than the latter, and I suggested that they would be worth trying intravenously in malaria. MacGilchrist³ found that the sulphate of cinchonine orally was slightly more efficient in malaria than the sulphate of quinine, but

the former has the disadvantage of being more irritant to the gastro-intestinal mucous membrane.

During the past year I have made a number of trials of cinchonine salts in malaria by the intravenous, intramuscular, and subcutaneous routes and have carried out some further experimental researches, with the results to be very briefly reported in this communication. I found the two cinchonine salts already mentioned to be practically painless by intramuscular and subcutaneous injection and to be rapidly absorbed, as shown by cinchonism being produced by full doses of 15 grains within one or two hours and the early appearance of the alkaloid in the form of quinine in the urine. I was therefore led to think that these cinchonine salts might be more suitable for intramuscular injection than the corresponding quinine ones; for it has been repeatedly demonstrated that even the most soluble quinine salts are largely precipitated in the muscles, from which much of the original dose can be recovered unabsorbed after considerable intervals even running into several days.

Experiments to ascertain the Rapidity and Completeness of the Absorption from Muscle of Quinine and Cinchonine Bihydrochloride respectively.

For this purpose 0.2 gram doses of each salt were injected into separate rabbits of approximately equal weight. Three pairs of animals were used, and they were chloroformed and killed after twelve, twenty-four, and seventy-two hours respectively, and analyses were very kindly made for me by Kerner's elaborate but accurate method by Assistant-Surgeon Madan Mohan Dutta, Demonstrator of Physiology, Calcutta Medical College, to whom I am greatly indebted. I also desire to express my great obligation to Mr. E. G. Shaw, B.Sc., for very kindly making the two cinchonine salts for me at the Government quinine factory in the Darjeeling Hills.

The results of the experiments are shown in Table I, which gives the amount of quinine recovered (1) from the muscle at the site of injection, showing the amount of unabsorbed precipitated alkaloid; and (2) from the organs, especially the brain, liver, kidneys, spleen, and adrenals, showing the amount absorbed and present in the tissues of the body at the different periods of time after the injections.

TABLE I.

	Quinine Bihydrochloride.		Cinchonine Bihydrochloride.	
	Muscle (unabsorbed).	Organs (absorbed).	Muscle (unabsorbed).	Organs (absorbed).
After 12 hours ...	80 mg.	30 mg.	40 mg.	88 mg.
After 24 hours ...	65 ..	26 ..	30 ..	65 ..
After 72 hours ...	28 ..	8 ..	10 ..	2 ..

The figures in Table I are very striking and clearly show the much greater rapidity and completeness of the absorption of the cinchonine as compared with the quinine salt. Thus in the pair of animals killed twelve hours after the injection 88 mg. of absorbed alkaloid were recovered from the organs in the case of the cinchonine salt, as compared with only 30 mg. in the quinine animal, showing approximately three times as great absorption in the practically important first twelve hours. On the other hand, 80 mg. of the precipitated quinine was recovered from the muscle after twelve hours, as against 40 mg. of precipitated alkaloid in the cinchonine animal. At the end of twenty-four hours 65 mg. were recovered locally from the quinine animal against only 30 mg. from the cinchonine one, while 65 mg. were recovered from the organs of the cinchonine animal (where the alkaloid would come into contact with the malarial parasites) against 26 mg. in the quinine one. At the end of seventy-two hours the organs only showed 2 and 8 mg. respectively, showing that absorption must have now nearly ceased, and most of the drug had already been eliminated from the body, presumably through the kidneys. The injected muscle now showed no less than 28 mg. of precipitated quinine still remaining in it, against only 10 mg. of alkaloid in the cinchonine animal, thus indicating that the absorption of the cinchonine salt was much more complete at the end of three days than of the quinine one. This fact,

taken with the three times as rapid absorption during the first twelve hours of the cinchonine bihydrochloride, indicates that the latter is far superior to quinine bihydrochloride when given by the intramuscular route with a view to rapid absorption and action in a severe malarial infection. Dr. M. M. Dutta, on examining microscopically the muscles at the site of the injection, found signs of necrosis of the tissues in the quinine but not in the cinchonine animal.

The clinical effect on the animals was even more striking, for whereas the animals injected with the quinine salts appeared to suffer from no definite symptoms of poisoning, the cinchonine animals, on the other hand, became so violently convulsed within half an hour of the injection that I was surprised that they survived, indicating very rapid absorption of the drug, a relatively very large dose having purposely been given. In this connexion it is interesting to note that MacGilchrist found the subcutaneous minimal lethal doses in guinea-pigs of quinine sulphate and cinchonine sulphate respectively to be 0.525 and 0.425 gram per kilo, whereas I found the soluble cinchonine salts to be very slightly less toxic intravenously in rabbits and pigeons than the corresponding quinine ones. The more rapid absorption of cinchonine salts from the tissues above shown explains the differences noted.

Clinical Experience of Intravenous, Intramuscular, and Subcutaneous Injections of Soluble Cinchonine Salts.

Exigencies of space will only permit of a very brief summary of the main points brought out by an analysis of my clinical experience with injections of cinchonine salts. The acid hydrobromide has been mainly used for intravenous and the bihydrochloride for intramuscular and subcutaneous injections. The most important practical points are the rapidity with which the fever and the parasites respectively disappear, while the time of relapses after from one to four injections has also been worked out in most of the cases. I am much indebted to Assistant-Surgeon Jogesh N. Mukherji, M.B., for kind help in examining daily blood films from most of the cases.

By each method of injecting the cinchonine salts rapid disappearance of both the fever and of the parasites from the peripheral blood was obtained in all three varieties of malaria. An examination of the records does not reveal any differences in the effects obtained by the various methods of administering the drugs, which is what might be expected in view of the rapid absorption of intramuscular injections of cinchonine salts already demonstrated, and also apparently of the subcutaneous doses as judged by the early appearance of cinchonism in the patients after full doses. In Table II I have given the time of cessation of the fever and of the disappearance of the malarial parasites from the blood respectively for each type of malaria treated by injections of soluble cinchonine salts. As the effects are more rapid in benign tertian and quartan cases than in malignant tertian, the combined figures of the two former are also shown for comparison with those of the last named more resistant variety.

TABLE II.—Day of Cessation of Fever and Disappearance of Parasites after Cinchonine Injections.

Fever.	Fever Disappeared in			Parasites Disappeared in		
	24 hrs.	48 hrs.	72 hrs.	24 hrs.	48 hrs.	72 hrs.
Benign tertian ...	5	—	1	3	2	—
Quartan ...	3	2	—	3	2	—
Benign tertian and quartan	8	2	1	6	4	—
Malignant tertian ...	4	4	2	3	3	2
Totals ...	12	6	3	9	7	2

The data in Table II may be briefly summarized by saying that in the benign tertian and quartan cases the parasites always disappeared in one or two days, and in all but one the fever ceased within the same time, and in the remaining one within three days. In the malignant tertian variety the parasites generally disappeared within two days and always within three, and

the fever ceased within the same period of time. The immediate results of the injection of the cinchonine salts were thus very satisfactory, and will be found to compare favourably, especially as regards the more serious malignant tertian variety, with those of administering quinine by various methods in the army in England as reported by J. W. W. Stephens and his colleagues.⁴

With regard to relapses the patients could not be kept in hospital long enough to furnish complete data. Four were discharged free from relapses on from the fifth to the twenty-fourth day, while in other cases after from one to four injections relapses were recorded from between the sixth to the thirty-third days, very much in the same way as in the army cases after similar quinine treatment. I did not use the cinchonine salts with the object of or expectation of preventing relapses by a few injections, but in order to rapidly control the fever and cause the parasites to disappear from the blood, after which a prolonged course of oral administration of quinine is indicated to prevent a recurrence of the fever.

The following recent case will serve to illustrate the value of preliminary intramuscular injections of cinchonine salts in cases of malaria in which oral administration cannot safely or conveniently be relied on.

A lady consulted me for what was obviously a benign tertian malaria, from which she had suffered on and off for over a year. Recently the attacks had become more frequent and severe, and she had to go to bed every other day during them; while, when she took quinine, she vomited, and it failed to control the fever. The blood showed benign tertian parasites in every field of an oil immersion lens, indicating a severe infection, not without danger if unchecked. I injected $7\frac{1}{2}$ grains of cinchonine bihydrochloride into the deltoid muscle on the day before an attack was due, and warned the patient that this could not be expected to stop completely the attack due the next day. Twenty-four hours later she felt quite well, and her blood was quite free from parasites, and, as a matter of fact, she had no attack. Three more 10-grain doses were given at daily intervals, after which she could take quinine by the mouth without trouble. On inquiry regarding the amount of discomfort after the injections, she said it was so little that she could with difficulty locate the spot the day after the injection. There was some cinchonism after the 10-grain doses.

CONCLUSION.

Cinchonine bihydrochloride in a 1 in 2 solution carefully sterilized in an autoclave is so rapidly absorbed that I consider it to be almost as quick and effective in its action in severe malaria as quinine or cinchonine salts intravenously, without the inconveniences and possible dangers of the latter, although in such rare extreme infections as that which I reported last year⁵ intravenous injections are advisable. In severe cases of malaria and during the prevalence of pernicious cases, as well as in patients who vomit orally administered quinine, I suggest the further trial of intramuscular injections of $7\frac{1}{2}$, 10, and in adult males up to 15 grains of cinchonine bihydrochloride (or in less severe cases, if preferred, the cinchonine acid hydrobromide, which produces less cinchonism) during the first few days of an attack of malaria, to rapidly control the fever and the infection, to be followed by a full course of quinine orally to prevent relapses.

REFERENCES.

¹ BRITISH MEDICAL JOURNAL, September 22nd, 1917. ² *Ind. Journ. Med. Research*, January, 1918, p. 463. ³ *Ibid.*, vol. 3, No. 1, p. 1, 1915. ⁴ *Ann. Trop. Med. and Parasit.*, vol. xi. ⁵ *Ind. Med. Gaz.*, November, 1917, p. 385.

EPIDEMIC ENCEPHALITIS.*

BY

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In the early part of the year an epidemic appeared in this country. Its nature was from the first somewhat obscure. Those who saw the earlier cases were faced with a similar difficulty to that which faced the courtiers in the story of Cinderella. They could not find amongst the diseases of their acquaintance a foot which would go into this newly found glass slipper. A search was therefore made amongst diseases which, so to say, did not move in Court circles, and were not personally known to the seekers. Amongst these it was at first thought that the owner of the slipper had been found, and that her name was Botulism. After

many painstaking efforts to force her foot into the slipper, it was found to be impossible, and the attempt was abandoned. Botulism was not Cinderella.

The botulism episode is, however, not without its bearing on this discussion. It emphasizes the inability of early observers to recognize in this epidemic a familiar known disease, and it reminds us of a fact which cannot be entirely ignored—namely, the alteration in quantity and quality of our foodstuffs under the present war conditions.

In dealing with the clinical aspects of the epidemic I propose to give an account of my own experiences rather than to attempt a review of the epidemic as a whole from the incomplete data as yet at our disposal. From the cases I have had the privilege of seeing in other districts, and from the excellent records which have appeared in the press, I think that the epidemic as seen in Sheffield and district may be taken as a fair sample of the whole. In one respect this is not true—there was not one fatal case throughout.

Sixteen undoubted cases came under my immediate observation. One of these was under my colleague Major Yates, in the Royal Infirmary. Besides these cases I have heard of some half-dozen other undoubted cases in the area, and I am satisfied that there have been several mild or abortive cases which passed unrecognized at the time.

List of Cases.

No., Sex, Age.	Date of Onset.	Lethargy.	Asthenia.	Ophthalmoplegia.	Paralysis Seventh Nerve.	Fever.	Remarks.
1. M. 15	1918. ?Mar. 7	+	+++	+	R. L. - -	?	Myasthenia gravis-like.
2. F. 23	Mar. 11	++	++	++	+	++	Like tuberculous meningitis.
3. F. 26	Mar. 17	-	-	-	++	++	
4. M. 26	Mar. 17	++	++	++	+	++	Like tuberculous meningitis.
5. M. 37	Mar. 25	+++	+++	++	+	+	Polyneuritic symptoms.
6. F. 56	Mar. 21	-	++	-	+	?	Severe tremor; Parkinson mask.
7. F. 70	Mar. 30	++	+++	+	-	-	Sudden onset, like stroke.
8. F. 17	?Mar. 7	++	++	++	-	?	Meningitis suspected.
9. M. 55	Mar. 25	++	++	+	+	+	Speech hurried.
10. F. 9	Mar. 31	+++	++	+	-	++	Katatonias, type of Batten and Still.
11. F. 16	Mar. 29	+++	++	+	-	+	Slept 48 hours on end.
12. M. 50	Apr. 15	+++	++	++	+	+	Very ill whilst in hospital.
13. F. 65	Apr. 16	+++	++	++	+	++	Left ptosis for a long time.
14. M. 12	May 2	++	++	++	-	+	Considerable delirium.
15. F. 5	May 13	+++	++	++	-	++	
16. M. 44	May 1	?	+++	+	+	+	Polyneuritic symptoms.

+ , Present; ++, marked; +++, very marked; -, absent.

The cases included persons of each decade up to seventy years. Only two were under ten. The sexes were about equally represented. The epidemic began early in March, and was practically over by the end of April.

MODE OF ONSET.

This varied considerably. In most of the cases the date of onset could be fixed quite easily. In five the onset was sudden, in the rest it may be described as gradual.

SYMPTOMS AND SIGNS.

The three cardinal signs in a typical case are lethargy, general asthenia, and cranial nerve palsies. From the combination of these three a clinical picture arises which is characteristic. It is difficult to say to which of the cardinal signs the picture is due, but as a rule it is chiefly to the asthenia and lethargy. The clinical picture, as a whole, is one of immobility. In my early paper I used the expression, "lying like a log." The attitude in bed suggests an effigy on a tomb; the immobile head and face a mask. This mask-like appearance is increased where there is facial diplegia, but a definite facial palsy is not necessary to produce it.

* Contribution to a discussion at the Royal Society of Medicine on October 22nd.