little attention to the natural protective forces of the patient in the treatment of malaria: an injection, even more powerfully than coloured water, can buoy up the hopes and faith of the patient, and thus strengthen his vital forces and natural protective powers.

As regards correct and complete diagnosis, the more the therapeutic action of quinine is controlled by scientific methods (concurrent examination of the blood), the better does quinine come out of the tests. In my experiments upon convicts, where quinine by mouth failed to reduce the temperature to normal on the fourth day of treatment, the continuation of the fever, on closer examination, was found to be due to some complication, the commonest complications being tuberculous glands, tonsillitis, pharyngitis and middle-ear disease. A single instance of a resistant type of malarial parasite *(quinine-fast)* I have never come across: in hundreds of cases of malaria, where treatment (10-15 grains thrice daily after food) was controlled by concurrent examination of the blood, the parasites disappeared from the peripheral blood, and the temperature dropped to normal on the fourth day of treatment at latest. It is, in a sense, unfortunate that the first therapeutic effect of quinine is to check sporulation, and thus check the fever; for after fever disappears, patients are apt to consider themselves cured, and yet their peripheral blood even is not free from parasites.

The following clinical or therapeutic classification of types of malarial infection will be found useful:—

I Febrile
- (*a*) Fresh infection. Infection can be completely cured by quinine properly administered.
- (*b*) Acute exacerbation of chronic infection.

(i) Fever can always be completely controlled by quinine, but the infection may, and usually does, remain.

(ii) Not infrequently the fever is quickly controlled by the patient's natural protective forces unaided by quinine—"spontaneous cure."

II Feverish, 99°—100°F
- (i) Obstinate low fever, but little influenced by quinine alone: a "change of air" usually necessary to brace up the patient.
- (ii) Its malarial origin usually determined by mononuclear count.
- (iii) Infection is active in spleen and bone-marrow, the natural protective forces being weak owing to the patient being "run down."

III Afebrile.—Infection is latent and quiescent, because the natural protective forces are strong.

A person with III, *afebrile chronic latent malaria*, when "run down" and "seedy," is liable to get II *feverish chronic malaria*—a persistent low fever which is so difficult or impossible to control until the patient's strength and vitality are restored: a person with III *afebrile chronic latent malaria*, when subjected suddenly to great fatigue or exposure to excessive heat or cold, is liable to get I (*b*) an acute attack of *febrile malaria*, the fever of which is easily controlled by quinine and occasionally by the patient's natural protective forces unaided by quinine. It must be remembered that II *feverish chronic malaria* is a comparatively rare condition: it is not common in civil life, and still less common in military, and is usually met with amongst officers who have been subjected to continuous worry and responsibility.

In chronic malarial infections a cure (sterilisation of the patient) is impossible, unless quinine is aided by the patient's natural protective forces; hence the value of tonic, *e.g.*, arsenic, change of air, sea voyages, etc. Very little quinine can reach the parasites in the venous sinuses of the spleen and bone-marrow where circulation is slow, and, to reach which, quinine—with its strong affinity for serum proteins—has a long way to go.

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## NOTES ON AN ANOMALOUS TYPE OF KALA-AZAR.

BY G. DODDS PRICE, M.R.C.S., L.R.C.P.

IT is conceded by most observers that in kala-azar the chief incidence of the disease falls upon the liver and the spleen, the latter organ rapidly obtaining a very large size, and the liver in the majority of the cases also being considerably increased in dimension. In a certain number of cases the liver is enormously enlarged, much more so than the spleen, so that one is almost justified in speaking of an hepatic type of the disease.

In October 1914, when Rogers was staying with me, I showed him four cases which I believed to be early cases of kala-azar though they were of a somewhat puzzling nature, in that they had never had very high continued fever, and their spleens were but slightly enlarged.

I punctured the spleens of these cases, and Rogers examined the slides. No parasites were found, and I felt somewhat chastened. By the end of the year three of the cases were dead, and the course they had run was compatible with that usually seen in kala-azar, though no further enlargement of the spleens took place, the organs being only just felt below the margin of the ribs.

By the end of March I had collected 23 cases of a similar nature, and as at the time Major Mackie, on special kala-azar duty, was spending a day or two with me, I asked him to see the cases.

He did so, and frankly confessed that he would not call them cases of kala-azar, though he admitted that they were of a very puzzling nature. To satisfy me, however, he took their peripheral blood, and slides were duly prepared.

Now before proceeding further I would like to remind my readers that the presence of leishmania in the peripheral blood is not commonly met with. Rogers has repeatedly told me that he has only found the parasite in the peripheral circulation in about six per cent. of his cases, Major Mackie's figures are ten per cent. in all cases, twenty per cent. for specially selected ones.

I will now give the result of his examination of these 23 slides. He writes on April 30th :—

"I am enclosing a list from which you will see what will astonish you as it did me, that 15 out of 23, that is to say over 60 per cent., show the presence of leishmania in the peripheral blood; that is three times as many per cent. as I have ever found before in Assam, even in selected advanced cases, and I can only conclude that there is something very extraordinary about this series of cases, I presume we have to deal with either an anomalous type of the disease, or else with an early stage when peripheral infections are taking place, and before the stage of visceral enlargement. In none of the blood films was any other abnormal condition noted, though several showed a mild eosinophilia, not a single malarial parasite or pigmented leucocyte could be found."

These cases all came from one line with a population of about 600, and where many cases of the usual type of the disease were to be found. Of these 23 cases, fourteen are dead, three are in *status quo*, and six are improved. The spleen was removed in two cases immediately after death, smears were taken, and were found to be swarming with the parasites of kala-azar. The weights of these spleens were 10 oz. and 13 oz. respectively—enlarged you will say; yes, but you must bear in mind that an average kala-azar spleen weighs between 35 and 40 ounces. It will be seen that the mortality of these cases corresponds with what is met with in the usual type of disease, and although some of the cases have now lasted eight months, yet the spleens of the majority have undergone very little further enlargement, and in one or two the organ cannot be felt below the margin of the ribs. The liver is not markedly enlarged in any of the cases.

Major Mackie's suggestion that the cases were in an early stage when peripheral infection is taking place, and before the stage of visceral enlargement occurs, cannot be considered tenable, for it must be borne in mind that splenic enlargement proceeds with startling rapidity in kala-azar, the organ doubling its size in a few days, and reaching several inches below the margin of the ribs at the end of the first few weeks of the disease. This I have seen occur repeatedly, and was most marked in two European cases I have lately had under my care.

I agree with Major Mackie that we have probably to deal with an anomalous type of the disease and its great importance must not be lost sight of, for the disease might very easily be overlooked. Why such a type should have arisen in lines previously infected with the usual type of kala-azar is a most difficult question to answer.

Major Mackie and his staff have been carrying out a number of inoculation and other experiments for some months past, and their work in this direction will be published in due course.

From this infected line 400 coolies were moved out in March and April last, and so far no cases of kala-azar have taken place, though the test cannot be considered complete until one year has elapsed. The peripheral blood of every coolie transferred to the new lines was examined by Major Mackie and his staff, and in none have any signs of leishmania been demonstrated.

Major Mackie states that among the Assamese 80 per cent. of his cases are under 16 years of age, and Major McCombie Young's figures are much the same. This has never been my experience on the tea estates of Nowgong. The majority of my cases have been adults, though nobody will deny that garden coolie lines swarm with children, and it is interesting to note that of the 23 cases of this anomalous type 18 were adults, and 5 were children. Sixty per cent. of the adult cases are dead, 40 per cent. of the children. In these infected lines there were 484 adults and 116 children; case percentage worked out: adults over 10 per cent., children 6 per cent. I have never seen this type of the disease in a European.

Since writing the above notes in October 1914, I have had little opportunity of following up this type of the disease, as the remainder of the healthy coolies from their infected lines were drafted into new lines at the end of following cold season, and the disease was finally stamped out. Major Mackie was recalled to military duty and his laboratory was closed down. I believe I am correct in stating that his researches threw no light on the subject. Of the 23 cases originally referred to 18 died and 5 recovered. I collected 35 altogether but I omit reference to the remaining 12 as they were not seen or examined by Major Mackie, he having been recalled. Kala-azar is still endemic in the Nowgong District, and I have seen a few cases in the past two years of this type of the disease. Kala-azar is very bad in the Sibsagar District,

many villages suffering badly, and as a survey of the infected villages is about to be undertaken it is of the utmost importance that those placed on special kala-azar duty in connection with this survey should be on the look-out for this anomalous type of the disease. It may, and probably does, occur in a very small percentage of those attacked, but it is just as capable of transferring the disease and is consequently a much greater source of danger to the healthy community, as this particular type is so difficult to recognize.

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## ON THE PRESENCE OF AN EASILY PRECIPITABLE ANTI-COMPLEMENTARY GLOBULIN-LIKE SUBSTANCE IN HUMAN SERUM AND ITS IMPORTANCE IN THE DIAGNOSIS OF KALA-AZAR.

BY U. N. BRAHMACHARI, M.A., M.D., Ph.D.,

*Teacher of Medicine at the Campbell Medical School, Calcutta.*

WHEN human serum is diluted with excess of distilled water it becomes cloudy owing to partial precipitation of the serum globulin. Under certain circumstances, a copious precipitate forms instead of a mere cloudiness. This precipitate is due to a globulin-like substance as is evident from the following facts:—

(1) It is soluble in normal saline, in dilute acids, and in dilute soda bicarb. solution. It is also soluble in sodium hydrate solution.

(2) It is precipitated from its solution in normal saline when the solution is treated with equal parts of a saturated solution of $(NH_4)_2 SO_4$ or when it is saturated with $MgSO_4$ or NaCl.

(3) It is not precipitated by $NH_4OH$ from its solution in dilute acids.

(4) It is insoluble in distilled water.

On chemical analysis, this substance is found to contain C, N, H, O, but so far I have not been able to detect in it the presence of S, P, or any halogens. After being thoroughly washed in distilled water it can be collected as a white precipitate having a granular appearance under the microscope.

If further investigations confirm the observation that this substance does not contain any phosphorus or sulphur, then it will be found to be different from serum-globulins in chemical composition.

We hope to enter, at a future date, into the chemical nature of this substance and at present shall content ourselves by assuming that it is globulin-like in nature.

In the *Indian Medical Gazette* last September, I pointed out that this copious precipitate is frequently observed when the serum of a kala-azar case is mixed with excess of distilled water. I also pointed out that a precipitate apparently similar to this has sometimes been observed in other diseases, *e.g.*, chronic malaria, phthisis, cancer of the liver, etc. I was not, therefore, then able to state whether the presence of this precipitate was of any diagnostic importance in kala-azar. Further observations lead to the conclusion that, if instead of using an excess of distilled water (which in my original experiments consisted of 15 to 20 times the amount of serum used) one uses two or three volumes of distilled water then the precipitate appears almost exclusively in kala-azar. Thus in a series of 20 cases of kala-azar, the following results were obtained:—

One part of serum plus two parts of distilled water produced a copious precipitate.

(In some cases one part of serum plus one and-a-half parts of distilled water gave rise to a distinct precipitate.)

Similar experiments were made with the serum of a series of cases suffering from other diseases and a negative result was always obtained.

| | One part of serum plus two parts of distilled water. |
|---|---|
| (1) Phthisis ... | No pp. |
| (2) Malarial fever ... | No pp. |
| (3) Cirrhosis of the liver ... | No pp. |
| (4) Enteric fever ... | No pp. |
| (5) Brights' disease ... | No pp. |
| (6) Anchylostomiasis ... | No pp. |
| (7) Pernicious anæmia ... | No pp. |
| (8) Dengue ... ... | No pp. |
| (9) Dysentery ... ... | No pp. |
| (10) Pneumonia... ... | No pp. |
| (11) Catarrhal jaundice ... | No pp. |
| (12) Broncho-pneumonia with enlarged spleen (No L. D. bodies in the spleen) | No p. |

In a few cases with enlarged spleen in which no L. D. bodies were found on spleen puncture, a similar precipitate was obtained, though clinically they looked like kala-azar.

Whether these are cases of kala-azar in which the parasites could not be found on spleen puncture, as sometimes is the case as pointed out by Leishman or whether some of them are cases of spontaneous cure from kala-azar can not be definitely stated in the present state of our knowledge.

I have also found that if distilled water is gently poured on to the top of the serum of a kala-azar case a distinct white ring is formed at the junction similar to the ring of albumen that is found on addition of nitric acid to a solution of albumen. This test also appears to be of diagnostic importance in kala-azar. A similar test is also observed in some obscure cases of enlarged spleen mentioned before.

To make the above two tests proceed as follows:—

(1) Two cc. of the blood from a prominent vein of a kala-azar case are drawn by a glass syringe and