THE UTILITY OF ENZYMES IN MALARIA.

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I take up a recent book [1], which mirrors accurately enough current opinion, and there I read, "Quinine is the one specific for all kinds of malarial fevers, as it absolutely destroys the malarial parasites." This is the general teaching of the schools, and when one first begins tropical practice one relies upon quinine as a certain cure for malaria. Some ten years ago experience led me to doubt this infallibility. In Hong-Kong about that time malaria was the chief cause of sickness among the troops. The admission rate to hospital for malaria was about 2,400 per thousand. A startling number! The equivalent of every man in garrison being a patient in hospital nearly two and a half times every year! Quinine in various forms, orally and hypodermically, in different courses of treatment was tried, but no method could be relied upon to obviate a relapse. During my service in Hong-Kong I should have had no difficulty in producing many cases showing records of seven or eight relapses.

These relapse cases have been a matter of concern because of the ensuing inefficiency, and recently with the troops in India efforts have been made to systematize the quinine treatment, to ensure that quinine is taken in sufficient doses, and that the treatment is spread over a sufficiently long time. These measures are complete enough, as the following details will show:—

1) No case of fever is diagnosed as malaria until the parasite has been discovered in the blood.

2) No case of malaria leaves hospital until the peripheral blood shows no plasmodium.

3) After leaving hospital all malaria patients are placed on a "malaria register," and attend for further treatment.
   (a) Benign cases receive quinine sulphate in acid solution, 10 gr., daily for one week, and afterwards three times weekly, until four months of quinine treatment have been completed.
   (b) Malignant cases receive quinine in the same form, 10 gr., daily for one month, and afterwards thrice weekly for three months longer.

And yet relapses occur. Patients return to hospital deaf from cinchonism, ill with fever, and showing parasites in the peripheral blood.
I think the impression is very general that benign cases are easily cured and relapses rarely. Here in Upper Burma there seems little distinction between benign and malignant cases as regards their curability under quinine. Relapses seem as frequent in the one infection as in the other, the only difference being in the cachexia, which is persistent and progressive in bad cases of malignant infection. Major Lelean, R.A.M.C., writing in the *Journal of the Royal Army Medical Corps* (November, 1911), had the same experience in the 7th Division in India. I quote his figures, as they show the importance of the subject: "Statistics have been kept which show the relapses occurring among a total of 1,053 malaria patients, who attended hospital at Meerut for three months subsequent to their discharge. During that period they received 15 gr. of quinine on two days per week. The drug was administered in solution and in the presence of an assistant surgeon, who kept a roster of these men and strictly enforced their regular attendance. We do not know what the mean daily strength was exactly, but it must have been approximately 170 for the eighteen months during which the results were kept. In that period there were 734 recurrences among these men, i.e., at the rate of 489 per year. It is, of course, obvious that this is but an approximate calculation, but it shows a per mille per annum attack rate amongst these men of no less than 2,876, which affords a considerable margin for error without losing its startling character." And continuing, he reiterates in slightly different form the question I have already suggested: "Within comparatively recent years it had been taught that the action of quinine upon malaria parasites was so certain that quinine could be relied upon for clinical diagnosis. Was that teaching correct?" I think not. Quinine has its sphere of usefulness, but it is an empirical remedy—a fundamental fact we have forgotten because the remedy is so time honoured.

In the foregoing I have used the word *relapse* in the ordinary medical acceptation of the term as applied to any disease—a recurrence. Colonel R. H. Firth, in the *Journal of the Royal Army Medical Corps* (February, 1913), in speaking of apyrexial malaria wishes a distinction to be drawn between *relapse* and *recrudescence*. By *recrudescence of infection* he speaks of a recurrence of the fever due to increased schizogony of the parasite after a period of apyrexia. By *relapse of infection* he indicates a recurrence of the fever due to a reversion to schizogony after the establishment of sexual forms in the blood. Professor Minchin [2] in his "Introduction to
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the Protozoa," says: "In the 'incubation' period of the disease schizogony alone occurs in all probability, but when the numbers of the parasite are sufficient to affect the health of the host, the reaction of the host against the parasite probably stimulates the production of the propagative phases, and Schaudinn has described the changes of the trophozoites which become sporonts."

In the light of the recent work [3] of Dr. John Beard, on the recurrence of dextro-rotatory albumins in organic nature and the part played by ferments in the protection of the animal body, all these things find a ready explanation. Schizogony of the parasite produces the clinical disturbance we call fever, the sexual forms are harmless, and the asexual growth of the parasite, as is the common feature with all asexual growths, can proceed to an unlimited number of generations or cell divisions, until checked by the natural protective ferments of the animal body. Just as the trophoblast is checked in its growth by the ferments of the developing embryo, so the natural protective ferments of the host react against the asexual phase of the parasite and sexual forms begin to appear. The varying degree of immunity, the degree to which the malaria remains dormant, is a measure of these natural protective ferments. In like manner, as these ferments are insufficient to destroy the asexual forms, the disease recurs. There is no essential pathological difference between the cases termed "relapse" and those called "recrudescence." Clinically, there is a difference only as to the time which has passed since infection. Before leaving this portion of the subject reference should be made to the recent publication [6] by Professor Emil Abderhalden on "Protective Ferments of the Animal Organism." In this work the author has gone a long way in the same direction as Dr. Beard's researches have led him.

In 1907 it was foreseen and foretold by Dr. Beard that the plasmodium of malaria would be readily destroyed by the enzyme trypsin, and the scientific principles involved have been enunciated by him in papers, published in 1907 and 1913 [3 and 4]. It may be of interest to cite one scientific conclusion from his recent memoir. In this Beard writes: "Since the organisms underlying the chief tropical diseases, such as malignant malaria, trypanosomiasis, sleeping sickness, yellow fever, relapsing fever, kala-azar, &c., are, so far as these attack human beings, asexual generations, it follows that the natural means of destroying the organisms of such tropical diseases, and of curing the patients, are the use in combination of the powerful pancreatic ferments, trypsin and amylopsin, as represented by the '1912' Fairchild injections."
Not until January, 1913, did the opportunity come to me of putting these principles into practice in cases of tropical disease and of seeing whether under treatment by ferments these relapses in malaria were preventable. To test this enzyme, treatment cases of severe infection and those showing relapses were selected. Clinically, the results are most marked, the change in the patient within a few hours remarkable, and the benefit permanent. As circumstances have arisen which have interrupted this work, and as I do not know when I can carry the observations further, I think that these clinical results demonstrating the utility of the pancreatic ferments in the severer forms of malarial infection should be recorded.

The method of treatment has been by intramuscular injections of the enzymes, trypsin and amylolysin. The injections employed in the following cases were prepared by Messrs. Fairchild Brothers and Foster and are stable in the Tropics. Both ferments are supplied in glass ampoules holding about 1 c.c. The injectio trypsini has a digestive value of 1,250 Roberts units and it is the most potent preparation of trypsin made. The injectio amylolysini is of maximum potency and contains 500 Roberts amylolytic units. The preparations are sterile and stable. I have kept some of these ampoules for nine months in Central India without appreciable loss of strength. Before injection the contents of each ampoule should be diluted with normal saline 1 in 5. My usual practice is to take up the contents of one ampoule of trypsin and of one ampoule of amylolysin in a 10 c.c. syringe, and then fill the syringe with sterile normal saline. This amount I usually give as a single dose. Baetzner [5], using the same preparations in surgical tuberculosis, gives his injections hypodermically, but I prefer to give the injections intramuscularly, and select the buttock, finding that patients suffer the least inconvenience in this way. Using ordinary surgical technique in giving these injections, I have made some hundreds after this fashion, and no harm has ensued. The ferments diffuse slowly from the tissue, into which they are injected, and some local oedema remains for twelve to twenty-four hours, when it disappears. The local pain is little more than that due to the needle-prick. The effect of the trypsin on the normal tissues at the site of injection is practically nil. But the general effect, as seen in the cerebral type of case, is marked. The headache vanishes, the patient's restlessness ceases, the skin becomes moist and the temperature falls, the patient's aspect is totally changed in a few hours, and he feels fresh and looks bright. As a rule, a single injection is sufficient to clear
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The peripheral blood of parasites. But in severe infections I think that three injections, given at intervals of about four days, are necessary to effect a cure. My previous experience [7] in the use of ferments in malignant disease has led me to repeat the injections, until the injections themselves cause a rise in the patient's temperature. This I have elsewhere called a "trypsin reaction." When this happens, I know that the patient is fully under the influence of the treatment. Usually this occurs in malaria with the third injection, and having proceeded so far the worst cases I have had to deal with have remained free from relapse.

The following cases were all British infantry soldiers. Three natives (Gurkhas) were also treated, but my notes of these cases are too fragmentary for inclusion:

Case I.—Private C., No. 9457. Malignant tertian malaria with hæmaturia. Contracted malaria in Maymyo, Burma, November, 1912. December 5, 1912: Admitted to hospital; temperature 101° F.; malignant tertian rings found in peripheral blood. Quinine 10 gr. thrice daily. December 6: Morning temperature 103° F., evening temperature 102.4° F. Hæmaturia appeared; quinine stopped; arsenic given. December 7 and 8: Temperature normal, but hæmaturia continuing. December 16: Apparent recovery; discharged from hospital, but ordered to attend daily and to receive a dose of 10 gr. of quinine for one month. Relapse: January 11, 1913: Readmitted to hospital; evening temperature 100° F. Malignant tertian rings and crescents found in peripheral blood; quinine 10 gr. given thrice daily. January 13 to 16: Evening temperature 100° to 102° F. each evening. January 17: Quinine treatment stopped; first injection of trypsin and amylopsin. Evening temperature 100° F. January 19: Evening temperature 101° F.; blood shows crescents. January 21: Evening temperature 101.6° F. January 23: Evening temperature 96° F. January 24: Second injection of trypsin and amylopsin. Six hours after this injection the patient's temperature rose to 100° F., but the peripheral blood showed no parasites. January 25 and 26: Blood negative; no symptoms. January 31: Third injection of trypsin and amylopsin; discharged from hospital. The patient was seen by me on March 16, April 27, and May 31; he has had no further symptoms.

Case II.—Private G., No. 9876. Malignant malaria with relapses. Contracted malaria in August, 1912, and was treated in hospital from August 22 to September 2, malignant tertian rings being found in the peripheral blood. The first relapse
occurred in December. Patient was in hospital from December 13 to December 19, when again malignant tertian rings were found. The man was continuously under quinine treatment from August 22, 1912, to January 2, 1913, the regulation four months' course of treatment. Second relapse took place in January, patient being admitted to hospital on January 29. He was deaf from cinchonism, the blood smears were repeatedly negative, showing no parasites, but his temperature each evening rose to about 100° F. He was discharged from hospital on February 11, and ordered to attend daily for further quinine treatment. Third relapse. On March 2, patient was attending for his daily dose of quinine, when he appeared to me to look so ill that I detained him in hospital. His evening temperature was 99·2° F., and blood examination negative. March 3: Admitted to hospital complaining of pains all over, worst in bones and joints. March 4: Blood showed malignant tertian rings. In the evening the temperature rose to 103° F., and patient became delirious, showing cerebral symptoms. March 5: Very severe headache; first injection of trypsin and amylopsin. March 6: Headache gone; feels well; temperature in evening 99·6° F. March 7: No headache or other signs. Second injection of trypsin and amylopsin given. March 9: Temperature normal, neither signs nor symptoms, blood negative. March 12: Temperature continuing normal, no symptoms. Third injection of trypsin and amylopsin given. This was followed by a rise of temperature to 102·4° F.; blood smear negative. March 13: Blood smears again taken, no parasites found; leucocyte count: polymuclear, 50 per cent.; large mononuclear, 17·3 per cent.; lymphocytes, 24·7 per cent.; eosinophile 8 per cent. The changes in the large mononuclear and eosinophile white blood cells are noteworthy. March 18: Discharged to duty. On April 16 and May 19 I examined the patient. He had no further symptoms.

Case III.—Lance-Corporal J., No. 8459. Contracted malaria in October, 1912. Was treated in hospital between October 25 and 30, 1912, benign tertian rings being found in the blood. The quinine treatment was continued from October, 1912, to February 28, 1913, i.e., a four months' course. On March 8, patient had a typical attack of ague in barracks and was not seen by a medical officer. On March 10 he was brought to hospital with a temperature of 104·2° F., and malignant tertian rings were found in the blood. March 12: First injection of trypsin and amylopsin. March 15: Second injection of trypsin and amylopsin. March 18: Third injection of trypsin and
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Amylopsin. March 25: Discharged to duty. Up to June 16, 1913, the patient had no relapse and no further symptoms. Query: Was this case a mixed infection of benign and malignant malaria, or a fresh infection of malignant malaria whilst the patient was taking quinine?

Case IV.—Private T., No. 9141. Benign tertian malaria. States he first had malaria in Rangoon some two years ago, and that he has been stationed in Mandalay since June, 1912, arriving in Maymyo, Burma, on March 8, 1913. Whilst in Mandalay he had five relapses of malaria. Maymyo, March 11: Detained with severe ague; temperature 103.8° F. Benign tertian rings and gametes in peripheral blood. March 12: Admitted to hospital; evening temperature 103.8° F. March 15: First injection of trypsin and amyllopsin. March 18: Second injection of trypsin and amyllopsin; blood negative. March 22: Third injection of trypsin and amyllopsin. March 25: Discharged to duty. Up to June 16, he had no relapse, and no further symptoms.


Case VII.—Private S., No. 9600. Benign tertian malaria, quinine seemed to give no benefit. Contracted malaria in September, 1912. States that he has had three relapses out of
hospital. Returned from manoeuvres on March 6, 1913. March 21: Reported sick; temperature 102·4° F. *Benign tertian gametes* found. Quinine 4 gr. four-hourly ordered. March 22: Temperature, morning 101·2° F., evening 101·6° F.; quinine continued. March 23: Temperature, morning 100° F., evening 101·6° F.; quinine 10 gr. thrice daily. March 24: Temperature, morning 99·6° F., evening 100° F.; quinine continued. March 25 to 29: Temperature normal; quinine continued. March 30: Evening temperature 100° F.; severe headache and joint pains. March 31: First injection of trypsin and amylopsin; evening temperature 100·2° F. April 1 to 4: Temperature normal, no symptoms. April 5: Second injection of trypsin and amylopsin. April 8: Discharged to duty. Up to June 16, no relapse and no further symptoms. After nine days of quinine treatment in this case the parasites were still able to produce fever, severe headache, and joint pains, all of which vanished after *one injection* of the ferments, trypsin and amylopsin.

**Case VIII.**—Private W., No. 9402. *Benign tertian malaria.* Contracted malaria in September, 1912, being treated in hospital from October 2 to 11. Completed a four months' course of quinine treatment in February, 1913. On March 27, reported sick, with a temperature of 102° F., *benign tertian rings* being found. On April 1 and 5 he received injections of trypsin and amylopsin. On April 10 he returned to duty, since when he has had no further symptoms.

**Case IX.**—Lance-Corporal F., No. 9327. *Benign tertian malaria.* Contracted malaria in October, 1912, being treated in hospital from November 1 to 12, and continuing the quinine treatment out of hospital until about the middle of January, 1913. On March 24, reported sick, temperature 104·8° F., and *benign tertian rings* were found. On April 1 and 5 he received injections of trypsin and amylopsin, the second injection causing a rise of temperature to 100° F. On April 10 he returned to duty, and has since had no further relapse.

**Case X.**—Private T., No. 8014. *Malignant tertian malaria.* First admission, severe double infection. May 19, 1913: Headache and colic; temperature 102·2° F.; quinine treatment begun. May 20: *Malignant tertian rings* found in peripheral blood. May 21: Temperature, morning 103·6° F., evening 102·4° F.; headache severe. May 22: Temperature, morning 104° F., evening 102·4° F. May 23: Temperature, morning 101° F., evening 100° F. May 24: Temperature, morning 99·4° F., evening 100·4° F. May 25:
Temperature morning 99.2° F., evening 99.2° F. May 26: Temperature, morning 98.6° F., evening 100° F. Quinine treatment stopped. First injection of trypsin and amylopsin. Compared with the eight days of treatment with quinine the progress made after one single injection of trypsin and amylopsin is marked. May 27: Better and brighter; evening temperature 98.6° F. May 28 to June 3, temperature normal. No further symptoms.


Case XII.—Private H., No. 9535. Malignant tertian malaria with cerebral symptoms; first admission; severe cerebral type of case and double infection. May 12, 1913: Detained; temperature 102°F. at noon, 104° F. at 3 p.m., blood smear negative. May 13: Temperature, morning 101.6° F., evening 104° F. May 14: Temperature, morning 100°F., evening 102.4° F. May 15: Temperature, morning 99.6° F., evening 105° F. May 16: Temperature, morning 98°F., evening 103° F. May 18: Malignant tertian rings found; quinine treatment ordered. May 19: Transferred to my care; headache very severe; restless; continuing the quinine treatment. May 20: Headache and restlessness more marked, and patient became comatose. First injection of trypsin and amylopsin. May 21: Headache gone; patient looks fresh and eyes bright; temperature now 99°F.; all symptoms vanished. May 26: Second injection of trypsin and amylopsin. June 5: Discharged from hospital to duty.

"If a doctrine be challenged," said Pasteur, "it happens seldom that its truth or falsehood cannot be established by some crucial test. Even a single experiment will often suffice either to refute or to consolidate the doctrine" [8]. Again, the great investigator, Emil Fischer, set up the doctrine of "lock and key" regarding
the action of ferments by two experiments, and two only. The first experiment was to observe the fact, the second to confirm it [9]. In the foregoing pages twelve experiments are set forth, and every single one of these confirmed the scientific conclusions which led to their being made. For, as Carl Ernst von Baer wrote long ago, "That which always repeats itself cannot be conditioned by chance or passing caprice, but must depend upon a necessity."

REFERENCES.