THE JUBILEE OF SIR PATRICK MANSON.

(1878—1938.)

A Tribute to his Work on the Malaria Problem.

By PHILIP MANSON-BAHR, C.M.G., D.S.O., M.D., F.R.C.P.

(*Physician to the Hospital for Tropical Diseases, London; Director, Clinical Division, London School of Hygiene and Tropical Medicine.*)

It is not generally realized that knowledge of malaria is even older than its name. The term malaria (an Italian colloquial word from *mala*, bad and *aria*, air) was introduced by MacCulloch in 1827 as a substitute for the more restricted "marsh miasma" or "paludal poison."

The history of malaria is wrapt in antiquity and takes us back to classical Grecian times. Many famous names have been connected with it—from Hippocrates and Galen to Ehrlich and his school of chemotherapy. What great personalities do these memories call to mind—Sydenham, courtier, soldier and physician; Laveran, the precise army surgeon; the bearded Grassi, medical zoologist; Marchiafava, scholar and physician; Ronald Ross, mathematician, musician, playwright—a versatile genius; and, lastly, the sturdy figure of Patrick Manson, looking more like a country squire than a pale-faced scholar—a practical and prophetic Scotsman with a magnetic personality. He played a vital part in many medical problems; whilst his contribution to malaria was not the least of his achievements and well merited the many tributes which have been paid to him. It was his pupil, Ronald Ross, who wrote of him in his Nobel Prize Essay, "without his work I am convinced that the malaria problem would not have been solved at all and we should still be engaged in a laborious search for the parasite in water and in air."

Already in the fifth century before Christ, Hippocrates had recorded the existence of periodic fevers and had divided them into quotidian, tertian, subtertian and quartan: subsequently Galen, Celsus and other writers recognized the substantial accuracy of this classification, but from that time onwards knowledge of malaria was at a standstill, a motley of patchwork and make-believe. Cinchona was introduced about 1640 and in the hands of Thomas Sydenham (1624-1689) the "Peruvian bark" served as a therapeutic weapon to separate the miasmatic fevers from other febrile diseases. Later the talented Richard Morton was able to demonstrate that some continued and remitting fevers were of the same nature as the so-called intermittents and was able to separate malarial fevers from them.

The next step forward was the discovery of the characteristic blood pigment of malaria in the viscera. The credit of this is given to Meckel (1847) who found the pigment-bearing cells in the spleen and blood. (This was undoubtedly the first record of the crescent stage of the subtertian malaria parasite). Later, in 1849, Virchow was able to confirm this discovery.

Following upon Koch's many discoveries of bacilli as the cause of acute disease, it is small wonder that malaria was also ascribed to this cause by the Italian workers Lanzi and Terrigi (1876), and later by Tomasi, Crudeli and Klebs (1879). However, shortly afterwards the riddle was solved by C. L. A. Laveran, a French army surgeon, who on the 6th of November, 1880, at Constantine in Algeria, first observed the parasite of malaria. He had the good fortune whilst watching a

pigmented body in the blood, to witness the eruption of long motile filaments, and thus was able to recognize its living and parasitic nature. It was this vital observation which lent colour to the greatness of his discovery. Referring to this fact in his later years Manson remarked "Laveran had the luck to see the particular crescent he was observing undergoing exflagellation and was therefore able to recognize its parasitic nature. Had I had the luck of Laveran what a swell I should have been."

It was in Hong Kong that we find records of Manson's incipient interest in the elucidation of malaria which subsequently became the predominating factor in his scientific life. In these fruitful and momentous years (1880-1889), although the anxieties of his private practice were enough to absorb the energies of most men, he found time to devise in his private work-room those "fool experiments" with malaria blood. He endeavoured to test the temperature of blood extracted from malaria patients with fowl's blood maintained under the same conditions and made trials to grow something from malarial blood in sterilized water from malaria-infected marshes. He searched for the elusive *Bacillus malariae* in vain (1881). It was not until 1884 that he heard or read of Laveran's work and set about looking for the *Plasmodium*, but it was not till his return to England, when he had opportunities of studying malaria cases at the Albert Dock Hospital in 1892, that he became fully aware of the true importance of Laveran's discovery.

The malaria-mosquito theory was essentially no new thing. H. H. Scott in his Fitzpatrick Lectures (1937) has pointed out that it was Columella (116 B.C.) who suggested that the virus of malaria emanated from marshes and associated it with insects born from them which attacked man in swarms. The Italian peasants had for centuries believed that fever was produced by the bite of a mosquito—a fact that was noted by Lancisi (1717), whilst Robert Koch pointed out that the natives of the highlands of Central Africa declared that on visiting the unhealthy lowlands they were bitten by an insect called *Mbu* with the result that they acquired a fever which they recognized by the same name.

In 1883, A. F. A. King, a sagacious American observer, brought together a mass of evidence indicting mosquitoes as accessories in the causation of malaria fevers. In the latter eighties of the last century the recognition of the malaria parasite in the peripheral blood had been traced by Italian scientists, chiefly by Bastianelli and Golgi—the three main species had been identified and their peculiarities described (1889). It had also been observed that some of the fully grown individuals of Laveran's parasite (the crescent) did not break up, as he originally described, but when the blood was withdrawn these assumed a spherical shape, whilst the others exflagellated, and it was to this phenomenon that Manson from 1892-1894 directed so much attention. He was then able by means of his carbol-fuchsin technique to obtain permanent preparations of the whole process and to make microphotographs, and these observations received remarkable confirmation at the hands of N. Saharoff (1894-1895).

By Koch, Blanchard, Labbé, Bignami, Golgi and a whole host of others this peculiar process was recognized as the "swan song" of the dying malaria parasite, but by Manson on the other hand the flagellum was regarded as a vital phase in its life-history, hence his well-known slogan and watch-word, when writing to Ross, "watch the flagellum." But the full and vital meaning of *ex-flagellation* as a *sexual act*, was not fully appreciated till it was explained by MacCallum in America (1897)—a veritable milestone in the history of malaria.

In retrospect it is not generally recognized that all this had been anticipated by Pfeiffer (1892) who, from a study of the coccidium in the rabbit's liver, had

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“Practical and Prophetic Scotsman.”

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"Versatile Genius."

PATRICK THURBURN MANSON

Born at Amoy, China, 20 August, 1878.
Died at Christmas Island, Straits Settlements,
8 March, 1902.

by analogy adumbrated the probable life-history of the malaria parasite *outside* the human body and had also suggested that it took place in blood-sucking insects capable of transmitting the progeny in the act of biting; and, as a matter of historic interest this had been shown to be the case in the matter of *Babesia Bovis* in its transmission through ticks by Theobald-Smith and Kilborne in 1893.

It must be remembered at this stage the true nature of the malaria parasite had not been generally recognized in India. This is made fully clear by the numerous writings of Ronald Ross at this time. As late as 1893 the very existence of the malaria parasite was doubted and Ross considered the supposed parasites to be the outcome of postmortem changes in the normal elements of the blood.

The true position at this time may be gauged by the following reference (R. Ross, Ind. Med. Gazette, 1896, XXXI. 353):—"Going to England I submitted my precious article together with a number of photomicrographs which had cost me about a year's labour to Dr. Patrick Manson. He said the kindest things possible about my work, but showed me a malarial crescent. I was bound to confess, in spite of my studies, I had never seen such a thing before."

In 1894 and again in 1896 Manson definitely formulated his mosquito-malaria hypothesis. Being a parasite, he argued, the germ of malaria must pass from host to host; in other words, it must at some time lead an extracorporeal life. From the fact that the flagellated body does not appear till the blood has left the bloodstream, he concluded that the function of the flagellum lay outside the human body and that it was the first phase of this extracorporeal development of the malaria parasite. As this parasite, whilst in the blood, is always enclosed in a blood corpuscle and is therefore incapable of leaving the human body by its own efforts, it must be removed by some blood-sucking insect. That insect Manson believed to be a mosquito, which from its habits was specially adapted for the purpose and which, from the association of malaria with swamps and marshes ("miasma," "paludism") conformed with the well-known habits of malaria. Furthermore, by analogy with the case of *Filaria bancrofti*, which Manson had already shown in 1878 required the intermediation of a winged insect (a mosquito, *Culex fatigans*), he reasoned that it was only one particular species of mosquito which was capable of subserving particular species of malaria parasite.

The mosquito-malaria hypothesis was generally noised abroad so that it was linked with him in the nick-name "Mosquito Manson." He enunciated his ideas and spoke about them with conviction to the young and enthusiastic, amongst them the late Sir Patrick Hehir (I.M.S.)*

The seed mostly fell on barren soil, but it was otherwise with Major Ronald Ross who called upon Manson one day in April, 1894, and this visit occasioned the following letter which has been preserved.

Sir Patrick wrote:—"I am certain, judging from your observations, that you have not seen the *Plasmodium malarie*, otherwise you would never have failed to recognize its pathological character, and the reason you have not seen it is the technique you employ. It will give me great pleasure to be of any service to you, for I am quite sure you can do good work and you have the patience to do it."

In August, 1897, at Secunderabad, Ross found pigmented cells in the stomach of the brown mosquito, *Anopheles stephensi* and there could be no doubt that these

* Sir Patrick Hehir, K.C.I.E., C.B., C.M.G., who died on May 1, 1937, at the age of 78, had a very distinguished career in India, mainly on the administrative side of the Indian Medical Service. He served in most of the contemporary Indian wars and was taken prisoner at Kut in 1916. He subsequently directed the medical services in the Afghanistan War of 1919. In 1927 he issued a monumental work on Malaria in India.

were living and growing malaria parasites. The preparations were fixed in 40 per cent. formalin on sealed slides and were despatched to Manson. How this momentous step forward was regarded by him may be judged by the reply Ross obtained in due course. 21st October, 1897, "You seem to be on it at last. The slides arrived a fortnight ago while I was away in Scotland. I examined them at once on my return and found them in good condition enough to recognize the cells you describe. But the preserving material was evaporating, and, fearing the cells might perish, I had them drawn at once by a good artist and I hope that they will appear soon in the 'British Medical Journal' along with your paper. I showed them to Thin and Bland-Sutton, who at once recognized their likeness to the malaria parasite and the great importance of your find. Personally I believe you are on the road to a great discovery, but first you must be sure of where you are."

Finally Ross' perseverance, patience and sagacity triumphed and he was able to trace the whole and intricate malaria cycle, not as he had first hoped with human malaria parasites, but with the analogous parasite of birds (*Plasmodium præcox*), as Manson had first suggested to him.

Ross' observations were quickly confirmed and elaborated by Grassi, by Daniels and by Koch.

In this momentous history due credit must be given to Grassi who showed definitely that several species of *Anopheles* mosquito, particularly *A. maculipennis* are the special mosquito hosts of the human species of malaria parasite. He found that, in their evolution, they closely resembled that which Ross had already demonstrated for the plasmodium of the bird (*Pl. præcox*) and had further so clearly foreshadowed and partly demonstrated for the malaria parasite of man. Together with Bignami (1900), Grassi was successful in conferring malarial fever to human volunteers by mosquito bite in Rome.

Finally it was Manson who, with the assistance of the Colonial Office and with the organization of the newly-founded School of Tropical Medicine in the Albert Docks, instituted the experiments which finally clinched the mosquito-malaria theory in the popular mind.

This final, and what he termed, the experimental proof of the mosquito-malaria theory was carried out in 1900, partly in London and partly in Italy. The underlying idea was to afford a practical demonstration to the ordinary citizen that the apparently vague and purposeless meanderings of scientific study were absolutely true. Special mosquito cages were devised and *Anopheles* mosquitoes which had been fed on patients infected with benign tertian malaria in Rome were sent to London to bite two volunteers, one of them being Manson's eldest son (Patrick Thurnburn Manson)* with the result that, after a due period of incubation, both had malaria fever and the parasites were demonstrated in their blood.

Footnote.—The circumstances surrounding this piece of medical history are interesting and worthy of record. In 1894, both Ross and Hehir competed for the Parke's Memorial Prize which the former won. The subject was "The causation, prevention and treatment of malarial fevers." Manson, President of the Committee of Adjudicators, awarded the prize to Ross, especially for his exposition of the mosquito-malaria hypothesis. It was this event which led later to his interview with Hehir in which he expounded to him his views illustrated by slides and arguments regarding this subject which carried both conviction and enthusiasm. (Letter from the late Sir P. Hehir, December 5th, 1925.)

* Patrick Thurnburn Manson, who died on Christmas Island in the Indian Ocean in 1902 at the age of 25, had already shown evidence of a keen scientific spirit and had had a brief but brilliant career at Guy's Hospital. The result of this crucial malaria experiment on himself was published in "Guy's Hospital Gazette" in 1900 together with a record of his illness in his own words and illustrated by his temperature chart.

At the same time an expedition was organized to prove that people who are well protected from mosquito bites can live in a highly malarious country without contracting the infection. For this expedition, in which Dr. G. Carmichael Low, the late Dr. L. W. Sambon and Signor Terzi took part, a special wooden hut with mosquito-proof doors and windows was constructed in England and erected near Ostia in the Roman Campagna. The experimenters remained there three months in the autumn of 1900.

They moved freely abroad in the daytime, but retired to the hut one hour before sunset until one hour after sunrise, and in consequence remained in perfect health, in contrast to the native peasantry and members of the Red Cross Malaria Service, who were living in the locality at the same time.

Thus did Manson contribute in no niggardly fashion to the basic and fundamental facts of the great story of malaria. To him must be given the credit, because of his initial observations and the logical deductions resulting therefrom, of affording the necessary stimulus which lead to the solution of the life history of the malaria parasite outside the human body, and by the institution of the two simple, but ingenious experiments which have just been described, of indicating the methods by which the disease could be prevented.

In the treatment of malaria Manson, in his various writings, had succeeded in producing order out of chaos. His fundamental principles are well set out in the first edition of his book, "Tropical Diseases," in 1898. "So soon as a diagnosis of malaria has been arrived at, unless there be some very manifest contra-indication, the first duty of the practitioner is to set about giving quinine. There are many ways of exhibiting the drug; however, great care must be taken that it is given in such a way that there can be no mistake about its being absorbed. If the patient for any reason, such as inability to swallow, or persistent vomiting, cannot take quinine by the mouth, and the existing condition be grave, it should be injected by the rectum: but if the circumstances of the case are such that a rapid action of the drug is imperative, it must be injected at once subcutaneously, or into a vein."

"A fever fit, once begun, cannot be cut short by quinine, and to give the quinine during the early stages aggravates the headache and general distress; but so soon as the skin is moist and the temperature begins to fall, the sooner the drug is commenced the better."

The dose advocated was ten grains in solution three times daily at the commencement of the sweating and thereafter twenty grains for the next three days or longer. For anti-relapse treatment he advocated fifteen grains should be taken at intervals of from five to seven days for six weeks or thereabouts, together with iron and arsenic.

These were the main points in Manson's attitude as regards quinine therapy and it may be said that, in spite of all the heart-searchings and the tergiversations regarding the dosage of quinine during and since the Great War, Manson's main ideas regarding the amount of quinine and mode of dosage remained unchanged.

That his attitude to quinine therapy was not by any means hide-bound, may be seen by the perusal of successive editions of his text-book. He tested out all the new preparations or salts of quinine which were introduced.

In many ways, owing to this open-minded attitude to therapeutic problems, he unconsciously gave a necessary stimulus to the science of chemotherapy then in its infancy. For many years he had employed methylene blue in his laboratory as a blood-stain: indeed, although unsatisfactory in its differentiation, it was the

only one he possessed at that time. In this direction he must be credited with anticipating the discovery of the polychromic Romanowsky method—by producing his borax methylene blue (methylene blue 2 per cent., borax 5 per cent.), by which the stain acquired the property of picking out the chromatin of the parasite. This stain is still employed and is found to give satisfactory results, especially in Germany, where it is still known as "Manson's stain." At the time of a quinine famine in Hong Kong in 1887 he had tentatively employed this dye in the actual treatment of malaria. The dose was 2-3 grains in pill form, pushed till the urine became deeply tinged, or signs of kidney irritation appeared.

Medicinal methylene blue (methylthioninæ hydrochloricum) was independently suggested in 1891 as a therapeutic measure by Ehrlich and Guttman. Various observers have pointed out that it is important to ensure that the preparation employed should be free from metallic impurities, especially zinc chloride, which may cause vesical or rectal irritation. It was tried out by Ziemann in Italy in 1897 in all forms of malaria with inconclusive results. Reitler, as the result of a trial in 44 cases, concluded that it assisted in preventing relapses when given in combination with quinine and thus allowed the therapeutic dose of quinine to be reduced.

This treatment is referred to in the first edition of "Tropical Diseases" (1898), but does not seem to have been pursued further in this country, but in Germany it appears to have enjoyed a fair reputation as a therapeutic agent; thus M. Mayer (1919) recorded three cases of quartan infection in which it appeared to exert a specific action. The drug was given five times daily in doses of 0.2 grm. at two hourly intervals, the daily dose being continued for seven days. Thereafter it was given in an intermittent manner for three days at a time on the lines of Nocht's fractional treatment with quinine. The polychromic properties then discovered led Manson to speculate upon the underlying chemical affinities of these aniline stains, and he formulated the opinion, subsequently frequently expressed, that the staining affinities of dye for a particular parasite, were correlated with its therapeutic efficiency, and therefore led him to advocate the extended use of methylene blue as a therapeutic agent. That this, a mere speculation, was a spark of genius which has been justified by subsequent developments, is set out in the sequel.

These were the first attempts at the employment of an aniline dye in the treatment of protozoal disease in humans. It may be said, however, that their influence on the course of future developments was very considerable. Thus in 1908 G. H. Nuttall and G. S. Graham-Smith exhibited methylene blue to dogs in experimental piroplasmosis and this led to the employment in 1909 of allied aniline dyes, *Trypanblue and Trypanrot (Meister, Lucius and Brüning), which proved to be highly efficient remedies in an infection for which no drug or mode of treatment had hitherto been proved to exert any appreciable effect. As Schulemann informs us, these tentative and rather hesitant enquiries regarding the therapeutics of methylene blue had far-reaching and quite unexpected results. The initial factors in the modern chemotherapy of malaria are based upon the fundamental work of Roehl, who in 1926 showed that canaries infected with *Proteosoma* could be used to assess the therapeutic action of many groups of drugs. He devised a method by which accurate amounts of drugs could be administered to the birds by injection directly into the crop, and the results of this medication accurately gauged.

* Trypanblue has the formula:—

$C_{32}H_{16}N_4O_{14}S_4Na_4$ and has several features in common with the structure of methylene blue.

Trypanrot has the formula:—

$C_{32}H_{16}N_4O_{15}S_5Na_5$.

Previously Giemsa and the Sergents had demonstrated that the action of quinine upon the proteosoma *Plasmodium relictum* of the canary was the same as that of this drug upon the human malaria parasites.

Schönhofer, Winger and Schulemann based their chemotherapeutic experiments on methylene blue. They took as the formula for this dye the following structure:—

The results of the experiments with the compound were then transferred to the quinoline group. (The quinoline ring is the basic structure in the formula for quinine.)

By changing the position of the amino groups in the quinoline rings, they introduced every conceivable substitute in the quinoline nucleus in addition to the amino group, and also used many heterocyclic rings. Contrary to the views of earlier workers, they did not unite the basic aliphatic radicles by a carbon bond in the fourth position, but with a nitrogen bond to the quinoline nucleus. The basis of **plasmoquine**, as well as of quinine, is six (6) methoxy-quinoline, but in the latter there is a carbon bond in the fourth position, whilst in plasmoquine an amino acid is the bond in the eighth position. Then Roehl discovered that plasmoquine destroyed the gametocytes (crescents) of **Plasmodium falciparum** within a few days—a result which could not be achieved by quinine alone. Furthermore it was realized that the drug does not produce the same effect upon all species of malaria parasites and, if anything, had a selective action upon **Plasmodium vivax**. The following are the formulæ now generally accepted for quinine and plasmoquine:—

The constitution of plasmoquine, as announced officially in 1928, is 6-methoxy-8-diethylamino-*iso* pentylaminoxy quinoline. A considerable number of similarly constituted drugs have been synthesized in several countries. In France they are known as **Fourneau 710 (Rhodoquine)**, **Fourneau 574,664** and **852**. The Russian **plasmocide** is the same chemical formula as Fourneau 710.

The success which was encountered in the insertion of a dialkylamino-alkylamino side chain in 6-methoxyquinoline led to such insertions in other heterocyclic nuclei, and thus atebryn was produced which is 2-chloro-diethylamino-*iso*-pentylamino-7-methoxyacridine (**quinacrine** appears to be identical with **atebryn**). In the production of atebryn the triple ring was used, in place of the double ring system of the quinoline nucleus, and it is said that the widening of this in atebryn was aimed at with the object of getting rid of the toxic properties associated with the quinoline nucleus.

Practical results of treatment with the new synthetic remedies.

The earlier experiments on men with plasmoquine were vitiated by using too large a dosage (0.12 grm. daily), an amount twice as large as that now generally advocated; consequently unpleasant toxic sequelæ made their appearance.

It was soon discovered too that in early subtertian malaria infections with large numbers of the ring (trophozoite) forms in the circulation, this drug had little or no effect in banishing them from the blood. On the other hand, its effect upon the gametocyte forms, and especially the crescent stage of the subtertian parasite were very striking. The chromatin granules and the protoplasmic structure of the parasite became affected after even minute doses and, furthermore, the property of **exflagellation** is immediately destroyed. The writer has shown that crescents commence to disintegrate and vanish from the circulation after 0.08 grm. of plasmoquine ($1\frac{1}{3}$ gr.)—when in previous cases in which daily observations had been made, they remained visible in the bloodstream for 28 days and after 56 grm. (840 gr.) of quinine hydrochloride.

In all four species of malaria parasite the same effect on the gametocyte stages has been observed; but the drug acts undoubtedly more potently in overcoming the infection and in preventing relapses in benign tertian and quartan malaria, than in the other species.

The drug appears to exert a special action upon the spleen which shrinks in size more rapidly than in cases treated by the traditional quinine method. The toxic effects are a peculiar cyanosis which at first becomes visible on the inner surface of the lower lip and at the base of the nails. This is a true drug poisoning and is due to the conversion of hæmoglobin into methæmoglobin. In some cases even a methæmoglobinuria results, as in the fatal case of plasmoquine poisoning reported by W. K. Blackie (1935). (S. African Med. J., ix, 147.)

In other cases who exhibit an idiosyncrasy to the drug abdominal pains are produced, which may be so severe as to resemble the clinical picture of a gastric ulcer. Acute pains in the left hypochondrium are probably connected with its action upon the spleen. The parenteral injection of plasmoquine, both by the intramuscular and intravenous routes, has not been generally employed on account of the toxic manifestations they are apt to produce. De Langen and C. J. Storm have shown that circulatory disturbances also may eventuate; thus 0.02 grm. when injected, causes a fall of 50 mg. of mercury in the blood pressure.

Plasmoquine-compound. It was soon found that the toxic properties of plasmoquine can be effectually counter-balanced by combining it with small

quantities of quinine. This mechanical mixture is now known as plasmoquine-compound.

The combination is dispensed in tablet form, each containing 0.01 grm. of plasmoquine with 0.125 grm. of quinine sulphate. The idea of combining the quinine is to render the drug effective in the treatment of subtertian malaria so as to destroy the younger ring forms of the parasite and so as to permit the plasmoquine to exert its full action upon the gametocytes. However, in actual practice, plasmoquine-compound has been shown to be the method of election in treating benign tertian and quartan malaria; its use in subtertian infections having been superseded by that of atebirin. This combination is comparatively tasteless and produces few of the disagreeable symptoms, usually associated with quinine therapy. In subtertian infections it is now used as an adjunct to atebirin, when three days treatment with plasmoquine-compound serve to get rid of the crescents which are unaffected by atebirin alone. This compound is well tolerated by children as well as by pregnant women, and it is therefore to be welcomed in those cases where the older quinine therapy was at a considerable disadvantage. The underlying principle in plasmoquine-compound administration is what is known in Germany as the *stoss-therapie*—that is, the administration of the drug in alternate weeks.

The maximum dosage for an adult man or woman is 6 tablets daily (i.e. 0.06 grm. plasmoquine+.75 grm. quinine). In actual practice however, in the anti-relapse treatment of benign tertian malaria the following scheme is advocated:—

For an adult.

- (1) 7 days—2 tablets of plasmoquine-compound twice daily.
- (2) 4 days interval and then 7 days—2 tablets twice daily.
- (3) 4 days interval and then 7 days—2 tablets twice daily.
- (4) 4 days interval and then 7 days—2 tablets twice daily.
- (5) 4 days interval and then 7 days—2 tablets twice daily.

This suffices to prevent any further relapses in most cases of benign, tertian and quartan malaria. It is most important that the tablets should be taken directly after meals on a full stomach, and it is now realized that the abdominal symptoms, formerly noted, were probably due to the direct action of the drug upon the unprotected gastric mucosa.

In children between 4 and 5 years of age, the dose advocated is one tablet twice daily, or between 5 and 10 years of age, 1 tablet three times daily.

In those rare cases with an idiosyncrasy to plasmoquine, the administration of glucose, 1 oz. daily, is advocated. In the case of infants Sudet has shown that up to 6 months of age the dose of plasmoquine (Rodoquine) should be .0025 grm. daily.

Quinoplasmine (chinoplasmin) is the combination of the same dosage of plasmoquine with a greater amount of quinine in the proportion of plasmoquine—quinine of 1:30. Each tablet contains 0.01 grm. plasmoquine+0.3 grm. (4½ gr.) quinine sulphate. The dose is three tablets daily for adults given in the same formula as already detailed. It has been widely used in India and in Palestine where the majority of the infections are benign tertian and where a greater proportion of quinine is considered more effective. The method was tested out in India by Manifold in 1930 in 3,187 British and Indian soldiers, and it was stated that this course was more efficacious in preventing relapses than the more lengthy and tedious anti-relapse quinine therapy.

Atebrin is a yellow powder which dissolves in water at 40° C. in a 7 per cent. solution. Chemically, it is the dihydrochloride of alkylamino-alkylaminoacridine

and was synthesized by Mietsch and Mauss in 1930 on the same lines as plasmoquine. It is said that in the process more than 12,000 compounds were evolved and that only one—atebrin—proved satisfactory. The formula is given as follows:

It was first demonstrated by Kikuth that atebrin exerts a definite and peculiar action upon the schizonts of all the known species of malaria parasite, and this was first worked out, as in the case of plasmoquine, upon the blood parasites of the canary; but in contrast to the latter drug, it exerted no comparable action upon the gametocytes, especially upon the crescent stage of the subtertian malaria. It attacks the immature ring stages first, next the developmental forms and finally, if exhibited over a sufficiently long period, the gametocyte stages disappear—but at no time is the power of exflagellation affected—as has been observed in the case of plasmoquine.

Clinically, its most striking effects are seen in the treatment of heavy infections of subtertian malaria, and here it has opened up a new avenue of therapeutics. There is also a considerable amount of evidence which is rapidly accumulating, that it is a safe drug to exhibit when a rapid hæmolytic, or blackwater fever, is threatening; because, though it does not absolutely preclude it, yet it has undoubtedly diminished the incidence of this catastrophe. A further advantage is that the modern preparations of atebrin (which have been elaborated during the past year) are comparatively devoid of toxic properties, and appear to be followed by few, if any, untoward results. The drug is excreted in the urine, to which it imparts a bright yellow colour, and it is stated that it can be demonstrated there for a period of 36 days. It is also passed in the fæces. The method of detecting atebrin chemically is comparatively simple:—

“The urine, rendered slightly alkaline, is extracted with ether, desiccated and the residue is treated with concentrated sulphuric acid which turns yellow and shows distinct fluorescence.”

Atebrin staining of the skin (or atebrin pigmentation) was commonly noted on the first introduction of the drug, but during the last one and a half years the tablets have been treated with a preparation of lacquer, and this has become far less noticeable. Atebrin pigmentation, which is first noticed behind the mastoid process, never occurs before the third day. The factors concerned in

this process are due to slow excretion and the accumulation of this dye-pigment in the skin, and it has been remarked that constipation and intercurrent infections modify the intensity and character of the discoloration. Naturally atebirin pigmentation has to be distinguished from the icterus of pernicious anæmia, acholuric jaundice and carotinæmia. This is a proposition which well merits the attention of the practical physician.

According to Hecht, atebirin is absorbed in the duodenum, and carried to the liver, whence it is excreted with the bile back into the duodenum to pass once more into the liver with the portal blood, so that, according to this theory, little atebirin reaches the general circulation, till the liver has been saturated with it, and this explains the fact that none appears in the urine until it has been exhibited for several days. The diet taken by the patient on atebirin treatment also requires supervision, for F. M. Peter has shown that food containing large quantities of cellulose is apt to absorb it.

Attention has recently been directed to the fact that in some susceptible individuals atebirin, even in therapeutic doses, acts as a cerebral excitant. This is especially liable to occur in native races, such as Malays, Tamils, Indians and Chinese. In England, amongst Europeans, such phenomena have rarely been noted. Some of these patients exhibit mild, or transient psychoses, whilst others become maniacal. As an explanation Kingsbury has suggested that it is due to the too rapid liberation of malarial toxins and their effect upon the cortical centres. The combination of atebirin and plasmoquine is by no means satisfactory and is apt to give rise to poisonous symptoms, such as intense depression, excruciating abdominal pains and colic, and is therefore not recommended.

On the other hand, atebirin is compatible with quinine and the two drugs may, with advantage, be given in combination, when they act beneficially in bringing down the temperature and combating the serious toxic manifestations of subtertian malaria, especially in delirious cases. Thus atebirin may be exhibited with quinine 5 gr. two or three times daily. In atebirin-treated malarial cases the shrinkage in the size of the spleen is phenomenally rapid.

Atebrin is put up in tablets each containing 0.1 grm. and should be given to an adult three times daily on a full stomach. This is very important, because on an empty viscus it apparently causes acute gastric pain. The daily dose is 0.3 grm. (4 gr.). Until recently it was considered that a five day course of treatment (1.3 grm.) sufficed to cure an average case of subtertian malaria, but it is now realized that a longer period is necessary, up to ten days as a primary course (3 grm.). It is much safer to repeat this course after an interval of one week in order to permit the excretion of the drug from the body. It is important that the tablets should be swallowed whole with a drink of milk or water, as the taste, when chewed, is intensely bitter. For children a useful method is to conceal the tablet in a raisin. The dosage is given as follows:—

From 6 months to	1 year	...	...	0.05 grm. daily
„ 1 year	„ 2 years	...	...	0.10 „ „
„ 4 years	„ 8	...	...	0.15 „ „
„ 8	„ 10	...	...	0.25 „ „
„ 10	„ 15	...	...	0.3 „ „

The drug is well tolerated by children and pregnant women—both very important aspects in therapy, and in the latter it is not accompanied by the risk of premature abortion, as it exerts no special action upon uterine contraction. The most important effect of atebirin is in the prevention of relapses in which it is undoubtedly superior to quinine.

Green (1932), treated 21 cases of subtertian malaria without any further relapses, whilst in a similar period there were 13 amongst 34 quinine treated cases used as controls. Janes and Nicol recorded eminently satisfactory results in 15 cases of therapeutically induced cases.

Atebrin is used for intravenous or intramuscular injection though this method is now rarely necessary. The soluble preparation is known as atebrin musonate and is put up in ampoules, each containing 0.125 grm. dissolved in 3 c.c. of water. One such ampoule is used for intravenous and three for intramuscular injection. Atebrin musonate 0.125 grm. corresponds to 0.1 grm. of solid atebrin dihydrochloride. Injections up to 0.2 grm. have been given in cerebral malaria without any noticeable deleterious effects. Field and Niven (1936) have given intravenous and intramuscular injections up to 0.3 grm. on two successive days, and have noted the rapid disappearance of the parasites from the circulation without any toxic results. On the other hand Udalagama in the Ceylon epidemic recorded the supervention of severe mental derangement in some of his cases from this procedure.

In some individuals atebrin musonate, given intramuscularly, provokes abscess formation, and the writer has observed a large sterile abscess in the buttocks of a patient which supervened three months after such an injection.

Advances in the Diagnosis of Malaria.

Perhaps the most important and outstanding event has been the recognition of a fourth species of malaria parasite, now known as *Plasmodium ovale*. In 1922 Stephens described the species from E. Africa, though it is by no means certain that it was not the same as had been previously noted by Ahmed Emin at Camaran in the Red Sea in 1914. In 1927 Stephen confirmed his belief in the authenticity of *P. ovale* by describing a further case from Nigeria. In 1930 Yorke and Owen demonstrated that the peculiar morphological features were preserved when the infection was directly transmitted from one person to another by blood inoculation, whilst later James and Shute succeeded in transmitting it through *Anopheles maculipennis*, and describing several peculiar features in this process. Janes Nicol and Shute (1935) have laid down criteria for regarding *P. ovale* as a separate species; namely that the character and arrangement of the pigment in the oöcyst in the stomach wall of the mosquito 72 hours after feeding is specifically diagnostic, whilst the sporozoites are much smaller than those of *P. vivax*. Furthermore, the morphological characters of the parasite, the periodicity of its asexual cycle in man and the characteristic clinical course of the disease are unaltered by repeated passages through insect and human hosts.

P. ovale somewhat resembles the benign tertian parasite, *P. vivax*, and it produces a tertian periodicity, but does not cause a marked enlargement of the host cell in which it produces the peculiar granular degeneration, known as "Schüffner's dots." The small schizonts (or rings) have no special features, but they lie in red cells which are usually oval and have irregular fimbriated margins. The "sporulating body" is formed by the maximum number of twelve merozoites which lie in a decolourised and degenerated corpuscle with many Schüffner's dots. The clinical course in man appears to be a particularly mild one and the infection tends to die out after several paroxysms, which come on in the evening or at night. The writer and Muggleton have now described cases from Uganda, Nigeria, the Belgian Congo and Sierra Leone. A feature of the fever is to produce abdominal pain, which may simulate appendicitis and rheumatic pains in the back, resembling lumbago.

As regards the actual methods of making a diagnosis in the latent phases of malaria infection, there are very few major improvements to record. Many workers, especially in Germany, prefer the thick-drop method of blood examination, especially when the parasites, as so often, are particularly sparse in the peripheral blood. The objection to this method is the distortion and partial destruction of the delicate parasites which occurs during the process of dehaemoglobinization, which makes their subsequent detection by the polychromatic stains particularly difficult. De Langen and others have shown that the number of parasites in the peripheral blood may be greatly increased after physical exercise which drives out the parasites from the blood reservoir in the internal viscera where they tend to accumulate.

In Germany and other continental countries it has been found that the most efficacious method of provoking a fresh malarial attack, and thereby demonstrating the causative parasites, is by the intravenous injection of 2 cc. of adrenalin hydrochloride, dissolved in 300 cc. of normal saline. This process results in a rapid contraction of the spleen whereby the parasites are driven into the peripheral circulation.

The diagnosis of malaria by spleen puncture has not found universal favour. According to Knowles, Acton and das Gupta, the spleen is to be regarded more as the graveyard, than as the nursery of the malaria parasite. Consequently, on spleen puncture, only malarial pigment and fragmented parasites can be identified. The recent experiences of Foy and Kondi in Macedonia in this direction would also appear to be disappointing.

Henry's sero-flocculation test, by providing us with a definite serological test, to be used in the quiescent stages and latent period of malaria, has aroused considerable interest; but unfortunately the results do not appear to be by any means consistent. From an examination of the two forms of pigment derived from haemoglobin—the ochraceous ferruginous pigment and the melanin, it was thought that they might produce antibodies in the blood of diagnostic importance and thus give a flocculation test. Accordingly the ferro-flocculation and the melano-flocculation tests came into being.

Malarial sera give flocculation reactions with **Metharfer**—an albuminate of iron with a suspension of melanin. In other tests **melanin** alone is used, which is obtained from the choroid of the ox eye scraped and ground up with twice its volume of distilled water, then filtered through cotton wool, and finally centrifuged for eight minutes at 4,000 revolutions.

The flocculation is said to persist long after the disappearance of the parasite and the subsidence of the clinical signs of malaria.

Benhamou and Gille consider that Henry's reaction depends really upon an increase in the euglobulin in the serum and a diminution of the cholesterol and serum-albumin. Brandt and Horn, using albuminate of iron, consider that Henry's reaction gives a very useful indication in inoculated malaria. In 50 malaria-treated cases all were positive during the duration of the malarial cure.

Conclusion. It must not be thought that, although so much has been accomplished in the study of malaria during the last 58 years since Laveran's momentous discovery, that the end is yet in sight. Even in the limited field which has been covered by this survey there are many *lacunæ* which have still to be filled in and many directions in which fresh advances have to be made. There is still much important research work to be performed in almost every aspect of the malaria problem, the truth of which assertion Patrick Manson himself would have been the first to admit.