REPORT ON THE LEAGUE OF NATIONS' COURSE ON MALARIA HELD IN SINGAPORE.

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The Course included theoretical and laboratory study at the Medical College, Singapore, and about twenty-five field demonstrations in and around Singapore and in Johore. The teaching covered the following eleven subjects:—

I.—ENTOMOLOGY.

Three hours a day for twenty days was devoted to this subject. The whole of the instruction was given by Professor B. A. R. Gater, M.C., Professor of Biology in the Medical College.

The points brought out in the lectures that seemed most important were: The wing venation terminology; the longitudinal veins of my earlier acquaintance were discarded and the names used by Christophers and Barrand, viz. subcosta, radius 1, radius 2 and 3, radius 2, radius 3, radius 4 and 5; media, media 1, media 2; cubitus, cubitus 1, cubitus 2, and analis were used instead. The cross veins were named humeral, subcostal, radial, sectorial, radio-medial, and radio-cubital.

The wing-scaling was another matter particularly stressed by the lecturer, as he bases his classification of anophelines in part on the variations of dark spots and pale areas of the wing.

In the description of the larva, the demonstration of the protrusible "notched organs" in the thorax, which are characteristic of all anopheline larvae was of interest. Attention was also particularly directed to the posterior clypeal group of hairs and to the sutural and trans-sutural hairs of the head which are used, together with the thoracic pleural and the abdominal palmate hairs, to enable a rapid identification of the different species of anopheline larvae to be made.

The classification of the family culicidæ was gone into fully, that based on the work of Edwards in 1922 being used. The somewhat clumsy method of Swellengrebel and Rodenwaldt of 1932, employing the terms "groups" and "super species," was also mentioned as this classification is used in the Dutch East Indies. It was also interesting to note that there is now a tendency to attach importance to the maxillary index as a means of distinguishing between possible malarial anopheline species and non-malarial. This index is based on the number of teeth on the maxilla; fourteen is taken as the dividing line, and those with less than fourteen are found to be man-biters, whilst those with more are animal biters.

A considerable number of the lectures was devoted to the ecology of the anopheles mosquito, and a great many references were made to recent experimental work which has been and is being done in the effort to learn
more about the life history and habits of the mosquito. The points brought out which were of interest in so far as they concerned the anopheles of Malaysia were: in Malaya a mosquito flight range of half a mile is considered the maximum effective range of the insect; in the Netherlands East Indies a control area of one and a half miles is considered necessary.

In the latter country, *A. sundaicus* (formerly called *A. ludlowi*) is the chief danger, and this mosquito is strong on the wing. In Malaya the most dangerous mosquito is *A. maculatus*. This species likes the clear seepage water of lightly shaded valleys for breeding in, just the ones provided for it by rubber estates. Seepage is plentiful owing to the almost daily showers of rain which raise the water table. The adult insect is apparently most active in a humidity of over 80 per cent. Indeed, in a humidity as low as 65 per cent it cannot survive more than a day or two. In Malaya Professor Gater has listed some 34 species of anopheles and 6 or 7 varieties: of these, only 3 are held to be important carriers, viz. *A. maculatus*, *A. umbrosus*, and *A. sundaicus*, while 5 more have been found to be infected in nature.

In the Dutch East Indies the same species practically are the proved carriers. It is noteworthy that although there are no marked seasonal changes in Malaya, yet there is a marked seasonal prevalence of all the commoner species of anopheles which is not the same for all, but the *A. maculatus* peak, which is in March, is followed closely by the parallel curve of malaria incidence. The species of anopheles which are only to be found in the Malay Peninsular are *A. asiaticus*, *A. wellingtonianus*, *A. watsoni* and *A. aurirostris*.

The first part of the laboratory course was devoted to external anatomy; this was followed by several days of study of the internal anatomy of the anopheles mosquito and dissection, including the dissection of infected insects. The larva was then studied in detail and a method of identification was taught, using for the purpose Professor Gater's "Aids to the Identification of Anopheline Larvae in Malaya" (p. 52 et seq.), published by the Government Printing Office, Singapore, price one Straits dollar. For the identification of adult mosquitoes the class used a key produced in the form of a trial table for rapid identification.

Valuable hints were given relating to the technique and apparatus recommended for the collecting of adult mosquitoes and larvae and the rearing of larvae. A number of copies of *Bulletins* from the Institute for Medical Research, Federated Malay States, and Reprints from the *Transactions of The Royal Society of Tropical Medicine and Hygiene* were issued showing the trend of the most recent experimental work going on in the subject.

Dr. R. Green, of the Institute, provided a most illuminating demonstration of malaria parasites in the monkey, bird and human being in a long series of slides which included a demonstration of oocysts in the mid-gut stained by a method which he is perfecting but which has not yet been published.
For dissecting the insect and identifying the adult each member of the class had a new binocular microscope of the Greenough type which gives stereoscopic vision. For larval work the monocular instrument used for haematology was used. With the binocular instrument a dissecting lamp was provided for illumination; this was a gas-filled bulb with daylight equivalent glass fitted to a flexible arm and provided with a reflector.

For use with the monocular microscope, both in this class and in the protozoology class, an extremely good type of microscope lamp was used. This lamp is a modification of a type suggested by Gordon and Welch. It consists of a 100 watt projector bulb (with a concentrated filament) which can be burnt cap down in any position within 45° from the vertical. The bulb is contained inside a double casing which prevents light entering the eyes and provides a large cooling surface with plentiful aeration. In the front of the outer casing is an adjustable sleeve which carries a glass rod specially selected for freedom from "bubbles" and faults, and finely ground on the end nearest the bulb. The sleeve is moved by means of the slide to which it is attached, so that the rod is exactly opposite the concentrated filament. The rod is then moved in and out until the outer end is seen to present an evenly illuminated area. A spot of intense and practically uniform light is then available which can be focused by the substage condenser, the outer end of the rod being used as the source of light. A light filter "neutral" or "daylight equivalent," e.g. for blood work, or both, is placed in the carrier which is clamped to the end of the glass rod. The apparatus is not difficult to make and could probably be constructed locally anywhere.

II.—HäMATOLOGY AND PROTOZOOLOGY.

In this class of seven lectures and seven two-hour periods of practical laboratory work, Dr. G. V. Allen gave the lectures and Dr. H. O. Hopkins the laboratory instruction.

This was a very valuable series of lectures despite the fact that the lecturer only reluctantly decided to make the course a résumé of the whole subject rather than confine himself to recent advances in the subject, because some members of the class were probably not engaged in laboratory work and might want their knowledge of the subject revised and brought up to date.

The points brought out in this class that claimed attention as being recent knowledge were as follows: *Plasmodium ovale*, which was first described by Stephens in 1922, has now apparently been recognized as a separate species. Its morphology is not altered by successive passages and it can only be identified in thin films when contrasted with *P. vivax* from which it differs in having a smaller number of merozoites, in that the red blood-cells are very often oval in shape and their margins fimbriated, and in the brown black colour and granular nature of the pigment and so on. The lecturer was able to get a blood slide with
P. ovale through the agency of the League of Nations and demonstrate it to the class.

The pigment produced by the parasite is now being employed in certain interdermal reactions (such as Rocchi's Test) as a test for the presence or absence of infection. This test is claimed to give a positive skin reaction in the majority of non-malarial and cured cases and no reaction in malaria cases. The formula for the pigment is given as C 84 H 152 N 20 Fe 0·82, but how it is prepared for the test is not stated.

Recent and detailed knowledge referring to such matters as the differences in the character of the pigment in the four different species of plasmodium in the oocyst, the Maurer's spots in the cells containing P. falciparum, the Zieman's stippling seen in those containing P. malariae, and the Schüffner's dots of P. ovale, all were discussed. The many facts, also, learned in recent years from the use of the malaria parasite for therapeutic purposes such as the differences, clinical, immunological and biological between Indian and Italian strains of P. falciparum, and the more accurate knowledge of the incubation period were mentioned. Culture methods and blood changes in malaria were both dealt with in this course of lectures.

The outstanding features of the laboratory course were the use of Shute technique for the staining of malaria parasites, both for use with Leishman's and Giemsa's stains; and the use of defibrinated blood films in examining blood for malaria parasites.

By means of the Shute technique we were enabled to bring out the various spots and stippling of the different species of the plasmodium at the first attempt. The technique depends principally on the adjustment of the distilled water to a suitable degree of alkalinity by the addition of lithium carbonate and on the testing of the methyl alcohol. The method is described by S. P. James, in the Transactions of The Royal Society of Tropical Medicine and Hygiene, xxiii, 269, of 1929, and again in an Addendum to the same article circulated privately.

Defibrinated blood films offer a means of obtaining the highest possible concentration of parasites on a film. The method is to take three or four cubic centimetres of blood from a vein and quickly introduce it into a small, clean, dry test tube containing a few glass beads. This tube is then shaken gently and continuously for three or four minutes, whereupon the defibrinated blood is poured into a small centrifuge tube, leaving the fibrin clot behind in the tube with the beads. The red cells are packed by spinning for a few minutes and the supernatant serum pipetted off. A drop of the centrifuged red cells is put on a slide and spread into a "thick" thin film, dried, and stained with Giemsa.

III.—CLINICAL.

As the Army Medical Service has its own large store of clinical material to draw upon for experience in this disease, it is not necessary to
describe this course in detail, particularly as there happened to be rather a
dearth of clinical material in the Tan Tock Seng Hospital during the
period, but in the lectures, Professor Hawes, with his great clinical
experience, adopted a distinctly conservative attitude towards the use of
the newer drugs, atebrin and plasmoquine, in contrast to certain of the
other lecturers, who came from up-country estates and who were keen
advocates of the use of these drugs in preference to the longer known drugs
of the quinine group. Professor Hawes pointed out that there is a type
of liver necrosis preceded by fatty degeneration in the central zone and
spreading towards the periphery, which is found in blackwater fever and
also when patients are treated with phenyl hydrazin? This fact should
be borne in mind when liver poisons such as atophan, plasmoquine and
atebrin are being used.

The low birth-rate associated with untreated malaria referred to by
the lecturer is the reason why the indigenous Malay population is being
out-bred by the Chinese immigrant population in Malaya. Is it not
possible, therefore, that if preventive malaria measures were intensified
in rural districts, the Malay population might become more prolific after
a generation or two and so offset this disproportion. For although the
Chinese are less immune to malaria than the Malays, they tend to concen­
trate in and around the towns where anti-malaria measures are more
effective than in the villages and so they are proportionately less affected
by malaria.

IV.—Pathology.

Dr. Tull, in his lectures, gave a very comprehensive account of the
histology, physiology and pathology of the organs of the body, especially
the spleen, liver and kidneys in so far as they are affected by malaria. This
lecturer also stressed the similarity of a malaria paroxysm to anaphylaxis
and was evidently inclined to think that the toxin is provided by the
pigment. He also suggested that supra-renal insufficiency might be the
determining cause of pernicious malaria, as the supra-renal cortex shows
degenerative changes evidenced by the partial or complete loss of its normal
yellowish colour.

V.—Synthetic Drugs.

This was naturally a most welcome series of lectures in view of the
great interest that is now being displayed in medical circles in the use of
the new synthetic drugs for the treatment of malaria. Dr. Green, who is
one of the staff of the Research Institute at Kuala Lumpur, and an
authority on this subject, confined himself in his lectures largely to Malayan
experience. We had also the experience of the Formosan School in this
matter through the kindness of Dr. Morishita, the Director of the Malaria
Research Institute of Taihoku, who was a member of the class and who
provided us with some of the publications of this institute which had a
bearing on this subject. As the general literature on these drugs is
already so extensive it will suffice here merely to summarize the Malayan view.

Plasmoquine was the first drug dealt with; it is considered to have a specific action on gametocytes and in particular renders crescents non-viable. The present-day tendency is to reserve it for use as a prophylactic against crescents and as a means of preventing the infection of mosquitoes by humans; moderately large doses at three-day intervals will effect this. A dose of 0.03 gramme given daily over a period produces methaemoglobinæmia in some cases and such a dose cannot be given safely without supervision. Gametocytes of benign tertian and quartan malaria are destroyed equally well by quinine and atebbrin, both of which drugs are less toxic than plasmoquine.

Atebrin, which has now been in use since April, 1932, appears to be much less toxic than plasmoquine and to be highly effective against the asexual forms of all species of plasmodium. Its dose is 0.3 gramme daily, either all at once or divided into two or three doses. It has a cumulative effect and is stored in the liver and tissues. It has been found in the urine up to thirty-six days after cessation of treatment. It is therefore unsuitable for prolonged administration; this, however, is less necessary as its cumulative action subjects the parasite to prolonged action and so the drug is very efficient in preventing relapses. As it has not the temperature-reducing properties of quinine it is now the custom in Malaya to treat a patient for the first two days of his malaria attack with quinine and then to continue with atebbrin instead of quinine for the next five days. Atebrin should not be continued for more than seven days, because it is liable to lead to toxic symptoms which are often delayed for six or seven days after the atebbrin has been stopped. These toxic symptoms consist of headache, abdominal pains and yellowish discoloration of the skin and whites of the eyes and, most important of all, cerebral excitation. This last takes the form of a delirium lasting from one to several days; during which time the patient is in a hiliarious, excited state and is not accountable for his actions. On recovery he has no recollection of the period spent in this condition. A seven-day course has produced this effect. A research experiment showed that while the relapse rate with quinine treatment was 38 per cent, that with atebbrin was only 4 per cent.

Japanese experience was generally in the same direction as regards these two drugs except that they found that plasmoquine had no power to prevent relapses.

The other synthetic drugs dealt with were Tetrabren, C 77, Fourneau 710, and Fourneau 852, of which only the last-named was considered to be effective.

Dr. Green also gave a lecture on the subject of bird and monkey malaria in which his conclusion was that cross infections of malaria from monkey to man were possible but far from common. The use of monkey malaria was permissible for tuition, as, for instance, the oocysts of
monkey-infected mosquitoes showed no structural difference, but for research monkey malaria was not sufficient and human controls in addition were required.

VI.—HISTORICAL.

Dr. Hoops gave a paper on the history of malaria. It was interesting to learn that Anna, Countess of Chinchon, from whom quinine received its name, cannot ever have taken the drug, because she apparently died in Spain before her husband ever left for South America as Viceroy of Peru. It was his second wife, Francesca de Ribera who was cured by quinine given her by the Viceroy’s physician Juan del Vego. It was Linnaeus who gave the drug the name cinchona in 1742.

VII.—EPIDEMIOLOGY.

This course of lectures was given by Professor Walch, of Batavia, Dutch East Indies. In the lectures he followed mostly the work of Ross, Christophers, and Gill and MacDonald of the English workers; Schüffner and Rodenwaldt of the Continental; and Darling of America. For the mathematics of hygiene we were referred to Ferguson and Udney Yule.

The lectures on the comparative study of the spleen rate in endemic and hyperendemic malaria were of the greatest interest and for this purpose malaria in British India, the Dutch East Indies, South Africa and the Southern States of U.S.A. was taken for purposes of comparison.

Christophers’ theory of the spleen rate was discussed in detail, and his work, along with that of Sinton and Covell in Section VII of Health Bulletin, No. 14, Government of India Malaria Bureau, was recommended to be followed.

VIII.—CONTROL.

To an officer belonging to such a service as the Army Medical Service with its predilection for preventive medicine it is natural that the subject of control should be held to be most important and an acquaintance with the malaria control work done in Singapore is necessary for anyone aiming at a complete knowledge of this subject. There is probably no one who has had a wider experience than Dr. Scharff in devising and carrying out underground drainage schemes and so the class was fortunate to have the benefit of his teaching both in his lectures and in the numerous outdoor demonstrations. In Singapore antilarval oiling is looked upon as a temporary measure, only to be carried out until permanent subsoil drainage in the area has been effected. Earth filling is expensive by comparison with draining and is not considered effective, though it is useful at times when soil happens to be available from engineering projects being carried out in the neighbourhood.

In brief the method whereby Singapore has almost eradicated malaria is by means of putting in lines of agricultural tile drains from 4 to 8 inches in diameter, according to size required by the flow, at a depth of from
4 to 7 feet below the surface, laid roughly along the line of the lowest contour of a valley above the height of the exit from the valley. These pipes, which are each 12 inches in length, are laid end to end against each other, leaving a space of about \( \frac{1}{10} \) to \( \frac{1}{4} \) inch between them through which the water enters from below. They are laid on rubble at the bottom of a trench to prevent silting and between the joints of the pipes a sausage of puddle is laid to prevent surface water, roots, etc., entering from above. The pipes are laid as straight as possible and an inspection chamber is placed where the gradient has to change to prevent scouring. The pipes are laid from the outlet backwards and the trench is filled in as soon as they are laid. Down the centre of the valley is laid a cement invert to lead off the surface water. This runs as straight as possible and into it the subsoil pipes discharge when they come to the surface at the bottom of the valley. The central invert consists of a curved cement invert one-third the circumference of a circle in shape with cement slabs leading back from the upper border of this at an angle of 45°. Unlike the subsoil pipes, these slabs and the invert sections are cemented together, but weepholes are left open at the lowest points of the invert curve.

This system of drainage is particularly applicable in Malaya where the water table is generally less than three feet below the surface as the result of the constant rainfall throughout the year and the presence usually of an impermeable layer not far below the surface. These subsoil drains are just sufficient to lower the water table and so prevent the water out-cropping as swamps in the floor of the valley and as springs and seepages at the bottom of the sloping sides. It is just in such seepages of crystal-clear water that the anopheles, and particularly the dangerous \( A. \) maculatus, love to dwell.

In addition to Dr. Scharff's lectures, Dr. Demeny of the Asiatic Petroleum Company spoke on the chemistry of anti-larval oils and demonstrated spreading powers, etc., of different oils. Dr. Smart gave one lecture on propaganda, which is used extensively in this country. As a means of bringing knowledge of disease prevention to the villages, there are cinema films, health weeks at agricultural shows, visits from health officers, lady health officers, dressers on motor bicycles, travelling dispensaries, lectures at schools. Dr. Smart also dealt with special control measures such as brush spraying and oiling, bamboo subsoil drains, medical examination of labourers and measures applicable to temporary engineering contracts, sluice gates for flushing streams, the use of Paris green in such places as ponds in botanical or other ornamental gardens, and larval eating fish.

Dr. Wallace, who has much experience of estate work, lectured on mass treatment of cases and carriers. He had had on his estates good results with plasmoquine and its combinations with quinine, but few other workers had been able to confirm his results. He had also had good results with plasmoquine for three months after an initial five-day course with atebrin.
He had not tried atebrin alone. In this case it was interesting that his parasite rate remained at nil for a month after the cessation of atebrin and then reappeared gradually although plasmoquine continued to be given for another two months.

There is already some evidence in the Third General Report of the Malaria Commission of the League of Nations (The Therapeutics of Malaria) that atebrin is a true prophylactic. There is also evidence of its sustained action up to something like thirty days, which is doubtless related to the slowness with which it is excreted, already referred to in Section V above. It would be interesting to see whether a five-day course of atebrin at intervals of six weeks would be sufficient to prevent both fresh attacks and relapses. The only drawbacks to such a method would be the occasional occurrence of a yellow tint in the skin and the possibility that the cumulative effect of taking the drug over a long period might in the end do damage to the liver. So far there is no evidence that this is likely to be so. The advantages are that the daily dose (0.3 gramme) can be taken at one time, and the total cost is small, the period of administration being so brief.

IX.—EXPERIMENTAL MALARIA, ETC.

Professor Ciucu, of Bucharest, who came from the Secretariat of the Malaria Commission of the League of Nations to carry out the administration of this course, gave a series of lectures on various subjects, including experimental malaria and the value of malaria therapy in the study of malaria, on experimental malaria and the study of malaria immunity and its contribution to the treatment of malaria, totaquina, bonification in Italy and the work of the Malaria Commission.

For instance, experimental malaria has enabled us to confirm the specificity of four species of parasite; it has established accurately the incubation period of malaria; it has verified observations on acquired immunity, e.g. that immunity to one strain of a parasite is not effective against another strain of the same species, and so on. As regards totaquina, the League of Nation's cheaper substitute for quinine, it is well established that Types I and II are both about equal to quinine sulphate in their efficacy.

Bonification has, by means of large scale drainage and cultivation, converted the Roman Campagna and other places in Italy from uninhabitable malaria swamps into populous and prosperous districts, the State and co-operative societies having advanced the necessary money for the work.

X.—MALARIA IN INDO-CHINA.

Dr. Morin, the Director of the Malaria Bureau of the Pasteur Institute in Saigon, gave a series of lectures on the above subject. The science of malaria prevention is still in its youth in French Indo-China, as it was not until 1929 that anti-malaria measures were taken in hand to any great extent. The chief reason for this was that jungle was hurriedly cleared in
many places for the purpose of planting rubber from 1926 onward, and this led to a bad malaria epidemic in 1928. Thus it is that even now the measures taken consist chiefly of oiling and surface drainage combined with quinine prophylaxis and by means of these measures a very fair measure of success has already been obtained.

The transmitting species of anophelines are *A. minimus*, *A. jeyporiensis* and *A. maculatus*. Dr. Morin illustrated his lectures by means of numerous slides and his detailed information, graphs, etc., are set forth in a book compiled by himself and Dr. Robin, who was a member of the class. The book is entitled "Essai sur la Prevention Pratique du Paludisme dans les exploitation Agricoles en Indochine" and is a publication of the Chambre D'Agriculture de l'Annam. Dr. Morin kindly gave a copy of this book to each member of the class.

XI.—Malaria in the Dutch East Indies.

Professor Walch also gave a further series of lectures on malaria in his country. He, too, illustrated his lectures with numerous lantern slides, and so most of the time was speaking in a darkened room, but the points of importance he brought out were the following:—

Malaria is hyperendemic in many of the places in Dutch East Indies, but whereas the spleen-rate in most of the towns in these areas was from 80 to 100 per cent. in 1922, in 1932 the spleen-rate in the same places had fallen to 0 to 40 per cent. The country is not swept by generalized epidemics but localized epidemics are common. The responsible mosquitoes are *A. sundaicus* (ludlowi), *A. hyrcanus* (sinensis) *A. maculatus* and *A. aconitus*. Control is for the most part on a big scale and consists in narrowing the river beds, deepening the creeks and rivers at their mouths, and building out piers to carry the stream out to the sea because these creeks are often blocked at their mouths by sand bars, and so the stream meanders along in a line parallel to the coast forming a swampy delta before it finds an outlet for its waters. Canals are also made to prevent lagoon formation. Rice fields are drained periodically; this simple method removes their dangerous larvæ effectively. The numerous fishponds in which fish are bred for profit were also rendered innocuous by making proper canals and sluice gates, through which the water could be drained off occasionally, and the aquatic plant which half filled these ponds, and afforded security for larvæ, killed and removed by drying.

XII.—General Conclusions.

In addition to the above summaries of the subjects listed in the Course, there was also instruction given in the form of cinematograph films, demonstrations, pamphlets, papers and discussions.

The course of study as a whole was a most interesting one and of great value to anyone concerned with tropical medicine. As will be seen from the syllabus it was very intensive, but this was due to the comprehensive
nature of it and was no hardship as the lecture rooms and laboratories of the Medical College were so well adapted for their purpose in this climate.

The League's professed object in establishing the Course was to make malariologists of those who attend it, and for those who aimed so high, there could be little time for idleness or rest during the few weeks available. With only one or two exceptions the class consisted of malaria research workers and medical officers of health, who were selected by their countries or governing bodies to attend the Course. As was fitting, the class was international in nature and was composed of some 8 British, 2 Australian, 2 French, 2 Siamese, 2 Japanese, 2 Chinese, 5 Indians, 2 Straits Indians, 2 Straits Chinese Medical Officers, and 1 Chinese lady doctor.

My own object in applying for permission to attend the Course was a limited one. I had recommended a number of subsoil drainage schemes to the C.R.E. for the Changi area, then in process of extending, and I wished to learn the principles of anti-malaria subsoil drainage and their application, so that I could see these schemes carried out to the best advantage. That the course took me further afield I hold to have been no misfortune. One of the cinematograph films I mentioned above was produced by the Health Department of the Singapore Municipality and showed this drainage being carried out in all its aspects. Through the kindness of the Deputy Health Officer (Dr. Dawson) I was enabled later to take with me all the Royal Engineer officers, foremen of works and native overseers of labour who are concerned in the carrying out of these subsoil drainage schemes in Changi to see this film, and this demonstration was undoubtedly of benefit to both them and myself.