forward to a defatted vaccine of *Bacillus leprae*, which procedure has been made hopeful by the recent work of Professor Dreyer.

I am indebted to Dr. Lobo, the late resident medical officer of the hospital, who carried out the treatments and recorded the notes of the cases.

THE CURATIVE DOSE OF ANTIMONY TARTRATE IN SCHISTOSOMIASIS (BILHARZIA DISEASE).

BY

J. B. CHRISTOPHERSON, C.B.E., M.D., F.R.C.P.,
ASSISTANT PHYSICIAN TO THE CITY OF LONDON HOSPITAL FOR DISEASES OF
HEART AND LUNGS, VICTORIA PARK; LATE MEDICAL DEPARTMENT,
SUDAN GOVERNMENT.

I RECEIVED recently from Africa the account of a series of 103 cases of *Schistosoma haematobium*, including one of *S. japonicum*, treated by intravenous injections of antimony tartrate. It raises questions of general interest and presents some points needing comment, therefore I venture to write a few words about the treatment.

The case of *S. japonicum* quoted was a man of 39 who had had the disease for thirteen years. He was apparently cured by a total of 20½ grains of antimony tartrate administered in thirty-one days; as it was impossible to keep him under observation, no definite conclusion regarding the permanency of the cure for *S. japonicum* could be drawn. (Two years ago the same investigator had another case of *S. japonicum* certainly cured by injections of antimony tartrate. The man was seen later in England and the cure fully investigated.)

Of the remaining 102 cases, 5 were of 10 years and under; 30 of 11 to 15 years; 27 of 16 to 20 years; 40 over 20 years. Of this total, 23 "failed to cure"—in other words, living ova were found in the urine after the injections.

In cases of "failure to cure" the question which immediately occurs to one is, How much antimony tartrate was given? None of the 23 cases of "failure" in the series had more than 13½ grains. One had only three-quarters of a grain, others had totals of 1½, 2, and 2½ grains only. Three "failures" were under 11 years of age; they had 8½, 3/4, and 2½ grains respectively. The "failures" of over 20 years—adults (four)—had a total of only 10½, 7, 12½, and 2 grains respectively. A cure could hardly be expected in any of the 23 cases because none had a complete course.

The question thus arises, What is a full or complete course of antimony tartrate for schistosomiasis in adults? In discussing this point two things should be remembered:

1. Bilharzia is a multiple infection—as many as, or even more than, 400 worms are sometimes present in the portal veins of a patient. These worms, although they are the same age (unless reinfection has taken place), have different longevities and resistances. Some die every year; those endowed with the greatest longevity live longest. Some are killed by small doses of antimony tartrate, whilst others are more resisting and require larger doses. The "curative" dose in any case of bilharzia is therefore the amount required to kill the most resisting worm present.

2. During or shortly after a course we have no means of ascertaining whether all the worms are dead. If live ova are present in urine or faeces, at least one worm is alive. Therefore, in cases where live ova are found after treatment, the length of the interval between treatment and re-examination is immaterial, because if the worms are not killed during treatment they are unlikely to die afterwards. But when no ova, or only dead ova, are found in the case of a "cure," it is important to state after what interval re-examination is made, because the effect of the antimony is to stop the automatic movement of deposited ova, preventing live ova appearing in the urine. Ova granular or not present does not necessarily mean that the worms are dead—their activities may be temporarily suspended by the drug, and on recovering they will become active again, after a month, three months, nine months, etc. It is not possible to state definitely that a permanent cure has been made until a year has elapsed, but it is impossible in Africa to examine all cases after a year. A good idea may be formed after three or six months, but it is not conclusive. The complement fixation test and eosinophilia are of no

practical value for diagnosis of life or death of the worms during treatment. Microscopic examination is only of precise value where live ova are found.

So we are reduced to a degree of empiricism with regard to treatment of bilharzia disease. By experience we know that some adult cases are cured permanently by a total of 20 grains given during a period of twenty-eight days; a greater proportion are cured by a total of 25 grains; and only a very few cases are not cured after a course of 30 grains. Therefore 30 grains administered over twenty-eight to thirty days remains the curative (adult) dose. I have seen one case of long standing which required a modified second course after 30 grains, but I believe such cases to be rare, especially in recently infected cases in Africa.

There was, no doubt, a good reason why the full course was not given in any of the 23 "failures" in the list. African patients frequently will not attend for treatment after they themselves think they are cured—that is, when the urine becomes clear and the pain has disappeared. Occasionally a course of treatment must be discontinued owing to "bad arm," or, less often, owing to toxic manifestations. A few patients cannot take antimony owing to idiosyncrasy; others cannot take a full single dose (2½ grains), and some cannot take a full course of 30 grains, but these are exceptional and more commonly met with in England than among African natives. A total dose of 30 grains of antimony tartrate (adult dose) may be considered large, and a month or six weeks a long time for a cure. In time no doubt a remedy will be produced which will act by smaller dose in a shorter period; but in the meanwhile it must not be forgotten that many patients who come for treatment have had the disease for some years; without treatment it would last for five, fifteen, twenty, or more years, with the risk of serious complications always present.

Notwithstanding the exceptions mentioned, however, it does not seem fair to classify as "failure to cure" cases which have in no sense received a full course of treatment and in which live ova continue to be present. The class "failure to cure" should be reserved to failure after a complete course, and not used in cases where, for some exceptional reason, the complete course has not been given; only failure attributable to the drug itself should be classified "failure to cure."

THE SIGNIFICANCE OF THE DIFFERENTIAL COUNT.

Eosinophilia.

In tropical medicine eosinophilia is regarded as a sign of helminth infection; it must not be forgotten that it is not exclusively so. In England, where examination of faeces is not yet regarded as of so great importance as in tropical countries, eosinophilia would probably suggest asthma, a chronic skin disease such as psoriasis, or maybe spring catarrh. The difficulty in Africa, however, lies chiefly in the fact that a patient may have several different helminths, including bilharzia, each causing an eosinophilia; so until other helminth infections are excluded eosinophilia in bilharzia disease is unreliable, for they as well as bilharzia may be causing it.

The helminths do not themselves directly produce eosinophilia. When it is present it is a sign that the body tissues are responding (against the toxins of the helminths). Recent cases of bilharzia disease as a rule show a higher eosinophilia than cases of long standing, but heavy infections of bilharzia are not always accompanied by eosinophilia, and slight infections are sometimes accompanied by a large eosinophilia. Eosinophilia means tissue response.

Some chronic cases of bilharzia in British pensioners who had had the disease for twenty years we found had only a scanty infection and a heavy eosinophilia, while some of the heavy chronic infections had none. Some patients who had none before acquired eosinophilia during treatment, no doubt owing to the tonic effect of the antimony, the body responding to the treatment. One case, infected in 1901, had in 1921 eosinophilia 18 per cent.; during treatment with antimony tartrate 42 per cent.; after treatment eosinophilia dropped down to 3 per cent.†

* Patients who cannot take antimony at all may be given emetine. Emetine is more toxic than antimony tartrate in the large doses necessary in bilharzia disease, and its after-effects are certainly more serious. Cardiac weakness and peripheral neuritis are fairly common after-effects.

† Cases infected in 1900, 1901, and 1903 gave in 1921 18 per cent., 16 per cent., 15 per cent., and 12 per cent. eosinophilia; while several war cases gave no eosinophilia when counted in 1921, although ova were present in the urine. During treatment eosinophilia appeared in some of the latter cases and increased as the course proceeded. One man infected in 1902 had no symptoms or ova in the urine in 1921, but he gave a 14 per cent. eosinophilia; he had no other helminth infection.

Similarly large mononuclear increase in malaria means tissue response to the malaria parasite. Absence of a large mononuclear increase is not a sign that malaria is not present; it is simply a sign that the patient is not reacting.

Both large mononuclear increase in malaria and eosinophilia in bilharzia are indications of the response of the tissues—both are signs of good omen, but neither is a specific sign. Absence is in neither case a reliable sign that either malaria in the one case or bilharzia in the other is absent.

The Complement Fixation Test.

The complement fixation test for bilharzia is diagnostic of bilharzia disease—it is not always present. It cannot be used as a test for the presence of live bilharzia during treatment—(1) because it is difficult to obtain antigen in many places; (2) like eosinophilia the test remains positive for some time after the elimination of the worms. In short, there is no method of deciding when the worms are all dead during the treatment with antimony tartrate. The worms* probably die during all stages of treatment, a small total number of grains killing the less resisting and a larger total amount the more resisting.

The curative dose is the amount which will kill the most resisting worm (this is approximately 30 grains, given in about twenty-eight days). Adult patients should therefore be given this dose, and the few who require more than this should have another modified course later, when the remaining worms become active again, as indicated by live ova in urine or faeces. The fact that the symptoms have cleared up and no ova (or no live ova) are found in the urine is in itself no indication to suspend injections until the full dose has been given.

Antimony tartrate commences to stop the ova appearing in the urine at about 5 grains. At 10 grains some of the ova which appear in the urine are dead. The antimony tartrate acts on the ovum (the motor mechanism) first, and also affects the worm so as to suspend its egg-producing activities; but the worm is not killed till later—if too little antimony is given it recovers and recommences egg laying, and hence a relapse takes place after an apparent cure.

Cases are sometimes reported in the medical periodicals (and these are more frequent now owing to more complete examinations of patients) of vesical bilharzia where there is also rectal bilharzia with papillomata, both due to *Schistosoma haematobium*, or it may be to *S. haematobium* and *S. mansoni* in the same patient. It would be interesting for those who have the opportunity to make examinations and take specimens of the rectal papillomata at intervals to watch the local effect of the injections of antimony tartrate.

KANGRI-BURN CANCER.†

BY

ERNEST F. NEVE, M.D., C.M., F.R.C.S. EDIN.,
SURGEON, MISSION HOSPITAL, KASHMIR.

SINCE the year 1881 operations for epithelioma performed in the Kashmir Mission Hospital have numbered 2,491; of these approximately 2,000, or 84 per cent., were for kangri cancer. The kangri is an earthenware bowl five or six inches in diameter, surrounded by basket-work and surmounted by a wicker handle. It is heated by means of wood-charcoal, and is worn, by the poorer class of Kashmiris, against the skin, under a single loose garment not unlike a smock-frock. The primary factor in the causation of kangri cancer is, doubtless, heat, but it is possible that the volatile substances resulting from the combustion of the wood play a secondary part. The seats of election of the growths are the inner sides of the thighs and the anterior surface of the abdomen above or below the umbilicus. The disease is considerably commoner in men than in women, probably owing to the less continuous use of the kangri by the latter in their mostly domestic occupations. The average age for the onset of the cancer is 55; in a few cases it occurred before the age of 40, and in 7 per cent. of the cases over the age of 70. Many elderly

Kashmiris show a great tendency to localized superficial overgrowth of the epithelium; small, slightly scaly, pigmented patches or papules may be found scattered over the entire surface of the body. Owing to the constant application of heat the skin of the thighs and abdomen often appears dry and horny, the course of the superficial veins is marked out by a brown discoloration, and every degree of chronic dermatitis may be met with, from a mere redness, with or without desquamation, to thickened patches, warty projections, or horny outgrowths from the surface. Scars, resulting from previous kangri burns, are frequent, and are apt to undergo a malignant change.

Kangri-burn cancer is never found on the back or on the extensor surface of the limbs. It may be single or multiple, and the skin around it usually shows scarring. In the early stages ulceration is absent, and the growth consists of a mere horny or warty thickening, beneath which an epithelial infiltration is demonstrable microscopically. The cancer is met with in three forms, the commonest of which consists of a circular or oval ulcer about an inch and a half in diameter, with deep crater-like centre and raised edges. In some cases part of the tumour is fungating and the rest deeply excavated. In a somewhat less common form the growth consists of a cauliflower excrescence, which may project one or two inches from the surface and measure three or four inches across. A less usual form, which occurs generally in the aged, consists of an excavation with very little evident sign of overgrowth. It presents small or large ulcerated areas with irregular steep edges, in places undermined, and a rugged floor rendered uneven by deep recesses.

These cancers are always very foul and the skin around is sodden with septic discharge, which dries and becomes adherent at the margin of the growth and to some extent on the surface. The glands are usually involved in cases in which the ulceration is advanced. In cancer of the thigh they are affected generally in the following order: those along the internal saphenous vein, deep in Scarpa's triangle, near the spine of the pubis, transversely below Poupart's ligament, and, in advanced cases, the deep femoral and external iliac glands. In cancer of the abdominal wall the inguinal and then the external iliac glands become involved if the growth is below the umbilicus, the anterior axillary glands if it is above that level. In more advanced cases the deep glands beside the axillary vessels may become infected. The subscapular glands are rarely involved, but occasionally small glands are found across the side of the chest from the epigastrium to the axilla. The glands frequently attain the size of a pigeon's egg and often soften early. When they break down diffuse infiltration results. The overlying skin becomes red and brawny, and finally gives way from suppuration. A secondary deposit in this condition presents an appearance similar to that of the primary growth, except that the ulcer is deeper and the subcutaneous tissues are infiltrated. There is an abundant foul discharge, and after months of suffering the patient dies of exhaustion, septic intoxication, or haemorrhage. In the case of such deposits in the groin or axilla, the femoral or axillary artery may be perforated by ulceration comparatively early in the course of the disease.

The average duration of life in kangri-burn cancer is about fifteen months; in about 10 per cent. of the cases, from one to five years; and, as an exceptional event, as long as twenty years. The malignancy varies. As a rule a small growth, if superficial, is slow to grow and still slower in infecting the glands. There are, however, striking exceptions, and at times a slowly growing tumour will suddenly show a rapid increase. More than 50 per cent. of the cases show secondary infection of the glands when first seen.

In operating on cases of kangri-burn cancer the glands should be dealt with in the first place, because the primary tumour is always septic. The glands also are likely to be septic and require careful handling during removal in order to avoid rupture. Small glands are apt to escape notice, especially the external pubic group and those in the axilla in cases of epigastric growths. In order to avoid septic contamination of the operation wound during removal of the primary tumour the surrounding skin should

* The fact that some cases of bilharzia disease are cured by quite a small dose of antimony tartrate, whilst others require a total of 20 to 30 grains, is explained by the fact that the power to resist antimony tartrate varies in different worms. This may be also the explanation of the varying opinions about the curative dose.

† In order to ensure the publication of Dr. Neve's clinical observations this paper has been curtailed by the omission of certain paragraphs discussing general questions.