microscopical examination (even a hasty one, without waiting for a sediment to form and without the help of the centrifugal machine) may prove of extreme value. At examinations for appointments and life assurance the discovery of minute quantities of blood, not sufficient to produce any reddish coloration of the urine, may lead to the detection of renal tuberculosis, as in the case of a young man whom I recently examined for a clerkship. In such cases the correct diagnosis must of course be confirmed by special examinations, such as by cystoscopy and by catheterizing the ureters, to see if only one kidney is affected. On repeated examinations in cases of this class the urine may sometimes be found apparently free from albumin (by the ordinary boiling and acidifying test), though its slight opacity when freshly passed should lead to a microscopical examination being made. On rare occasions, in such cases, even the slight obvious opacity may temporarily be absent from urine, which by microscopical examination of the centrifuge sediment is found to contain minute quantities of blood or pus.

I understand from Dr. Lister (though I have not observed it myself) that the urine at the commencement of an attack of gonorrhoea (congestive stage) may sometimes contain a little albumin even before the appearance of any purulent discharge.

After the subsidence of an attack of haematuria of uncertain causation the presence of a little pus in the urine by microscopical examination may indicate grave disease, such as a malignant tumour involving the pelvis of one kidney.* This whole subject, however, I need not further discuss here.

ON THE ACTION OF CERTAIN SPECIAL PREPARATIONS ON MALARIAL PARASITES AND THEIR EMPLOYMENT IN THE TREATMENT OF MALARIA.

BY

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THESE investigations were carried out at No. 4 General Hospital, S.A.M.C., Roberts Heights, during 1917-19 on malarial patients invalided from the German East African campaign. The majority of the cases were of a severe type, associated with marked anaemia and debility, numerous relapses occurring in hospital while under quinine treatment (25 to 30 grains daily). Of 8,788 hospital cases 61 per cent. showed benign tertian parasites in their peripheral blood, 23 per cent. malignant subtertian, 16 per cent. both benign tertian and malignant subtertian parasites. The average period in hospital and convalescent camp of these cases was fifty-one days, during which time the blood was examined at weekly intervals and the patients kept on routine daily quinine treatment. Parasitological relapses occurred during this period of observation in 24 per cent. of the benign tertian cases, 11 per cent. of the malignant subtertian cases, and 39 per cent. of the mixed infections. The circumstances under which these cases contracted malaria (a particularly strenuous military campaign in the tropics) suggested a special terminology to meet this resistant clinical condition—namely, "campaign malaria," which apparently owes its intractability to repeated reinfection associated with severe physical strain in unacclimatized individuals only partially protected from a tropical climate and frequently insufficiently supplied with suitable food.

The frequency with which relapses occurred and the slowness with which these patients recovered a condition of good health emphasized the importance of testing any

remedy which might cut short the period of treatment necessary and reduce the number of relapses. Accordingly these investigations were initiated, with the object of providing if possible a more effective treatment. It is not proposed to deal in this paper with the comparative studies made of the results of treatment of different infections with varying doses of quinine administered by the oral, intramuscular, and intravenous routes. The practical outcome of this work, however, was the adoption of a standard treatment for all average cases of malaria. This treatment consisted of 30 grains of quinine in solution by the mouth daily for three weeks, followed by 20 grains daily for one month and subsequently 10 grains daily for two months.

NEO-SALVARSAN, SALVARSAN, NEO-KHARSIVAN, KHARSIVAN, GALYL.

In view of the debilitated condition of many of the cases selected for treatment it was necessary to exercise the greatest care in the employment of these toxic preparations. Accordingly the patients were specially prepared, and the dose of the "606" preparations employed was invariably about half that dose commonly used for the treatment of syphilis (neo-kharsivan, neo-salvarsan, 0.45 gram; salvarsan, kharsivan 0.3 gram; galyll 0.2 gram).

Until some experience of these preparations had been obtained in malarial patients it was customary at first to give intravenous injections at weekly intervals. Subsequently, however, it was found that intravenous injections could with safety be given on alternate days for three or four injections, and in one of the cases reported in this series fourteen intravenous injections of 0.2 gram galyll were administered during an inclusive period of twenty-two days, as many as five injections being given on successive days without any obvious harmful effects.

During the past three years some thousands of intravenous injections of these preparations have been administered in malarial subjects without a single fatality. It is therefore clear that the employment of intravenous injections of the above preparations in malarial subjects is not attended by any appreciable or special risk, provided the doses and methods recommended are used and the precautions enumerated are fully observed.

Apart from the general contraindications in regard to the employment of these preparations commonly recognized when considering the treatment of syphilis, it is necessary specially to consider the following points in regard to the employment of these preparations in malarial subjects.

(a) *Tachycardia and Dilatation.*—These are symptoms of the disease resulting from anaemia and toxæmia. They improved, however, rapidly as a result of intravenous injections of salvarsan and galyll, and in 154 cases subjected to this treatment, the majority of whom had some cardiac embarrassment, not a moment's anxiety on this score was experienced.

(b) *Pyrexia.*—Some observers have held that following an injection of "606" or galyll the temperature often rises 1 to 1.5 degrees, sometimes accompanied with slight rigor, nausea, and vomiting as part of the general reaction to the drug. In a series of over 790 injections these phenomena were observed only seven times with the above doses.

(c) *Renal Complications.*—As these drugs are toxic, it is necessary for the patients' safety that they should be eliminated fairly rapidly. Where, therefore, there is a history of recent nephritis, or where the symptoms of such a condition are present (albumin, oedema, etc.) an injection should not be given.

(d) *Gastro-intestinal Conditions.*—As vomiting is also a fairly frequent symptom of reaction after injection, severe vomiting, diarrhoea, or obstinate constipation should be corrected before an injection is given.

Preparation of the Patient.

Sufferers from malaria should have complete rest in bed for at least twenty-four hours before an injection. Their diet should be light and easily digested during this period. The bowels should be opened either by a purgative pill (for example, pil. hydrarg. coloc. co. with hyosc.) the previous night, followed by saline (mist. alba) the following morning or by an enema in the morning before injection. A light breakfast—one egg, two slices of toast, and one cup of tea—given at least four hours before injection, may be allowed, but no food should be

* In one such case, a man, aged 35 years, under my observation in 1918, the patient (owing to some mistake) was forced to join the army, but was soon transferred to a military hospital and then set free. He died in March, 1920, and the post-mortem examination showed a malignant tumour and pyonephrosis of the left kidney, with secondary tumours elsewhere in the body. This was Case II in a paper which I published (in regard to another subject) in the *International Clinics*, Philadelphia, 1920, series 30, vol. iii, pp. 43-51.

given again till four hours after the injection, when a cup of tea with a slice or two of bread-and-butter may be taken. A complete meal should not be allowed until next day. A sample of urine of the preceding twenty-four hours should be tested on the morning before injection, and if this is found to contain albumin or sugar the injection should not be given.

Considering the small doses that are advocated in these cases the above precautions may seem excessive, but in view of the great debility of these patients and the frequency of dosage advocated, it is important to carry out such preparatory measures if untoward incidents are to be avoided.

Reactions.

Some of the reactions have been alluded to. With such small doses, 0.2 or 0.3 gram, anything approaching a marked reaction has not been seen. A few cases complained of congestive headache. In 650 injections of galy, only on one occasion was an actual rigor observed to follow an injection, and as in this case a tertian paroxysm was expected on this day, it was in all probability quite unconnected with the injection. Vomiting was observed in one case in which 0.5 gram salvarsan had been given.

Results.

The total number of patients treated for purposes of investigation was 154. The clinical action of "606" preparations may be considered under the following headings:

1. *Nervous*.—Headache frequently disappeared not to return even with subsequent rigors.
2. *Pyrexia*.—Where rigor and pyrexia followed an injection at the usual period of the vegetative cycle of the parasite they were invariably milder in degree, and frequently aborted—in fact, experience has shown that these drugs are of considerable diagnostic value in differentiating the two main types, benign and malignant, the former being almost invariably aborted.
3. *Tonic Effect*.—Generally speaking, the tonic effect of "606" preparations is well marked, and rapidly becomes apparent; anorexia, lassitude, and debility soon give way to a feeling of well-being, while tachycardia and shortness of breath, consequent upon anaemia and cardiac dilatation, rapidly improve.
4. *Spleen*.—Splenic enlargements under the influence of these drugs disappear with remarkable rapidity.
5. *Liver*.—In cases where enlargement of the liver was marked with icterus of skin and conjunctivae, rapid improvement has generally followed a single injection, bilious vomiting, furred tongue, and foul breath clearing up within a short period.
6. *Lungs*.—A number of men with malaria were admitted suffering from a dry bronchitis with severe cough. It was noted that rapid improvement followed an injection, though the same frequently occurred after a few doses of quinine had been taken.

Action of "606" Preparations on Malarial Parasites.

1. *Benign Tertian Malaria*.—As a result of numerous observations on the blood after intravenous injections with the above preparations in the doses advocated, without any other medicinal treatment, it was definitely determined that "606" preparations exert a marked parasitocidal action on the benign tertian parasite. Thick blood smears showing numerous parasites commonly become negative within twenty-four to thirty-six hours. No appreciable difference was observed in these different "606" preparations, the result of treatment being closely similar in each case. The action of these preparations is closely analogous to the action of quinine, although "606" preparations appear to be more active and to produce much more rapid effects, especially in chronic resistant infections associated with enlarged spleen and marked anaemia.

2. *Malignant Subtertian Malaria*.—The action of "606" preparations on tropical malaria exhibits a very marked difference from their action on benign tertian malaria. Observations showed that "606" preparations have no definite parasitocidal action on any stage of the malignant subtertian parasite. When employed, however, in association with quinine, these preparations appear to render the parasites more vulnerable to the action of quinine, the

infection being controlled and cured with smaller doses of quinine than would be required without these preparations. The employment of "606" preparations in malignant subtertian malaria appears to be specially indicated in resistant infections with marked anaemia and cachexia, owing to their action in breaking down resistance to quinine and their tonic effects.

Relapses.

The selective action of "606" preparations for benign tertian infections is very marked. In spite of this, relapses are common even when this preparation is combined with quinine treatment. Total eradication is doubtless possible with "606" preparations alone in early simple infections, but the majority of the cases treated were chronic cases resistant to treatment, of which a considerable number relapsed even while under treatment in hospital. Relapses, however, are much less frequent when several injections are given on alternate days in addition to quinine treatment.

It is not possible with "606" preparations alone to effect Ehrlich's *therapia magna sterilisans* except in the earliest infections. Freedom from relapses and total eradication of the infection cannot therefore be promised after treatment with numerous intravenous injections of "606" preparations.

In malignant subtertian malaria quinine must be employed in addition, as "606" preparations have little direct destructive action on the parasites. When these preparations are used in addition to quinine the action of the latter is intensified, and the progress towards recovery is much more rapid.

Detection of Parasites.

The thick smear was always employed in searching for parasites in the peripheral blood; it is a rapid and efficient method of controlling the results of treatment. It is possible to demonstrate parasites easily by this method when it may be impossible to find them on examination of thin films even after a prolonged search. Using this method it was found that in 4,043 cases of malaria admitted into hospital with positive thick smears, 23 per cent. showed parasites persisting in the blood on the eighth day of treatment with an average daily dose of quinine of 23 grains. The average persistence of parasites in thick smears in these cases was nineteen days. This fact indicates the severe nature of the cases and demonstrates the slow action of quinine in reducing heavy infections in markedly debilitated individuals. Resistant benign tertian infections responded readily to "606" given intravenously together with quinine by the mouth owing to the parasitocidal action of "606" on the benign tertian parasites. Intramuscular injections of soamin and quinine orally offered no advantage over quinine and inorganic arsenic in these resistant cases, as the following statistics indicate:

Results of re-examination of blood, after an average interval of eight days, in cases of benign tertian malaria, positive on first examination—34 cases treated with quinine and an average of one injection of "606"—compared with 3,171 cases treated with quinine only, and 44 cases treated with quinine and an average of two injections of soamin. In the 44 cases treated with quinine and soamin the blood was re-examined after an average interval of 6.5 days.

	Quinine + 606.	Quinine.	Quinine and Soamin.
Number of cases positive on first blood examination	34	3,171	44
Number positive on re-examination	Nil	710	10
Percentage of cases positive on re-examination	Nil	22	22.7
Average daily quinine (grains) in interval before re-examination	11.6	23.2	23.6
Average persistence of asexual forms in cases positive on re-examination	Nil	19	19.2

Mixed Infections.

The failure of treatment with "606" preparations alone to prevent relapses in mixed infections, even when the treatment is pushed, is shown by the following cases:

Case 1.—Mixed infection (benign tertian and malignant tertian). Intravenous injections of 0.20 gram galy on the 1st, 2nd, 3rd, 4th, 6th, 7th, and 8th days. Parasite relapse of

malignant rings on the 16th day, and benign tertian parasites together with malignant rings on the 24th day. A few crescents were also found on the 21st day. No other treatment given.

Case 2.—Mixed infection (benign tertian and malignant tertian). Intravenous injection of galyi 0.35 gram on the 1st day. Parasite relapse of benign tertian on the 12th day. Further injections of galyi 0.20 gram on the 17th, 19th, 21st, 23rd, 25th, 29th, 31st, and 33rd days. Parasite relapse on the 39th day of benign tertian parasites. Crescents were daily found in the blood from the 21st to the 39th day. No treatment other than galyi given during the period of observation.

Case 3.—Mixed infection (benign tertian and malignant tertian). Intravenous injections of galyi 0.20 gram on the 1st, 2nd, 3rd, 5th, 6th, 7th, 9th, 14th, 16th, and 9th days. Parasite relapse on the 20th day, benign tertian parasites and numerous malignant rings. Crescents found daily from the 5th to the 15th days, and not found from the 16th to the 23rd days. Treatment, galyi only.

Case 4.—Mixed infection. Intravenous injections of galyi 0.20 gram on the 1st, 2nd, 3rd, 4th, 6th, 7th, 8th, 14th, 15th, 16th, 17th, 18th, 20th, and 22nd days. Parasite relapse with numerous malignant rings on the 14th day to the 23rd day. On the 24th day benign tertian parasites were also found. Crescents were found almost daily. Treatment, galyi only.

SOAMIN.

Numerous intramuscular injections of soamin were administered in severe resistant cases of various types of malaria. Soamin exhibits no parasitocidal action on the parasites of either benign tertian or malignant subtertian malaria. Its beneficial action is confined to the breaking down of the resistance of parasites to quinine.

TARTAR EMETIC IN "CRESCENT INFECTIONS."

A small series of twenty-seven cases of malignant subtertian malaria with crescents in finger blood were treated by tartar emetic injections, the total number of injections administered being 137.

No demonstrable effect attributable to the injections was observed on crescents. Even repeated doses of 20 cg. of tartar emetic did not appear to produce breaking down of the crescents in the blood.

No advantage as to the rapidity of elimination of crescents from the blood could be demonstrated between a group of cases treated by quinine only and a group of cases treated by quinine together with an average of five injections of tartar emetic. The most rapid and certain method of eradicating crescents from the finger blood is to treat the patient thoroughly with quinine (30 grains daily). Under such treatment crescents disappear in an average of fifteen days. Supplementary treatment with arsenic and iron is indicated, and in unusually resistant cases intravenous injections with "606" preparations, or intramuscular injections of soamin, are advisable to break down the resistance to the action of quinine, of the "ring" forms from which the crescents arise.

In regard to the prevention of relapses, these have occurred in both benign tertian, malignant subtertian, and mixed infections after treatment with an average of four to six injections of tartar emetic in each infection. Tartar emetic has no demonstrable effect on the asexual forms of the parasites of either benign tertian or malignant subtertian infections, and exerts no influence on the clinical course of the disease.

MERCURY AND ANTIMONY OINTMENT.

A small series of eleven cases were treated with quinine and inunctions with an ointment composed of antimony 2 parts, mercury 30 parts, lanoline 68 parts. About 1 drachm was rubbed in daily for fifteen minutes. Inunctions were continued for an average of twenty-five days. The inunctions did not appear to have any direct action on the parasites or to intensify the action of the quinine which was administered at the same time. No therapeutic effects were observed.

CONCLUSIONS.

1. Neo-salvarsan, salvarsan, neo-kharsivan, kharsivan, galyi, administered intravenously, may be employed with safety in the treatment of all forms of malaria, provided the doses and methods recommended herein and the precautions enumerated are fully observed.

2. These preparations, in the doses recommended, exert a marked parasitocidal action on the benign tertian

parasite, thick blood smears showing numerous parasites usually becoming negative within twenty-four to thirty-six hours.

3. These preparations have no definite parasitocidal action on any stage of the malignant subtertian parasite. When used in addition to quinine, the action of the latter is intensified and the progress towards recovery is much more rapid.

4. Generally speaking, the tonic effect of these preparations is well marked in all cases of malaria; anorexia, lassitude, and debility soon give way to a feeling of well-being, while tachycardia and shortness of breath, consequent upon anaemia and cardiac dilatation, rapidly improve. Splenic enlargements disappear with remarkable rapidity.

5. The employment of these preparations is recommended, in addition to quinine treatment, in chronic resistant infections and malarial cachexia. Three or four injections at weekly intervals are recommended. Freedom from relapses cannot be promised even after numerous intravenous injections. In regard to the preparation of the solutions and technique of administration, the usual methods are followed in each case.

6. Soamin exhibits no parasitocidal action on the parasites of either benign tertian or malignant subtertian malaria. Its beneficial action is confined to the breaking down of the resistance of chronic infections to quinine.

7. Tartar emetic has no demonstrable effect on the sexual or asexual forms of the parasites of either benign tertian or malignant subtertian malaria, and exerts no influence on the clinical course of the disease. The most rapid and certain method of eradicating crescents from the finger blood is adequate quinine treatment (30 grains daily) and arsenic.

8. Inunctions of mercury and antimony ointment do not appear to exert any therapeutic action in malaria.

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Memoranda:

MEDICAL, SURGICAL, OBSTETRICAL.

SPASMODIC HICCUGH.

In view of the recently reported plague of hiccough in Montreal and Paris an account of two cases which have recently come under my care, and are, so far as I am aware, the first cases to be noted in England, may be of interest to your readers.

Case 1.—A man residing near high downland, accustomed to easy open-air life, who had not recently been away from the district, presented as the initial symptoms frontal headache and slight rise of temperature. On the second day a cough developed, and the hiccough first began at the end of a fit of coughing and lasted an hour. In an hour's time another attack occurred, lasting an hour and a half. These recurrent attacks continued for two days. On several occasions the hiccough continued until retching was set up, and, although no material was vomited, the act of retching appeared to stop the hiccough for a time. It was noted that the hiccough was more violently spasmodic than is usual in an ordinary mild persistent attack. The temperature throughout remained at 101° F., and finally dropped by crisis. The frontal headache continued and heavy night sweats occurred. After trying all the usual homely remedies my advice was sought at the end of the first day, and a mixture containing potassium citrate, bismuth subnitrate, tincture of belladonna, and dilute hydrocyanic acid was given every four hours. Very little relief was obtained, and the attack finally yielded at the close of the second day to a mixture of sodium, potassium and ammonium bromide, leaving the patient weak and shaken.

Case 2.—A young man employed in business near the docks. The symptoms differed from those in the previous case in that a smart attack of diarrhoea occurred coincidently with the onset