TABLE 6

STAINING RESULTS [a] (INDIRECT METHOD) AFTER EXPOSURE OF BLOOD SMEARS TO WHOLE ANTISERUM OR GAMMA-GLOBULIN FROM MONKEYS, EITHER INFECTED WITH *P. BASTIANELLII* OR NON-INFECTED CONTROLS, FOLLOWED BY FLUORESCEIN-LABELLED RABBIT ANTIHUMAN GAMMA-GLOBULIN

Smear		Sera			
Parasite	Host	*P. bastianellii* immune serum 227	Control serum	*P. bastianellii* immune γ-globulin 200	Control gamma-globulin
P. bastianellii	Monkey	+++	–	+++	–
P. vivax	Human	+++	–	+++	–

[a] For explanation of symbols see Table 2.

tion of *P. gallinaceum* sporozoites, when labelled, stained the erythrocytic stages of *P. gallinaceum* but not those of *P. bastianellii*.

Fluorescent stippling of the infected red blood cell was a feature common to the mammalian malarias (Fig. 1 and 2) but was not observed in the avian infections (Fig. 3). Tobie & Coatney [d] suggested that the stippling, which they observed in infections of *P. vivax* and *P. bastianellii*, represented Schuffner's dots. In the present work larger fluorescent granules were found in *P. berghei* infections, in which Schuffner's dots have not been shown by Giemsa staining. It is clear that the stippling marks the position of antigenic material in or on the infected host cells.

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Classification of Antimalarial Drugs in Relation to Different Stages in the Life-cycle of the Parasite: Commentary on a Diagram

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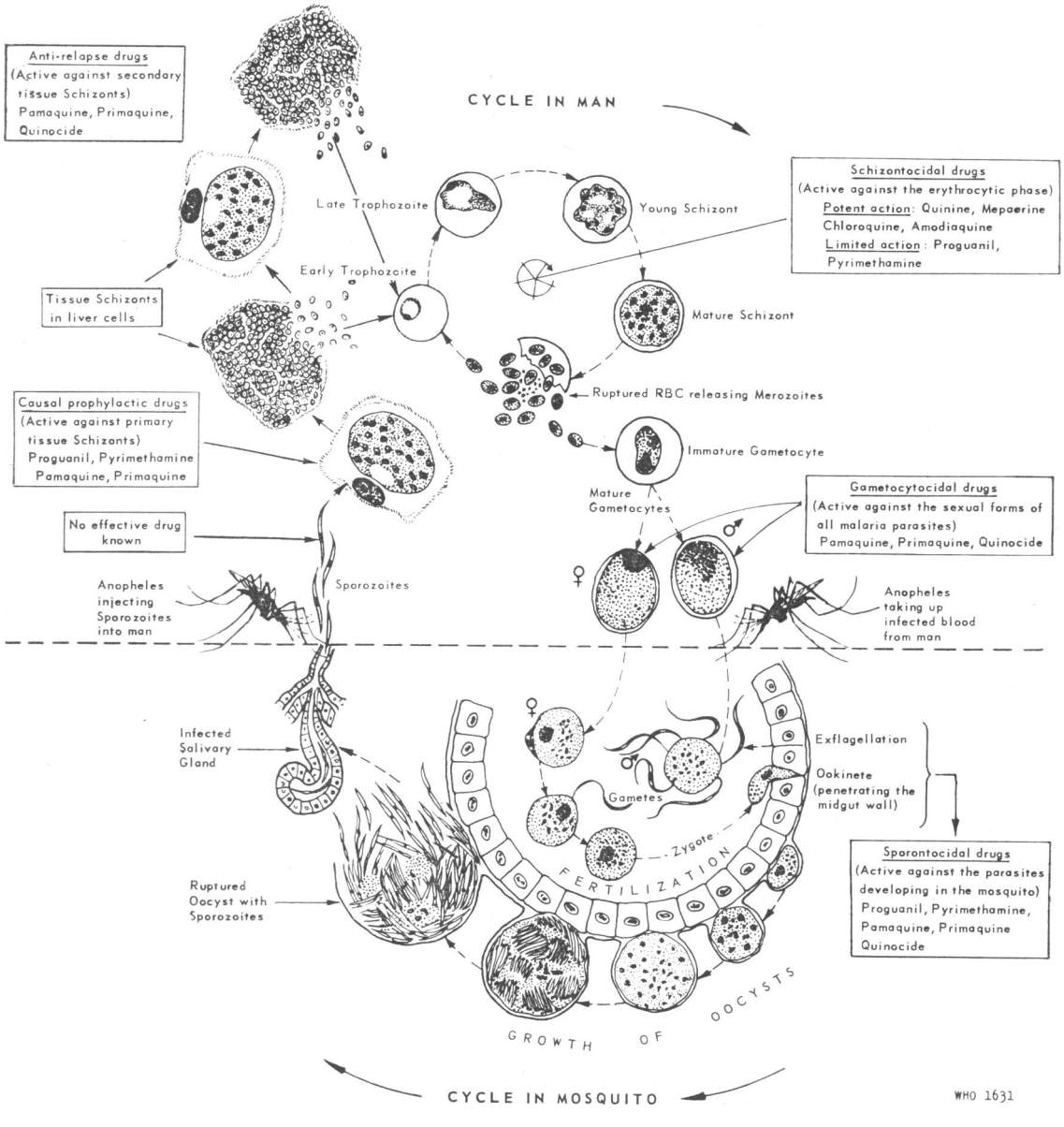
One of the ways of classifying antimalarial drugs is according to their action on particular stages of the life-cycle of the parasite. The teaching of the principles of chemotherapy of malaria can be greatly facilitated by the use of a diagram indicating clearly the rationale of the use of different antimalarials for different purposes, both in the prevention and cure of individual infections and in the two principal phases (attack and consolidation) of malaria eradication programmes.

Such a diagram is shown here, illustrating the classification of the most common antimalarials and accompanied by some comments on these. A number of less known or not generally used compounds have not been included.

All the data concerning the rationale of chemotherapy of malaria, the description of individual compounds in common use, guidance as to dosage and so on will be found in the monograph *Chemotherapy of malaria.* [a] A large amount of recent information on the use of chemotherapy in malaria eradication and on the trends of research in this field

[a] Covell, J., Coatney, G. R., Field, J. W. & Singh J. (1955) *Chemotherapy of malaria*, Geneva (*World Health Organization: Monograph Series*, No. 27).

CLASSIFICATION OF ANTIMALARIAL DRUGS IN RELATION TO THE DIFFERENT STAGES OF THE LIFE-CYCLE OF THE PARASITE



is contained in the report of the WHO Technical Meeting on Chemotherapy of Malaria.[b]

Terms pertaining to the action of antimalarial drugs have now been redefined by a WHO drafting committee on malaria terminology[c] and some of relevant definitions are as follows:

Causal prophylaxis [True causal prophylaxis]: Complete prevention of erythrocytic infection by the administration of drugs destroying either sporozoites or primary tissue forms.

Gametocytocide [Gametocytocidal drug]: A drug which destroys the sexual forms of human malaria parasites. [According to this definition, all antimalarial drugs are gametocytocides because they all eliminate *P. vivax* gametocytes. Gametocytocidal and schizontocidal action should be defined in relation to particular species. The practice of describing the action of antimalarial drugs with general reference to all three species might be confusing.]

Radical treatment [Anti-relapse therapy]: Treatment adequate to achieve radical cure [i.e., complete elimination of erythrocytic stages and persisting tissue stages of the parasite from the body so that relapses cannot occur]. In the case of vivax, malariae and ovale infections, this implies the use of drugs which destroy the secondary tissue phase of the parasite.

Sporontocidal drug: A drug which, when given to the malaria-infected vertebrate host, prevents or interrupts the development of the parasite in the mosquito.

Classification of antimalarial drugs

Taking into account their main action on the relevant stage of the life-cycle of the malaria parasite drugs can be classified into five groups :

Causal prophylactic drugs (primary tissue schizontocides) act on the pre-erythrocytic forms (primary tissue phase) of the malaria parasite. Although primaquine and pamaquine (probably also quinocide) are active on the primary tissue schizonts of *P. falciparum* and *P. vivax* they are not used in practice as prophylactic drugs because of their possible side-effects. On the other hand, proguanil and pyrimethamine are highly active against the primary tissue forms of *P. falciparum* and have some action on these forms of *P. vivax*.

Schizontocidal drugs sensu stricto (blood schizontocides) act on the asexual erythrocytic forms of all species of malaria parasites. Quinine, mepacrine and 4-aminoquinolines such as chloroquine or amodiaquine have a potent and rapid action and are used for treatment and for temporary prevention (suppression) of clinical symptoms. Although proguanil and pyrimethamine have an action on the erythrocytic phase of *P. falciparum* infection, this effect is slow and probably varies in relation to the strain of the parasite. Both drugs (as also chlorproguanil) are particularly useful as suppressants of all species of malaria parasites, especially *P. falciparum*;[d] in the latter case suppressive cure may be achieved.[e]

Gametocytocidal drugs (gametocytocides) *par excellence* are the 8-aminoquinolines, of which pamaquine, plasmocide, primaquine and quinocide are most active on sexual forms of all species of malaria parasites. The last two compounds are much less toxic than the others. Quinine, mepacrine, chloroquine and amodiaquine have an action on gametocytes of *P. vivax* and *P. malariae* but no direct action on gametocytes of *P. falciparum*.

Sporontocidal drugs inhibit the sporogonic phase of development of the parasite in the mosquito. (This effect is also called " anti-sporogonic action " or " gamostatic action " by some workers.) Proguanil, chlorproguanil and particularly pyrimethamine act on the gametocytes of *P. falciparum* and *P. vivax*, rendering them non-infective to mosquitos; with pyrimethamine this effect may last for two to three weeks after a single dose.

Pamaquine, primaquine (and probably quinocide) have the same effect, though the action is somewhat slower and the duration less because of the faster excretion of 8-aminoquinolines.

Anti-relapse drugs or *secondary tissue schizontocides* have a pronounced action on the secondary exo-erythrocytic phase of *P. vivax* and *P. malariae* infections in the liver. The only compounds of high

[b] World Health Organization, Technical Meeting on Chemotherapy of Malaria (1961) *Wld Hlth Org. techn. Rep. Ser.*, **226**.

[c] *Terminology of malaria and malaria eradication*, Geneva, World Health Organization (in preparation).

[d] In some cases proguanil and pyrimethamine can produce a suppressive cure of *P. vivax* infections. Many 8-aminoquinolines show an activity on asexual forms of malaria parasites in the blood but only in doses which are likely to be followed by undesirable side-effects.

[e] *Suppressive treatment* (suppression, chemosuppression, clinical prophylaxis, chemoprophylaxis, drug prophylaxis, etc.): treatment the aim of which is the prevention—or elimination—of clinical symptoms and parasitaemia, and which does not necessarily prevent eliminate the infection. *Suppressive cure*: complete elimination of the parasite from the body while the patient is receiving continuous suppressive treatment.

activity are pamaquine, primaquine and quinocide. They effect radical cure of all relapsing infections and are usually administered after the treatment of the primary attack, though they can also be given during a relapse or at the time of latency. The completeness of the curative effect in vivax infections depends somewhat on the strain of the parasite.

Primaquine and quinocide are better supported and have fewer side-effects than pamaquine or plasmocide.

Primaquine and Quinocide as Curative Agents against Sporozoite-induced Chesson Strain Vivax Malaria

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Primaquine, 8-(4-amino-1-methybutylamino)-6-methoxyquinoline, was synthesized by Elderfield (1946)[c] and its pronounced effectiveness as a curative agent against Chesson strain vivax malaria was demonstrated by Edgcomb et al. (1950).[d] In military installations in the USA it was highly effective for the radical cure of Korean vivax malaria (Garrison et al.;[e] Alving et al.;[f] Coatney et al.[g]). It was first used on a large scale when the US troops returned home from Korea by ship. Over 330 000 men each received a single 15-mg (base) dose, daily, during the 14-day Pacific crossing. The regimen was highly successful in preventing the introduction of this malaria into the USA (Archambeault [h]). The total American experience resulted in a regimen which is generally accepted throughout the world for the radical cure of vivax malaria, i.e., a single 600-mg (base) dose of chloroquine or the standard 1500 mg (base) given over 3 days, to remove the circulating asexual parasites responsible for the illness, followed by primaquine, 15-mg (base), single dose, daily for 14 days. The 14-day regimen permitted a relapse rate of less than 1% against vivax malaria of Korean origin (Alving et al., *loc. cit.*). There is, however, a paucity of such data against the Chesson strain. The senior author carried out the first part of this study in 1956 with 24 white male volunteers infected by the bites of 10 heavily infected mosquitos. When an infection became patent, the subject was given a single 600-mg (base) dose of chloroquine followed by the standard 14-day primaquine treatment. Of the 24 subjects, nine (36%) exhibited an initial relapse, three (12.5%) had a second attack, and one (4%) had a third attack during an observation period of over two years.

In 1949, Elderfield [i] synthesized another 8-aminoquinoline with the methyl group in the 4-position of the aliphatic side-chain, in contrast to primaquine where the methyl group is in the 1-position, and identified it as CN-1115. It did not receive an early trial in man because toxicity tests in rhesus monkeys showed its toxicity was approximately equal to that of pamaquine.

The Russian chemists Braude & Stavrovskaya [j] synthesized the same compound in 1952 and gave it the name quinocide. In 1955, investigators in the

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[c] Elderfield, R. C., Gensler, W. J., Head, J. D., Hageman, H. A., Kremer, C. B., Wright, J. B., Holley, A. D., Williamson, B., Galbreath, J., Wiederhold, L., Frohardt, R., Kupchan, S. M., Williamson, T. A. & Birstein, O. (1946) *J. Amer. chem. Soc.*, **68**, 1524.

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[f] Alving, A. S., Hankey, D. D., Coatney, G. R., Jones, R., jr, Coker, W. G., Garrison, P. L. & Donovan, W. N. (1953) *Amer. J. trop. Med. Hyg.*, **2**, 970.

[g] Coatney, G. R., Alving, A. S., Jones, R., jr, Hankey, D. D., Robinson, D. H., Garrison, P. L., Coker, W. G., Donovan, W. N., DiLorenzo, A., Marx, R. L. & Simmons, I. H. (1953) *Amer. J. trop. Med. Hyg.*, **2**, 985.

[h] Archambeault, C. P. (1954) *J. Amer. med. Ass.*, **154**, 1411.

[i] Elderfield, R. C., Mertel, H. E., Mitch, R. T., Wempen, I. M. & Werble, E. (1955) *J. Amer. chem. Soc.*, **77**, 4816.

[j] Braude, M. B. & Stavrovskaya, V. I. (1956) *Ž. obshch. Khim.*, **26**, 378.