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CHEMOTHERAPY OF RODENT MALARIA EVALUATION OF DRUG
ACTION AGAINST NORMAL A. (U) LIVERPOOL SCHOOL OF
TROPICAL MEDICINE (ENGLAND) DEPT OF PARAS. W PETERS

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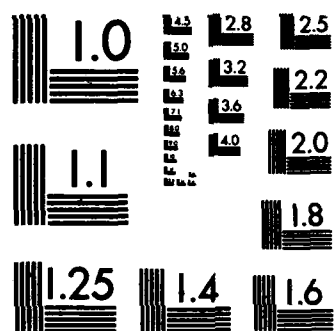
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CHEMOTHERAPY OF RODENT MALARIA
EVALUATION OF DRUG ACTION AGAINST NORMAL AND
RESISTANT STRAINS INCLUDING EXO-ERYTHROCYTIC STAGES

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Final

Summarising Report

by

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1. BASIC QUESTIONS INVESTIGATED

→ (i) New compounds are no

- (*) New compounds are needed for the prevention and treatment of malaria parasites that are resistant to chloroquine and other standard antimalarials, i.e. P.falciparum.
- (14) Safer antirelapse drugs are needed to replace primaquine in the treatment of P.vivax infections.
- (11) In order to open the way to the rational design of new antimalarials more needs to be known of the mode of action of existing compounds, and the manner in which the parasites can become resistant to them.
- (17) In order to answer these questions we need to know more about the matabolic pathways of normal malaria parasites.
- (17) Ways of combating drug resistance by the use of drug combinations are required, especially as a means of preventing the further development of resistance to new compounds.

study

1.1. Chemotherapy

1.1.1. The establishment of in vivo models

A. Blood schizontocides

The work of this group was based on the use of rodent malaria parasites in mice. From an old strain of P.berghei Kyberg 173 (N) lines were derived with resistance to the following compounds:-

RC	highly resistant to chloroquine
NS	low level resistance to chloroquine, cyclically transmissible
PYR	Highly resistant to pyrimethamine
B	highly resistant to proguanil and cycloguanil
ORA	highly resistant to sulphonamides
P	moderately resistant to primaquine

These lines and the drug-sensitive N strain were used to infect random bred Swiss albino mice by the intraperitoneal or, more recently, intravenous inoculation of infected donor blood, in order to evaluate the action of a variety of potential blood schizontocides. The technique employed for this work was the "4-day test" established by the writer in 1965.

Baseline data of drug response were established firstly with the N strain, and subsequently a spectrum of response to the resistant lines was determined as a means of forecasting the potential effectiveness of new compounds against drug-resistant human malaria parasites. Experience has largely confirmed the predictive value of this procedure. (41)

Over the past 12 years we have evaluated some 350 compounds in these models. Recently a line of P.berghei resistant to mefloquine (the 1100-line) was established and added to the battery of resistant lines used for screening.

B. Tissue schizontocides

Cyclically transmitted rodent malaria parasites were required in order to determine whether a compound would exert any action on the pre-erythrocytic stages of the parasites in the liver, on

the assumption that this would have predictive value for (i) true causal prophylactic action against human malaria parasites and (ii) radical curative (antirelapse) action against P.vivax and P.ovale. Three parasites were exploited for this purpose, the NS line of P.berghei, P.yoelii 17X, and P.y.nigeriensis. The mammalian host throughout was the same random-bred Swiss albino mouse. The insect host was Anopheles stephensi, a colony of which has been maintained for this purpose in a special insectary.

The screening procedure (10) developed for this work proved to be simple and efficient with one exception. Compounds that have an inherently long half-life extending beyond the duration of the pre-erythrocytic cycle may exert an effect also on the first generation of erythrocytic merozoites to emerge from the liver. In spite of this limitation on the technique some 300 compounds were examined and the predictive value was found to compare favourably with that of the more complex P.cynomolgi-rhesus model utilised by Schmidt. (42) Data could be compared on a qualitative level although major differences in parasite and host metabolism obviously rendered a quantitative comparison invalid.

C. Long-acting compounds

As a possible means of utilising antimalarials for the protection of large indigenous populations, or smaller defined groups, e.g. military forces, without the necessity of regular and frequent drug administration, compounds or formulations of antimalarials with a very long duration of action are being explored. It was felt that current primary screening procedures might be inadequate to detect inherently long action in a test compound but, rather, might be causing us to gloss it over as inactive, or only of very low grade activity. A screening system was therefore devised (not yet published) which would permit the detection of potential long duration activity, against blood stages of P.yoelii. Work is continuing on an extension of this screen to detect also long duration of action against tissue schizonts. With the aid of this test marked activity has been demonstrated in such compounds as diformyl dapsone (now used as a positive comparison standard drug), the pyridine methanol WR 172435, the phenanthrene methanol WR171669, and a quinazoline WR 180872.

Active steps have also been taken towards developing and testing both single drugs in repository formulations and, recently, drug mixtures. Siloxane rubber implants and certain biodegradable polymer formulations have proved of value in extending the duration of action of pyrimethamine (up to 10 months in polymer) and various sulphonamides. Silastic implants so far have proved less effective than polymers.

1.1.2. Drug combinations

A number of studies were made to determine whether or to what degree the use of drug combinations would overcome the problem of drug resistance in the blood and tissue stages. As anticipated a variety of combinations composed of a dihydrofolate reductase inhibitor together with a sulphonamide or sulphone proved successful. (4, 5, 9, 21, 23) In addition, however, several unexpected types of drug potentiation were discovered. The first of these was a combination of menoctone with cycloguanil (14) the reason for which has yet to be clarified. The second was the combination of chloroquine with erythromycin (45) which was found to have a high level of potentiation against the highly chloroquine-resistant RC line, a lesser potentiating power against the NS line, and no potentiation against the N strain.

1.1.3. Establishment of lines resistant to new drugs

In view of the history of the development of resistance to existing drugs it was obviously important to attempt to predict the ability of malaria parasites to evolve resistance to any promising new compounds that might be developed. Consequently experiments were carried out to induce resistance to a variety of new compounds used singly, and to several different drug combinations. (3, 11, 12) Resistance was found to develop very readily to menoctone, but less readily to the new phenanthrenemethanols and quinolinemethanols. (46, 48) However, when we used as starting material not the drug sensitive N strain of P.berghei but the NS line, P.yoelii, P.y.nigeriensis or other parasites that are partially resistant to chloroquine it was found that resistance could readily be produced to the new compounds. Moreover resistance to compounds such as WR 122455 and WR 142490 (mefloquine) was cyclically transmissible and became stable after a moderate number of passages under drug selection pressure. Such resistant lines were cross-resistant to quinine, although they tended to retain their responsiveness to chloroquine and other compounds (e.g. antifols).

On the basis of these observations we believe it is necessary to use a compound such as mefloquine alone in man with great caution because of the danger that P.falciparum which is already resistant to chloroquine may also become resistant to mefloquine within a relatively short time under field conditions. (40, 47, 48, 52)

1.1.4. The dissemination of drug resistance

One of the puzzling things about chloroquine resistance as seen in P.falciparum is the apparent rapidity with which it seems to be extending geographically. A partial explanation for this was provided by our observations that chloroquine appears to have a stimulatory action on sporogony of strains of P.yoelii the asexual blood stages of which are already resistant to this compound. (6) This observation has since been confirmed in P.falciparum by other workers. The explanation for this phenomenon has not yet been forthcoming. In the past two years also it has been shown by other investigators that chloroquine-resistant asexual blood stages of P.chabaudi have a biological advantage over and overgrow drug-sensitive parasites in mixed infections.

1.1.5. The prevention of drug resistance

It has long been recognised that the combination of chloroquine with pyrimethamine in field use against P.falciparum has not prevented the emergence of resistance to one or both of these compounds, in spite of predictions to the contrary which were based on the assumption that the two drugs have quite different modes of action.

We were able to confirm this lack of mutual protection in a P.berghei model but, on the contrary, could demonstrate that a mixture of mepacrine (7) or chloroquine (28) with a sulphonamide did inhibit the emergence of resistance. Subsequently we examined various drug combinations, including antifols with sulphonamides with and without chloroquine (40) and, more recently, mefloquine (48) in various combinations. These experiments established the value of the model for such long-term studies and showed that one can select (by trial and error at least) appropriate combinations of drugs which will at least greatly slow down the rate at which resistance to a drug will develop. The practical value of such a measure is self-evident.

1.2. Mode of drug action

1.2.1. Chloroquine and chloroquine-like compounds

The first and most conspicuous effect of chloroquine on asexual erythrocytic stages of malaria parasites is a clumping of the haemozoin (malaria pigment). This phenomenon was investigated extensively and forms the basis of a procedure for studying a variety of physiological processes in the parasites. and of comparing the modes of action of antimalarial drugs. (26,31,34,35,43,51) It has been described as the "CIPC" or "Chloroquine-induced Pigment Clumping Test".

This test has proved invaluable for separating in vitro drugs that exert a chloroquine-like effect from those that possess a quinine-like action, and from others that have neither type of activity. The CIPC was also of value in establishing physico-chemical characteristics of the chloroquine binding sites within the erythrocyte-parasite complex, and correlating these with the molecular structure of a variety of antimalarial drugs.(43) The precise nature of the binding sites however has not yet been defined, and work is continuing on this question both in Liverpool and London.

1.2.2. Quinine, quinoline-methanols and allied compounds

Quinine and a variety of drugs with comparable structures retain their activity against malaria parasites that are resistant to chloroquine.. With the CIPC we have shown that such compounds are competitive inhibitors of chloroquine. WR 142490 (mefloquine), WR 122455 and quinine itself appear to share the same binding site(s) as chloroquine but, in addition, have a separate binding site.(36) They exert a different type of action on the haemozoin which results not in a gross clumping of the pigment granules in a single cytolysosome, but in an apparent decrease in the electron density of the granules with the subsequent formation of smaller conglomerations of the residues which are inconspicuous at the light microscope level.(38) Changes are also induced in the nuclear and other membranous structures. Mefloquine and WR 122455 are many times more effective than quinine but otherwise appear to act in precisely the same manner.(46,49) Not surprisingly therefore quinine was found to be inactive against the mefloquine-resistant L/1100 line of P.berghei. None of these compounds has any inherent activity against pre-erythrocytic liver stages of rodent malaria.

1.3 Parasite metabolism

1.3.1. Parasite-induced changes in host cell permeability

Early in our studies on parasite metabolism we found that much of the work of earlier investigators was rendered invalid by their failure to ensure the complete freeing of their preparations from white cells, and from a failure to appreciate the full significance of the presence of host reticulocytes.

Having overcome these technical problems we were able to demonstrate that L-glucose rapidly enters parasitised erythrocytes. but not intact, unparasitised ones.(44) The presence of functional "micropores" in infected red cells would be of obvious benefit for an

intracellular parasite such as Plasmodium, as it would facilitate the passage to the parasite of a variety of metabolites through the "leaky" host cell membrane.

1.3.2. Utilisation of haemoglobin

Intraerythrocytic malaria parasites are known to obtain a high proportion of their amino acids through the digestion of host cell haemoglobin. We were able to demonstrate the presence of parasite cathepsins in red cells infected with P.berghei. (37) A critical analysis of the pigment isolated from the parasites strongly suggested that it did not contain haemoglobin peptide remnants as suggested by other workers, but that it consists essentially of 40% haemin plus about 10 amino acid molecules per molecule of haemin giving a unit molecular weight of about 1000. This unit is probably repeated, perhaps as a polymer to produce a characteristic microcrystalline substance. (39)

1.3.3. Parasite DNA

The buoyant density of the DNA of the rodent malaria parasites is of limited value in separating the different species and subspecies, but the hybridisation of DNA isolated from different lines, plus various cross-immunity experiments, proved invaluable in determining their phylogenetic relationships. Thus, for example, the famous NS line originally derived from an old laboratory line of P.berghei N proved to have very close affinities with P.y.nigeriensis, but not to be identical to this parasite. (50)

Other experiments confirmed that, whereas chloroquine and quinine do intercalate with DNA, mefloquine does not do so. (49) This adds weight to the argument that DNA intercalation is not the prime mode of action of any of these compounds, a point of view that we have always supported.

The pyrimidines thymidine and cytidine were shown to enter infected red cells but they are not incorporated into parasite DNA. Purines on the other hand are readily incorporated. It seems likely that the necessary kinases for pyrimidine uptake are lacking.

1.3.4. Glycolysis and electron transport

The intraerythrocytic stages of rodent malaria parasites produce energy from glucose essentially through the anaerobic Embden-Meyerhof pathway, the terminal product being lactate. Several enzymes belonging to the citric acid Krebs cycle that were previously thought to be of parasite origin have been demonstrated (through isoenzyme characterisation) to be of host cell origin (29, 30), as too are enzymes of the pentose phosphate shunt. We have shown that during the evolution of the macrogamete and its growth in the mosquito, enzymes of the Krebs cycle are "switched on" and the sporogonic stages of the parasites utilise the citric acid cycle fully. (8, 15, 16) This activity continues in the sporozoite but ceases again with the establishment of the pre-erythrocytic schizonts in the liver parenchyma cells. (19)

1.4. Mechanisms of drug resistance

1.4.1. Chloroquine

Highly chloroquine-resistant rodent malaria parasites concentrate this compound to a significantly lesser degree than do drug-sensitive parasites. The fact that pigment is lacking in the highly resistant RC line of P.berghei originally led us to suggest that the high affinity binding site for chloroquine in normal parasites is associated either with the pigment itself or in the pigment vacuole membranes. (20) We suggested that, in normal parasites, chloroquine is concentrated partly by passage up a pH gradient into the relatively acidophilic lysosomal vacuoles that contain the pigment, and that this mechanism is somehow disturbed in resistant parasites, possibly through a mutant affecting parasite membrane permeability to chloroquine. (32) This hypothesis still remains unproven. It is clear however that there is a marked change in the high affinity chloroquine binding sites in resistant P.berghei and the nature of this change is still being investigated.

Once the parasites have developed an ability to survive in the presence of an otherwise lethal concentration of chloroquine, they require other metabolic modifications in order to survive. This is due partly to the fact that they appear less capable of utilising host haemoglobin or, alternatively, do not need to do so to the same degree as normal parasites. We observed that P.berghei RC line parasites living in reticulocytes are able in some manner to influence the host cells to increase their output of certain Krebs cycle enzymes which it seems likely are then utilised by the parasites (or perhaps the host cells) to utilise glucose beyond lactate as they normally do in the sporogonic stages. (29,30) Other workers have shown similar examples of host enzyme induction by malaria parasites e.g. folate pathway enzymes and adenylate kinase in avian malarias.

Thus it seems possible that a common phenomenon in drug resistant Plasmodium may be the ability to induce abnormal enzyme activity in the host cells to help them overcome their own deficiencies of certain enzymes or the metabolites the production of which they mediate. This may explain to some degree the commonly observed mixed resistance e.g. of P.falciparum towards chloroquine and pyrimethamine, the basic modes of action of which are so different from each other. (28)

1.4.2. Pyrimethamine

In the course of investigating the genetic nature of drug resistance we were obliged to refute the hypothesis of "synpholia" proposed by other investigators to explain the rapidity of spread of

pyrimethamine resistance. On the contrary we could confirm that pyrimethamine-resistant P.berghei possesses a mutant dihydrofolate reductase with a reduced affinity for this compound.

2. CONCLUSIONS

Although a number of loose ends remain to be tied up and we have still not satisfied ourselves how chloroquine acts, or how malaria parasites become resistant to it, we believe that the collaboration between WRAIR and the Department in Liverpool has been a fruitful and stimulating one. The Principal Investigator would like to take this opportunity of expressing his great appreciation of the generous financial support, the spirit of ready and frank cooperation, scientific stimulation and friendship that have been provided by a succession of Directors and various colleagues at WRAIR ever since the start of this programme. He would also like to say how much he is indebted to his academic and technical staff in Liverpool for their imagination, hard work and skill that have made this programme so rewarding. Special mention must be made of Drs Carol Homewood, Bob Howells, David Warhurst (shortly to become, once again, a member of the writer's staff, in London), a succession of graduate research students including the late K. Gregory, Dr Ken Neame, Mrs June Portus and Mr Brian Robinson. In recent years the Reports have been typed by Mrs Diana Steedman, a key member of our team.

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