that antimalarial drugs, in the form in which they circulate in the body, do act on the malaria parasite in vitro. The remarkable feature of the result is that the individual drugs act on the parasites in various stages of their development. It is probable that a series of enzymatic processes are going on during the development of the malaria parasites in the red cells and that the known antimalarial drugs antagonize different enzyme systems.

Arsenic exerts its toxic effect on living cells by attacking some essential sulphydryl component in the pyruvate system. Riboflavine has been shown to be an atebrin antagonist and pantothenic acid antagonistic to pantoyltaurine.

It appears probable from these results, that antimalarial drugs exert their effect on various enzyme systems concerned with growth on the one hand and division of the schizonts on the other.

Hawking (1947) has recently used this method to demonstrate that Paludrine acts on the exo-erythrocytic forms of P. gallinaceum developing in vitro.

(A figure (Black 1946) was shown to illustrate the typical degenerative changes produced by Paludrine on P. falciparum in vitro, and it was pointed out that these forms are analgous to forms of P. vivax found in the circulation of patients with vivax malaria after the administration of Paludrine).

Intervention du Dr. M. Ciuca (Roumanie):

Tous les malariologistes apprécient au plus haut degré les travaux du Centre de Recherches de Cairns (Australie). L'auteur de l'intervention demande les concentrations actives des médicaments. L'atebrine et la mésochine à 1/5000 n'ont pas d'action «in vitro» sur le sang virulent, où se trouvent toutes les formes d'évolution du parasite. L'avantage de la méthode de Black en utilisant les cultures du parasite est évident.

The Mode of Action of 8-Hydroxyquinoline (Oxine) a Chemical approach,
Dr. Adrien Albert (*England*).

The work described in this and the following paper has been carried out during the last two years in the Universities of Sydney and Melbourne, and some of it has recently appeared in the British Journal of Experimental Pathology.

The main thesis presented here is that the antibacterial action of 8-hydroxyquinoline, the active constituent of chinosol, depends on the ability to remove a vitally important heavy metal from the bacterial cell. This metal is probably cobalt.

Certain organic compounds can react with metal ions to give ring structures with entirely new properties. This process is termed chelation and the complexes thus formed often have great stability. Their metallic nature is masked and they resemble organic, rather than inorganic, compounds. Oxine (8-hydroxyquinoline) is such a chelating agent, capable of removing the following biologically important ions from solution at pH 7: Mn, Zn, Fe, Cd, Co, Pb, Cu.

The antibacterial properties of oxine undoubtedly depend on its ability to chelate with trace metals in bacteria, for the following reasons.

We have prepared all the isomeric hydroxyquinolines and found that oxine

was the only isomeride capable of chelation, and that it was the only isomeride with strong antibacterial properties. We then showed that antibacterial activity in oxine was completely abolished by blocking either of the groups on which the chelation depends (the —OH and the =N—). Then we showed that both chelating power and antibacterial activity could be conferred on other heterocyclic nuclei by the insertion of these two groups in the relative positions wich they occupy in oxine.

Professor Rubbo will tell you of his experiments when he attempted to reverse the antibacterial action of oxine on Gram-positive organisms by the use of various biologically important metals. Only cobalt had any reversing effect, but it had this in a very high degree. In the case of Gram-negative rods, not cobalt but zinc, copper or iron were required to achieve reversal. This shows that the reversing action of cobalt on Gram-positive organisms is not due to some favourable stability of the oxine-cobalt complex, but is specific for this class of organisms. It strongly suggests that cobalt may be a vital constituent of Gram-positive bacteria and that oxine owes its antibacterial action to the removal of cobalt.

This reaction apparently takes place at a bacterial surface, since the biological effect of oxine can be greatly diminished by substituting inert groups in the 2-position although such substitution does not interfere in any way with the chelating action on metals. When these inert substituents were placed elsewhere in the molecule, antibacterial activity reappeared in full.

What could be the function of cobalt in bacterial metabolism? The answer may be derivable from the singular property of oxine solutions to be rapidly bactericidal (e. g. 5 minutes), when dilute, and slowly bactericidal (e. g. 24 hours) when concentrated. One is reminded of the work of Baur and Preis who studied the autoxidation of cysteine which does not occur in the absence of metals but proceeds rapidly in the presence of a trace of copper. When, however, both copper and cobalt are present, the rate is greatly reduced.

Could it be, then, that the function of cobalt in the cell is to act as a guardian for a metabolically important group, possibly a thiol (—SH) group, that is rapidly oxidized when this metal is withdrawn by oxine? In such circumstances it is quite likely that oxidative destruction is being effected by another metal, for example copper or iron, and that stronger solutions of oxine, by removing both the cobalt and the other metal, greatly retard the rate of destruction.

If this hypothesis is to be upheld, it would be necessary to show that oxine is not antibacterial under conditions where oxidation, particularly atmospheric oxidation, is made difficult. Professor Rubbo will tell you of his experiments where organisms grew in the presence of several lethal doses of oxine, provided the oxidation-reduction potential were maintained below a certain figure.

Whatever modifications of these hypotheses may take place in the light of fresh experimental work that they may stimulate, it seems that the mode of action of this drug is now becoming understood, more than half a century after its introduction.