EXPERIMENTAL BILHARZIASIS IN ANIMALS*

IV. CHEMOPROPHYLAXIS IN BILHARZIASIS

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Chemoprophylaxis as a means of combating and preventing parasitic disease is rapidly gaining ground. The great success that has been achieved with this technique in the fight against malaria is a wonderful example of its value, not only in preventing infection of the human host but also of the vector.

Quite independently and unknown to each other the two laboratories mentioned above have been investigating chemoprophylaxis in bilharziasis in experimental animals. Both used the drug S.616† (Farbwerke Hoechst) in albino Swiss mice.

Since their experimental procedures and techniques were slightly different it is necessary to report the results separately.

I. *Technique* (*Farbwerke Hoechst AG*)

Twenty-three groups, each containing 10 albino Swiss mice of about equal weight, were infected with approximately 200 cercariae per mouse from a Liberian strain of *S. mansoni*. Treatment with S.616 (Hoechst) was undertaken before and after infection in different groups of mice, the drug being administered in a single dose of 40 mg./kg. by means of a stomach tube. Continous examination of the faeces was carried out. On the 72nd day following infection the mice were sacrificed. The percentage effect (Fig. 1) is calculated from the ova in the faeces during life, and the worms in the mesenteric

* Articles I, II and III of this series appeared in S. Afr. Med. J., 1952, **26,** 1005; 1953, **27,** 950; 1956, **30,** 79.

† For patent reasons, the chemical composition of this drug cannot at present be revealed.

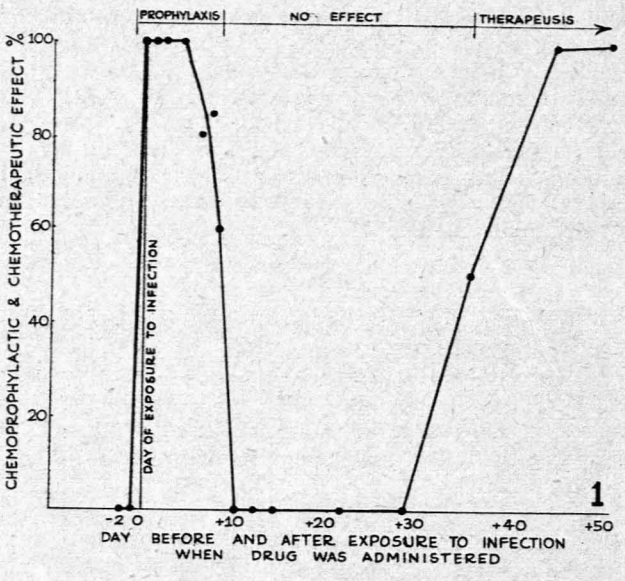

Fig. 1. Showing the chemoprophylactic and chemotherapeutic effect of S.616 (Hoeschst) on a Liberian strain of S. mansoni in mice.

and portal veins and the ova and worms in squeezed liver preparations at autopsy.

After the successful demonstration of S.616 (Hoechst) on cercariae *in vivo*, experiments were performed *in vitro*. The cercaricidal properties are well illustrated by Table I.

TABLE I. THE CERCARICIDAL EFFECT OF S.616 (HOECHST)

Dilution of S.616 in water	*Time elapsed to death of cercariae*
200 μg/ml.	Dead immediately.
100 μg/ml.	Dead in less than 1 minute.
50 μg/ml.	Dead in about 1 minute
25 μg/ml.	Dead in about 4 minutes.

II. *Technique* (*S.A.I.M.R.*)

Six to 10 albino Swiss mice of approximately equal weight were used in each test. Each mouse received by intraperitoneal injection about 180 cercariae of an Egyptian strain of *S. mansoni*, maintained in *Australorbis glabratus*. The drug S.616 (Hoechst) was administered by means of a stomach tube, each mouse receiving a single dose of 50 mg./kg. The faeces of the mice were examined regularly, and cure or failure to cure judged by the absence or presence of living ova. Surviving mice were killed at different times and search made for living adult worms. The results are shown in Table II. It will be noted that the drug was inactive when given one week before exposure of the mice to infection, active when given on the day of exposure to infection and again inactive until the schistosomes had matured sexually and ova were being passed by the mice.

In an additional experiment using a South African strain of *S. mansoni* maintained in *Biomphalaria pfeifferi* it was shown that all of 6 mice infected 56 weeks previously were cured by a single dose of 50 mg./kg., *per os*.

DISCUSSION

The insusceptibility of sexually immature schistosomes to drugs which are effective against mature infections has recently been the subject of a paper by Standen[1] in which he reviews the literature on the subject and reports his own experiences. Briefly, it appears that only Schubert[2] has been able to produce some effect on immature infections in mice. This was achieved by 5 successive daily intraperitoneal injections of antimony preparations. Standen's own experience is that neither tartar emetic nor 3 of the most active p-aminodiphenyoxyalkanes has any effect on schistosomes under 28 days of age. Standen produces highly conclusive evidence that it is the sexually mature worms which are susceptible. He also shows that although unisexual male infections respond at the expected stage of development, unisexual female infections are still resistant after 173 days because, unlike males, they do not mature sexually in the absence of the opposite sex.

It is, of course, not to be assumed that the mode of action is the same for all drugs. It is clear from both series of experiments reported above that the schistosomes are susceptible before they reach the liver and after they leave it. Hence it is possible that the liver itself protects the parasites. In this connection it is worth recalling that sexually mature worms migrate from the mesentric veins to the liver when drugs which

TABLE II. SHOWING THE CHEMOPROPHYLACTIC AND CHEMOTHERAPEUTIC EFFECT OF S.616 (HOECHST) ON AN EGYPTIAN STRAIN OF S. MANSONI IN MICE

Day	*Mouse Groups* A	B	C	D	E	F	G
−7	Dosed						
0	Infected	Infected and dosed	Infected	Infected	Infected	Infected	Infected
+7			Dosed				
+14				Dosed			
+28					Dosed		
+48	All+ve	All−ve	All−ve	All−ve	5/6+ve		All−ve
+56	—	„	2/6+ve	All+ve	All+ve	Dosed	All+ve
+65	—	„	3/6+ve	„	4/6+ve		„
+80	—	„	All−ve	„		1/10+ve	„
+90	—	„	1/6+ve	„			„
+119 }	—						1/10+ve
+134 }							

— = not examined

are active against them are administered to the host. Use can be made of this phenomenon when screening drugs for activity.[3]

Attempts in Johannesburg to interfere with the presumed protective power of the liver by the administration of varying doses of carbon tetrachloride, atropine and adrenaline were unsuccessful.

SUMMARY

1. Experiments performed quite independently in Johannesburg, South Africa, and Frankfurt, Germany, have showh that the drug S.616 (Hoechst) acts as a prophylactic in experimental *mansoni* bilharziasis in white mice.

2. The drug prevents infection from developing when administered on the day of, or up to 4 days following, exposure to cercariae.

3. The drug does not prevent development of the disease and subsequent passage of ova when administered from about the 10th to the 35th day after exposure to cercariae. During this period the schistosomes are principally located in the liver, which *may* play a protective role.

4. From about the 35th day after exposure to infection, and when the schistosomes are sexually mature and have migrated to the mesenteric veins, a single oral dose of 40-50 mg./kg. of S.616 effects approximately a 100% cure.

5. It has been demonstrated, *in vitro*, that S.616 has a cercaricidal effect.

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2. Schubert, M. (1948): Amer. J. Trop. Med., **28**, 157.
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