THE POSITION TO-DAY IN CHEMO-THERAPY AND CHEMO-PROPHYLAXIS OF ANIMAL TRYPANOSOMIASIS

The compounds in use throughout Africa to-day are Dimidium bromide, ethidium bromide, antrycide sulphate, and antrycide pro-salt, which consists of a mixture of the quickly absorbed sulphate and the more slowly absorbed chloride to give a longer protective effect.

When it is stated that these are in use, it means that these compounds are being manufactured and sold on a commercial scale, having passed laboratory and field trials before reaching that stage. Practically every big chemical firm in Britain and elsewhere is working on new and probably more effective drugs, but most of these are not at the stage where they can be issued for general use.

In some cases drugs which are curative in experimental small animals do not produce the same result in cattle. In others, large scale manufacture leads to batches being produced which are unstable and cause a more severe illness in the animal than Trypanosomiasis itself, or such severe reactions at the site of injection that the animal is sick for weeks after, and abcessation and necrosis of the tissues follows. These factors will no doubt be eliminated in course of time but large scale experiments on bovines are lengthy and expensive and the collection of data, etc., in Africa is not always easy.

DIMIDIUM BROMIDE is to a large extent now falling into disuse in Africa. The drug is a curative one and any prophylactic property it may have is of short duration. The mortality encountered with its use, due to a type of photo-sensitisation leading to liver and othere tissue damage, is the chief reason why it has been largely replaced by one of the newer drugs.

ETHIDIUM BROMIDE is also purely a curative drug but it has the advantage of being less toxic than dimidium; and its chief use now is probably to destroy trypanosomes which have become resistant

ANTRYCIDE in its two forms is now the most widely used drug throughout Africa, and the one which has marked the first piece of real progress in the chemical control of trypanosomiasis.

As mentioned above there are two forms in which the drug is administered:-

Antrycide methyl sulphate is very soluble, acts rapidly and passes out of the body rapidly (probably in 3 - 4 weeks)

The chloride salt however is relatively insoluble and forms a deposit in the tissues from which it slowly passes into the body (over 2 - 3 months). To combine the advantages of these two they are mixed and used as the "pro-salt" which, as can be seen, has a curative and prophylactic effect.

However the sulphate (which is cheaper) can be used as a prophylactic where infection is sporadic and infection is from flies carried to the cattle by some means (cars, game etc) or when mechanical transmission by biting flies takes place. If the challenge of tsetse flies becomes too heavy of course, the pro-salt would be used.

DRUG RESISTANCE.

With most drugs the microbe, insect, etc tends to develop a degree of resistance to the drug which is trying to destroy it. This happens chiefly in circumstances where dosage or concentration of drugs is too low to kill outright, so that the microbe, etc has time to organise its resistance. This phenomenon is known in such cases as arsenic - resistant ticks, D.D.T. resistant flies, penicillin - resistant streptococci, and the trypanosome is no exception.

Resistance occurs with all the drugs referred to above, but has not proved as serious as was first expected, as the "stopper" drugs, can be used as alternatives. It occurred with one of the earlier drugs, tryparsamide, used in human medicine, which, in spite of the developement of resistant strains has been used with success for over thirty-six years.

Turning now to the experiments being carried out on new compounds,

a drug that will cure trypanosomiasis without harming the animal, and at the same time will stay in the animal's system for a long enough period to protect the animal from reinfection and make frequent re-treatments unnecessary.

Having established the tryp-killing drug, the problem is to make it relatively insoluble so that it will stay at the site of injection or elsewhere for some time.

There is a great deal of activity in this field at the moment and a permanent panel to co-ordinate information and the results of experiments in the field and laboratory has been formed, known as the Chemotherapy Panel sitting in London. Regular communications of great interest are received from this Panel which are confidential, but a summary of trials on the more hopeful new compounds is given below.

It was found that the combination of Suramin with some of the known trypanocidal drugs already described made the compounds more active as prophylactics and less toxic than these drugs alone.

The table given below gives a quick impression of the encouraging results.

No. of beasts.	Treatment.	Dose mg./kg.	1st. break-throug
5	Antrycide pro-salt	5	2 months
3	Antrycide dimethyl-sulphate (ADMS)	5	1 months
5	Suramin ADMS	10	3 months
5	Suramin - ADMS	20	4½ months
5	Suramin - ADMS	40	5½ months
4	Ethidium bromide	5	2 months
2	Suramin - ethidium	5	7 months
3	Suramin - ethidium	10	13 months
5	Suramin - Berenil	5	1 months
5	Suramin - Berenil	40	1½ months
4	RD.2801	2	5 months

No. of beasts.	Treatment	Dose mg./kg.	1st. break-through
3	Suramin - RD.2801	10	Still protected after 2 months.
3	Suramin - RD.2902	10	Still protected after 2 months
3	Suramin - RD.2902	20	Still protected after 2 months.

A note on the approximate cost of each compound is interesting. To effect 6 months protection.

	s.	d.
(1) Antrycide pro-salt (3 times in 6 months)	8	3
(2) Suramin - antrycide D.M.S. complex (given once)	12	10
(3) Suramin - ethidium complex (given once)	2	9

The suramin antrycide complex does not give a full 6 months protection, and this together with the higher cost possibly will preclude its use.

In this connection a curative and prophylactic drug for T. Simiae in pigs has been found for the first time, being antrycide pro-salt and suramin - antrycide complex.

In cattle the ethidium bromide - suramin complex has not yet reached the stage where it can be manufactured and used on a large scale. Extensive trials in cattle are in fact still proceeding in Africa.

It is found at the moment that local reactions at the site of injections are severe and lead to a considerable swelling followed by necrosis. However no other signs of toxicity have been observed and trials are continuing.

Fairly extensive trials have been going on with Prothidium Chloride produced by Boots, but up till now the drug has not lived up to its earlier promise.

With some batches issued for use in Africa results were not

prophylactic property is also very variable as will be seen by the table below.

Animal No.	8.	Positive after 98 days	
	7	" " 122 "	
	6	" " 97 "	5 mg/Kilo.
	5	" " 122 "	
	1	Positive after 12 days.	
	2	" " 117 "	
	3	" " 118 "	3 mg/Kilo.
	4	" " 38 "	

Further tests are going on, and recent observations indicate that only some batches appear to cause the severe reactions, but as with the complexes described above they are not ready for general issue.

Stylomycin produced by Lederle's is designed for the treatment of humans and animals, and can be given orally. Results have not been incouraging in humans up till now. Animal trials are confined at the moment to laboratory small animals. The indications on that margin between the curative and the toxic dose are extremely narrow

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