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CLOSING REMARKS

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Before closing this symposium I should like to review the conclusions that seem to be indicated by our work. The individual investigators' comments have interpreted their own findings and will suggest starting points for future studies.

The development of nitrothiazolyl-imidazolidinone (CIBA 32644-Ba) constitutes an important advance in the treatment of schistosomiasis and amoebiasis. This compound differs from the classical drugs in several respects.

In the treatment of severe schistosomal infections, a parasitological cure is usually obtained, even though black eggs may continue to be excreted for several weeks or months. Once the elimination of viable eggs has been completely arrested for 2-3 weeks, relapses do not appear to have occurred. Experimental studies also suggest strongly that the non-viable eggs found were laid before, or very soon after, the start of treatment.

In amoebiasis, CIBA 32644-Ba has an extra-intestinal amoebicidal effect; it thus marks an important step forward in the treatment of amoebic dysentery and represents a valuable alternative to emetine in the treatment of the hepatic forms of the disease.

Thanks to its activity, its good tolerability at active dose levels, and its therapeutic margin, CIBA 32644-Ba is undoubtedly superior to the classical antischistosomal agents, and at least as good as the best anti-amoebic drugs available.

This new compound is active against all species of schistosome and its activity does not appear to be influenced by the age or the severity of the infection, or by the age, race, or sex of the patients.

Like every other active substance, CIBA 32644-Ba gives rise to side effects.

We shall not dwell on the minor side effects, such as moderate headache, nausea, dizziness, etc., the incidence and intensity of which vary.

The following symptoms of genuine intolerability, however, deserve mention:

— painful epigastric cramps;
— severe headaches;
— anorexia and vomiting.

Some side effects, such as myalgia, arthralgia, and skin affections may be attributable to allergic reactions. Here again, the incidence varies.

Three types of side effects have attracted special attention:

1. Frequent E.C.G. changes, involving mainly the T waves.
2. Neuropsychic effects, ranging from severe headaches to convulsive attacks, with infrequent hallucinations.
3. Transitory impairment of spermatogenesis.

The remarkable thing about these side effects is that they are all reversible. Experience has shown that they are not incompatible with the use of the drug, especially when one compares them with the side effects encountered in the classical treatments.

The immunological reactions observed in schistosomiasis patients treated with CIBA 32644-Ba are consistent with the production of a specific antigen that causes an antibody reaction. The biological significance of these immunological reactions is now being studied.

The predominant site of attack of CIBA 32644-Ba is the reproductive organs of the schistosome: oviposition is arrested and the parasites are autolysed in the liver within 1-6 weeks. The biochemical mechanisms by which the antiparasitic action is produced are as yet unknown. Experimental and immunological findings indicate that a genuine parasitological cure takes place.

The non-metabolised substance possesses a specific affinity for the schistosomes and their eggs as well as for the zones of proliferation of the amoebic abscess. In these sites, cumulation occurs that is not observed in any of the host tissues. The metabolites appear to be parasitologically inactive.

According to the type of infection and the clinical form of the disease, the investigators have tried various dosage schedules based on an average dose of 25 mg/kg, given in 2 fractional doses daily for 7 days.

In *S. haematobium* infections, doses of 20-25 mg/kg daily, given in one single or two fractional doses for four to ten days, have yielded excellent therapeutic results.

Comparable results have been achieved in *S. mansoni* infections with doses of 20-40 mg/kg daily, given in one single or two fractional doses, for 5-15 days.

In *S. japonicum* infections, treatment with doses of 15-25 mg/kg daily, in two divided doses, for 5-10 days has so far produced encouraging results; subsequent studies will confirm this.

In cases of acute amoebic dysentery and liver abscess, an excellent response has been obtained with doses of 25 mg/kg daily, given in two divided doses for 9-10 days.

It is noteworthy that doses equal to twice the accepted active dose have been relatively well tolerated. The toxic effects, however, appear to be proportional to the dose and the duration of treatment.

To sum up, the investigators have shown that CIBA 32644-Ba yields positive results in the treatment of schistosomiasis, acute amoebic dysentery, and amoebic liver abscess. We consider that research should be continued along the following lines:

1. Large-scale trials with low doses of the compound;
2. Evaluation of the results after longer follow-up periods;
3. Study of relapsed cases, and of the possibility of reinfection and immunising effects;
4. Biochemical study of the mechanism of action.

These aspects should be investigated with a view to the possible future use of the compound in mass-treatment.