THIRD INTERNATIONAL PHARMACOLOGICAL MEETING

VOLUME I

Mode of Action of Anti-parasitic Drugs

Edited by

J. RODRIGUES DA SILVA

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and

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INTRODUCTORY REMARKS

J. RODRIGUES DA SILVA

Rio de Janeiro, Brazil

THIS Symposium will consider the mode of action of drugs which interests not only individuals affected by different species of parasites but also mankind as well, since most of the topics to be considered in this Symposium will deal with mass diseases—mainly those which cannot be controlled by immunization procedures. As a matter of fact the parasitic diseases to be considered during this Symposium are those of highest interest to Brazil and other Latin American countries situated in the tropics such as malaria, Chagas disease, schistosomiasis, intestinal parasitic diseases and leishmaniasis. Besides this, all these parasitic diseases, with the exception of Chagas disease, are also of great interest to all other countries situated in the tropical areas of the world—mainly in Africa and Asia—where not only their respective native peoples struggle for life, but also people who have moved there for different purposes.

In all these areas, intensification of trade between nations and the improvement and speed of means of transportation have changed the old concepts so as to make it an imperative and vigorous interest on the part of the nations which lead the destinies of the world to solve the health problems of the undeveloped countries. The control of these diseases is important from different angles, since it will affect the health and hence the economy of the country. On the other hand it will change the local or regional conditions of the area, in respect to trade, military actions, etc.

For all these reasons, it was certainly a precise and valuable decision of the Organizing Committee of the Third International Pharmacological Congress to have among the different symposia one dedicated to the "Mode of Action of Antiparasites".

It is well known and has been restated recently by Browning, that to the genius of Ehrlich the world owes chemotherapy. Early this century, he set out to find drugs which would cure infections aiming also to achieve the maximum effects with the least toxicity. This was a unique task requir-

ing coordination of great resources, mental and material, in the fields of biology and chemistry, and later on with new scientific developments with the more precise help of the specific knowledge of enzymatic mechanisms, genetics, radioisotopes, etc.

At first, it might seem that the control of the diseases caused by parasites with drugg was an objective to be achieved very soon, were it not for the emerging appearance of resistance of parasites to drugs. This phenomenon was found to occur even before Ehrlich, who used it to build the foundation for his famous theory of the mode of action of antiparasitary drugs.

With the advance of progress in the field of chemotherapy—which had much of its impetus during the last two great wars—came also the increase of the phenomenon of drug resistance. According to Schnitzer and Grumberg, drug resistance has accompanied the development of chemotherapy "like a faithful shadow and the history of chemotherapy is also a history of drug resistance".

So, a very serious threat has been created regarding the control of diseases which are not yet amenable to immunization procedures—as is the case of those to be considered in this Symposium. The phenomenon requires more and more effort to solve the different situations. To overcome these difficulties new drugs must be synthetized and carefully studied at the same time that other measures, such as environmental sanitation, health education and, when applicable, anti-vector measures, are effective.

In spite of these alternatives there are situations in which chemotherapy is the only procedure to be resorted to, a reason why more and more effort is needed to study the mode of action of the antiparasites.

This has been, I presume, the reason why this Symposium has been planned and will take place, under so modest a chairmanship, with the participation of such outstanding authorities to whom we are eager to listen.

I. GENERAL

CHEMICAL STRUCTURE AND MODE OF ACTION OF ANTIPARASITES

QUINTINO MINGOIA

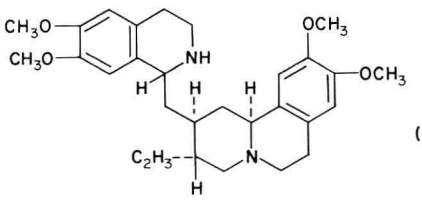
Department of Pharmaceutical Chemistry, Faculty of Pharmacy and Biochemistry, U.S.P., São Paulo, Brazil

In accordance with the organizer of the present Symposium, Prof. J. Rodrigues da Silva, and due to the extensiveness of the topic, this report is restricted to chemotherapeutic and antibiotic drugs which are employed in human parasitoses of major interest to the South American continent. No reference is made to the agents employed against malaria and Chagas' disease because they constitute other topics of this Symposium. Excluding the older and less employed drugs against human parasitoses, the more recent can be divided into two classes: antiprotozoarian antibiotics and anthelmintics.

I. ANTIPROTOZOARIANS

1. Amebicidal Drugs

The treatment of infections due to *Endamoeba histolytica* began in 1912 by Vedder[155] and Rogers[126] using emetine chlorhydrate. Today there are a great number of natural and synthetic chemotherapics which are used as intestinal or hepatic amebicidal drugs. Among the former we may remember, besides emetine (I), *conessine*[22] an alkaloid from *Holarrhena antidyssenterica* with a steroid nucleus (II), the stereospecific synthesis of which was achieved in 1962,[106, 146] and *glaucarubine*,[49] an active principle of



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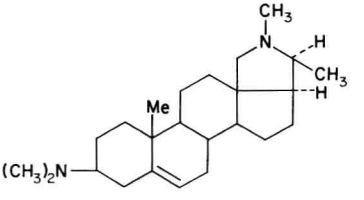

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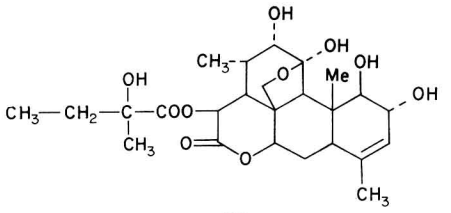


III

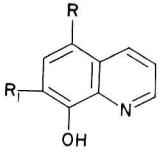
Simarouba glauca, whose exact chemical constitution (III) was demonstrated in 1964 by X-ray studies of the crystalline *p*-bromobenzoate.[91] After the work by Brossi,[28] the natural emetine was substituted by *2-dehydroemetine*, under the commercial name of Mebadin. It differs from the natural alkaloid only by a double bond in position 2–3, but is six times more active and two times less toxic; furthermore dehydroemetine is used by the oral route against the parenteral route employed for emetine.[20, 21]

Emetine and its dehydroderivative, conessine, etc., constitute the diffusible amebicidal drugs reaching, by the blood stream, *E. histolytica* (pathogenic form) in the parenchyma, the site of its necrotizing action. Like schistosomicidal drugs, the above are excreted in the urine: they cure the symptoms due to amebiasis but do not sterilize the infection and are not able to prevent reinfection.

Among the natural amebicides we find some antibiotics, especially *fumagillin*,[7, 108] of polyenic structure, and *paromomycin*,[37, 152] a non-macrolidical heteroside of the kanamycin type. An amebicidal activity is also displayed by bactericidal antibiotics as tetracyclins, erythromycin, bacitracin, etc.

There are many important synthetic drugs which constitute the contact amebicides, which, when administered by oral route, act directly on *E. histolytica* at the level of colic ulcers. They cannot act on the deeper layers of the intestinal wall or even the hepatic parenchyma. They belong to several chemical groups:

(a) *8-quinolinol and 8-quinaldinol derivatives* — Mostly they are di-halo-



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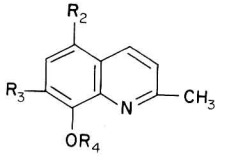
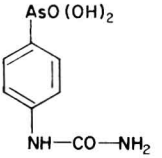


V

genated derivatives of the general formulas (IV) and (V); the more recent are *halquinol* and the mixture AI-306/307, known commercially as Intestopan. Studies by Carvalho *et al.*[39] on the comparative tolerance and efficacy have demonstrated that AI-306 and AI-307 show minimal side-effects. Regarding therapeutic efficacy, positive results have been obtained in 80% of the treated cases.

(b) *Arsenicals* — Practically out of use are: *carbarsone* (VI),[8] *glycobiarsol* (VII),[14] and *diphetarsone* (VIII).[48, 136]



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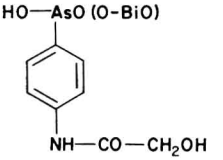

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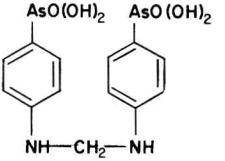
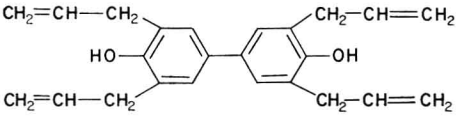


VIII

(c) *Aminoquinolines, aminocresols and quinones* — The 4-aminoquinolines are diffusible amebicides; because of their elective accumulation in the



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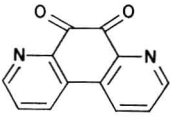


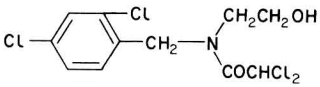
X

liver, they are used in the treatment of the hepatic amebiasis. *Chloroquine* is the one most used.[46]

Biallylamicol (IX), patented in 1949 under the name of Camoform, acts rapidly in intestinal amebiasis in man and in apparent hepatic amebiasis.[61 88]

A *phenantrolinedione* (X), known since 1960 as Entobex, is active against human intestinal amebiasis.[55]

(d) *Haloacetamides* — The amebicidal activity of chloroderivatives was



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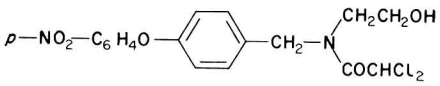

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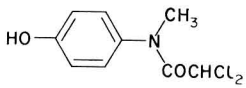

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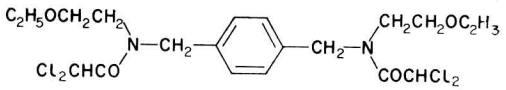
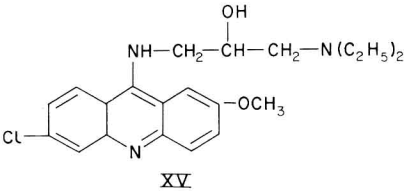


XIV

demonstrated during the synthesis of structural chloramphenicol analogs with a dichloroacetyl radical. The first of these compounds was synthesized by Surrey[148] and named officially *chlorbetamide* (commercial name Mantomide) (XI).[78,102] Others more active and less toxic followed recently, among which were *clefamide* or Mebinol (XII),[42, 57] *diloxanide* or Entamide (XIII) used as such[26] or as the furoate (Furamide)[86, 140, 163] *teclozan* (XIV), etc.

2. *Chemotherapy of Lambliasis*

The first drugs utilized against infections by *Giardia lamblia* were the antimalarics like atebrine and then chloroquine and amodiaquin; later on in the group of the acridines, atebrine was substituted by *Acranil* (XV).[32]



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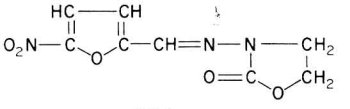


XVI

More recently new excellent chemotherapeutic agents were found among heterocyclic nitroderivatives especially *furazolidone* (XVI) with the furan nucleus, *aminitrozole* (XVIII) with a thiazolic ring, and *metronidazole* or Flagyl (XX) with an imidazolic nucleus.[54, 105, 134]

Studies of comparative tolerance and efficacy of the different lamblicides by Carvalho *et al.*[38] led to the following conclusions:

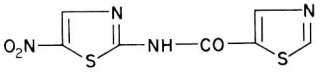
1. Regarding tolerance, Acranil and furazolidone were responsible for the more serious side-effects when used in adults; side-effects of metronidazole were negligible.

2. Concerning the therapeutic efficacy in 179 cases, the following percentages of cures were obtained: 92·3% for Acranil, 89·6% for furazolidone, 84·3% for metronidazole, 50% for aminitrozol. The authors recommended metronidazole with an efficacy almost identical to furazolidone and much better tolerated.

3. Chemotherapy of Trichomoniasis

Of the trichomones, only *Trichomonas vaginalis* which is found frequently in the mucosa of the genito-urinary tract must be remembered.

Trivalent arsenicals, mercurials, quaternary ammonium compounds, antibiotics, like trichomonycin[43] were used as trichomonicides. The most effective were the heterocyclic nitroderivatives,[12, 53] especially metronidazole.[114, 160]



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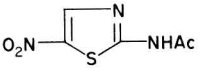

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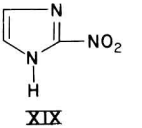

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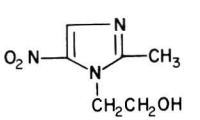

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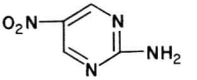
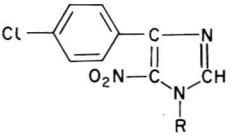


XXI

2-amino-5-nitro-pyrimidine (XXI) is characterized by its long survival in the organism.[109] Atrican is effective against both *T. vaginalis* and *Candida albicans*, differing therefore from metronidazole.[142]

In 1964, Ellis *et al.*[63] found new amebicides and trychomonicides, which were more active than metronidazole. These new drugs belong to the arylnitroimidazoles of the general formula (XXII).



XXII

$R = CH_3$ (Comp. I) or CH_2CH_2OH (Comp. II)

The minimum doses which kill the protozoa after 48 hours at 28°C are the following, expressed in μg/ml:

Compound	*Trychomones*	*Histomones*	*Entamoeba*
Metronidazole	0·3	2·5	2·5
Compound I	0·1	1·25	2·5
Compound II	0·05	1·5	1·5

Trychomycin, not sufficiently effective by oral administration, gives good results in women when administered both orally and intravaginally.[80]

4. Chemotherapy of Toxoplasmosis

Toxoplasmosis due to *Toxoplasma gondii* affects, normally, warm blooded animals associated with men; human infections (especially in children) have been observed in Brazil and other American countries.

In 1941, Sabin and Warren[128] successfully tried sulfas in the chemotherapy of toxoplasmosis, especially those of the pyrimidine group (sulfadiazine, sulfamerazine and sulfamethazine). In 1943, Biocca[18] assayed various acylderivatives of 4-nitro-4′-amino-diphenylsulfone synthesized by us,[110] among which five showed a distinctly higher activity than the sulfas.