No new effective drugs for trypanosomiasis, human or animal, have been brought into field use for 20 years; increased drug development costs, the generally small drug budgets of developing countries and widespread evolution of drug resistance are primary causes. The topic covered briefly here deal with data accumulated since an earlier review (Williamson, 1970). A more extended account will be published elsewhere.

Existing drugs

For human trypanosomiasis, the situation is now exacerbated by restricted commercial production of suramin, tryparsamide and melarsen. Pentamidine, effective only in early infections, and melarsoprol, requiring hospital admission because of toxicity, are not satisfactory treatment substitutes. Effective and safe Berenil treatment of early Rhodesian and Gambian sleeping sickness has been reported (Temu, 1975).

In animal trypanosomiasis, Gill and Malhotra (1971, 1974) showed that suramin-Antrycide complex could protect Indian ponies against surra for up to 23 months. Where drug resistance conditions are favourable, Prothidium and Samorin continue in sporadic use for treatment of cattle (Bott, 1971; Touré, 1973; Fineille, 1973; Lovemore, 1974). Deep intramuscular injection is required to circumvent the dermonecrotic properties of these drugs; intravenous injection of Samorin has also been reported as beneficial (Touré, 1973). Pharmacological investigations with Berenil (Raether and Seidenath, 1971; Raether et al, 1972, 1974a and b; have shown that it is capable of prolonged tissue retention. Berenil is hydrolysed extensively in the stomach, but the effects of oral dosage on prophylaxis appear to be variable.

New drug developments

An analogue of the water soluble Mel W has been reported as active, orally and subcutaneously, in Gambian sleeping sickness (Friedheim and Cavier, 1973). A Berenil analogue, 6-amidino-2-(4-aminophenethyl)-indole, (102/198; DAPI) was found to be active on Trypanosoma congolense-infected zebu cattle (Dann et al, 1971) and had activity equivalent to Berenil in experimental infections (Fink and Dann, 1974). Ross and Jamieson (1975) described a novel nitrovinylimidazole drug series, of which an amidine derivative had activity in experimental infections comparable to that of standard drugs. Trials of the adenine nucleoside, Cordycepin, in tsetse-induced T. vivax infections (Aylodun et al, 1973) revealed therapeutic but not curative activity.

Drug resistance

Numerous accounts of resistance in both human and animal infections continue to be reported, implicating pentamidine, suramin, and Samorin among others. Gray and Roberts (1971) showed that T. vivax and T. congolense strains, resistant variously to Berenil, Ethidium, Antrycide and Samorin, retained resistance after tsetse transmission for periods of up to 16 months.

Combination chemotherapy

The dearth of new drugs forces consideration of the possibilities of combined treatment. Development of hypersensitivity to one trypanocidal drug in a strain made resistant to another, appears to be related to synergistic activity (Williamson, 1970). In addition, existing data on drug action may be used to select combinations of drugs with different loci of cellular lethality; the combination need not be restricted to known trypanocides, as several inhibitory compounds, such as some RNA synthesis inhibitors (Williamson and Scott-Finnigan, 1975), may serve as ancillary potentiating agents.

Modes of drug action

Few new findings derive from work with trypanosomes; most are indirect, from other cell systems. A structural context for drug action studies (Williamson et al, 1975) showed that a guide to intracellular drug targets could be provided by analysis of specific drug-induced lesions in trypanosome fine structure. Cytoplasmic cleft induction by nucleoside drugs such as Cordycepin appears to involve selective inhibition of unsaturated fatty acid uptake (Williamson and McLaren, 1974).

Diamidines and Ethidium cause different kinds of kinerplast DNA condensation in T. cruzi in vitro (Delain and Rieu, 1969; Delain et al, 1971; Brack et al, 1972) and in T. rhodesiense in vitro (Williamson et al, 1975). These effects may reflect a difference in mode of binding, which is intercalative for Ethidium and external for diamidines (Festy et al, 1975). Berenil appears to bind to T. cruzi kinerplast circular DNA at four equidistant sites which also bind RNA polymerase (Brack and Delain, 1975). Another important cytotoxic property of diamidines, the ability to precipitate nucleoside phosphates and nucleotide coenzymes, has been emphasized by Makulu and Waakhees (1975).

The vulnerability of RNA synthesis in pathogenic trypanosomes is enhanced by an inability to synthesize purines de novo; examination of a series of known inhibitors of cellular RNA synthesis has revealed high trypanocidal activity in a number of antitumour antibiotics such as Daunorubicin, Distamycin A, Chromomycin A, Chromomycin C (Williamson and Scott-Finnigan, 1975).

The probability that suramin enters trypanosome lysosomes is strengthened by demonstration of its lysosomotropic properties in other cells (Davies et al, 1971; Buyse et al, 1973; Jacques et al, 1975; Hart and Young, 1975). Exploitation of drug lysosomotropism, by encapsulation or attachment to carrier compounds, has potential for selective delivery, toxicity reduction and controlled release for prophylaxis. At concentrations comparable to those affecting trypanosome infectivity (10-100 μM), suramin specifically inhibits a number of adenosine triphosphatases (Fortes et al, 1973); the isolated glycerophosphate oxidase of T. brucei is even more sensitive to suramin (Fairlamb and Bowman, 1975).
Losos and Ikede (1972) have stressed the different distribution within the mammalian host of the T. vivax-T. congolense (haematoic) and T. brucei (humoral) trypanosomes. Much of the difference in drug reactivity of the two trypanosome groups may be explained on this basis, as both groups are qualitatively sensitive in vitro to Antricyde, Ethidium and Berenil; of these, only Berenil shows considerable tissue retention and hence is more active in vivo against T. brucei tissue forms. This consideration is likely to become even more crucial with the recognition that cattle can be reservoirs for T. rhodesiense infections in man, which cannot be eliminated by drugs active only on haemato parasites (MWAMBU, 1973).

References


Immunological research and the problem of immunization against African trypanosomiasis

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Many people still doubt the feasibility of producing suitable vaccines and disrupt their value in relation to current methods of trypanosomiasis control. Vaccines would do little to reduce the reservoir of infection in wild hosts or the continuous threat of trypanosomiasis to livestock. There is little evidence of antigenic uniformity among the different trypanosome species and several vaccines would probably be required. Man and the domestic animals in most instances are incapable of an effective immune response to natural infection with pathogenic trypanosomes and vaccination might be required repeatedly. However, complete tsetse control is unjustified even though it is doubtful if any vaccine of practical value will be produced in the immediate future.

In seeking to achieve vaccination the following considerations are important: (1) trypanosomiasis is an insect-borne disease and the antigenicity of metacyclic trypanosomes is likely to be a factor of primary importance in the immune response and (2) the nature of immunity to Trypanosoma brucei, which causes inflammatory and degenerative changes in connective tissue and the reticulo-endothelial system, might differ significantly from immunity to T. congolense and T. vivax, which are primarily parasites of the circulatory system, associated with the development of anaemia and tissue anoxia (Goodwin, 1970; Losos and Ikede, 1972).

Trypanosomal antigens

The properties of trypanosomal antigens and their availability for immunization purposes have been considered in several reviews (Lumbers, 1967; Weitz, 1970; Gray and Luckins, in press). One group of internal antigens which are probably mainly enzymes and structural proteins occurs in different strains and species of trypanosomes, but these are unsuitable for vaccine production because they lack immunogenicity. A second group of external antigens which vary during infections and differ from one population of a strain to another are of more interest because they stimulate the formation of specific protective antibodies. These antigens are associated with a trypanosomal surface coat (Vickerman, 1974) and are thought to be low molecular weight glycoproteins (Allsopp and Irogu, 1974). A third group of antigens like host-serum proteins, also closely associated with the cell surface, have been noted, but their significance in immunity is not yet clear (Seed, 1974).

Strains of trypanosomes

The possibility of immunoprophylaxis also depends on the number of antigenically different strains of trypanosomes circulating in infected areas and techniques are being developed for classifying strains. Tsetse flies infected with serological variants of T. brucei, T. gambiense and T. congolense transmit trypanosomes with strain-specific basic antigens (Broom and Brown, 1940; Gray, 1975; Uilenberg and Giret, 1972). Strains of T. brucei and T. gambiense also persist in a recognizable antigenic form in the field for several years (Gray, 1970, 1975). Comparisons of cyclically transmitted trypanosomes from different areas have shown that there are many different strains of T. brucei in circulation (Gödeblöd et al, 1973), but T. gambiense seems to be a more uniform species (Gray, 1975). Strains of T. brucei also produce different series of variant antigens in infected hosts (Van Meirvenne et al, 1975) and can be typed on this basis. Comparisons of T. congolense and T. vivax are technically more difficult and few reliable results have been obtained, but tsetse flies apparently harbour many different types of these organisms (Dar et al, 1971).

Immunization against isolated populations of trypanosomes

Laboratory and domestic animals have been immunized against infection with one or limited numbers of antigenically different populations of trypanosomes by many