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Recent Research on the Biological Activity of Suramin

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I. Introduction

Suramin is a symmetrical polysulfonated naphthylamine derivative of urea and is known by many other names: Antrypol, Bayer 205, Belganyl, Fourneau 309, Germanin, Moranyl, Naganin, Naganol, and Naphuride. It was originally synthesised in approximately 1916 by German workers at Farbenfabriken Bayer AG among a series of approximately 2000 compounds that were tested for trypanocidal activity. These researchers had previously noted trypanocidal activity in some symmetrical polysulfonated naphthylamine azo dyes, e.g., trypan red, trypan blue, and afridol violet. The problem of colouring was avoided with the colourless compound suramin. This compound has amide linkages rather than azo linkages.

Suramin has been widely used since the 1920s for the prophylactic treatment of human trypanosomiasis in Africa and for the treatment of the early stages of the disease before the nervous system is involved. In vivo it is very active against trypanosomes of the subgenus

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Trypanosoon, comprising the human parasites *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense* and the cattle parasites *Trypanosoma brucei brucei*, *Trypanosoma equiperdum*, and *Trypanosoma evansi*. Suramin is relatively ineffective against infections of the cattle trypanosomes *Trypanosoma vivax* and *Trypanosoma congolense* (Hawking, 1963). Van Hoof et al. (1947) observed that Congolese patients with trypanosomiasis and onchocerciasis were cured of both diseases following treatment with suramin. The fact that suramin is an effective chemotherapeutic agent for *Onchocerca volvulus* was confirmed in many field trials in Africa. It is still the only effective macrofilaricide considered for use in the treatment of human onchocerciasis, and its action on microfilariae, although slower and less complete than that of diethylcarbamazine citrate or ivermectin, is still substantial (reviewed by Gibson et al., 1977).

An extensive review of suramin's antiparasitic action and therapeutic use in trypanosomiasis and onchocerciasis was provided by Hawking (1978). Since then, research on suramin has gained considerable momentum due to the finding of De Clercq (1979) that suramin is a competitive inhibitor of RT†, the DNA polymerase of retroviruses, and, subsequently, the demonstration of Mitsuya et al. (1984) that suramin can block the infectivity and cytopathic effect of HIV in vitro at doses that are clinically attainable in human beings. Because of previous clinical experience with the drug, suramin could be used without the need for time-consuming animal toxicity studies, and suramin was entered into clinical trials as a treatment for AIDS (Broder et al., 1985; Cheson et al., 1987; Yarchoan and Broder, 1987). Suramin treatment for hepatitis B virus infections was studied by Loke et al. (1987). In the AIDS trials, suramin was shown to have adrenal toxicity which led several workers to test suramin as an anticancer drug for adrenocortical cancer (Allolio et al., 1989a,b; Vierhapper et al., 1989; La Rocca et al, 1990b) and other cancers (Stein et al., 1989; Klijn et al., 1990; Van Oosterom et al., 1990; La Rocca et al, 1991a,b; Myers et al., 1992; Reed et al., 1992). La Rocca et al. (1990c,d) has written reviews of suramin as an anticancer drug.

II. Chemistry

Suramin is the symmetrical 3″-urea of the sodium salt of 8-(3-benzamido-4-methylbenzamido)naphthalene-1,3,5,-trisulfonic acid (fig. 1). The synthesis of suramin was described by Fourneau et al. (1924), Bär (1948), and Wacker (1966). Suramin is a white, pinkish white, or faintly cream-coloured powder; it is odourless, tastes alkaline and slightly bitter, and is hygroscopic. It is readily soluble in water. Suramin should be kept in a well-closed container, protected from light, and stored in a cool place (British Pharmacopoeia, 1968). Suramin in commonly used infusion fluids (1 mg/ml) is stable when stored in glass container bottles at 4°C in the dark, at 22°C under normal light conditions in a day-night rhythm, or when protected from light for at least 7 days (Beijnen et al., 1990).

A. Structure-Activity Relationships

Since the structure of suramin was established by Fourneau et al. (1924), many analogues have been prepared. Any deviation, however slight, from the structure of suramin reduced the trypanocidal activity considerably or gave an inactive compound (Fourneau et al., 1924; Bauer and Becker, 1928; Adams et al., 1956). The specificity of the structure of suramin in relation to trypanocidal activity and host toxicity was reviewed by Fairlamb (1975). The antifilarial activity and antagonist properties of suramin at purine receptors are also sensitive toward small structural variations (Nickel et al., 1986; Urbanek et al., 1990). In contrast, the inhibition of HIV-I RT is much less sensitive to molecular modifications. Structural features such as overall molecular size, acidity, size of the central group, and certain substitution patterns determine the RT inhibitory activity of a compound. A number of suramin derivatives were superior to suramin in a RT inhibition assay, and preliminary antiviral evaluation in susceptible human T-cells inoculated with HIV-I demonstrated in vitro therapeutic efficacy for some derivatives having lower drug-related toxicity than suramin (Jentsch et al., 1987).

B. Analytical Methods

In some pharmacological studies, nonspecific analytical techniques for suramin measurement were used that were both time-consuming and subject to high background interferences. Since clinical trials started in which suramin was used for the treatment of AIDS, new more accurate methods of monitoring suramin levels in body fluids were developed. During trials of suramin as an anticancer drug, a narrow therapeutic window and variable kinetics in individual patients were found, and frequent drug monitoring has become essential.

A number of high-performance liquid chromatography assays for the determination of suramin in body fluids have been described (Edwards et al., 1985; Klecker and Collins, 1985; Ruprecht et al., 1986; Stolzer et al., 1986; Teirlynck et al., 1989; Supko and Malspeis, 1990; Tjaden et al., 1990; Tong et al., 1990; Beijnen et al., 1991; Brandsteterová et al., 1991; De Bruijn et al., 1991). Reversed phase ion pair chromatography has commonly been used. In one assay, a gradient elution was used (Klecker and Collins, 1985). Sample pretreatment included deprotonation by an organic solvent and addition

† Abbreviations: RT, reverse transcriptase; HIV, human immunodeficiency virus; HIV-I, HIV type I; AIDS, acquired immunodeficiency syndrome; CSF, cerebrospinal fluid; DFMO, DL-α-difluoromethylornithine; LDL, low-density lipoprotein; PKC, protein kinase C; PDGF, platelet-derived growth factor; $[Ca^{2+}]_i$, intracellular free Ca^{2+} concentration; SSV, simian sarcoma virus; RBC, red blood cell; ACTH, adrenocorticotropic hormone; ATP, adenosine 5′-triphosphate; GTP, guanosine 5′-triphosphate; UTP, uridine 5′-triphosphate.

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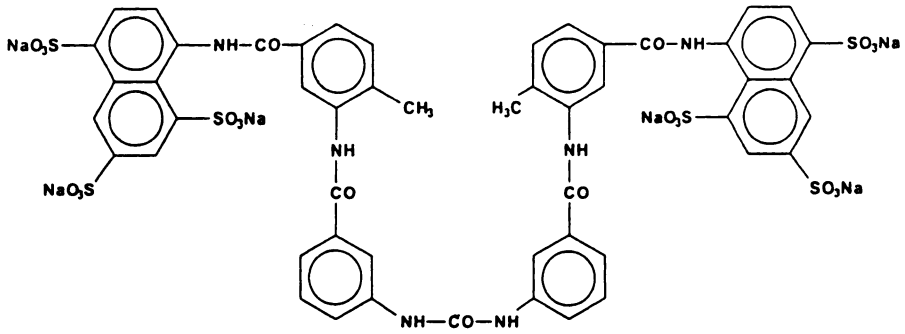

FIG. 1. Structure of suramin.

of an ion pairing agent. In earlier reports, triple and double extractions were used. Single extraction was used in later studies. In two assays, plasma samples were injected directly onto the column (Tong et al., 1990; Brandsteterová et al., 1991).

III. Absorption and Distribution

A. Dosage

Suramin is usually given by slow intravenous injection in 10% aqueous solution for the treatment of trypanosomiasis. It is not absorbed when given orally. Intramuscular or subcutaneous injection is irritating and painful. The normal dose for adults is 1 g. Because of rare instances of an immediate hypersensitivity reaction, a test dose of 0.1 g should be given before proceeding with the full course of treatment; the latter involves the administration of a normal dose on days 1, 3, 7, 14, and 21. Weekly doses may be given for an additional 5 weeks. Patients in poor condition should be treated cautiously during the first week. A second course of treatment should not be given earlier than 3 months after the first. In children, a 2-mg/kg test dose is used, and injections of 20 mg/kg are given on days 1, 3, 7, 14, and 21.

Suramin may be used as a chemoprophylactic agent. A single dose of 1 g gives protection for about 3 months. In the treatment of onchocerciasis, a trial dose of 0.1 g should be followed 1 week later by a dose of 1 g, and then 1 g is given weekly up to a total dose of 4 to 6 g (Apted 1980; Webster 1985; White 1989).

In the AIDS trials, commonly a test dose (200 mg) was given, followed within 1 to 3 days by an induction regimen of 0.5 to 1.5 g for 6 weeks. This was followed by a maintenance programme of 0.5 or 1.0 g per week (Levine et al., 1986; Cheson et al., 1987).

In antitumour trials, very different administration regimens are used. Because many of their patients had very advanced or rapidly growing malignancies, Stein et al. (1989) found it necessary to develop techniques for rapidly "loading" patients with suramin. They found that bolus administration of suramin, in contrast to a continuous infusion, was associated with a high incidence of fever, malaise, and rash. As a result, these authors now make it a practice to load patients at a dose of 350 mg/m^2/day by continuous infusion until dose-limiting toxicity, usually anticoagulation, develops. Because of the perceived correlation between anticoagulation and response, they allow prothrombin time to increase to 17.5 to 18 s before discontinuing drug administration. Suramin is then withheld until toxicity abates. A maintenance infusion 50 mg/m^2/day is used and is continued until evidence of disease progression appears.

The possible development of a Guillain-Barré syndrome prompted Stein et al. (1989) to place major emphasis on continued pharmacokinetic monitoring during suramin administration, with cessation of therapy occurring when a steady-state plasma level of 300 μg/ml is achieved (Stein et al., 1989). Data from protein-binding studies explained in part the development of severe toxicity associated with plasma levels beyond 300 to 350 μg/ml: at that point, the free fraction of suramin sharply increases from 500 ng/ml at a total plasma concentration of 500 μg/ml to 10 μg/ml at a total plasma concentration of 1000 μg/ml, which corresponds with a 20-fold dose increase (De Bruijn et al., 1991).

Because of the need for individualised dosing regimens based on pharmacokinetic parameters measured for each patient, Scher et al. (1992) developed an adaptive control strategy. The approach utilises both previously derived population data and concentrations determined prospectively for an individual patient. This procedure permits drug concentrations to be maintained in a defined range. Data from individual patients are fit using a maximum likelihood technique to determine the mean and standard deviation for the pharmacokinetic parameters. This initial population pharmacokinetic model requires full data sets for each patient. The derived model estimates are then refit using an iterative two-stage Bayesian approach to refine the model. The model is constantly updated by repeating the process as more data become available. The more data included for an individual patient, the less attention is paid to the population parameters. Once derived, the iterative two-stage parameters can be used to determine a limited sampling strategy that includes the most informative or optimal sampling times to measure plasma concentrations of suramin in individual patients.

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B. Pharmacokinetics

Initial plasma concentrations following intravenous injection decline rapidly during the first few hours and then more slowly during the next few days. A low concentration of drug, tightly bound to serum proteins, is maintained for up to 3 months (Gutteridge, 1985). Biochemical studies have provided evidence that suramin can form strong complexes with many proteins, including serum proteins, and will inhibit a large number of enzymes (Müller and Wollert, 1976; Vansterkenburg et al., 1989; Bos et al., 1990); tight complexes are also formed with LDLs (Vansterkenburg et al., 1993).

Tissue concentrations of suramin are about the same as the plasma concentration. Two notable exceptions to this are the brain, which contains little or no suramin, and the kidney, which contains approximately double the concentration of other tissues (Fairlamb, 1975). In two experiments by La Rocca et al. (1990b), the concentration of suramin in the adrenals 7 days after a single intravenous bolus injection in mice was 4.1- and 5.4-fold higher than that detected in plasma. With the exception of the kidneys, suramin accumulation in the adrenal glands was from 3- to 20-fold higher than that in a variety of other organs evaluated including lung, muscle, liver, brain, spleen, and large bowel.

It is generally assumed that suramin cannot cross the blood-brain barrier because of its large molecular size and because at physiological pH suramin is highly charged (−6). This strongly anionic nature of suramin possibly accounts for its inability to enter erythrocytes or to be absorbed from the gastrointestinal tract after oral administration. However, Stein et al. (1989) measured a suramin level in the CSF of 3 μg/ml in a patient at a time when the serum suramin level was in excess of 350 μg/ml. Rees et al. (1982) reported the presence of membranous inclusions within neurones and neuroglia of the suramin-treated rat brain. This indicates that whenever large doses of suramin are administered sufficient drug crosses the blood-brain barrier to affect neuronal metabolism. Furthermore, Raseroka and Ormerod (1985b) found that in an early infection in mice infected with *T. brucei* suramin clears the brain of parasites. They argued that, in a later stage of the infection, *T. brucei* are protected from the action of suramin because the trypanosomes are harboured intracellularly within the ependymal cells and that these intracellular trypanosomes are responsible for relapses after chemotherapy.

Until recently, because of analytical limitations, little was known of the pharmacokinetics and metabolic fate of suramin, and this has compounded the lack of understanding of the action of suramin in trypanosomiasis and onchocerciasis. Collins et al. (1986) studied the clinical pharmacokinetics of suramin in patients with HIV infection. They found the plasma half-life of suramin to be 44 to 54 days; they did not find any metabolites in plasma. Collins et al. (1986) found a renal clearance of only 0.3 ml/min. This is a small quantity compared with a volume of distribution of 40 liters. Nonetheless, it accounts for 80% of the total drug removal from the body.

Edwards et al. (1986) treated six Ghanian patients suffering from onchocerciasis with radiolabeled suramin. Plasma concentrations declined in a multiexponential fashion. The plasma clearance calculated from ^{14}C data was 0.072 ± 0.012 liters/h. The terminal half-life was 865.1 ± 154.2 h (36 days), and the apparent volume of distribution was 98.6 ± 21 liters.

In pharmacokinetic studies by Scher et al. (1992), a two-compartment open model adequately fit the available data. The model's values for the volume of central (4.53 ± 0.67 liters/m^2) and peripheral compartments (10.32 ± 1.42 liters/m^2) suggest limited drug distribution outside the extracellular fluid. The distributional half-life was 25.2 ± 5.4 h, and the elimination half-life was 29.7 ± 6.9 days.

Coleman and Adjepon-Yamoah (1986) determined the hepatic disposition of suramin, free from influences of other organs, using an isolated perfused rat liver preparation. They studied the disposition of suramin during 5 h following an 18-mg bolus dose containing 8 mCi of ^{14}C-labeled drug by monitoring the perfusate plasma level and bile. The subcellular localisation of suramin and ^{14}C radioactivity at the end of the experiment was determined. During the course of the experiment, approximately 50% of the ^{14}C radioactivity taken up by the liver was eliminated in bile. However, unchanged suramin could not be detected in the total biliary radioactivity, which was composed of unidentified and highly polar suramin derivatives. These studies indicate that, although hepatic handling of suramin is limited and the drug is localised in lysosome-rich liver fractions, previously undetected suramin metabolites may well account for much of the unidentified ^{14}C radioactivity excreted in the bile.

IV. Pharmacological Actions of Suramin

A. Action on Trypanosomes

Although suramin has been in use for the treatment of African trypanosomiasis since 1920, its mode of action on the trypanosomes is still far from clear. The effects of the drug on *T.b. rhodesiense* have been reviewed by Williamson (1979).

A variety of trypanosome enzymes have been reported to be inhibited by suramin in the range of 1 to 100 μM. These include *Trypanosoma cruzi* thymidilate kinase (Al-Chalabi and Gutteridge, 1977), *T.b. brucei* glycerol-3-phosphate oxidase (Fairlamb and Bowman, 1975, 1977), and a number of enzymes associated with the trypanosome's plasma membrane (3′-nucleotidase and protein kinase), its flagellar pocket membrane (acid phosphatase, and acid pyrophosphatase), and its digestive apparatus

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such as the lysosomes (phospholipase A1) (reviewed by Opperdoes et al., 1987).

The majority of the glycolytic enzymes in trypanosomes is located inside microbody-like organelles called glycosomes (Opperdoes, 1987). This contrasts with the situation in other organisms in which the glycolytic enzymes are present in a soluble form in the cytosol. Misset et al. (1986) noted that most of these glycosomal enzymes were characterised by a high isoelectric point, rendering these enzymes with positive charge at physiological pH. By modeling the available amino acid sequences of several glycosomal enzymes in the three-dimensional structures of the respective glycolytic enzymes from other organisms, Wieringa et al. (1987) noticed that the positive charges were concentrated in two so-called hot spots on the surface of the proteins at a distance of about 40 Å (Wieringa et al., 1987). With its two symmetrical negatively charged polysulfonated naphthylamine groups at each side of the molecule also approximately 40 Å apart, suramin is expected to interact with positively charged hot spots of the glycosomal proteins. Therefore, Opperdoes and coworkers measured the effect of suramin on all of the glycosomal enzymes. Suramin almost invariably inhibited the glycolytic enzymes of the trypanosome with I_{50} values <100 μM and was much less effective on the homologous enzymes from mammalian origin (Misset and Opperdoes, 1987; and Lambeir et al., 1987). In most cases, the kinetics of inhibition were quite complex, revealing both competitive and noncompetitive modes of inhibition, suggesting multiple sites of interaction with the drug. This remarkable specificity for almost all glycosomal proteins strongly suggests that an excess of positive charge on their surface might play an important role in the enzyme-drug interaction.

Fairlamb and Bowman (1980) investigated whether suramin is taken up in vivo by bloodstream trypanosomes and at what rate and whether glycolysis and respiration are inhibited by exposure to suramin. Progressive accumulation of suramin within the trypanosome is associated with an increasing inhibition of oxygen consumption. The results are compatible with their hypothesis that suramin inhibits glycolysis in vivo by a combined action against two enzymes: glycerol-3-phosphate oxidase and NAD^+-dependent glycerol-3-phosphate dehydrogenase. These investigators found a linear inhibition of oxygen consumption associated with an increasing duration of exposure to the drug in vivo; inhibition was also dependent on the dose of suramin administered. It was suggested that suramin is taken up by endocytosis as a complex bound to plasma protein. This presumably occurs as a result of a combination of fluid phase and a more specific type of uptake because suramin uptake is 18 times faster than that calculated for the fluid phase endocytosis of inert macromolecules, such as polyvinylpyrrolidone. When within the cell, the endocytic vesicles fuse with lysosomes to form secondary lysosomes in which the protein carrier molecule is degraded, thereby releasing suramin into the cytoplasm. Suramin then inhibits production of ATP by its combined action on the glycerol-3-phosphate oxidase and the NAD^+-dependent glycerol-3-phosphate dehydrogenase. As the amount of free suramin increases within the cell, the rate of ATP generation decreases, leading to a diminished rate of uptake of more drug from the plasma. Eventually, sufficient suramin is released from the secondary lysosomes, further decreasing the rate of production of ATP, leading to disorganisation of metabolic function and death of the organism.

The brain is the main, and probably the only, source of infection in relapses of *T. brucei* following chemotherapy. A number of studies have recently demonstrated synergism among trypanocidal drugs. For example, individual drugs only had activity against early-stage infection, whereas activity was extended to include effects against stages with central nervous system involvement when individual agents were given together with suramin. In addition, this synergism generally permitted the use of lower dosages of the drugs, decreasing toxicity. Jennings and Urquhart (1983) found that a single dose of 20 mg/kg of suramin followed by four daily doses of 30 mg/kg fexinidole (a 2-substituted 5-nitroimidazole) will effectively eliminate all the trypanosomes from the brains of chronically infected mice.

Jennings et al. (1983, 1984) evaluated the efficacy of combination drug treatment (suramin and one of three 2-substituted 5-nitroimidazoles) in mice with chronic infection in which trypanosomes were localised in the central nervous system. None of the three 5-nitroimidazoles tested alone cured mice when administered 21 days after the onset of the infection. Permanent cures were obtained, however, when treatment was carried out with suramin followed by the substituted 5-nitroimidazole compounds. Zweygarth and Röttcher (1987) reported that Ro 15–0216 (a 5-substituted 2-nitroimidazole compound) acted synergistically with suramin in *T.b. evansi*-infected mice. This was observed when suramin was combined with Ro 15–0216 in the suramin-resistant stock CP-893, although very high doses of suramin had to be administered. Raseroka and Ormerod (1985a) reported that a combination of suramin and metronidazole (a substituted 5-nitroimidazole) can clear trypanosomes from both brain tissue and ependymal cells. Mice with a 28-day infection are cleared of parasites, without relapse, by a single dose of suramin (40 mg/kg) followed, 3 days later, by five daily doses of metronidazole (500 mg/kg). Metronidazole alone has no effect on the infection, but its combination with suramin clears blood, tissues, brain, and ependymal cells.

Studies with two ornithine-decarboxylase inhibitors, DFMO and α-monofluoro- methyldehydroornithine methyl ester, have also shown a synergism of these

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compounds with suramin. Clarkson et al. (1984) reported trials of the combination of suramin and DFMO in mice with brain invasion. Bacchi et al. (1987) compared DFMO with α-monofluoro-methyldehydroornithine methyl ester for their ability to cure two distinct *T.b. brucei* central nervous system murine model infections. Both inhibitors cured the TREU 667 and LUMP 1001 isolates, if used in combination with a single (20 mg/kg) injection of suramin. When used in combination with suramin, α-monofluoro-methyldehydroornithine methyl ester was far more effective than similar doses of the DFMO combination.

The inhibition of ornithine decarboxylase by DFMO results in a complete elimination of putrescine and a 60 to 75% reduction of spermine levels, followed by a decrease in trypanothione biosynthesis. Trypanothione is used by trypanosomatids to reduce oxidised glutathione which is formed to scavage free radicals produced from H_2O_2 and superoxide anion. Trypanothione is also used for the enzymatic removal of peroxides by trypanothione peroxidase. In that way trypanothione is responsible for a sufficiently high intracellular thiol level and for the removal of peroxides and other toxic oxygen metabolites. Nitroimidazole compounds are believed to induce the production of radicals and the sequestering of trypanothione (Van Bogaert and Haemers, 1989).

It is striking that a synergism exists between suramin and compounds that inhibit the production of trypanothione and compounds that sequester trypanothione. The mechanism of DFMO synergism is unknown, but there are several observations that may be related. Preliminary experiments (Bacchi cited by Clarkson et al., (1984)) showed that the curative effect of suramin in non-central nervous system-infected mice can be abolished by exogenous polyamines. These polyamine reversal experiments with suramin, and their synergism with DFMO and α-monofluoro-methyldehydroornithine methyl ester, argue for a common basis of action relating to the intracellular polyamines.

Opperdoes et al. (1987) showed that the bloodstream form of *T. brucei* is capable of interiorising macromolecular material. This either occurs by fluid endocytosis, as is the case with an abundant protein such as albumin, or occurs by receptor-mediated endocytosis, as is the case for two less abundant proteins, LDL and transferrin. Suramin was found to inhibit the rate of endocytosis of transferrin in rabbit reticulocytes and to decrease the amount of membrane-bound transferrin; the latter effect could be explained by a reduced affinity of the receptor for transferrin (Bowen and Morgan, 1988). Suppressed cell surface binding of transferrin and the uptake of iron via receptor-mediated endocytosis in two distinct cell lines was also reported (Forsbeck et al., 1986). In addition, inhibition by suramin of the interaction of LDL and LDL receptors from bovine adrenal cortex membranes was reported (Schneider et al., 1982), as was a suramin-induced inhibition of lipoprotein binding to the putative lipoprotein receptor of *Schistosoma japonicum* (Rogers et al., 1989). Vansterkenburg et al. (1993) found that suramin decreases the binding of LDL to specific receptors located on the membranes of *T. brucei* and decreases the uptake of LDL by 50% at suramin concentrations ranging from 0 to 100 μM, thereby leading to the death of the parasite due to depletion of cholesterol and/or phospholipids.

B. Action on Filaria

A number of filarial enzymes involved in carbohydrate metabolism are inhibited by suramin, among which are lactate dehydrogenase from *Dirofilaria immitis* (Walter, 1979), lactate dehydrogenase and malate dehydrogenase from *O. volvulus* (Walter and Schultz-Key, 1980), NADP-linked malic enzyme from *O. volvulus* and *D. immitis* (Walter and Albiez, 1981), and glucose-6-phosphate dehydrogenase from *O. volvulus* (Titanji et al., 1988); these enzymes are possible targets for the action of suramin in the treatment of onchocerciasis. The above studies were made with (partially) purified enzymes. In contrast Howells et al. (1983) found that suramin had no effect on the glycolytic activity of *Brugia pahangi* in vitro and that the lack of effect was correlated with the failure of suramin to penetrate the worms in vitro.

The lack of effect of suramin at 200 μM on glycolysis in intact worms in vitro suggested an impermeability of the worms to the drug. This was confirmed by the failure of worms to progressively accumulate suramin in vitro and the ability of the aromatic polyanionic trypan dyes, trypan blue and red, to displace suramin from the worm surface. In the absence of the dyes, worms in serum-free incubation media adsorbed [^{14}C]suramin to a level 4-fold greater than the amount of drug in the surface inulin space of the body; in media containing trypan red or blue at 5 mg/ml, the surface adsorption of suramin was inhibited and residual suramin was associated with the inulin space. Worms in TC199 with 10% serum accumulated drug only to a level equivalent to that of the inulin space volume, and this drug level was not significantly influenced by the presence of trypan blue up to concentrations of 10 mg/ml. It was concluded from these studies that, although in vitro worms do not progressively accumulate, nor are they permeable to, suramin, the surface of the worm can adsorb the drug. Adsorption was competitively inhibited by high concentrations of other polyanionic compounds or by serum proteins in the incubation medium.

The observations of worms recovered from suramin-treated jirds indicate that suramin does not exert its primary effect on intact worms in vivo by inhibition of glycolysis. Worms recovered from jirds as late as 5 weeks after suramin dosage showed no obvious reduction from the control value in their rates of glycolysis or in the rate of uptake and incorporation of D-glucose, L-leucine, or

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adenosine. Embryogenesis in the drugged worms was also unimpaired. A significant mortality occurred among female worms between 5 and 7 weeks after the commencement of treatment, and a significantly lower lactate production was observed in moribund worms at week 7. The presumption that such a delayed lethal effect was the result of a gradual accumulation of suramin by the worms was, however, not supported by the experimental data which showed that the concentration of suramin in worms decreases with increasing time postadministration. The reduced levels of glycolysis observed in some worms, surviving week 7, was, therefore, unlikely to represent a primary result of drug action. This was further supported by the observation that the rate of glycolysis was unimpaired in worms 2 weeks after intraperitoneal dosing with five separate 100-mg/kg doses.

The presence of a [^{14}C]suramin level greater than the mean inulin space value on worms 1 h after intraperitoneal dosing suggests that the drug concentration obtained in the peritoneal cavity at the time of dosing is sufficient to saturate both the high-affinity binding sites of the peritoneal fluid proteins and the worm surface. At 3 and 6 h, the level of [^{14}C]suramin on the worms was equal to or less than the amount of label in 0.1 μl of peritoneal fluid but, from 24 h onward, there was evidence of a true "net" uptake of suramin by the worms. It has been assumed that in vivo the amount of drug associated with the worm surface will approximate that observed in worms incubated in vitro in medium containing 10% serum. Direct evidence of an oral uptake of polyanions in vivo was obtained from the observation of trypan blue in the intestinal lumen of worms recovered from jirds 6 to 24 h after dosing with the dye.

An exclusion of suramin from the tissues of the worm during the primary phases of drug effect is consistent with the observed lack of drug effect on glycolytic activity and with the pattern of ultrastructural changes found in drugged worms. These ultrastructural observations suggest that the intestinal epithelium itself might be the site of action of the drug, with marked degenerative changes observed in the plasma membrane of the adluminal surface of the cells. The primary action of suramin on *B. pahangi* is considered to differ from that described on trypanosomes and mammalian macrophages. Ingested free suramin or suramin liberated from serum-protein complexes is not thought to rapidly penetrate the intestinal epithelium or other tissues of the worm because the macrofilaricidal action of the drug is not associated with either an inhibition of glycolysis during the first weeks after treatment or those processes concerned with the uptake and incorporation of glucose, leucine, and adenosine.

It should be stressed that the subject of investigation, *B. pahangi*, resembles the agents of Bancroft's and Malyan filariasis, in which suramin is not used in treatment, rather than the agent of onchocerciasis, in which it is used. Although all of the agents involved are filarial worms, they may be just enough apart biologically that there are some physiological differences, including differences in the ability of suramin to inhibit metabolic enzymes.

In a study by Wolf et al. (1980), patients suffering from onchocerciasis received five or six weekly doses of suramin (15 to 20 mg/kg). Nodulectomies and enzymatic isolation of adult worms were performed 1 to 6 weeks after the last dose. The examination of the living worms revealed a significantly lower proportion of males with sperm and females with eggs, or eggs and embryos, after suramin treatment, thus indicating an early effect of the drug on the more sensitive germ cells and developing stages in the adult parasites. The median microfilarial density in the skin decreased from 37.3 microfilaria/mg before treatment to 10.5 microfilaria/mg 1 to 3 weeks and 1.7 microfilaria/mg 4 to 6 weeks after the end of treatment.

From a similar investigation (over a longer period), Duke (1991) reported the nature and timing of the changes in adult *O. volvulus* leading up to their death after a 7.1-g course of suramin. The numbers of microfilaria reaching the skin every 16 days remained at about the pre-suramin level for 96 days and only reached zero by day 224 after the start of drug treatment. The histopathology of nodules excised from patients before and at intervals of 56 to 335 days after the start of the suramin course revealed changes in the worms that correlated over time with the disappearance of microfilariae from the skin. Nodules removed at 56 and 77 to 91 days showed that suramin acted first by impeding the vitality, and subsequent development of small morulae, and by virtue of its toxic sterilising and lethal action on the male worms, an action that terminated insemination; treatment also prevented further fertilisation of the continuing supply of ova. Embryos already at the large morula or later stages were not directly affected by the drug. Likewise, the ovaries were not affected until late, and they continued to give rise to unfertilised ova, albeit in declining numbers, until just before the worms died. At 120 days, live microfilaria and some live brezels could still be seen in utero, but by 187 days, no live microfilaria remained in the worms, and almost all of the females were moribund or dead.

C. Action on Human Immunodeficiency Virus

Suramin is a potent inhibitor of the RNA-directed DNA polymerase (RT) of several retroviruses (De Clercq, 1987). It causes a 50% inhibition of the RNA-directed RT activity at a concentration of about 1 μg/ml (0.7 μM). Yet, the effect of suramin on RT is not specific. Other DNA polymerases, viz., DNA polymerase α and DNA primase, are also strongly inhibited by suramin (Ono et al., 1985; Chandra et al., 1987), whereas DNA polymerases β and γ and terminal deoxynucleotidyl transferase

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are relatively resistant to the drug (Ono et al., 1985). The inhibition of RT by suramin is competitive with respect to the template-primer, i.e., poly(A)·poly(dT), for the avian myeloblastosis virus RT. This suggests that the drug interacts with the template-primer-binding site of the enzyme. Through its naphthalenetrisulfonic acid groups, suramin may bind to basic amino acid residues at or near the active center of the RT.

Basu and Modak (1985) found that suramin is a non-specific inhibitor of viral and cellular DNA polymerases, including terminal deoxynucleotidyl transferase, and that inhibition is most readily reversed by the addition of serum albumin. No evidence to demonstrate specific domain interaction between DNA polymerases and suramin could be obtained. It seemed unlikely that suramin has any usefulness as a DNA polymerase-specific (or RT-specific) inhibitor. In the light of these results, the reported ability of suramin to block AIDS virus infection in cultured T-cells is rather difficult to attribute to selective inactivation of viral RT as suggested by Mitsuya et al. (1984).

Spigelman et al. (1987) reported that suramin can inhibit the three constitutive DNA polymerases of mammalian cells, DNA polymerases α, β, and γ, and the special DNA polymerase of primitive lymphoid cells, terminal deoxynucleotidyl transferase, at levels comparable to those required to inhibit viral RT. They found that suramin inhibits all DNA polymerases tested. The mechanism was uncompetitive with respect to substrate as determined by Lineweaver-Burk plots for avian myeloblastosis virus-RT, terminal deoxynucleotidyl transferase, and α-polymerase. These authors also reported that multiple cell lines in culture, particularly lymphoid cells, are growth inhibited when exposed to suramin. The apparent selective lymphocytotoxicity of suramin represents an important property of the drug and may account for the persistent immune suppression reported in suramin-treated patients with AIDS.

Polyanionic substances, such as polyacrylic acid, polymethacrylic acid, polyvinyl sulfate, dextran sulfate, and polyphloroglucinol phosphate, are all known to interfere with the virus adsorption process. Being a hexasulfonic acid derivative, suramin might also affect virus adsorption to the cells. Inhibition of cell binding of HIV has been found; however, higher concentrations are necessary for inhibition than are needed for suppression of infectivity and replication of HIV, and the inhibition of cell binding is not complete (Mitsuya et al., 1988; Schols et al., 1989a).

Multinucleated giant cell (syncytium) formation induced by the interaction between the gp120 glycoprotein expressed on the surface of cells infected with HIV-I and the CD4 receptor of uninfected $CD4^+$ cells may play an important role in the depletion of T4 lymphocytes in patients with AIDS (Haseltine, 1988). Suramin proved capable of blocking giant cell formation and protected uninfected $CD4^+$ MOLT-4 cells against destruction by HIV-I-infected HUT-78 cells (Schols et al., 1989b; Baba et al., 1990). Suramin may directly interact with the viral glycoprotein gp120 that is involved both in HIV binding to cells and to syncytium formation. Suramin proved to have an inhibitory effect on the binding of anti-gp120 monoclonal antibodies to the gp120 epitope of HIV-I-infected HUT-78 cells that is required for cell fusion. This inhibitory effect could be ascribed to a specific interaction of suramin with gp120. However, the inhibitory effect is easily neutralised by fetal calf serum (Schols et al., 1990).

Yao et al. (1991a,b) emphasised that physiological concentrations of serum albumin in in vitro experiments significantly attenuated suramin's antiviral effects, suggesting that only free suramin has antiviral properties. Neutralising effects of albumin on suramin blockade of gp120-CD4 binding and on the inhibitory effect of suramin on HIV replication and RT activity were reported. It was suggested that discrepancies between in vitro and clinical activities of suramin may be due to differences between free suramin levels in experimental assays and those achievable clinically.

Results from Fields et al. (1988) indicate that HIV-induced phosphorylation of CD4 precedes, or occurs concomitantly, and could be involved in the mechanism of viral entry. Blockade of HIV-induced CD4 phosphorylation with the PKC inhibitor, H-7, effectively inhibits viral infectivity in long-term cultures, possibly by interfering with the entry of cell surface-bound virus particles. Hence, PKC may be a potential target for anti-HIV therapeutic agents. Suramin has been found to be an inhibitor of PKC (Hensey et al., 1989; Mahoney et al., 1990). Kinase activity of PKC types I to III was inhibited by suramin in a concentration-dependent manner, with type I (IC_{50} = 29 μM) being approximately 2-fold more sensitive to suramin inhibition than were types II and III (IC_{50} = 50 μM). Kinetic analysis of the inhibition indicated that suramin competitively inhibits kinase activity with respect to ATP with K_i values of 17, 27, and 31 μM, respectively, for PKC types I to III (Mahoney et al., 1990). These results are in agreement with a previous study (Hensey et al., 1989) and suggest that suramin may act by preventing HIV entry into T-cells via inhibition of PKC and phophorylation of the HIV CD4 receptor.

D. Action on Other Viruses

Apart from inhibition of HIV, suramin has been tested for antiviral action against a number of other viruses. Suramin was reported to block the activity of the RNA-directed DNA polymerase encoded by the duck hepatitis B virus (Tsiquaye and Zuckerman, 1985). The inhibition of DNA polymerase activity associated with core particles from infected liver and circulating virions is irreversible and occurs in a dose-response fashion. Similar

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findings were presented by Offensperger et al. (1988), who showed that suramin reduced the activities of endogenous DNA polymerase, RT, and exogenous DNA polymerase by 90% and more at a concentration of 1 mM; a 50% inhibition was achieved by 0.2 μM suramin. Tsiquaye et al. (1986) examined acyclovir and suramin for their efficacies alone and in combination against duck hepatitis B virus in persistently infected Peking ducks. Because the activity of DNA polymerase is proportional to the titres of circulating infectious virus, the inhibition of specific DNA polymerase activity was used as a measure of the HBV response to antiviral drugs. A five-dose course of suramin administered intravenously to carrier ducks produced a pattern of markedly decreased levels of DNA polymerase activity. However, enzyme activity returned to pretreatment levels during the follow-up period. A combination treatment, which proved more effective in maintaining suppressed levels of polymerase activity in the ducks after treatment, was acyclovir followed by suramin. The basis of the response to this particular regimen is unclear (Tsiquaye et al., 1986).

Petcu et al. (1988) examined the effect of suramin on in vitro infection by duck hepatitis B virus and obtained an unexpected result. Suramin irreversibly blocked infection by this virus when present at the time of virus absorption but, contrary to expectations, had no comparable effect on synthesis of viral DNA when added after the absorption period. To further clarify the action of suramin, they examined the effect of the drug on in vitro infection of chick embryo fibroblasts by Rous sarcoma virus (a retrovirus) and of woodchuck hepatocytes by the hepatitis δ virus (an RNA virus). Suramin blocked infection by both viruses when present during virus absorption. The drug did not inhibit intracellular synthesis of full-length viral nucleic acids for Rous sarcoma virus or hepatitis δ virus when added following an initial absorption/uptake period. The results with Rous sarcoma virus were especially clear in indicating that suramin acted primarily at an early stage distinct from viral DNA synthesis/reverse transcription. Observations conducted with hepatitis δ virus further supported this interpretation, because this RNA virus does not appear either to use an RT or to precede through a DNA intermediate during its replication cycle. A more reasonable hypothesis is that suramin acts by inhibiting an intracellular process associated with virus uptake and uncoating. Such a situation is at least consistent with the lysosomotropic property of the drug. Possible targets include endocytosis of virus-receptor complexes, virus uncoating, and the cycling of receptors to the cell surface where they would be available to incoming viruses (Petcu et al., 1988). Similar results with hepatitis δ virus-infected woodchuck hepatocytes have been reported by Choi et al. (1989).

Ruprecht et al. (1985) reported the evaluation of suramin in murine retroviral sytems in vitro and in vivo, using the T-cell tropic virus SL3–3 and the erythropic Rauscher murine leukemia virus. In their murine systems, injection in the presence of suramin yielded viral titres several logarithms lower than control levels. A lesser degree of suppression of viral titres occurred if suramin was started only after infection, although suramin was still able to decrease viral amplification and spread throughout the cultures.

Alarcón et al. (1984) tested a number of compounds for antiherpes activity using a cell culture system, based on the infection of HeLa cell monolayers with Herpes simplex virus type 1 at a low multiplicity of infection (0.2 to 0.5 plaque-forming units/cell). The test compound was added with the virus, and after 48 h of incubation the cytopathic effect was recorded when examined with a phase-contrast microscope. The protein-synthesising capacity of the cell monolayer was estimated by using a short pulse of [^{35}S]methionine. A reduction of viral cytopathogenicity was observed with suramin at concentrations not affecting cellular protein synthesis. Suramin was active against Herpes simplex virus type 1, vesicular stomatitis virus, semliki forest virus, and encephalomyocarditis but not against poliovirus.

Sola et al. (1986) tested suramin, among other compounds, for its activity against African swine fever virus replication (in vitro). Both viral inhibitory potency and cytotoxicity were investigated. Suramin was second best in inhibitory potential and cytotoxicity but had the most favourable therapeutic index. No virucidal activity was observed against African swine fever virus with any of the compounds. Suramin also inhibits the multiplication of yellow fever virus (Croon and Wolff, 1980).

Cogan et al. (1986) investigated the effect of suramin in vitro against feline leukemia virus. Feline leukemia virus infection of domestic cats is common and causes considerable mortality and morbidity secondary to immunosuppression. Suramin was administered intravenously to two healthy adult cats infected with the naturally acquired feline leukemia virus. Although the experiment demonstrated that short-term suramin treatment can be given with relative safety to cats at large doses relative to those frequently used in humans, no long-term antiviral effect was evident, no enhancement of immunosurveillance was noted, and the cats reflected clinical disturbances including drug-related vomiting and transient anorexia. These results are analogous to observations made in humans infected with HIV and treated with suramin. The cats continued to have positive test results for feline leukemia virus internal antigens in their peripheral blood cells and serum, despite the absence of detectable infective viruses in their serum during suramin treatment; this antigenemia may represent noninfective viral particle debris or extremely low levels of infective virus undetectable by the 81 cell focus induction assay.

E. Interaction with Receptors

ATP released from sympathetic nerves as a cotransmitter can induce either contraction or relaxation of

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smooth muscle by activating P_{2x} or P_{2y} purinoceptors (Burnstock and Kennedy, 1985). Dunn and Blakely (1988) found suramin to be an effective and apparently selective antagonist at the P_2 purinoceptor of the mouse vas deferens. These smooth muscle cells contract after stimulation of ATP-sensitive receptors classified as P_{2x} purinoceptors. At a concentration of 100 μM, suramin antagonised the response to α,β-methylene-ATP, whereas responses to carbachol and noradrenaline were unaffected. Similar results were obtained by Von Kügelgen et al. (1990), and Hoyle et al. (1990) found antagonistic effects of suramin (100 μM to 1 mM) on P_{2x} purinoceptors in the guinea pig urinary bladder. In contrast, Hourani and Chown (1989) found no consistent inhibitory effect of suramin (100 μM) on P_{2x} purinoceptors in the guinea pig bladder. Suramin (300 μM) also inhibited the ATP-induced relaxation of smooth muscle cells of the guinea pig taeni caeci and taenia coli, actions that are assumed to be mediated via P_{2y} purinoceptors (Den Hertog et al., 1989a; Hoyle et al., 1990).

Antagonism by suramin does not always appear to be competitive. Hoyle et al. (1990) found a depression of the maximal response as well as a rightward shift of the concentration-response relationship for α,β-methylene-ATP in the guinea pig urinary bladder. The interaction of suramin with the P_{2x} receptor was further complicated by the potentiation of P_{2x} receptor-mediated activity seen at 1 μM suramin. Results by Von Kügelgen et al. (1990) showed that in the mouse vas deferens concentration-response curves for α,β-methylene-ATP, adenosine 5′-O-(3-thio)-triphosphate, UTP, and lower concentrations of ATP (0.1 to 1 μM) are shifted to the right by suramin (10 to 300 μM). However, at least in the case of α,β-methylene-ATP and adenosine 5′-O-(3-thio)-triphosphate, the effect of suramin was not a simple parallel shift: suramin increased the response to a maximal concentration of α,β-methylene-ATP and increased the slopes of the concentration-response curves of α,β-methylene-ATP and adenosine 5′-O-(3-thio)-triphosphate. Increases in the maximal response to α,β-methylene-ATP on the mouse vas deferens was also reported by Blakely et al. (1991). The reason for the increase in maximal effects and slopes is not clear, but suramin might abolish an inherent relaxant effect of α,β-methylene-ATP and adenosine 5′-O-(3-thio)-triphosphate, (which agrees with inhibition of ATP-induced relaxation of the guinea pig taenia caeci and taenia coli (Den Hertog et al., 1989a; Hoyle et al., 1990)). Another possibility is that suramin interferes with the desensitisation produced by high concentrations of the stable ATP analogues (Von Kügelgen et al., 1990). A report by Left et al. (1990) described an attempt to characterise the antagonist properties of suramin at P_{2x} receptors in the rabbit ear artery. Minimum incubation times for each concentration of suramin used in the Schild plot analysis were calculated to achieve >95% occupancy without agonist curve depression at each concentration. Under these conditions, suramin fulfilled all criteria for simple competition: parallel rightward displacement of α,β-methylene-ATP curves and a Schild plot slope of unity. The resulting pK_B estimate was 4.79 ± 0.05. This estimate of affinity was shown to be independent of the agonist used in another experiment in which L-β,γ-methylene-ATP was used (pK_B = 5.17) (Left et al., 1990).

Results by Hoiting et al. (1990) show that suramin acts on a common component in processes activated by ATP, probably at the level of the P_2 purinoceptor. Membrane currents and the formation of inositol tetrakisphosphate in DDT_1 MF-2 vas deferens smooth muscle cells are inhibited by suramin. An intracellular effect of suramin cannot be involved because the drug did not alter basic levels of the inositol phosphates. Competitive antagonism of ATP-activated current by suramin has also been found in PC12 phaeochromocytoma cells and suggests that suramin may compete with ATP for the receptor that seems directly coupled to the channel (Nakazawa et al., 1990).

Suramin reduces the inhibitory junction potential induced by exogenous ATP and by stimulation of nonadrenergic inhibitory nerves that are assumed to release ATP as a cotransmitter (Den Hertog et al., 1989b). In isolated strips of taenia coli in which a standard tone has been induced by carbachol (100 nM), suramin at both 100 μM and 1 mM significantly antagonised responses to ATP and relaxant responses to electrical stimulation of the intramural nonadrenergic, noncholinergic inhibitory nerves (Hoyle et al., 1990).

Intravenous administration of suramin caused a blockade of vascular P_{2x} receptors for at least 0.5 h (Schlicker et al., 1989). Suramin, which by itself produced a short-lived decrease, followed by a persistent increase in blood pressure, decreased the initial phase of the pressure response to ATP, to α,β-methylene-ATP, and to electrical stimulation without affecting the decrease and secondary increase in blood pressure elicited by ATP and the pressure response to noradrenaline. Suramin appears to inhibit the release from neurotransmitters of the postganglionic sympathetic neurons at a preganglionic site, because the drug inhibited the electrically evoked increase in blood pressure without affecting the pressure response to noradrenaline.

Suramin can reverse nondepolarising neuromuscular blockade through a competitive antagonism of nondepolarising relaxants, whereas it is ineffective on the paralysis evoked by the depolarising relaxant succinylcholine (Henning et al., 1992). Both the post- and presynaptic actions of nondepolarising relaxants are inhibited by suramin without increasing acetylcholine concentrations in the synaptic cleft, suggesting that suramin binds to a subunit of the acetylcholine receptor also occupied by nondepolarising relaxants but different from the succinylcholine-sensitive site.

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Suramin also interferes with the binding of LDL to its receptor. Schneider et al. (1982) described a procedure for the purification of the LDL receptor from bovine adrenal cortex membranes in which, during one step, the receptor is subjected to affinity chromatography on LDL coupled to Sepharose 4B. The receptor is eluted with suramin, which was found to be an inhibitor of LDL interactions. Lipoprotein binding to Sj 43, the putative *S. japonicum* lipoprotein receptor (which displays a wide range of cross-species lipoprotein binding and combines the specificity of the mammalian high-affinity LDL receptor and the low-affinity HDL binding protein), could be inhibited by suramin (Rogers et al., 1989). Vansterkenburg et al. (1993) found that suramin decreases the binding of LDL to specific receptors located on the membranes of *T. brucei* and decreased the uptake of LDL by 50% at suramin concentrations from 0 to 100 μM. They suggested that the interference of suramin with the LDL-receptor interaction was caused by a noncovalent binding of the drug to the high-affinity sites on LDL (Vansterkenburg et al., 1993).

Forsbeck et al. (1986) used suramin to analyse the growth effect of blockade of iron uptake on two established human cell lines U-937 (monocytoid) and K-562 (erythroleukemic). Suramin suppressed cell surface transferrin binding and uptake of iron via inhibition of receptor-mediated endocytosis. As a result, both lines accumulated in the S-phase. DNA synthesis and cell division were inhibited in the suramin-treated U-937 cells but not in the K-562 cells. Iron supplied to suramin suppressed U-937 cells, by a route alternative to transferrin, reinitiated DNA synthesis and cell division, although at a lower level than in control cells, suggesting that there are other disturbances introduced by suramin in the U-937 cells in addition to iron deprivation. In a study by Bowen and Morgen (1988) of the effects of osmolar and ionic factors on endocytosis and exocytosis of transferrin using rabbit reticulocytes, suramin accelerated the rate of exocytosis and inhibited the rate of endocytosis; these changes were associated with a decline in the amount of membrane-bound transferrin. This decline could be explained by a reduced affinity of the receptor for transferrin.

F. Disturbance of Growth Factor-Receptor Interaction

Growth factors are implicated in a wide variety of physiological and pathological processes. These include embryogenesis, growth and development, selective cell survival, hemopoiesis, tissue repair, immune responses, atherosclerosis, and neoplasia. An important link between growth factors or their receptors and oncogene products has also been established. Thus, the elucidation of the mechanism of action of growth factors has emerged as one of the fundamental problems in biological sciences and may prove a crucial prerequisite for understanding the cause or causes underlying the unrestrained proliferations of cancer cells (Rozengurt, 1986). PDGF, a cationic 32-kDa protein isolated from human platelets, is one of the principal mitogens in whole blood serum in a number of cells of mesenchymal origin in vitro. The mitogenic response to PDGF is mediated by the interaction of PDGF with specific high-affinity cell surface receptor sites which, in turn, activate intracellular events (Williams et al., 1984, and references therein).

Williams et al. (1984) examined the binding of PDGF to its receptor sites in membrane preparations to define the kinetics and equilibrium characteristics of the binding reactions in the absence of complicating reactions, such as receptor internalisation and metabolism. Suramin was found to reversibly dissociate PDGF from its high-affinity receptor sites. Hosang (1985) demonstrated that suramin inhibited cellular binding of PDGF by binding to PDGF itself, thereby inactivating it as a ligand, and showed that suramin inhibits PDGF-induced synthesis of DNA in quiescent Swiss 3T3 cells as well as induced proliferation of these cells. Hosang (1985) suggested that suramin may inhibit PDGF binding by interacting with those positively charged amino acid residues with which PDGF interacts with the receptor or, alternatively, acts allosterically, i.e., binds to another domain(s) of PDGF and induces a conformational change and, thereby, renders it unable to bind. The latter possibility is supported by the finding that suramin efficiently promoted dissociation of preformed ^{125}I-PDGF receptor complexes, whereas PDGF itself, which is presumably the most competitive inhibitor of ^{125}I-PDGF, had no effect.

Betsholtz et al. (1986) reported that suramin, in addition to inhibiting the binding of ^{125}I-PDGF, also inhibits the binding of ^{125}I-labeled epidermal growth factor, and dissociates the same cell-bound factors bound to cells at 4°C. Inhibition by suramin of the binding of transforming growth factor-β, heparin-binding growth factor type 2 (Coffey et al., 1987), basic fibroblast growth factor (Neufeld and Gospodarowicz, 1988), and insulin-like growth factor I (Pollak and Richard, 1990) to their receptors also has been reported. Inhibition of binding to and displacement from their receptors has been reported for epidermal growth factor (Betsholtz et al., 1986), brain-derived growth factor (Huang et al., 1986), and colorectum-derived growth factor (Culouscou et al., 1988).

The effects of PDGF on the $[Ca^{2+}]_i$ in chondrocytes were studied and compared with the effects of PDGF on mitogenesis and proteoglycan synthesis (Fukuo et al., 1989). PDGF evoked phasic and then tonic increases in $[Ca^{2+}]_i$ dose dependently in quiescent cultures of chondrocytes, and it also stimulated both DNA and proteoglycan syntheses dose dependently similarly to that produced by the somatomedins. Pretreatment with suramin caused a dose-dependent inhibition of the PDGF-evoked increases in both $[Ca^{2+}]_i$ and DNA synthesis. However,

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pretreatment with suramin enhanced the proteoglycan synthesis induced by PDGF without affecting the basal level of proteoglycan synthesis directly.

SSV is an acutely transforming primate retrovirus isolated from a woolly monkey fibrosarcoma. Structural analysis of the viral genome has shown that it arose by recombination of simian sarcoma-associated virus with a woolley monkey cellular gene segment, v-*sis*. The structure and function of the human cellular locus c-*sis* has been clarified; it encodes one of the constituent chains of PDGF (Betsholtz et al., 1986, and references therein). SSV-transformed cells provide one of the best models for studying the mechanism of autocrine transformation. The putative transforming protein of SSV, the v-*sis* gene product, shows growth factor activity identical with human PDGF and immunoreactivity to anti-PDGF antisera. The v-*sis* gene product and PDGF cannot be distinguished from each other with respect to cellular biological properties (binding to the PDGF receptor, K_d, effect on down-regulation of the receptor).

The PDGF receptor is a membrane glycoprotein whose biosynthesis and processing occur by the pathway common to other plasma membrane proteins. The 160-kDa precursor of the PDGF receptor, presumably synthesised in the endoplasmatic reticulum, possesses high mannose-type carbohydrate side chains. The 160-kDa precursor is converted to the 180-kDa receptor, which has complex-type carbohydrates, presumably in the Golgi apparatus. In normal NIH 3T3 cells and NRK cells, all of the 180-kDa receptor molecules appear on the cell surface 2 h after their synthesis. The cell surface 180-kDa receptor exhibits a half-life of approximately 4 h.

In SSV-transformed cells, the v-*sis* gene product is synthesised in a manner similar to other secretory glycoproteins, with transport through the endoplasmic reticulum and Golgi apparatus and addition and procession of oligosaccharide side chains. Because both v-*sis* gene products and the PDGF receptor undergo fast biosynthesis and processing, it is possible that the v-*sis* gene product interacts with the ligand-binding domain of the PDGF receptor in the lumen of the endoplasmic reticulum and/or Golgi apparatus during intracellular routing. This might result in the activation of the cytoplasmic protein-tyrosine kinase domain, leading to initiation and maintenance of the transformed state of SSV-transformed cells. In cells transformed by either v-*sis* or c-*sis*, the majority of newly synthesised receptors fail to reach the cell surface and are turned over with a shorter half-life (<30 min). The apparent processing alteration or rapid turnover of the PDGF receptor in SSV-transformed cells and c-*sis*-transformed cells is very likely due to the interaction of *sis* gene products and the PDGF receptor in the endoplasmic reticulum and/or Golgi apparatus (Huang and Huang, 1988, and references therein).

Garrett et al. (1984) found that when SSV-transformed cells are exposed to suramin the PDGF receptors reappear on the cell surface. Receptor up-regulation was also found by Johnsson et al. (1986). Huang and Huang (1988) found that suramin not only blocked the rapid turnover of the PDGF receptor in all of the SSV-transformed and c-*sis*-transformed cells tested but also increased the secretion of *sis* gene products into the media of SSV-transformed cells and v-*sis*-transformed cells. The increased secretion of the *sis* gene product by suramin (15 μM) is not due to the blocking of uptake of *sis* gene products secreted into the medium because, at 15 μM, suramin had no significant effect on the cell surface PDGF receptor. This is further supported by the observations that excess recombinant v-*sis* gene product or protamine in the culture medium did not augment the secretion of the ^{35}S-labeled v-*sis* gene product. The ED_{50} of suramin for inhibition of PDGF or recombinant v-*sis* gene product was estimated to be approximately 60 μM. However, suramin reversed the rapid turnover of the PDGF receptor and increased secretion of the v-*sis* gene product at a much lower concentration (15 μM). This further ruled out the possibility of an extracellular effect of suramin.

Huang and Huang (1988) suspected that the effect of suramin on potential intracellular ligand binding by the receptor is due to the accumulation of the inhibitor to a sufficiently high concentration in an intracellular compartment(s). Keating and Williams (1988) also found that suramin prolonged the half-life of the mature receptor in v-*sis*-transformed cells, but they did not find inhibition of intracellular receptor activation. Results by Fleming et al. (1989) established that suramin alters the interaction of the v-*sis* product and its receptor but that the suramin action was specifically localised to cell surface PDGF receptors. Their results suggested that suramin is able to strip ligands already bound to receptors and to down-regulate enzymatic activity of internally activated receptors as they reach the surface. Down-regulation of the basic fibroblast growth factor receptor was found with NIH3T3 cells that have been transformed as a result of transfection with basic fibroblast growth factor cDNA. Treatment of the transformed transfected NIH3T3 cells with suramin, which blocks the interaction of basic fibroblast growth factor with its receptor, reversed the morphological transformation and restored receptors almost to normal numbers (Moscatelli and Quarto, 1989).

Suramin (100 μg/ml) can inhibit the growth of human colonic adenocarcinoma cells, HT29-D4, and rapidly induce a typical enterocytic differentiation similar to the one obtained by growing these cells in the absence of glucose. Suramin also inhibits glucose consumption and lactate production. It is likely that external factors trigger or prevent cell differentiation and that altered glucose consumption is the consequence of these effects. By interfering with external signals, such as growth factors,

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suramin could elicit the effect of differentiation that was observed (Fantini et al., 1989). The differentiation has been found to occur in medium containing fetal calf serum and in a serum-free medium (Fantini et al., 1990d). A comparison of the states of organisation reached by the HT29-D4 cells after glucose starvation or after long-term suramin treatment demonstrated that a better state of organisation is obtained in the presence of suramin (Fantini et al., 1990c). Suramin was also able to interfere with the mode of release of carcinoembryonic antigen in HT29-D4 cells (Fantini et al., 1990b).

An interference of suramin with the transition of smooth muscle cells from a contractile to a synthetic phenotype in vitro has been found. It is unclear by what mechanism suramin affects this process; it may have a direct effect on the cell surface or it may interfere with the cellular binding of substances that take part in the control of the differentiated properties of the cells (Sjölund and Thyberg, 1989).

The growth of a well-characterised rat glioma cell line (C6) can be impaired in a dose-dependent manner by suramin, in serum-supplemented as well as in a defined serum-free medium. Moreover, the drug induced profound alterations in cell morphology, which may account for cell differentiation. Suramin increased the cell surface expression of adhesion molecules, N-CAM (Fantini et al., 1990a).

Suramin counteracts the growth stimulatory effects of both androgens and growth factors on androgen-sensitive tumour cells. The effects are reversible after withdrawal of suramin. Human prostate tumour (LNCaP) cell growth is inhibited by suramin (0.01 to 1.0 mM) in a dose-dependent way; growth was arrested in the G_0/G_1 phase of the cell cycle. Suramin inhibited PDGF- and basic fibroblast growth factor-stimulated cell growth of hamster ductus deferens tumour cells. In the presence of testosterone, however, suramin showed a biphasic effect: stimulatory at a low dose (0.01 mM) and inhibitory at a dose >0.01 mM (Berns et al., 1990).

G. Action on Cancers

The machinery that transduces the growth factor signal to the cell nucleus includes the growth factor receptors, their substrates, a number of key enzymes (including kinases and lipases), cytoskeletal proteins, transcriptional factors, DNA-binding proteins, and, finally, a complex of enzymes that channel deoxy- and ribonucleotide precursors into the growing forks of DNA replication (Goustin et al., 1986). In addition to its most important action on growth factors, suramin also disturbs other elements of the signal transduction process from the growth factor receptor to the nucleus leading to neoplasia.

G proteins make up a family of membrane-associated proteins that transduce extracellular signals, such as hormones or photons, into a diverse array of cellular responses. All of these proteins bind and hydrolyse GTP, and GTP, in turn, regulates their interactions with signal detectors (cell surface receptors) and effectors (membrane-associated enzymes and ion channels). Each G protein utilises a common GTP-dependent mechanism to transduce signals between unique sets of detector and effector elements (Masters and Bourne, 1986). Receptor-stimulated breakdown of phosphoinositide leads to the formation of a Ca^{2+}-mobilising second messenger, inositol 1,4,5-triphosphate, and an activator of PKC, diacylglycerol. Many different agonists utilise this signal transduction pathway for which the relevant effector appears to be phospholipase C. It is suggested that one or more G proteins couples the receptor to phospholipase C (Williamson, 1986). Butler et al. (1988), using a neuroblastoma × glioma hybrid cell line, demonstrated that suramin can noncompetitively inhibit the GTPase activity of certain G proteins, such as G_i, and hence disrupt the function of δ-opioid receptors which couple to this G protein.

Among the immediate consequences of the growth factor-receptor interaction are the activation of various ion transport systems in the plasma membrane and changes in intracellular composition. Mitogen-induced alterations in the levels of $[Ca^{2+}]_i$ and H^+ are of special interest, because these ions are thought to serve as second messengers that trigger and regulate cell proliferation. Addition of serum, PDGF, epidermal growth factor, or other mitogenic peptides to responsive cells evokes a rapid, but transient, several-fold increase in $[Ca^{2+}]_i$. Subsequent to growth factor binding, the $[Ca^{2+}]_i$ increase is without a detectable lag period (<1 s). In general, the rapid $[Ca^{2+}]_i$ signals in response to extracellular stimuli are mediated by the second messenger, inositol 1,4,5-triphosphate, which triggers the release of Ca^{2+} from the endoplasmic reticulum. It is generally accepted that Ca^{2+} plays an important role as a second messenger to regulate numerous cellular activities. Ca^{2+} may play a key role in mediating, either directly or indirectly, the early transcriptional effects of growth factors. Furthermore, one should consider the possibility that the rapid increase in $[Ca^{2+}]_i$ serves to trigger some of the early nonmitogenic responses to growth factors, such as cytoskeletal reorganisations, fluid endocytosis, or chemotaxis, reviewed by Moolenaar (1986). Suramin has been shown to inhibit dose dependently the PDGF-evoked increase in $[Ca^{2+}]_i$ in quiescent cultures of chondrocytes (Fukuo et al., 1989).

There are at least five growth factor receptors that have protein-tyrosine kinase activities and that are stimulated several-fold when binding their cognate ligand. Among them are those for epidermal growth factor, PDGF, CSF type 1, insulin, and insulin growth factor type 1. A number of general principles apply to the growth factor receptor protein kinases. Enhancement of their phosphotransferase activities is very rapid following ligand binding, and in every case, autophosphoryla-

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tion is an early event. The common function of these receptors strongly implies that tyrosine phosphorylation is an integral part of a mitogenic signal system (Hunter, 1986). Suramin treatment of PDGF-activated cells at 4°C caused dissociation of cell surface PDGF, and dissociation was rapidly followed by receptor dephosphorylation. It is suggested that, because of the dissociation of the ligand, the kinase activity of the receptor is switched off so that the phosphotyrosine-containing receptors remain exposed to the action of phosphatases that rapidly dephosphorylate them (Sturani et al., 1989).

Proteolytic processing of internalised growth factor, or its receptor, or both, can play a role in the transduction of the mitogenic signal. Suramin slows down the intracellular degradation of PDGF, a process that takes place within the lysosomes. This is probably due to the overall influence of the drug on the lysosomal system of the cell and may contribute to the inhibitory effect on the induction of DNA synthesis. By analogy, chloroquine and monensin, two other lysosomal inhibitors, have been observed to suppress intracellular degradation of PDGF and PDGF-induced DNA synthesis in rat arterial smooth muscle cells (Sjölund and Thyberg, 1989).

PKC, a Ca^{2+}- and phospholipid-dependent protein kinase, is involved in signal transduction from a number of cellular agonists, including certain mitogens, such as growth factors, and has been implicated in numerous biological processes, including tumor promotion and differentiation (Nishizuka, 1984, 1986). Suramin is an inhibitor of PKC (Hensey et al., 1989; Mahoney et al., 1990) (see section IV. C). At concentrations adequate to inhibit the isolated enzyme, suramin was seen to slow the rate of proliferation of neuroblastoma NB2A cells in vitro and to induce their differentiation, as evidenced by typical morphological changes (Hensey et al., 1989).

Stein et al. (1989) noted a close temporal correlation between the development of anticoagulation and measurable tumor shrinkage; this anticoagulation is due to circulating levels of heparan and dermatan sulfate (Horne et al., 1988). There is a growing amount of literature suggesting that the physiology of glycosaminoglycans plays a critical role in various aspects of tumor cell biology, and it may well be that the antitumor effect of suramin seen in their trial is a consequence of a suramin-induced accumulation of heparan and dermatan sulfate (Stein et al., 1989).

V. Pathological Actions of Suramin

A. Toxicity

Studies of the toxicity of suramin have been conducted mostly with patients treated for trypanosomiasis and have been reviewed extensively by Hawking (1978). Drug trials of suramin for anti-AIDS and antitumour action, and subsequent studies of toxicity found in these trials, revealed new properties of known and unknown toxicities of suramin.

A febrile reaction to the first one or two injections is almost invariable, and it may be severe. Subsequent injections produce a lesser reaction or are without incident. Although uncommon (1 in 2000 to 1 in 4500), a reaction, apparently due to a drug idiosyncrasy, may occur. In this case, the injection is immediately followed by vomiting, shock, and collapse which has on occasion proved fatal. For this reason it is advisable to routinely administer a small test dose before proceeding with the full course.

Other adverse reactions include pruritus, urticaria, a papular eruption, conjunctivitis, photophobia, palpebral edema, stomatitis, and hemolytic anemia. Rarely, desquamation of the skin, especially that of the palms and soles of the feet, may occur, and cutaneous hyperesthesia, with pain in the soles of the feet, is occasionally encountered. Some degree of nephrotoxicity is common, but the mild albuminuria, usually the only sign, is not an indication for the suspension of treatment. Only if there is evidence of more severe renal damage, e.g., increasing albuminuria, hematuria, and cylindruria, is there need to change treatment. Although there are many toxic reactions, their occurrence is relatively infrequent (Hawking, 1978; Apted, 1980). In drug trials with suramin for anti-AIDS and antitumour action (Broder et al., 1985; Levine et al., 1986; Cheson et al., 1987; Allolio et al., 1989a; Stein et al., 1989; Balbus et al., 1990; Klijn et al., 1990; La Rocca et al., 1990b,d, 1991a; Van Oosterom et al., 1990), many of these adverse drug actions have been encountered (tables 1 and 2). Most reported toxic actions found in AIDS trials occurred in the second to third week of therapy, resolved spontaneously, did not reoccur, and were rarely severe or life-threatening. Unexpected toxic effects included adrenal insufficiency and vortex keratopathy.

These reactions are also found in reports of clinical studies of the anticancer actions of suramin (Allolio et al., 1989a; Stein et al., 1989; Balbus et al., 1990; Klijn et al., 1990; La Rocca., 1990d, 1991a; Van Oosterom et al.,

TABLE 1
Clinical toxic effects of suramin therapy in AIDS (from Cheson et al., 1987)

Effects	% of patients ($N = 98$)
Fever	78
Rash	48
Malaise	43
Neurological*	33
Vomiting	20
Diarrhea	12
Stomatitis	5
Cardiopulmonary	5
Chills	4
Myalgias	3
Abdominal pain	3
Edema	2
Pruritis	1

* Headache, metallic taste, paresthesias, and peripheral neuropathy.

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TABLE 2
Laboratory abnormalities with suramin therapy in AIDS (Broder et al., 1985; Levine et al., 1986; Cheson et al., 1987)

Renal	Haematological	Hepatic
Proteinuria	Leukopenia	Bilirubin elevations
Microscopic pyuria	Anaemia	Hepatic aminotransferases elevations
Trace haemoglobinuria	Eosinophilia	
Creatine elevations	Thrombocytopenia	
Occasional granular casts		

1990). Because different dosing schedules and higher plasma concentrations were used in these studies, more unknown toxicities have been found. Suramin-induced coagulopathy is the most common dose-limiting toxicity. The most significant toxicity encountered has been the development of a severe polyradiculoneuropathy with variable recovery.

Suramin appears to induce immunosuppression and, in consonance, an increased incidence of local intravenous catheter site infections has been noted. Analgesic activity of suramin has also been reported (Ho et al., 1992). Some endocrinological effects were reported by Klijn et al. (1990): a significant decrease in both mean thyroxine and thyrotropin responses to thyrotropin-releasing hormone and, in men, an increase in mean plasma estradiol and a decrease in testosterone. Adrenal insufficiency, vortex keratopathy, coagulopathy, polyradiculoneuropathy, immunosuppression, and adverse skin reactions will be discussed in later sections.

B. Action on Blood

Eisen and Loveday (1973) found that a major part of the anticoagulant effect of suramin in vitro must be attributed to inhibition of the terminal clotting stage, the fibrinogen-fibrin conversion by thrombin. In a report by Horne et al. (1992), it was demonstrated that in plasma suramin inhibits factors V, VIII, IX, X, XI, and XII, whereas thrombin, prothrombin, and factor VII are unaffected. The inhibition of factor V is virtually irreversible, although the effects of suramin on the other factors are readily reversed by dilution. Suramin in vitro has also been found to inhibit the fibrinolytic activity of purified plasmin and of streptokinase-activated normal human plasma (Moroz, 1977).

A complex coagulopathy appeared during clinical trials with suramin as treatment for metastatic adrenocortical carcinoma (Horne et al., 1988). This was eventually shown to be caused by glycosaminoglycans (heparan sulfate and dermatan sulfate) that accumulate in the patient's plasma.

Constantopoulos et al. (1980) previously noted that suramin, given to rats intravenously in single, relatively large boluses (500 mg/kg), led to a 5- to 8-fold increase in hepatic glycosaminoglycans. The glycosaminoglycans appeared to be composed of heparan sulfate and dermatan sulfate. In these studies, suramin inhibited enzymes critical for glycosaminoglycan degradation, thus allowing accumulation of the substrates; however, no coagulopathy was described.

C. Suramin-induced Mucopolysaccharidoses

Mucopolysaccharidoses is a group of hereditary disorders of glycosaminoglycan metabolism. The biochemical defect is a deficiency of one of the lysosomal enzymes required for the degradation of glycosaminoglycans. The resulting diseases are characterised by intralysosomal accumulation of partially degraded glycosaminoglycans and excessive excretion of these compounds in the urine. In most types of mucopolysaccharidoses, a sequel of the enzymatic defect is accumulation of sphingolipids in the brain and organomegally.

Suramin is a potent inhibitor of the lysosomal enzymes iduronate sulfatase, β-glucuronidase, and hyaluronidase (Constantopoulos et al., 1980; Marjomäki and Salminen, 1986). In addition, suramin strongly inhibits β-hexosaminidase A, G_{M3} sialidase, acid phosphatase, cathepsin B, cathepsin D, and other enzymes (Buys et al., 1978; Rees, 1978; Constantopoulos et al., 1981; Rees et al., 1982). Rats given intravenous suramin, 250 to 500 mg/kg, accumulate glycosaminoglycans in the liver, kidney, spleen, and other organs and excrete excessive amounts of these compounds in the urine, thus simulating a mucopolysaccharidosis (Constantopoulos et al., 1980). The excess glycosaminoglycans were heparan sulfate and dermatan sulfate. Intracerebral injection of 250 μg of suramin resulted in a small increase of glycosaminoglycan and a larger increase of ganglioside G_{M2}, G_{M3}, and G_{D3} concentrations in the treated regions of the brain (Constantopoulos et al., 1980, 1981).

Pathologically, multisystem lysosomal storage is evidenced by liver parenchymal cells containing vacuoles with polymorphic content (Rees et al., 1982), as well as distinctive membranous inclusions within neurones and neuroglia of the brain and tubule cells in the kidney (Rees, 1978; Rees et al., 1982; Marjomäki and Salminen, 1986). A strongly positive staining with Alcian blue of the liver, spleen, kidney, lung, heart, and brain confirms that these organs contained higher amounts of glycosaminoglycans than did other organs from untreated rats. Highly vacuolated tissue macrophages were frequently observed in the liver, spleen, kidney, lung, and heart. Suramin also caused an abnormal enlargement of the kidney, spleen, lung, and liver, splenomegaly being most

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pronounced. All effects of suramin were expressed within 10 days after drug administration (Rees et al., 1982).

Buys et al. (1978) perfused isolated rat livers, injected with saline or with suramin (250 mg/kg) 24 h previously, with a medium containing radioactively labeled formaldehyde-treated albumin. Suramin-loaded livers released breakdown products at a much lower rate than did controls and contained about double the amount of undigested radioactive protein as many as 3 h after the start of the perfusion. This suggests that inhibition of proteolysis by suramin is not caused by the binding of the drug to the substrate in the bloodstream.

The effect of suramin on lysosomal enzymes was studied in vitro. When used at a concentration corresponding to the putative concentration in lysosomes in vivo, the drug inhibited the lysosomal endopeptidases cathepsin Bl and D as well as acid phosphatase. These results suggest that the observed storage phenomena may be mainly caused by inhibition of lysosomal enzymes. Electron micrographs of liver sections of suramin-treated rats showed that the lysosomes of sinusoidal cells resembled those seen in certain lysosomal storage disease (Buys et al., 1978).

A study of the histopathology of suramin toxicity in a chimpanzee (Gibson et al., 1977) demonstrated morphological alterations in the kidney, liver, and spleen similar to those described by Rees et al. (1982). However, these organs were not enlarged. This finding is presumably related to the lower dose of suramin used in these experiments.

Significant reversibility of both the biochemical and pathological changes induced by suramin was found within 6 months (Rees et al., 1986a,b). The extent and rate of suramin accumulation and the retention of the drug varied considerably between organs with the greatest drug concentration occurring in the kidney (4 mg/g) 2 weeks after injection. Suramin persisted at gradually decreasing levels in all organs for the duration of the experiment, remaining at the highest level (1.15 mg/g) in the kidney. The concentration of glycosaminoglycans peaked 10 to 18 days after administration of the drug in all organs. Within 6 months the level had returned to normal in the liver, spleen, and lung but remained elevated in the kidney. The activities of β-glucuronidase and acid phosphatase were decreased in all organs at diminishing levels throughout the experiment. There was a significant increase in the activity of arylsulfatase B, except in the kidney, where the predominant effect was a reduction of activity. Recovery of the morphological changes was evident in all organs except the lung within 6 months of suramin administration.

Christensen and Lüllmann-Rauch (1988) drew attention to a methodological pitfall concerning the use of cationic dyes for a histochemical analysis of the suramin-induced mucopolysaccharidosis. They found that suramin gives a strongly positive reaction with Alcian blue, and, accordingly, a positive staining reaction with Alcian blue observed in a given cell cannot be conclusively attributed to the storage of sulfated glycosaminoglycans as has been done.

D. Immunological Actions

In many disorders, the complement system is found to be in an activated state and this activation was associated with diseases of several organs, including skin and eye diseases. Examples of such skin diseases are pemphigus and hereditary angioneurotic oedema (Asghar et al., 1983). Suramin has been used for the treatment of pemphigus (Tomlinson and Cameron, 1938; Hawking, 1978). Hereditary angioneurotic oedema is characterised by a lack of regulative function of C1 inhibitor on C1 esterase; attacks of hereditary angioneurotic oedema can be prevented by suramin (Brackertz and Kueppers, 1973; Hawking, 1978).

Several actions of suramin on the complement system have been documented. Fong and Good (1972) showed that suramin interferes with the interactions of sensitised sheep erythrocytes (SHEA) and C1, leading to the complex denoted by SHEAC1. This complex may react with C4, giving rise to the SHEAC1C4 complex, which in turn may react with C2 to form SHEAC1C4C2. All of these complexes are inhibited by microgram quantities of suramin. Inhibition of SHEAC1 and C4, as well as SHEAC1C4 and C2 interactions, was shown to be competitive. In agreement with Fong and Good (1972), inhibition of the total haemolytic sequence was found when assays were carried out with suspensions of sensitised cells. However, the inhibition of this sequence was much weaker when measured by a plate method derived from a C4 assay (Eisen and Loveday, 1973).

The initial step in activation of the complement system by immune complexes involves the interaction of the Fc region of immunoglobulin with the C1q subcomponent of the macromolecular C1 complex. This binding process causes the activation of other subcomponents, C1r and C1s, to form activated C1, which in turn triggers the classical complement pathway via reactions on C4 and C2. Suramin inhibited C1q binding at moderately low concentrations with a sigmoidal inhibition curve. The C1q-suramin complex showed a dissociation constant on the order of 50 μM (Lin and Fletcher, 1978).

Suramin can prevent the binding of freshly opsonised immune complexes to specific receptors (CR_1) on RBCs and CR_2 on Raji cells, and it can also release the majority of the complexes from the cells when they are bound. The major complement component on these immune complexes is believed to be C3b. Suramin inhibits binding of immune complexes containing C3bi to RBCs and Raji cells also but not the binding of immune complexes containing C3d,g to Raji cells (Taylor et al., 1984). Once bound to RBCs, the release of immune complexes from CR_1 is mediated essentially by an interaction between

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CR_1 and factor I and is associated with degradation of immune complexes-C3b into immune complexes-C3d and fluid-phase C3c. Suramin was found to induce release of CR_1-bound immune complexes in the absence of ethylenediaminetetraacetic acid, whereas factor I-mediated release of CR_1 was inhibited by suramin in the presence of ethylenediaminetetraacetic acid (Thomsen et al., 1986).

Several groups have shown suramin to suppress experimentally induced tissue injury reactions mediated by immune complexes. Suramin was effective in inhibiting passive cutaneous anaphylaxis and the proteinuria manifestations of experimental glomerulonephritis and did not affect antibody fixation to tissue or histamine-mediated skin reactions (Fletcher and Lin, 1980). The Arthus reaction was used as a model, and suramin inhibited complement-mediated reactions in rabbits; cellular infiltration was inhibited by about 65%, reduction of complement deposits was shown, and suramin gave protection against destruction of the endothelium and basal lamina at the Arthus reaction site. The development of erythema was only slightly affected; a 20% reduction in size was found (Asghar et al., 1983; Asghar, 1984). Suramin has been evaluated in a series of in vitro and in vivo models of cartilage degradation. It appeared extremely efficacious in inhibiting the release of a cartilage proteoglycan-degrading enzyme from the mouse macrophage maintained in culture; it also prevented the autolytic breakdown of rabbit knee cartilage maintained in vitro. Suramin was, however, inactive in preventing the cartilage degradation observed during the pathogenesis of adjuvant arthritis in the rat (Ackerman et al., 1983).

Suramin is known to alter host responses to infections with facultative intracellular bacteria. Suramin exerts an inhibitory effect on the delayed-type hypersensitivity elicited in mice by sheep RBCs (Brandely et al., 1985). Several mechanisms, depending on the time of drug administration with respect to sheep RBC sensitisation, underlie this activity of suramin. When administered after antigenic sensitisation, suramin can interfere with the recruitment of phagocytic cells at the site of the inflammatory infection and, thereby, prevent the expression of delayed-type hypersensitivity. Reduced delayed-type hypersensitivity reactivity in mice treated with suramin 8 days before sheep RBC immunisation appears to result from the rapid degradation of the antigen, thus made unavailable to induce delayed-type hypersensitivity-mediating T-cells. In contrast, analysis of the spleen cell population from mice treated with suramin 1 h prior to priming with sheep RBC indicates that, under these conditions, delayed-type hypersensitivity-mediating T-cells are induced but are ineffective (Brandely et al., 1985). With a similar suramin treatment and sheep RBC sensitisation protocol, helper T-cells are generated but fail to collaborate with B-lymphocytes and macrophages for an antibody response, when activated by an antigen in vitro. Suramin administration results in a suppressive T-cell activity (Motta et al., 1985).

Following one intraperitoneal injection of suramin (400 mg/kg) in mice, biphasic alterations of the resistance to *Listeria monocytogenes* were observed, depending on the timing of the drug administration in relation to the intravenous challenge. Treatment with suramin, concomitantly or 1 day before, markedly enhanced the bacterial growth in spleen and liver. In contrast, an increased resistance was observed when suramin was given 8 days before the challenge. This late effect was associated with a stimulation of the mononuclear phagocyte system, as measured by the increase of the spleen index and accumulation of histiocytic cells in the lymphoid organs, such as peripheral nodes (Brandely et al., 1986). Suramin has been reported to be capable of activating murine B-lymphocytes in vitro in a fashion similar to the conventional B-cell mitogens (Kirchner et al., 1986).

Spigelman et al. (1987) reported that multiple cell lines in culture, particularly lymphoid cells, are growth inhibited when exposed to suramin and that in normal mice suramin causes profound and prolonged thymic atrophy and splenic lymphocyte depletion. Suramin caused variable degrees of cell growth inhibition; eight of 10 lymphoid cell lines were suramin growth inhibited and one of five nonlymphoid cell lines was suramin sensitive. Suramin given intraperitoneally daily at 60 mg/kg for 4 days caused >90% thymic loss by day 11. This thymic involution was prolonged beyond day 24. Suramin-induced thymic atrophy was a dose-dependent phenomenon for doses between 15 and 60 mg/kg.

E. Teratogenic Aspects

Suramin has been given to women for more than 60 years, and no case of infant malformation has been reported and no abortifacient action has been described in humans. Although teratogenic effects of suramin in rodents have been reported, the development of the placenta in humans is different from that of rodents, and the experimental data from the latter are not directly applicable to humans (Hawking, 1978).

Following treatment with suramin, a high proportion of kidney defects or hydrocephales among rat fetuses was observed. These malformations are commonly associated with teratogenic insult during the early organogenesis period of rat development (Freeman and Lloyd, 1986). Suramin accumulates in the visceral yolk sac after its injection into pregnant rats during organogenesis and, thus, is well placed to influence yolk sac function (Freeman and Lloyd, 1985).

Freeman and Lloyd (1985) found that suramin at a concentration of 5 mg/ml or higher decreased the total protein content of both embryos and yolk sacs at the time of harvesting and (after culture in [^{3}H]leucine-labeled serum) decreased the amount of conceptus-associated radioactivity by approximately 23%. In addition

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to the large decrease in the uptake of ^{3}H-labeled proteins, suramin also significantly increased the proportion of the total conceptus radioactivity that was associated with the yolk sac (Freeman and Lloyd, 1986). These data indicate that pinocytosis of protein by the yolk sac is inhibited by suramin as is the degradation of protein taken up by pinocytosis. Conceptuses exposed to suramin for the penultimate 6 h and to radiolabeled protein for the final 6 h of culture still exhibited a significantly impaired ability to capture radiolabel, suggesting that the site of suramin's action on pinocytosis may be intracellular (Freeman and Lloyd, 1986).

Suramin is an example of a teratogen that probably acts by interfering with histiotrophic nutrition in the early organogenesis-stage rat embryo. This mechanism has previously been proposed for anti-visceral yolk sac antiserum and leupeptin. However, other possible effects of the drug cannot be ruled out. For example, suramin, by virtue of its polyanionic nature, is an effective inhibitor of certain types of receptor-ligand binding and also is an inhibitor of some lysosomal enzymes other than proteinases (Freeman and Lloyd, 1986).

F. Adrenal Pathology

As was found following the treatment of pemphigus with high doses of suramin (Wells et al., 1937; Tomlinson and Cameron, 1938; Humphreys and Donaldson, 1941), adrenal toxicity was observed in the treatment of AIDS with high doses.

Stein et al. (1986) reported the development of hypoadrenalism in a patient with AIDS receiving high-dose suramin treatment. Levine et al. (1986) treated 12 patients who suffered from AIDS with suramin. Adrenal insufficiency developed in two patients after the weeks 25 and 29 of therapy, whereas five additional patients have had normal baseline cortisol levels but abnormal ACTH stimulation test results that occurred after many months of treatment.

The observation of Cheson et al. (1987) that adrenal insufficiency developed in one of their suramin-treated patients has stimulated a more systematic evaluation of subsequent patients. In their study, adrenal insufficiency was detected in 23% of patients, of whom 14% had clinically significant disease. Although routine testing revealed normal adrenal function in 13 patients, it is possible that additional cases of subclinical adrenal insufficiency may have been present in the untested cases. It is not clear, however, how many of these cases were directly attributable to suramin.

In an attempt to address this issue, Hawkins and coworkers (J. G. Hawkins, A. M. Levine, and J. LoPresti, cited by Cheson et al., 1987) compared a group of 14 suramin-treated patients with AIDS with seven non-suramin-treated patients with AIDS and similar clinical characteristics. Six of the 14 treated patients had both adrenal and gonadal insufficiency, and all had received at least 14 g of suramin sodium. In contrast, none of seven control patients had clinical or laboratory evidence of such endocrine abnormalities.

Feuillan et al. (1987) treated five cynomolgus monkeys with suramin (800 mg/m^2) once a week for 5 weeks. The treated animals had progressive elevations of plasma ACTH and plasma renin activity and decreased serum cortisol responses 30 min after the administration of synthetic ACTH compared to controls. There was a disruption of the architecture of the adrenal cortex, a diffuse inflammatory cell infiltrate, and a thinning of the zona glomerulosa and zona fasciculata.

Inhibitory actions of suramin on adrenal steroidogenic enzyme activities were reported by Ashby et al. (1989). The effect of suramin was concentration dependent, and a 50 μM or lower concentration was sufficient to inhibit the activity of five steroidogenic enzymes by 50%. Although concentrations of suramin within the adrenals have not been measured, the plasma levels in patients with AIDS ranged from 50 to 400 μg/ml (Collins et al., 1986; Cheson et al., 1987), and it was presumed that intraadrenal concentrations were sufficient for inhibition because 50 μM is approximately equivalent to 1.4 μg/ml. These in vitro data demonstrate a profound inhibitory effect on the cytochrome P-450 enzymes and suggest one mechanism of suramin's inhibitory action on adrenal function, i.e., a concentration-dependent inhibitory effect on several key P-450 steroidogenic enzyme steps in the glucocorticoid pathway.

Studies by Marzouk et al. (1990) made it appear unlikely that suramin affects corticosteroidogenesis via a blockade of the enzymes involved. Suramin inhibited ACTH-stimulated corticosteroid release by rat adrenocortical cells in a dose-dependent manner (IC_{50} = 200 μM). The effects of other stimulators that bypass the ACTH receptors were not significantly affected by suramin. Marzouk et al. (1990) suggested that suramin interacts with ACTH before or during its action at the receptors on the adrenocortical cells. Inhibition by suramin of ACTH-induced cortisol release (as well as growth) has also been found with normal adult human cortical cells in vitro (Dorfinger et al., 1991).

G. Vortex Keratopathy

Teich et al. (1986) observed a toxic keratopathy possibly due to suramin treatment in patients suffering from AIDS. The extent of keratopathy was related to the total dose of suramin administered. Two patients had been receiving suramin for approximately 4 months, with total doses of 17.2 and 15.2 g, and both had a diffuse subepithelial vortex keratopathy in both eyes, virtually identical with that seen in Fabry's disease and chloroquine keratopathy. Holland et al. (1988) reported the clinical findings of vortex keratopathy in six patients treated with high-dose intravenous suramin for adrenocortical carcinoma. The corneal findings were similar to those

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observed in Fabry's disease or the drug-induced keratopathies of chloroquine, amiodarone, and chlorpromazine. Three of the patients had additional findings of corneal epithelial toxicity: superficial punctate keratopathy in two patients and peripheral epithelial erosions in another. Stellate opacities of the anterior lens capsule developed in one patient. This patient had the highest serum level and total dose of suramin. In none of the patients did subepithelial opacities develop as was described for three of five patients with AIDS who were treated with suramin (Teich et al., 1986).

The histopathological and electron microscopic findings in the corneas from one of the above patients appeared similar to those seen in drug-related vortex keratopathy and Fabry's disease. Lipid deposition particles in the cornea, conjunctiva, and lens epithelia were demonstrated. The particles were lamellar inclusion bodies that had a lipid inclusion configuration in the cytoplasm. Similarly, electron microscopy of the cornea in patients taking chloroquine and amiodarone and patients with Fabry's disease demonstrate lipid-bearing concentrically arranged intralysosomal inclusions in the corneal epithelium. The idea that suramin could cause a vortex keratopathy is tenable, because it is a lysosomotropic compound that inhibits many lysosomal enzymes and has induced systemic mucopolysaccharidosis when given to animals in large doses.

Vortex keratopathy was seen in five of 15 patients treated by Stein et al. (1989), and in two of these patients this was associated with symptoms of photophobia, tearing, and blurred vision. The symptomatic patients were treated with artificial tears, and one required soft contact lenses. In both cases, the patients were incapacitated for 2 to 3 weeks by the toxicity before symptoms abated. Biopsy of these corneal lesions revealed changes consistent with lysosomal accumulation of glycosaminoglycan. In all cases, the vortex keratopathy cleared with the discontinuation of treatment and left no residual damage.

H. Suramin-induced Polyneuropathy

La Rocca et al. (1990a) reported the development of a severe polyneuropathy in four of 38 patients who were receiving suramin therapy for the treatment of various underlying malignancies. In two patients the clinical syndrome resembled that of a subacute Guillain-Barré syndrome. In both patients, progressive limb weakness developed with areflexia, leading to complete flaccid paralysis with bulbar and ventilatory involvement within 4 to 7 weeks. Nerve conduction studies documented the development of conduction blocks at multiple sites, implying demyelinating rather than axonal pathology. In one patient, there was good recovery within a few months, but in the other patient, conduction block and reduced conduction velocity were followed by extensive axonal degeneration and a severe residual neurological deficit. The nerve conduction studies in a third patient showed no conduction block at any stage, but the reduced motor conduction velocity in the peroneal nerve, together with delayed F waves, would be compatible with some degree of underlying demyelination in addition to the extensive axonal degeneration which was present. In patient 4, there was evidence of conduction block in the spinal roots or the proximal parts of the peripheral nerves, implying that demyelination was restricted to these areas. Although axonal degeneration was also present, the patient's relatively rapid recovery from severe upper limb weakness would be in keeping with a mainly demyelinating process. All four patients were treated with a 5-day course of plasmapheresis following the onset of neurological symptoms. No immediate therapeutic effect was demonstrated.

The maximum plasma levels in the four patients in whom polyneuropathy developed ranged from 386 to 465 μg/ml (mean, 424.5 μg/ml) compared with a mean of 272 μg/ml for all 38 patients entered in the study. The probability of significant polyneuropathy developing with a suramin level of >350 μg/ml was calculated to be 40%. No correlation could be made with the total dose of suramin administered or with the duration of therapy.

I. Skin Reactions

Adverse skin reactions have been found following suramin treatment for trypanosomiasis. These symptoms include pruritus, urticaria, papular eruptions, skin desquamation, especially to the palms and soles of the feet; cutaneous hyperesthesia with pain in the soles of the feet is occasionally encountered (Hawking, 1978; Apted, 1980). Skin eruptions have also been reported in patients with AIDS (Broder et al., 1985; Levine et al., 1986; Cheson et al., 1987) and those with cancer (Stein et al., 1989; La Rocca et al., 1990b,c,d, 1991a) who were treated with suramin. These rashes were mostly self-limited and resolved despite continued suramin therapy. However, in one report, a nonspecific papular skin rash was of sufficient severity to require specific treatment (Van Oosterom et al., 1990). A generalised exanthem that required cortisone treatment and discontinuation of suramin therapy was described in another report (Balbus et al., 1990).

Twenty patients with metastatic prostate carcinoma were evaluated retrospectively for evidence of skin toxicity (O'Donnell et al., 1992). Erythematous maculopapular lesions involving the trunk and, often, the proximal area of the extremities developed in 12. In each instance, the eruption faded within 3 to 5 days. Continuing suramin therapy did not affect the severity or the rate of resolution of the eruption. One patient complained of mild pruritus. There were no recurrences during subsequent treatment cycles. The findings of histological evaluation of punch biopsy specimens of skin lesions were consistent with a nonspecific drug eruption.

Mildly erythematous, annular lesions, with a periph-

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eral keratotic scale distributed predominantly over the legs developed in one patient. These lesions faded but did not resolve between the first and second treatment cycle. The lesions increased in number and severity when the second cycle of therapy was initiated. When treatment was stopped, the lesions faded without complete resolution. Histological examination of punch biopsy specimens confirmed the clinical impression of disseminated superficial actinic porokeratosis.

A 0.5-cm erythematous papule with a central depression on the posterior region of the neck developed in one patient during the first treatment cycle. This lesion doubled in size during the second treatment cycle. Multiple erythematous, dome-shaped papules with a central keratin plug on the dorsal aspect of each hand developed in another patient. These lesions arose within the first week of treatment. Histological evaluation of the lesions revealed features consistent with a keratoacanthoma.

May and Allolio (1991) reported a patient treated with suramin for metastatic adrenocortical carcinoma. Suramin plasma concentrations were between 179 and 246 μg/ml. During the third week of maintenance therapy, the an extensive rash developed. The onset was sudden, with eruption of urticarial plaques and erythema in the neck. Clear bullae appeared and became confluent with extreme congestive erythema and purpura. The epidermis came off in large sheets. The day after admission, acute respiratory distress due to a mucous plug in the upper airways developed, and cardiopulmonary resuscitation was necessary. Orotracheal intubation was difficult because of extremely oedematous mucous membranes. The patient died the same day of cardiac arrest.

VI. Chemotherapy with Suramin

A. Treatment of Trypanosomiasis

In African trypanosomiasis, suramin is used mainly for the early stages of *T.b. rhodesiense* infection; pentamidine is generally preferred for early-stage treatment of *T.b. gambiense* infection. Suramin is not used as a sole therapy for late-stage infections with central nervous system involvement because its penetration into the CSF is not considered adequate. Provided the test dose is well tolerated, early-stage trypanosomiasis is treated with a dose of 20 mg/kg body weight of suramin (up to a maximum of 1 g in adults) given every 5 to 7 days, usually for a total of five injections and not exceeding seven injections. In late-stage *T.b. rhodesiense* infection, two or three injections of suramin are often given before starting treatment with melarsoprol; combined treatment with suramin and tryparsamide has been used in late-stage *T.b. gambiense* infection. Suramin is of no use in Chagas' disease (South American trypanosomiasis, caused by *T. cruzi*) (Martindale, 1989).

Suramin has been used as a prophylactic agent. However, it is no longer used for this purpose because the period of protection is only 2 to 3 months, intravenous administration is necessary, and there is a risk of nephrotoxicity (Apted, 1980). A more disquieting hazard associated with chemoprophylaxis is the tendency to mask symptoms until central nervous system invasion occurs. The result is induction of advanced cryptic cases in which organisms are not found in the blood or lymph nodes but are present in the CSF at the time of diagnosis. Chemoprophylaxis may be considered only for individuals who will have constant, heavy exposure to the tsetse fly over an extended period in areas with known transmission of disease (Bales, 1991).

Drug combinations of suramin and nitroimidazoles have shown promise in treating trypanosomiasis in mice (Jennings and Urquhart, 1983; Jennings et al., 1983, 1984; Raseroka and Ormerod, 1985a; Zweygarth and Röttcher, 1987). Arroz and Djedje (1988) reported the combined use of suramin and metronidazole in a moribund patient with multidrug-resistent *T. b. rhodesiense*. Intravenous suramin was given on days 1 (0.2 g), 2 (0.5 g), 3, 7, 14, and 21 (20 mg/kg), and oral metronidazole was administered as a daily dose of 40 mg/kg for 10 days. On the day 11, CSF examination showed no trypanosomes. Metronidazole was continued at the same dose for a further 10 days. On day 21, CSF showed no trypanosomes. Examination of blood was consistently negative. The patient was much improved clinically, gaining 5.5 kg in weight. But 3 weeks after treatment, trypanosomes reappeared in the CSF (Arroz and Djedje, 1988).

B. Treatment of Onchocerciasis

Drug treatment of onchocerciasis was recently reviewed by Orme et al. (1988). Suramin remains the only macrofilaride available for clinical use against *O. volvulus*. To kill all adult worms, a total of at least 6 g of suramin must be given over 6 weeks. However, such a dosage can produce significant and dangerous side effects in 10 to 30% of patients and cannot be recommended for general use. The lower dose limit to achieve a high degree of therapeutic activity, combined with an acceptable level of safety for an adult weighing 60 kg or more, is 4 g given over 6 weeks. The weekly injections correspond to 0.2, 0.4, 0.6, 0.8, 1.0, and an additional 1.0 g of suramin in a 10% solution. In patients who do not show any signs of toxicity, the macrofilaricidal action can be improved by a final injection of 1 g, increasing the total dose to 5 g (Rougemont et al., 1984; WHO, 1987).

Suramin treatment of ocular onchocerciasis may be associated with a risk of developing optic atrophy. It is possible that suramin, with its partial microfilaricidal effect, may cause slow death of the microfilariae, which would be unfavourable to the optic nerve because of a prolonged period of inflammatory activity (Anderson and Fuglsang, 1978; Thylefors and Rolland, 1979). Treatment of sight-threatening onchocerciasis with suramin should begin with diethylcarbamazine citrate (given under corticosteroid cover) to reduce microfilarial load, followed

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by the course of suramin in the schedule given above (WHO, 1987; Anderson and Fuglsang, 1978).

Mass treatment with suramin of the millions of people infected with *O. volvulus*, many of whom are suffering from onchocerciasis, is unacceptable because of the high degree of risk involved, even though these individuals constitute a reservoir of the parasite (WHO, 1987, Orme et al., 1988). At present, ivermectin, a microfilaricidal rather than a macrofilaricidal agent, is the drug of choice for treating patients afflicted with onchocerciasis (Goa et al., 1991).

C. Treatment of Acquired Immunodeficiency Syndrome

Cheson et al. (1987) confirmed previous observations that suramin, at doses associated with moderately toxic reactions, can inhibit recovery of the virus from patients with HIV infection. In their initial report, Broder et al. (1985) treated 10 patients with AIDS-Kaposi's sarcoma or AIDS-related complex with 1.0 g/week suramin for 6 weeks. Detectable virus levels decreased in each of four patients who had a positive virus culture before therapy. In the study of Cheson et al. (1987), of 72 patients who were virus positive before therapy and who received suramin for at least 3 weeks, suppression of the virus was noted in 40% overall, including 13, 51, and 80% of those who received 0.5, 1.0, and 1.5 g/week, respectively. Despite the small number of patients in each group, this observation suggests a clinical dose-response effect. There was no apparent correlation between serum suramin concentrations and recovery of the virus. The concentration of suramin that results in HIV suppression in vitro is approximately 100 μg/ml. Inhibition of virus at suramin plasma concentrations of 100 μg/ml or less occurred in 10 patients. Nevertheless, concentrations as high as 400 μg/ml were not consistently associated with lack of viral recovery. Among the possible explanations are that viral protein determinations may provide a more accurate assessment or that trough determinations of suramin levels did not accurately reflect drug pharmacokinetics. Nevertheless, virus suppression did not appear to be associated with clinical response or immunological improvement.

There are a number of possible explanations for the failure of suramin to improve immune function. First, because suramin is virostatic, continued low-level proliferation and infection of lymphocytes may have occurred. Second, the failure of suramin to adequately penetrate the central nervous system allows for a sanctuary for continued viral replication and eventual reseeding of the systemic circulation. Third, in a number of in vitro and in vivo systems, suramin appears to have immunosuppressive effects of its own.

Although suramin exerted moderate antiviral activity in vitro, a low level of clinical activity and failure of immunological restoration have limited its clinical usefulness. Based on data from their study, Cheson et al. (1987) concluded that suramin is not recommended as therapy for AIDS.

D. Treatment of Hepatitis B Virus Infection

Loke et al. (1987) reported their experience with suramin in patients with chronic active hepatitis B and the drug's effect on hepatitis B virus replication. Three patients were treated. Each had severe chronic active hepatitis with cirrhosis. Serum HBV DNA polymerase was positive on at least two occasions during 3 months prior to treatment. Following a test dose of 200 mg on day 0, all patients were treated as outpatients and received a further 500 mg on day 7 and 1 g on days 14, 21, 28, and 35. In contrast to the observations in Peking ducks (Tsiquaye et al., 1986), there was no in vivo suppression of HBV DNA polymerase activity during therapy.

It is noteworthy that the two patients with the most marked toxic effects had the lowest serum albumin level; presumably blood levels of free suramin may have been undesirably high. Because of the observed side effects, Loke et al. (1987) do not believe that suramin has a role in the treatment of chronic active hepatitis.

E. Treatment of Metastasising Adrenal Carcinoma and Other Metastatic Carcinomas

The adrenal toxicity found in patients suffering from AIDS and treated with suramin and the finding of adrenocortical necrosis in suramin-treated cynomolgus monkeys suggested that suramin could be useful in treating conditions characterised by adrenocortical hyperfunction, such as adrenal carcinoma and Cushing's syndrome (Feuillan et al., 1987). Several studies of the potential therapeutic effect of suramin in patients with metastasising adrenocortical cancer (Allolio et al,. 1989a,b; Vierhapper et al., 1989; Balbus et al., 1990) and other metastasising cancers (Stein et al., 1989) have been made.

In combination with mitotane, suramin had a favourable clinical response in a patient with metastasising adrenocortical cancer (Vierhapper et al., 1989). Allolio et al. (1989a,b) used suramin in five patients with metastatic adrenal carcinoma not responding to mitotane. Suramin was given in a dose of 1.0 to 1.5 g intravenously at weekly intervals. In three patients, no response to suramin was seen. One patient showed a transient disease stabilisation and one had complete resolution of multiple pulmonary metastases for 5 months. In none of the nonresponders did suramin reach the concentration of 200 μg/ml, whereas in the patient with tumor regression concentrations >300 μg/ml were noted. Treatment of this patient with suramin was begun in August 1987. After a loading dose of 10.7 g was given for 6 weeks, the lung metastases regressed almost completely. But lung metastases were again demonstrated in January 1988 during a low-dose maintenance regimen of suramin. Increased dosage arrested further growth but achieved no regression of the metastases. The patient died unexpectedly in April 1988 of acute circulatory failure. In another

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report, a patient with an extirpated adrenocortical carcinoma and lung metastases was treated with suramin (350 mg/m^2/day) for 16 days. After 1 week, one maintenance dose of 700 mg/m^2/day was given; plasma levels of 210 to 251 μg/ml were found. Four and 8 weeks after stopping therapy because of toxicity, increasing regression of lung metastases was found (Balbus et al., 1990).

In a study by Stein et al. (1989), 10 patients with metastatic and surgically unresectable adrenocortical carcinoma, four patients with metastatic renal adenocarcinoma, and one patient with refractory acute T-cell leukemia-lymphoma (HTLV-1) received suramin. There were no complete responses, four partial responses (two of 10 adrenal cortex, one of four renal, one of one HTLV-1), and two minimal responses (two of 10 adrenal cortex). All 15 patients in this study received at least 3 weeks of parenteral suramin therapy. Patient 1 received a weekly intravenous bolus injection of 850 mg/m^2 for the first 3 weeks, followed by a dose escalation to 1.2 g/m^2/week. Patients 2 through 8 received 1.4 g/m^2/week via intravenous bolus injection, and patients 9 through 14 received 350 mg/m^2/day via continuous infusion. Patient 15 received 467 mg/m^2/day. Each of these regimens of drug administration represented loading schedules, and the alterations only served to shorten the drug loading time. After the initial loading phase, patients 10 through 15 were given a continuous maintenance infusion at a dose of 10 to 200 mg/m^2/day. The cumulative suramin dose administered to these 15 patients ranged from 8.8 to 39.3 g with a duration of therapy ranging from 5 to 20 weeks, including interruptions due to drug toxicity.

In their trial, Stein et al. (1989) found that patients with bulky tumors often required far larger cumulative drug dosages to attain the goal of 200 to 300 μg/ml than would be expected based on the AIDS studies. This is particularly remarkable in that all but one of their patients were uninephric. The mechanism behind this deviation remains to be determined, but it may well be that the drug concentrates within the tumor mass. Stein et al. (1989) noted a correlation between serum suramin level and response. Every patient who progressed through therapy had suramin levels of <200 μg/ml. Conversely, suramin levels of >200 μg/ml were associated with at least transient disease stabilisation. In the four partial responses, suramin levels were in excess of 240 μg/ml.

During the trial, Stein et al. (1989) noted a tight temporal correlation between the development of anticoagulation, due to circulating heparan and dermatan sulfate, and tumor shrinkage; each of the partial responses was associated with prolongation of prothrombin time, partial thromboplastin time, and thrombin time associated with circulating glycosaminoglycans.

Many of the patients in this trial had elevated levels of lactic dehydrogenase before treatment. Decline of this parameter was observed in many patients with adrenocortical carcinoma and in all patients who achieved a response. In several patients who required termination of therapy, increase in serum lactic dehydrogenase presaged a rapid regrowth of tumor. The ultimate use of this interesting marker remains to be determined.

The possible therapeutic efficacy of suramin in 12 patients with metastatic renal cell carcinoma has been examined. It does not appear to be an active single agent against this carcinoma, although >90% necrosis of multiple tumor sites was documented at autopsy in one patient and disease stabilisation did occur in two patients with normalisation of a markedly elevated tumor-related serum calcium level in one patient (La Rocca et al., 1991b).

La Rocca et al. (1991a) reported a study of 35 patients with metastatic prostate cancer refractory to at least one conventional hormonal manipulation, who have been treated with suramin. Of the 15 patients with measurable disease, three demonstrated complete disappearance of their sites of soft-tissue involvement following suramin therapy, and another three had a >50% reduction in the size of their measurable lesions for at least 1 month. Soft-tissue sites of tumor involvement included pelvic masses, lymph nodes, and biopsy-proven skin nodules. However, in only three of these 15 patients did the overall tumor response to suramin last >3 months. With regard to the bone involvement by prostate cancer, with a mean follow-up of 8 months, only three of the 35 patients (9%) demonstrated some improvement in abnormalities observed by bone scans with suramin treatment, and in each case, this change became manifest only after 9 months or more of suramin therapy. An additional six patients demonstrated areas of improvement, as well as areas of worsening, in their bone scans, and 11 patients had no change. The remainder manifested disease progress.

Serial measurement of prostate-specific antigen levels were performed on 32 suramin-treated patients. Of these, seven (22%) had normalisation of their levels, and six of these had metastatic disease limited to bone; only one has thus far had unequivocal improvement in his bone scan abnormalities. In only four of these seven patients has the duration of prostate-specific antigen normalisation been >3 months.

Of 21 patients with severe bone pain prior to the initiation of suramin therapy, 15 (71%) experienced significant relief, often in the course of the first cycle of treatment. However, this could be attributable to replacement doses of hydrocortisone which were given in view of suramin's adrenocorticolytic properties.

In each of the patients treated with suramin who eventually manifested some degree of tumor response, evidence of this nearly always appeared in the course of the first cycle of therapy (i.e., during the first 10 weeks of study), either as shrinkage of soft-tissue disease or as

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a significant decline in serum prostate-specific antigen levels.

VII. Concluding Remarks

Research on suramin has gained considerable momentum since the drug was found to be an inhibitor of the DNA polymerase of retroviruses and the demonstration that suramin could block the infectivity and cytopathic effect of HIV in vitro. The literature concerning suramin has been reviewed up to 1992. From this review the following conclusions can be drawn:

The renewed interest has resulted in new and more specific methods of monitoring suramin levels in body fluids and, as a result, a better understanding of the pharmacokinetics of the drug.

In anti-AIDS and anticancer therapy in which high-dosage regimens are used, new and unknown properties of suramin are revealed.

The pharmacological properties of suramin appear to be highly nonspecific, which results in many side effects and a complex toxicological profile. Because of the nonspecific actions of suramin, it is very difficult to ascribe a particular mode of action on any pathogen or in any disease state.

Therapeutic prospects are restricted by the many toxicities. In onchocerciasis, the use of suramin has decreased, because of its troublesome administration, in favour of ivermectin. High levels of suramin are not feasible because of serious toxicities, which appear to be related to the free fraction of suramin in the plasma.

Suramin can be very useful in the elucidation of pathological and pathophysiological mechanisms as a research tool.

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