INTERNATIONAL JOURNAL OF LEPROSY Volume 35, Number 4
Printed in U.S.A.

Antimalarial Studies on 4,4'-Diaminodiphenyl Sulfone (DDS) and Repository Sulfones in Experimental Animals[1]

Paul E. Thompson[2]

In contrast to the preeminent position of sulfones in the treatment of leprosy since 1941, they have become interesting in malaria only recently. A brief historic review explains this delayed interest. Coggeshall *et al.* (4) studied the therapeutic effects of Promin in malaria, near the time when it was first tried in the treatment of leprosy at Carville by Faget *et al.* (7). They found that Promin in intravenous doses of 15 to 20 gm. daily for 3 or 4 days was highly effective against *Plasmodium falciparum* but not very active against *P. vivax*. Although the effects against *P. falciparum* were a valuable clue, the overall results attracted little attention because, as compared with quinine, Promin had narrower action, was less potent, and less convenient to administer. The comparatively early switch from conjugated and rapidly excreted sulfones to DDS in the treatment of leprosy is well known to this audience. The impetus for this switch was lacking in malaria chemotherapy because of the introduction of many other effective drugs including quinacrine, chloroquine, amodiaquine, chlorguanide, and pyrimethamine.

Interest in sulfones as antimalarials was revived by the report of Archibald and Ross (1) in 1960. Their observation of lower prevalence of malaria in leprosy patients under treatment with DDS led them to compare the effects of 200 mgm. of DDS and 300 mgm. of chloroquine in single oral doses. They found that falciparum malaria was cleared by either drug, although somewhat more slowly by DDS. They found also that most cases of quartan malaria gradually responded to DDS, while all responded promptly to chloroquine.

These results suggested that sulfones were potent enough to be considered as one of the types of antimalarials that might be a source of repository drugs. Fortunately, test methods had been developed with *P. berghei* in mice and *P. cynomolgi* in monkeys, and reassurance on the feasibility of repository antimalarials had been gained through success with cycloguanil pamoate (16), a poorly soluble salt of the active dihydrotriazine metabolite of chlorguanide. Encouraging results were obtained quite early with 4,4'-diacetylaminodiphenyl sulfone (DADDS) (18). In view of the probability that parasites resistant to chlorguanide or pyrimethamine might also be resistant to cycloguanil salts, a series of basic studies (17) were conducted on the biologic relationships between cycloguanil hydrochloride and DDS, by use of *P. berghei*. This work showed (1) that resistance could be induced to either drug, (2) that only a low order of cross resistance occurred between cycloguanil hydrochloride and DDS, and (3) that induction of resistance was more difficult to a mixture than to the components individually. These results thus indicated that cycloguanil salts and sulfones act differently and have valuable complementary effects. The concurrent and independent work of Ramakrishnan *et al.* (11) contributed importantly to the developing position of DDS, by giving evidence that its mode of action is different from that of pryimethamine.

---

[1] Presented at Symposium on Sulfones, U. S.-Japan Cooperative Medical Science Program, San Francisco, California, 11 May 1967.

[2] P. E. Thompson, Ph.D., Department of Experimental Therapeutics, Biomedical Sciences Division, Parke, Davis and Company, Ann Arbor, Michigan 48106.

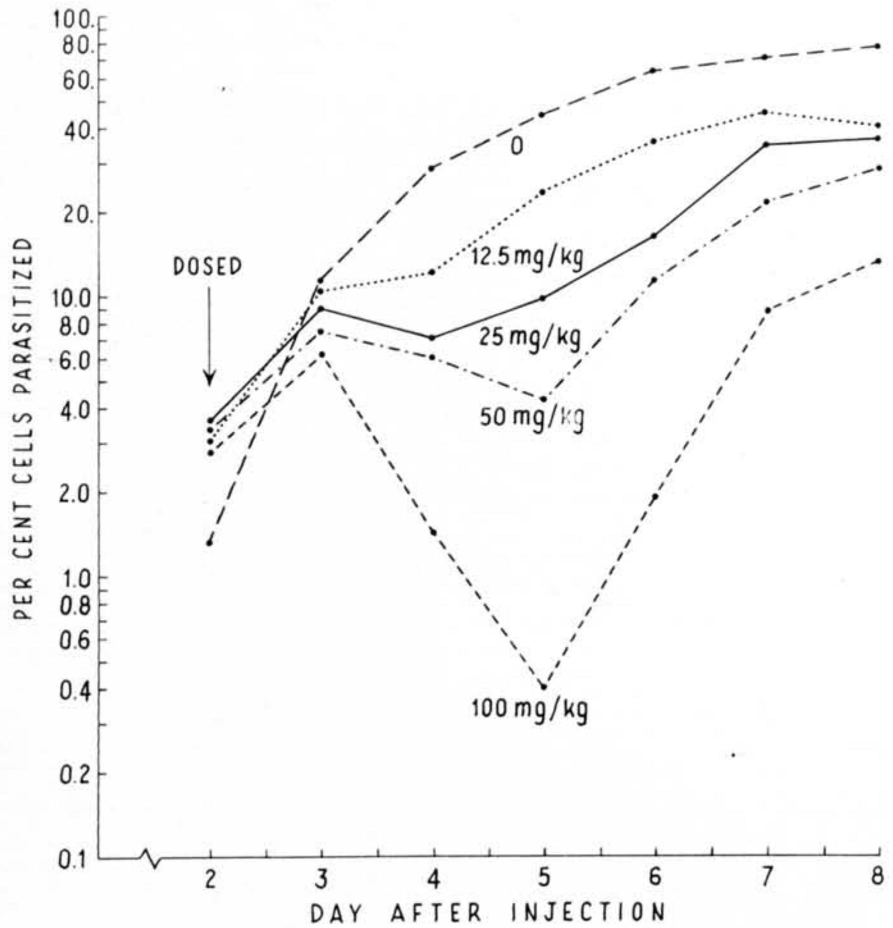


FIG. 1. Effects of a single oral dose of DDS against *P. berghei* in mice.

In the meantime drug-resistant parasites were becoming a more important problem in malaria. Although chlorguanide and pyrimethamine resistance had been known for some years, the problem increased progressively with the discovery that some strains of *P. falciparum* in South America are resistant to 4-aminoquinolines and acridines and that some in Southeast Asia are resistant to all four types of drugs. Chloroquine resistance was induced in *P. berghei*, and cross resistance studies showed that sulfones were effective against parasites that were resistant to 4-aminoquinolines and acridines ([20]). The sulfones thus appeared from these studies to represent a different mode of action from the other drugs just mentioned. The unique position of sulfones (or sulfonamides) has been demonstrated in many ways by others, particularly with multiresistant *P. falciparum* ([5]).

As a background for interpreting data on repository sulfones, it is desirable to review first the effects of DDS itself under various test conditions ([17, 20, 21]). The results of testing a single oral dose of 12.5 to 100 mgm./kgm. against patent *P. berghei* infections in mice are shown in Figure 1. All doses were active. The drug acted rather slowly, more than 24 hours being required for full effects. The periods of inhibition of parasite multiplication ranged from one to two days. The degree and duration of suppression were dose-related.

A very different order of suppressive potency by DDS occurred with more prolonged treatment. Thus when mice were given DDS subcutaneously twice daily for four days, the parasitemia was suppressed 51 per cent by doses of 0.16 mgm./kgm./day and more than 90 per cent by doses of 1.25 mgm./kgm./day. High potency was observed also with DDS treatment for six days by the drug diet method: 0.14 mgm./kgm./day (0.0001% diet) suppressed 50 per cent and 0.6 mgm./kgm./day (0.0005% diet) suppressed 94 per cent.

It is important to note that Shepard *et al.* ([14]) found the minimal effective level of DDS in the diet against *Mycobacterium leprae* in mice was about 5-fold less than we found necessary for activity against *P. berghei.* This strongly suggests that the *M. leprae* mouse test system is much more sensitive than the *P. berghei* mouse test system to DDS.

In tests for repository action, a 400 mgm./kgm. dose of DDS given subcutaneously failed to protect mice against a challenge with *P. berghei* one week after they had been dosed. ([18]).

DDS was studied by intramuscular administration in rhesus monkeys to give data on the relationship between blood sulfone levels and activity against *P. cynomolgi* ([21]). DDS was given in 40 per cent benzyl benzoate–60 per cent castor oil, and total sulfone levels in the plasma were determined by a modification of the Bratton-Marshall procedure ([3]). The results obtained following doses of 1, 4, 16, and 64 mgm./kgm. are summarized in Figure 2. Blood sulfone levels were dose-related over the entire range of doses. All doses had some suppressive effects, but they acted rather slowly. Suppressive effects were less by doses of 1 or 4 mgm./kgm. than by 16 or 64 mgm./kgm., but the effects by the two larger doses were comparable. Similar effects by the two larger doses suggested that beyond certain drug blood levels further increases were not proportionately more effective. The strongly suppressed infections recrudesced within one to two weeks after the amounts of sulfone in the blood fell below measurable levels.

A great many sulfones ([6]) have been tested in mice for repository action against *P. berghei.* The test procedure comprised the dosing of a group of mice subcutaneously and challenging subgroups intraperitoneally with *P. berghei* at one to two week intervals after dosing. The drugs were given as a suspension in a mixture of 40 per cent benzyl benzoate and 60 per cent castor oil. Many of them lacked repository activity. Eight of the active ones will be discussed. All of these compounds have also been found by Shepard ([15]) to be effective against *M. leprae* in mice when given subcutaneously semimonthly, monthly, or bimonthly.

DADDS (4,4′-diacetylaminodiphenyl sulfone) was the first member of the series and has been studied more extensively than the others. Data dealing with its repository antimalarial action in animals have been reported ([18]). It is adequate to mention here that significant repository action persisted in mice through 14 weeks following a 400 mgm./kgm. dose, through 10 weeks after 200 mgm./kgm., and through six weeks after 100 mgm./kgm. Mention should be made, however, that protection frequently was not complete during these intervals, as some of the mice developed low numbers of parasites. The period of practically complete protection by a 400 mgm/kgm. dose was estimated to be eight to ten weeks. All doses were well tolerated.

In contrast to mice, rats were not protected against *P. berghei* challenges by a subcutaneous dose of DADDS. Metabolic studies showed that this difference in activity between hosts was correlated with their capacity to deacetylate DADDS: mice deacetylated it efficiently, but rats did not ([21]). These observations agreed with other types of evidence indicating that at least one of the amino groups must be free for microbiologic activity by a sulfone.

The repository action of DADDS in lipid or aqueous vehicles has been studied in 16 rhesus monkeys ([18]). Challenges with *P. cynomolgi* trophozoites were given at intervals of one to three months after the intramuscular injection of the drug. A 50 mgm./kgm. dose prevented positive blood smears for an average of 158 days, and a 12.5 mgm./kgm. dose had such effect for somewhat more than 51 days. With either

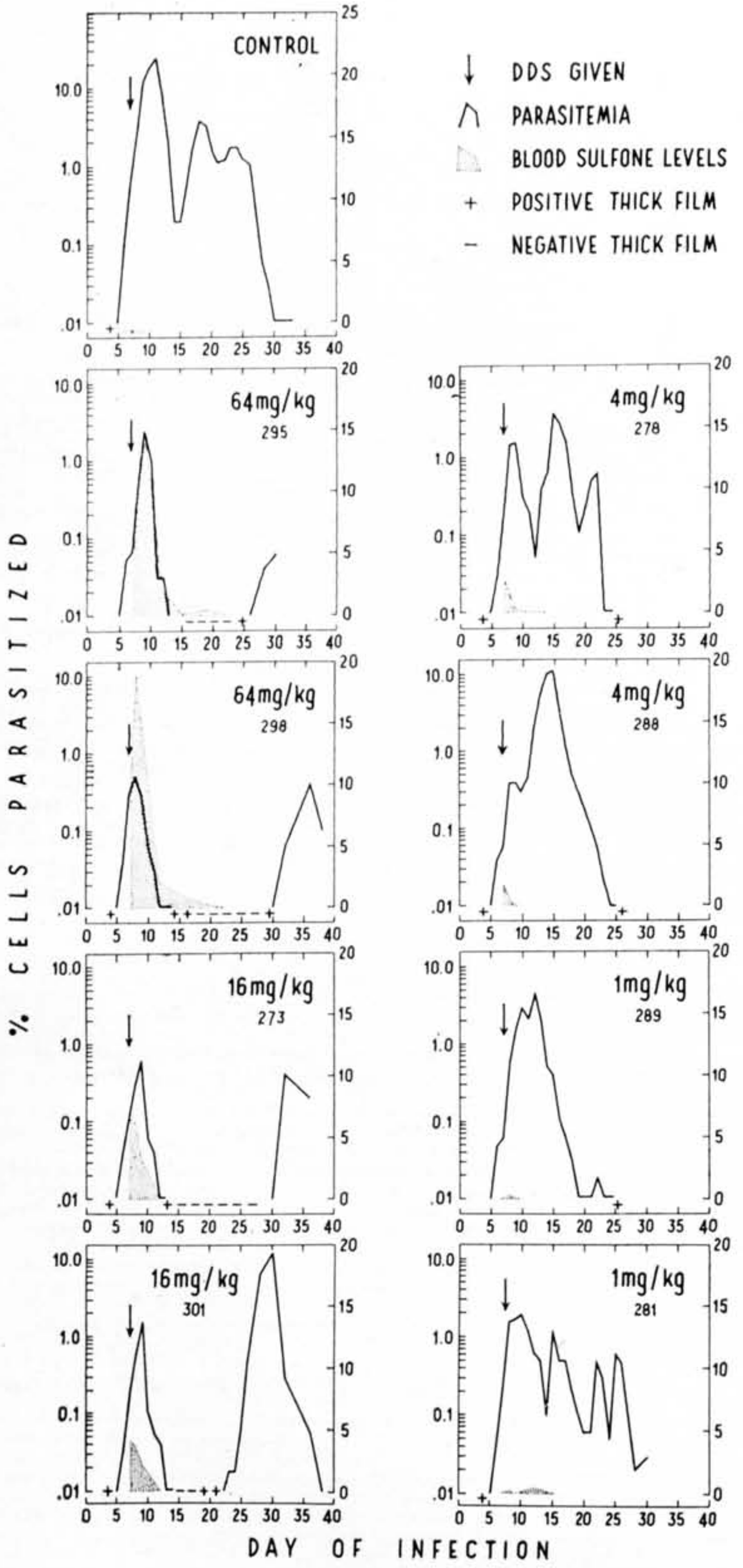


FIG. 2. Blood sulfone levels and effects on *P. cynomolgi* parasitemia in rhesus monkeys given an intramuscular dose of DDS.

dose, partial protection persisted for very much longer periods.

The therapeutic effect of DADDS intramuscularly has been studied in 27 rhesus monkeys with patent infections of *P. cynomolgi* [18, 21]. Typically, the parasitemias continued to increase for about 36 hours after dosing and then declined to submicroscopic levels during the next six days. The rate of action was thus similar to that of a 16 or 64 mgm./kgm. intramuscular dose of DDS.

It is evident from a variety of observations that DADDS is absorbed very slowly following intramuscular or intraperitoneal administration. Monkeys given 50 mgm./kgm. and rats given 400 mgm./kgm. have shown by chemical analysis only trace amounts of drug or derivatives in either the blood or urine [18]. Chemical assays of the injected muscle in monkeys at various intervals after dosage confirmed that the drug is absorbed slowly [8].

Thin-layer chromatography of the urine of mice, rats, and monkeys given DADDS parenterally showed that in each species some of the drug appeared in the form of DDS and of monoacetyl DDS, although the amount of DDS in rat urine was particularly low [21].

DADDS implanted subcutaneously in dialysis sacks had protective action in monkeys while the sacks were in place but not following their removal. Chemical analyses of the bag content showed that the average drug release rate during protection was only 1.0 mgm. per day [19].

Studies against sporozoite-induced infection of *P. cynomolgi* in rhesus monkeys [13] indicated that DADDS lacked appreciable activity against tissue stages, but had a long suppressive action against blood forms.

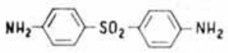
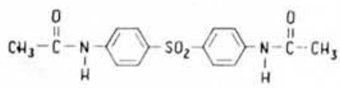
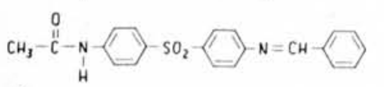
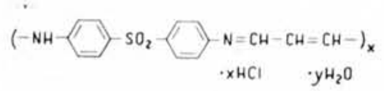
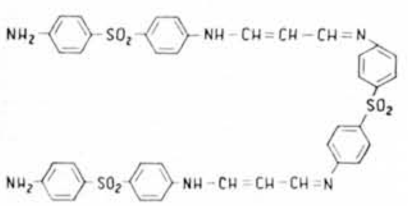
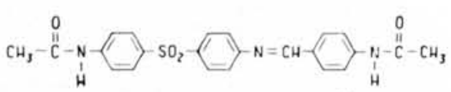
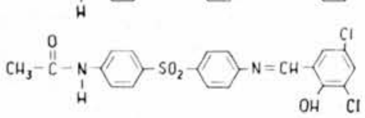
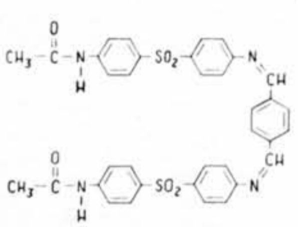
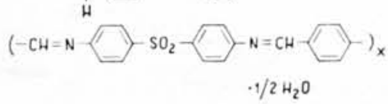
The other seven repository sulfones to be discussed are compounds PAM-1367, 1431, 1435, 1470, 1481, 1503, and 1513. The chemical structures of these compounds, their length of repository action against *P. berghei* in mice, and data dealing with their metabolism in rats, along with similar information on DDS and DADDS, are summarized in Figure 3 [21]. Their length of action in mice was intermediate between the short-acting DDS and the long-acting DADDS. Generally, the pattern of urinary excretion in rats also was intermediate between that of DDS and DADDS. The repository compounds also produced much lower peak blood sulfone levels and much lower methemoglobin levels than did DDS, which suggested that they should be much safer drugs.

The foregoing work has pointed to a series of repository sulfones that might be developed for medicinal uses. We have focused our attention on two representatives of the series, namely, the very long-acting DADDS and the intermediately long-acting PAM-1503 (CI-608). Preclinical toxicity studies [9] have been conducted on them.

The repository sulfones are of interest in malaria primarily as a mixture with cycloguanil pamoate. A 1:1 mixture of cycloguanil pamoate and DADDS, designated CI-564, is under study in human volunteers and in the field [2].

DADDS has been given separately by intramuscular injection in 40 per cent benzyl benzoate-60 per cent castor oil in two published field studies, primarily to clarify its position in malaria. Laing *et al.* [10] studied DADDS in 60 school children living in an area of East Africa where falciparum malaria is hyperendemic and pyrimethamine resistance is common. They gave a 150 mgm. dose to 30 children and a 225 mgm. dose to the other thirty. The injections were well tolerated. Significant suppression of falciparum malaria was observed for respective periods of about one month and two months.

Rieckmann [12] studied the effects of DADDS in 200 subjects in New Guinea. The doses ranged from 90 to 225 mgm. (3.8 to 7.5 mgm./kgm. of body weight). Injection site reactions (tenderness, swelling, or heat) occurred in only two of the subjects. No evidence was observed of systemic toxicity, including teratogenic effects, over a follow-up period of six months. Falciparum malaria was suppressed significantly for about three months. Vivax malaria, which is known to be not highly susceptible to sulfones, was only partially suppressed through 15 days and reappeared at near

DRUG	STRUCTURE	P. BERGHEI WEEKS PROTECTED MICE	P. BERGHEI WEEKS PROTECTED RATS	RATS: URINARY EXCRETION % EXCRETED IN 30 DAYS	RATS: URINARY EXCRETION ESTIMATED ½ LIFE (DAYS)	RATS: PEAK BLOOD LEVEL γ/ml	RATS: PEAK MET Hb gm./100 ml.
DDS		<1	1.5	56.6	9.0	13.76	3.87
DADDS		8-9	0	7.3	>200	0.20	0
1367		5	–	44.2	27	–	–
1431		7	–	32.5	25	–	–
1435		3	–	33.8	39	–	–
1470		5	–	85.0	10	–	–
1481		7	–	31.0	35	0.67	1.0
1503		5	3	40.0	38	0.40	0.25
1513		4	–	50.6	30	–	–

* EACH DRUG GIVEN SUBCUTANEOUSLY IN ONE DOSE OF 400 mgm./kgm. SUSPENDED IN 40 PER CENT BENZYL BENZOATE - 60 PER CENT CASTOR OIL

FIG. 3. Comparative antimalarial and metabolic data on DDS and eight repository sulfones. Each drug given subcutaneously in one dose of 400 mgm./kgm. suspended in 40 per cent benzyl benzoate-60 per cent castor oil.

the pretreatment level of prevalence by day 30.

It is desirable in conclusion to emphasize two major reasons for interest in repository sulfones. First, they act for much longer periods than oral sulfones. Therefore, through infrequent administration they offer the possibility of superior treatment of outpatients and of the protection of contacts by chemoprophylaxis. Second, they result in sustained low blood sulfone levels rather than the fluctuating levels characteristic of conventional oral administration. They may be advantageous because (a) the degree of efficacy or apparent potency associated with sustained drug blood levels can be vastly different from intermittent levels, and (b) sustained low drug levels have the possibility of greater safety than the temporarily high levels following other types of treatment.

SUMMARY

Conjugated, rapidly excreted sulfones were shown to be useful against falciparum malaria during the early documentation of their value in leprosy. Almost twenty years elapsed before sulfones began to attract attention as antimalarial drugs. This lag stemmed from belated recognition of the potency of 4,4'-diaminodiphenyl sulfone (DDS), unequal activity of sulfones in different types of malaria, and availability of superior alternative drugs. Recently, drug resistance has become an important problem in malaria, and evidence has been obtained indicating that sulfones have a different mode of action from conventional antimalarial drugs. Sulfones are thus emerging as useful adjuncts in malaria.

Concurrently, research on repository antimalarials showed that several types of sulfones have long action when given intramuscularly or subcutaneously. Data on antimalarial activity and metabolism in animals are presented on 4,4'-diacetylaminodiphenyl sulfone and seven other repository sulfones (PAM-1367, 1431, 1435, 1470, 1481, 1503, and 1513). These compounds provide a useful range of substances relative to patterns of drug release and duration of action. A dose of repository sulfone acts for much longer periods than an oral dose of DDS. Through slow absorption, it produces low blood drug levels with much less fluctuation than conventional oral administration. These patterns of drug release favor continuous suppressive action, with less likelihood of toxicity from high drug blood levels.

Repository sulfones may prove to be particularly convenient in the treatment and prophylaxis of leprosy.

REFERENCES

1. Archibald, H. M. and Ross, C. M. A preliminary report on the effect of diamino-diphenyl sulphone on malaria in Northern Nigeria. J. Trop. Med. & Hyg. **63** (1960) 25-27.
2. Black, R. H., Hennessy, W. B., McMillan, B., Dew, B. B. and Biggs, J. C. Studies on depot antimalarials: 2. The effect of a single injection of the depot antimalarial CI-564 on relapsing vivax malaria acquired in New Guinea. Med. J. Australia **2** (1966) 808-811.
3. Bratton, A. C. and Marshall, E. K. A new coupling component for sulfanilamide determination. J. Biol. Chem. **128** (1939) 537-550.
4. Coggeshall, L. T., Maier, J. and Best, C. A. The effectiveness of two new types of chemotherapeutic agents in malaria. Sodium p,p'-diamino-diphenylsulfone n,n'-didextrosulfonate (Promin) and 2-sulfanilamide pyrimidine (Sulfadiazine). J. American Med. Assoc. **117** (1941) 1077-1081.
5. DeGowin, R. L., Eppes, R. B., Carson, P. E. and Powell, R. D. The effects of diaphenylsulfone (DDS) against chloroquine-resistant *Plasmodium falciparum*. Bull. WHO **34** (1966) 671-681.
6. Elslager, E. F. and Worth, D. F. Repository antimalarial drugs: n,n'-diacetyl-4,4'-diaminodiphenylsulphone and related 4-acylaminodiphenylsulphones. Nature **206** (1965) 630-631.
7. Faget, G. H., Pogge, R. C., Johansen, F. A., Dinan, J. F., Prejean, B. M. and Eccles, C. G. The promin treatment of leprosy. A progress report. Publ. Hlth. Rept. **58** (1943) 1729-1741. *Reprinted in* Internat. J. Leprosy **34** (1966) 298-310.
8. Glazko, A. J. Parke, Davis & Company, unpublished data.
9. Kaump, D. H. Parke, Davis and Company, unpublished data.
10. Laing, A. G. B., Pringle, G. and Lane, F. C. T. A study among African school children of the repository antimalarial properties of cycloguanil pamoate, 4,4'-diacetylaminodiphenylsulfone and a combination of the two drugs. American J. Trop. Med. & Hyg. **15** (1966) 838-848.
11. Ramakrishnan, S. P., Basu, P. C., Singh, H. and Singh, N. Studies on the toxicity and action of diaminodiphenyl sulfone (DDS) in avian and simian malaria. Bull. WHO **27** (1962) 213-221.
12. Rieckmann, K. A new repository agent, CI-564, used in a field trial in New Guinea. Trans. Roy. Soc. Trop. Med. & Hyg. **61** (1967) 189-198.
13. Schmidt, L. H., Rossan, R. N. and Woods, J. University of California, Davis, personal communication.

14. SHEPARD, C. C., MCRAE, D. H. and HABAS, J. A. Sensitivity of *Mycobacterium leprae* to low levels of 4,4′-diaminodiphenyl sulfone. Proc. Soc. Exper. Biol. & Med. **122** (1966) 893-896.

15. SHEPARD, C. C. Activity of repository sulfones against *Mycobacterium leprae* in mice. Proc. Soc. Exper. Biol. & Med. **124** (1967) 430-433.

16. THOMPSON, P. E., OLSZEWSKI, B. J., ELSLAGER, E. F. and WORTH, D. F. Laboratory studies on 4,6-diamino-1-(p-chlorophenyl)-1,2-dihydro-2,2-dimethyl-s-triazine pamoate (CI-501) as a repository antimalarial drug. American J. Trop. Med. & Hyg. **12** (1963) 481-493.

17. THOMPSON, P. E., BAYLES, A., OLSZEWSKI, B. and WAITZ, J. A. Studies on a dihydrotriazine and a sulfone, alone and in combination, against *Plasmodium berghei* in mice. American J. Trop. Med. & Hyg. **14** (1965) 198-206.

18. THOMPSON, P. E., OLSZEWSKI, B. and WAITZ, J. A. Laboratory studies on the repository antimalarial activity of 4,4′-diacetyl-aminodiphenylsulfone, alone and mixed with cycloguanil pamoate (CI-501). American J. Trop. Med. & Hyg. **14** (1965) 343-353.

19. THOMPSON, P. E., WAITZ, J. A. and OLSZEWSKI, B. The repository antimalarial activities of 4,4′-diacetylaminodiphenylsulfone and cycloguanil pamoate (CI-501) in monkeys relative to local release following parenteral administration. J. Parasitol. **51** (1965) 345-349.

20. THOMPSON, P. E., OLSZEWSKI, B., BAYLES, A. and WAITZ, J. A. Relations among antimalarials from studies with cycloguanil-, sulfone-, or chloroquine-resistant *Plasmodium berghei* in mice. American J. Trop. Med. & Hyg. **16** (1967) 133-145.

21. THOMPSON, P. E., WAITZ, J. A., OLSZEWSKI, B., BAYLES, A. and BUTCH, A. Parke, Davis and Company, unpublished data.

DISCUSSION

Dr. Binford. Before opening Dr. Thompson's paper for discussion I would like to add something on the history of the use of DDS in malaria. Early last year we had a call from the State Department saying a foreign correspondent from Australia was in the office, who had been with a party of foreign correspondents in Hawaii, where they had been briefed by the Commanding General of the Tripler Hospital, who told them of a new drug for the treatment of malaria in Vietnam. This drug had come out of the work of a leprosy hospital in New Guinea. The correspondent, being from Australia, wanted to get the facts. I wrote to Major General Byron L. Steger, Commanding General of the Tripler Hospital, who replied that Major General Robert E. Blount, when in Hawaii, on his way to Vietnam, had told him the story. He referred me to Colonel William Tigertt, Director of the Walter Reed Army Institute of Research. Colonel Tigertt sent me a bibliography developed by a pharmacologist in Philadelphia working under contract to search the literature for clues on all drugs that had been used effectively in malaria. In this search he turned up Dr. Coggeshall's paper,[1] which has been mentioned earlier today, and a one-page article in *Leprosy Review*, written by Dr. D. L. Leiker in 1956,[2] who was in Netherlands New Guinea at that time. In this article Leiker commented on the fact that patients in the leprosy hospital were not getting malaria, while in the surrounding country malaria was rampant. Leiker suggested that DDS treatment might be responsible

---

[1] COGGESHALL, L. T., MAIER, J. and BEST, C. A. The effectiveness of two new types of chemotherapeutic agents in malaria. Sodium p,p′-diamino-diphenyl-sulfone n,n′-didextrosulfonate (Promin) and 2-sulfanilamide pyrimidine (Sulfadiazine). J. American Med. Assoc. **117** (1941) 1077-1081.

[2] LEIKER, D. L. Note on sulfone activity in malaria infection. Leprosy Rev. **27** (1956) 66-69.

for the absence of malaria in the patients with leprosy. In 1960, Archibald and Ross,[3] in Nigeria, published a paper on the subject. We who are in leprosy work are, of course, gratified to learn that this observation made first in a leprosy hospital has been useful in improving the treatment of falciparum malaria due to resistant strains of the parasite. The paper is now open for general discussion.

Dr. Shepard. Do rats form the monoacetylated compound from DADDS.

Dr. Thompson. Yes. The monoacetylate is formed in rats, monkeys, and mice.

Dr. Shepard. Is the difficulty that they do not take it down to DDS?

Dr. Thompson. There is very good evidence, as far as malaria is concerned, that the monoacetylated compound is not as effective as DDS or some conjugated DDS. We have some comparative data on the monoacetylate, but I cannot quite recall them now.

Dr. Peters. In injecting suspensions like those mentioned, is it possible to assess accurately the size of the particles injected, and is it possible to reproduce these injections?

Dr. Thompson. This has been one of the really difficult parts of the work. The earlier problem with cycloguanil pamoate has been resolved. It has also been resolved quite well with DDS. From the other sulfone, CI-608, we could make fine particles quite readily, but they should be larger and this had not yet been achieved. We were certainly aware that one could not extrapolate from monkeys to people in the case of particle size of cycloguanil pamoate, and I would be reluctant to do it with these sulfones. I think we should go ahead and get data on the ones we have, although there are some suggestions that possibly they might not be of the ideal size. In the case of the DADDS the size has not mattered much within a fairly wide range. The material is in the neighborhood of 20 to 40 microns in diameter, and can be reproduced quite well.

Dr. Mansfield. A symposium should be as comprehensive as possible, so that readers of the *Proceedings* of the symposium may derive maximum benefit by referring to one source. Thus, I would like to make a few comments on the use of sulfones in the therapy of diseases other than leprosy or malaria. This morning I had communication with physicians in San Francisco concerning the use of sulfones in the treatment of an infection of the left hand due to *Nocardia brasiliensis.* These physicians used DDS in a dosage of 50 mgm. daily in the treatment of this infection.[4] The most extensive clinical experience with sulfones in *N. brasiliensis* infections has been carried on by Dr. Gonzalez Ochoa in Mexico.[5-8] He recommends a daily dosage of 200 mgm. DDS for the treatment of this mycetoma, i.e., 100 mgm. following breakfast and 100 mgm. after dining in the evening. Clinical cure is often rapid, but relapses are common unless the drug is administered for two to three years after clinical recovery. Mycetoma lesions located in soft tissues, which are easily irrigated, respond more rapidly; such lesions often respond to smaller dosages of DDS, as in the case cited above. Lesions that involve bone, especially thoraco-pulmonary mycetoma, have a poorer prognosis and require prolonged therapy. Relapses are principally due to premature suspension of treatment

[3] ARCHIBALD, H. M. and ROSS, C. M. A preliminary report on the effect of diamino-diphenyl sulfone on malaria in Northern Nigeria, J. Trop. Med. & Hyg. **63** (1960) 25-27.

[4] BECTON, J. and NIEBAUER, J. Personal communication, 1967.

[5] GONZALEZ OCHOA, A., SHIELS, J. and VASQUEZ, P. Acción de la 4,4' diaminodifenil-sulfona frente a *Nocardia brasiliensis.* Gac. med. (Mexico) **82** (1952) 345-353.

[6] GONZALEZ OCHOA, A. Effectiveness of DDS in the treatment of chromoblastomycosis and mycetoma caused by *Nocardia brasiliensis. In* Therapy of Fungus Dieases: An International Symposium. Sternberg, T. H. and Newcomer, V. D., Eds. Boston, Little, Brown & Co., 1955, pp. 321-328.

[7] GONZALEZ OCHOA, A. Mycetomas caused by *Nocardia brasiliensis,* with a note on the isolation of the causative organism from the soil. Lab. Invest. **11** (1962) 1118-1123.

[8] GONZALEZ OCHOA, A. Personal Communications, 1967.

and are most common in the thoracopulmonary forms of *N. brasiliensis* infection. Recently, at the Fifth International Congress of Chemotherapy, in Vienna, a long-acting sulfonamide also, 4-sulfanilamide-5-6 dimethoxpirimide, was shown to be at least as effective as DDS in therapy of this mycetoma.[8] Other *Nocardia* infections do not respond to sulfone therapy; the treatment of choice for these infections is sulfonamides, often in combination with another chemotherapeutic agent.[9, 10, 11, 12]

Arnold[13] reported the cure of a case of cervicofacial actinomycosis with DDS therapy; the etiologic agent was not isolated, but was thought to be similar to *Actinomyces bovis*. DDS is now recommended also in the therapy of actinomycosis of the skin in penicillin-sensitive patients.[14] DDS may be useful in the treatment of infections caused by *Streptomyces madurae*[15, 16] and *Madurella grisea*.[17]

Promising results with DDS therapy have been obtained in the therapy of dermatitis herpetiformis (Duhring's Disease)[8, 18, 19, 20, 21] and pyoderma gangrenosum.[22] Experimental toxoplasmosis has shown response to sulfone.[23] Treatment of psoriasis with sulfones has not been encouraging.[24]

Gonzalez Ochoa[8] has used DDS in the therapy of chronic discoid lupus erythematosis and cutaneous tuberculosis. DDS may be particularly useful in those cases of chronic discoid lupus erythematosis where there is marked infiltration of the lesions; 200 mgm. DDS daily is recommended, with progressive reduction of the dosage to a maintenance dose of 50 mgm. daily once the lesions have cleared. In cutaneous tuberculosis Dr. Gonzalez Ochoa has used the same dosage as he recommends in therapy of *N. brasiliensis* mycetoma.

Karlson has studied the *in vitro* activity of DDS against various acid-fast microorganisms and has found a wide variation in sensitivity among various mycobacterial strains and relative insensitivity among strains of *Nocardia asteroides*.[25] Finally, some new experimental derivatives of DDS have been found to have *in vitro* chemotherapeutic effect against *Mycobacterium tuberculosis* and *Staphylococcus aureus*.[26]

Dr. Hanks. Dr. Mansfield might be interested to know that from the State of Massachusetts, by means of personal communication, he can get ancillary information. Dr. James Gray, mycologist for the State, has been isolating Nocardia from presumed cases of tuberculosis. Since the stand-

[9] HILDICK-SMITH, G., BLANK, H. and SARKANY, I. Fungus Diseases and Their Treatment. Boston, Little, Brown & Co., pp. 303-317.

[10] PEABODY, J. W. and SEABURY, J. H. Actinomycosis and nocardiosis. A review of basic differences in therapy. American J. Med. **28** (1960) 99-115.

[11] SEABURY, J. H. and DASCOMB, H. E. Results of the treatment of the systemic mycoses. J. American Med. Assoc. **188** (1964) 509-513.

[12] WILSON, J. W. and PLUNKETT, O. A. The Fungus Diseases of Man. Berkeley, University of California Press, 1965, pp. 143-161.

[13] ARNOLD, H. L., JR. and AUSTIN, E. R. Diasone therapy for actinomycosis of the jaw. J. American Med. Assoc. **138** (1948) 955-956.

[14] PIPKIN, J. L. Fungus diseases of the skin. Actinomycosis. *In* Current Therapy, Philadelphia, W. B. Saunders, Co., 1967, pp. 514-515.

[15] MARIAT, F. Action *in vitro* de 4-4'diaminediphenyl sulfone sur les actinomycetes aerobies pathogenes. Compt. Rend. Acad. Sci. (Paris) **244** (1957) 3095-3098.

[16] RIDDELL, R. W. and STEWART, G. T. Fungus Diseases and Their Treatment. London, Butterworth and Co., 1958, pp. 121-125.

[17] NEUHAUSER, I. Black grain maduromycosis caused by *Madurella grisea*. Arch. Dermat. **72** (1955) 550-555.

[18] ALEXANDER, J. The treatment of dermatitis herpetiformis with heparin. British J. Dermat. **75** (1963) 289-293.

[19] CORNBLEET, A. Dermatitis herpetiformis: chronic dermatosis yields to sulfones. Clin. Med. **70** (1963) 1483-1486.

[20] WEAKLEY, D. R. Dermatitis Herpetiformis (Duhring's Disease). *In* Current Therapy. Philadelphia, W. B. Saunders, Co., 1967, pp. 495-496.

[21] ZAIAS, N. Personal communication, 1967.

[22] ALTMAN, J. and MOPPER, C. Pyoderma gangrenosum treated with sulfone drugs. Minnesota Med. **49** (1966) 22-26.

[23] JACOBS, L., MELTON, M. L. and KAUSMAN, H. E. Treatment of experimental toxoplasmosis. Arch. Ophthal. **71** (1964) 111-118.

[24] PEREIRA, C. A. O emprego da sulfona na psoriae. Hospital (Rio de Janeiro) **66** (1964) 197-204.

[25] KARLSON, A. G. The *in vitro* activity of 4-4' diaminodiphenyl sulfone against various acid-fast microorganisms. Internat. J. Leprosy **31** (1963) 183-187.

[26] PRESCOTT, B. and CALDES, G. Some new derivatives of 4-4' diaminodiphenyl sulfone as potential antimicrobial agents. Antimicrob. Agents & Chemotherap. **4** (1964) 564-567.

ard drugs for tubercle bacilli were absolutely useless Dr. Gray has collected, but never published, a great deal of information on *in vitro* sensitivities of *Nocardia* to sulfonamides and on the results of treating of patients.

Dr. Rees. I wish to ask Dr. Thompson if he has information on the emergence of resistance, either in animals or man, during treatment with DADDS, as compared with DDS.

Dr. Thompson. We have only one limited observation; it indicated that there was no difficulty in inducing resistance to DDS. The strain was passed at weekly intervals, and had a generation time of about 28 hours. After about 12 passages we observed a significant increase in tolerance to DDS. DADDS is released at a rate that will occasionally kill the parasite, but occasionally does not. We made one study in which injected mice were followed daily for 43 days. Most seemed protected through the period. However, there were two in which quite-severe infections developed. We were curious to know if strains resistant to DDS had developed and ran a dose titration with those isolates against the parent line. Apparently the strain had not become resistant. Our doses were such that we could determine as much as a two and a half-fold shift in tolerance. The two isolates did not become resistant at the level, but we did not check below that point.