CORRESPONDENCE

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MODE OF ACTION AND METABOLISM OF SULFONES

To The Editor:

I have read with great interest the discussion on the mode of action and the metabolism of the sulfones to which various workers contributed in your correspondence section [1] and also the interesting editorial in the same issue.[2] You presented a very valuable discussion on a difficult subject, and I learned much from it.

Recent work has given more light on this subject, and I would draw attention to the work of Boyer, Rist and Saviard,[3] Boyer, Troestler, Rist and Tabone,[4] and of Francis and Spinks.[5] These papers support and amplify the findings of Titus and Bernstein [6] which you quoted.

Boyer, Rist and Saviard found that promin and sulphetrone are unstable in solution, particularly in solutions of 5 per cent or less; even at room temperature, on storage, a precipitate of DDS appeared. This instability had a marked influence on chemotherapeutic activity *in vitro*. They studied the activity of several complex sulfones against Proteus X19, one set of experiments being carried out with sulfone solutions sterilized by autoclaving, and the other with solutions sterilized without heat. They also studied the effect of incubation on the activity of the complex sulfones. They found that autoclaving increased the activity of a 50 per cent solution of sulphetrone by only a moderate amount, five times; with a 5 per cent solution the

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[1] Internat. J. Leprosy **18** (1950) 247-263 (correspondence).

[2] Wade, H. W. Internat. J. Leprosy **18** (1950) 237-244 (editorial).

[3] Boyer, F., Rist, N. and Saviard, M. Ann. Inst. Pasteur **77** (1949) 680-687.

[4] Boyer, F., Troestler, J., Rist, N. and Tabone. Ann. Inst. Pasteur **78** (1950) 140.

[5] Titus, E. and Bernstein, J. Ann. New York Acad. Sci. **52** (1949) 719-728.

[6] Francis, J. and Spinks, A. British J. Pharm. & Chemother. **5** (1950) 565-583.

increase was twenty times. During incubation the activity of these sulfones steadily and progressively increased. They attributed these increases to the liberation, by hydrolysis, of DDS, and concluded that there was no reason whatever to suppose that the distributed sulfones act by virtue of their full molecule, either *in vitro* or *in vivo*, without giving off DDS. In a still more recent paper [1] Boyer *et al.* have described a method, similar to that of Titus and Bernstein, for isolating DDS from solutions and body fluids in the presence of complex soluble sulfones.

Francis and Spinks [5] have carried out similar studies, with similar results. They studied the action of five different sulfones, including DDS, promin, diasone, and sulphetrone, against *Str. agalactiae*, one set of sulfone solutions being sterilized by heat and the other by bacterial filtration. They found that with the filtered sulfones, promin and sulphetrone were 250 times less active than DDS, while diasone was 27 times less active. With the heat-sterilized solutions, the activity of promin was increased 26 times, and that of sulphetrone 9 times; no figure was given for diasone. They used a method of benzene extraction to estimate the DDS content of solutions of soluble sulfones, and showed that the giving of soluble sulfones to animals, either by mouth or by injection, produced appreciable blood levels of DDS which, however, were much higher after oral administration. They added soluble sulfone to animals' blood and incubated it, and found very little hydrolysis to DDS. They concluded that disubstituted sulfones act by their DDS content, produced by hydrolysis during sterilization before injection, by hydrolysis in the stomach on oral administration, and possibly to a small extent by hydrolysis in the body.

Your editorial commented on the lack of similar data in human beings. I have been working for some time trying to remedy this lack, and this work is to be presented in a paper now in preparation. With human beings receiving sulfones, I have been using the method of benzene extraction as described by Francis and Spinks to estimate DDS in the presence of soluble sulfones. I have applied this method to a study of blood and urine, and also of aqueous solutions of sulfones.

Some of the main findings are:

(*a*) Both sulphetrone and diasone appear to contain traces of free DDS as an impurity.

(*b*) When even a neutral solution is stored or incubated, the free DDS content steadily rises. Strong solutions are more

stable than weak ones; acid solutions, even slightly acid solutions, are very unstable.

(*c*) Boiling or autoclaving causes an increase in the free DDS content, up to 20 or even 30 times in weak solutions of sulphetrone; with strong solutions, and with diasone, the increase is less.

(*d*) Sulphetrone solutions prepared for injection by autoclaving contain free DDS in small but appreciable amounts.

(*e*) The blood of patients receiving such injections of sulphetrone shows a definite but low free DDS content. This content is no higher than that of the blood of patients receiving *the same dose* by mouth, and this in spite of the very poor absorption of orally administered sulphetrone, less than 20 per cent. Also it is little higher than that produced by the administration of the amount of DDS contained in the sulphetrone injected.

(*f*) The oral administration of disubstituted sulfones in the usual doses produces blood levels of free DDS much higher than is produced by injections of the usual doses. In most cases it is about the same as the DDS level produced by the administration of 150-200 mgm. doses of DDS itself.

(*g*) In patients receiving DDS itself by mouth, the sulfone present in the blood is not all in the form of free DDS. A fraction appears to be in the form of a water-soluble derivative.

(*h*) In patients receiving DDS, either by mouth or by injection, between 75 per cent and 95 per cent of the sulfone in the urine is in the form of a water-soluble derivative. This is probably the same compound as is described in the urine of dogs by Titus and Bernstein[5] and of rabbits by Francis and Spinks.[6] It is not in a conjugated form, for it is very readily diazotised without previous acid hydrolysis. These findings are at variance with those of M. I. Smith,[7] who reported that in rabbits DDS is excreted unchanged, and of Michael Smith,[8] who though finding more DDS in the urine than appeared to be soluble, did not detect soluble metabolites of DDS.

(*i*) Of my patients receiving sulfones in the usual doses, in only about 20 per cent is the urine definitely acid; in most of them it is definitely alkaline. This is presumably the result

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[7] SMITH, M. I. Personal communication quoted by Wade (see Ref. 2 above).

[8] SMITH, M. Lep. Rev. **21** (1950) 17-29.

of alkalosis produced by sulfones as described by Brownlee *et al.*[9] in animals.

It is realized that the findings (*h*) and (*i*) recorded above make the study of the metabolism of sulfones still more complicated. It now appears that there are many different forms in which sulfone may appear in blood and urine. The water-soluble sulfones, such as promin, diasone and sulphetrone, are degraded in varying degrees to DDS, which is water-soluble. DDS, again, can produce water-soluble forms. The isolation and identification of these metabolites and the study of their chemotherapeutic activity will be a very difficult undertaking, but it is necessary for a full understanding of the action of this important group of drugs. Also, it might lead to improvements in sulfone treatment.

In the meantime, it appears that the simplest, cheapest, and most rational form of treatment is provided by the administration of DDS. The Nigeria Leprosy Service is now (Jan. 1951) treating over 15,000 patients in this way. Our great difficulty, as with other sulfones used here, is not the toxic effects of the sulfones usually described, anemia, hemolysis, etc.—these cause very little trouble—but a drug fever and dermatitis caused by patients becoming allergic to sulfones. Antihistamine drugs given orally have been of great value in the treatment of this condition, and desensitization is usually possible later. We now find twice-weekly treatment to be simpler, safer, and better tolerated than daily treatment, and probably no less effective; our standard dosage, attained slowly over several weeks, is 400 mgm. given orally twice weekly.

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[9] BROWNLEE, G., GREEN, A. F. and WOODBINE, M. British J. Pharm. & Chemother. **3** (1948) 15-28.