CORRESPONDENCE

This department is provided for the publication of informal communications which are of interest because they are informative or stimulating, and for the discussion of controversial matters.

EARLY EXPERIENCES WITH DDS IN MAN

An inquiry from a correspondent about how the idea became established that the parent substance of the sulfones is too toxic for use in human beings was submitted to two authorities in this field. One of them was Dr. Leon A. Sweet, of Parke, Davis & Co., who told of a trial by Dr. Perrin H. Long which led to a statement [*Bull. Johns Hopkins Hosp.* **62** (1938) 565] that, "Its toxicity, in our opinion, precludes its use in human beings." A statement from Dr. Long of his experience is given here. The other was Dr. George Brownlee, recently of the Wellcome Research Laboratories in England where Buttle and associates, in 1937, made one of the first studies of the substance. His reply is also given here, supplemented by information from another source.

From Dr. Perrin H. Long, Johns Hopkins University School of Medicine, Baltimore, Maryland:

About the early use of diaminodiphenyl sulfone in human beings, back in 1938 Doctor Bliss, Mr. Feinstone and I carred out an extensive study on the effectiveness of that substance in experimental infections. We found it to be highly effective against streptococci and pneumococci and, in retrospect, I can say that it was the most effective of the sulfa series that we ever worked with in the laboratory.

Even though we knew as a result of our animal experiments that it was quite toxic, we decided in the summer of 1938 to test its efficacy in several cases of subacute bacterial endocarditis. I do not have the details of the clinical investigation at hand but, as I remember it, we set our doses at a somewhat lower level than we had found to be effective in mice; i. e., based on a weight for weight comparison. I think about four patients were treated, and in each one we got into trouble within a few days after treatment was started because of severe anemia. This scared us off and we did no more with the compound. I should judge, though, that it would be possible to adjust the dosage so that it could be used in human beings.

From Dr. George Brownlee, Toxicology Research Unit, Medical Research Council, Carshalton, Surrey:

I think I may have one answer to the question of how the belief got established that DDS is so terribly toxic. It will be recalled that DDS was discovered before sulphapyridine or sulphathiazole or any of the later

sulpha drugs which proved to be effective in pneumonia. As soon as the efficiency of DDS against pneumococci in animals was discovered in these laboratories here, that substance was pressed into service in man. The blood level which was necessary to eliminate the pneumococcus in animals, i.e., somewhere about 5 to 7.5 mgm. per cent, is indeed toxic for man—terribly toxic. Doses of 1 to 2 gm. daily produced an acute hemolytic crisis on the third day, followed later by signs of central (cerebral) irritation. The pneumonia appeared to be successfully aborted.

The short explanation, then, of how the belief got established must be referred to the dose level. There is, of course, an extensive and well-documented literature upon the nature of the hemolytic poison which DDS is.

The new fact is that, provided one does not go above about 3 mgm. per cent in man, the acute hemolytic crisis seen with higher blood concentrations does not appear to intervene. Whether the second insidious toxicity which workers with laboratory animals have always seen with DDS, namely, slowly developing peripheral neuritis, will occur in man remains to be seen. It is quite clear that we must proceed cautiously with these studies in man, as indeed is being done.

I have been kept up to date, by correspondence and otherwise, with the work that is being done with this drug in leprosy. There is little doubt that this work, which seems to be started off by John Francis following observations of McEwen in cows, must be taken most seriously. I have been coming to the conclusion that we must find time to make a set-piece pharmacological study of DDS so that the clinical experimentation with it can be put on a sound basis.

[According to Dr. John Lowe, of the Nigeria Leprosy Service (personal communication), Buttle and associates of the Wellcome Research Laboratories, in their first report on experiments with DDS [*Lancet* **1** (1937) 1331], stated that after a single dose of 300 mgm. in man the blood had marked antibacterial properties. In a personal communication to Lowe, Buttle has said that a therapeutic trial was made in human beings suffering from acute infections, with doses of the order of 1 to 2 gm. a day. Because of the rapid production of methemoglobinemic and other toxic effects that treatment was promptly abandoned.—EDITOR.]