Comments

The Editor has invited my comments on Dr Sheshkin's paper, which I read with interest.

The care of the patient who is subject to recurrent and severe acute phases can be one of the most difficult problems confronting the leprologist, and one has every sympathy with the concern which prompted Dr Sheshkin's study. At the same time, the choice of thalidomide for a study of this nature is not a little surprising. The appalling results it may have in pregnancy have rightly discredited thalidomide in the mind of the general public, and the publicity surrounding it, and the emotional reaction associated with it, clearly call for the utmost caution in its use in any drug trial. It would be legitimate to ask whether the patients knew what they were receiving, and if so, how far their emotional response may have influenced the findings.

The report of promising results in any form of therapy, no matter how bizarre, is sufficient to stimulate enthusiasts to proceed with its use. Here the author has a considerable responsibility. The risk remains that sooner or later the drug will be administered during pregnancy. In any case, how certain is it that the drug is without danger apart from pregnancy. What for instance is its effect on spermatogenesis, a very cogent matter in the type of male leprosy patients who might be included in future trials. I can find no reassurance on this point in the literature. The more extensive use of the drug could be justified only if results with it in the most difficult cases were of such brilliance as to outweigh its known serious defects. The results published in this paper do not match up to such a standard. The number of patients is too few for much store to be placed on the clinical remissions recorded after its use. The history of leprosy is strewn with forlorn therapeutic hopes based on small trials. At the same time, the numerous side effects the author reports cannot be ignored.

There is another aspect of this paper which merits comment. It is not surprising that the author has encountered reactive phases of such difficulty as to prompt this trial while using a maintenance dose of DDS at the level of 100 mg. daily. Nowadays most leprologists would regard this dose as far too high, and would advocate a maintenance dose of not more than half this amount, with a very slow build up to that level. By such means the course of treatment is likely to be much more tranquil, and the incidence of reactive states materially reduced without loss of anti-bacterial activity. Where patients show any intolerance to lower doses of DDS some useful alternative drugs are now available for basic therapy. These facts provide additional fundamental grounds for questioning the necessity for this trial.

T. F. DAVEY

The Editor has asked me to comment on Dr Sheskin's paper which appears in this issue, and I would like to criticise it on the following grounds:

Firstly, the drug itself. Dr Sheskin is advocating the use of a drug which is so dangerous that, during the short time it was marketed, it left a trail of suffering and grief which stirred the conscience of the world almost as much as did the dropping of atom bombs on Japan in 1945. It is clear that Dr Sheskin confined his trial of thalidomide to males and to non-pregnant females, but, if more trials are carried out, there is a danger that the drug may inadvertently be given to females in the early stage of pregnancy, or, more likely, that it will find its way into households where it will not be kept under lock and key. Quite apart from thalidomide's teratogenic effects, it should be noted that the following side effects were encountered during the trial: drowsiness, constipation, dryness of oral and nasal mucosa, erythema of face and chest, oedema, and skin eruptions.

Secondly, the actual trial. In the first place, Dr Sheskin should describe what he means by the term 'lepra reaction'. Many use it to describe both types of reaction occurring in lepromatous leprosy, the one in which the actual leprosy

lesions rapidly become swollen and erythematous, and the other type characterised by erythema nodosum. I use the terms Type 1 and Type 2 to differentiate them (Jopling 1959), and at the 8th International Leprosy Congress in 1963 the respective terms 'lepromatous exacerbation' and 'lepra reaction' were recommended. Their response to treatment is different, and the reader of Dr Sheskin's paper needs to be told which of these two types of reaction was treated, or whether both types were included. Further, although we are told that the drug was given to 13 'unselected cases' we are not told what system was adopted to exclude bias. I do not think, therefore, that any conclusion can be drawn from this trial. However, recent work on skin homograft survival suggests that thalidomide possesses immunosuppressive properties (Hellmann *et al.*, 1965), so it is probable that more trials of the drug in lepra reaction will soon be under way and Dr Sheskin's results will either be confirmed or refuted.

I would like to say a final word on the use of dapsone (DDS) in patients who are reacting, for it would seem to me to be extremely hazardous to give 100 mg. daily to such patients. I would consider it unwise to give as much as 100 mg. *in one month*, let alone in one day, and anyone who tries giving 5 mg. twice a week will be taking the first step in getting the reactions under control and will be pleasurably surprised at the steady improvement in smears and biopsies.

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REFERENCES

HELLMANN, K., DUKE, D. I., and TUCKER, D. F. (1965). *Brit. Med. J.*, **2**, 687.
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I have carefully read the paper of Dr Sheskin regarding the effect of thalidomide on the lepra reaction. I must admit that I know very little about leprosy but I find it intriguing that thalidomide should be found to possess yet another type of biological activity in addition to its well known embryotoxic, neurotoxic and sedative effects. It would be interesting to know whether there is a common biochemical denominator in all these effects or whether they are independant of each other. At present, in spite of intensive research, we know very little about how thalidomide produces its effects.

Thalidomide under physiological conditions is known to be a very reactive (unstable) compound and in the body it undergoes spontaneous hydrolysis to give some twelve metabolites all of which are known. It would be of great interest to know whether it is the drug itself which is responsible for suppressing the lepra reaction or whether this effect is due to one or more of the metabolities.

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