'VADRINE' (S.131) IN THE TREATMENT OF LEPROMATOUS LEPROSY: A PRELIMINARY REPORT

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In 1956 Dr. H. Brodhage drew our attention to the possible anti-leprosy action of two new oxdiazolones which had been shown to have tuberculostatic activity in guinea pigs equal to that of isoniazid and to be less toxic (Brodhage and Wilder Smith, 1955). One of these compounds, the p-aminosalicylate of 2-pyridyl-(4)-1,3,4, -oxdiazolone-(5), had been shown to be active *in vitro* against isoniazid-resistant strains of *M. tuberculosis* and according to Dr. P. Geistlich (personal communcation) had proved to be non-toxic to humans in tuberculosis trials and had shown activity against leprosy in a preliminary trial in Angola.

It was decided to carry out a trial of this compound in a small number of leprosy patients at the Jordan Hospital, and a supply was sent to us by Edward Geistlich & Sons, Wolhusen, Switzerland, who had manufactured it in their Research Laboratories under the name S.131 later to be changed to Vadrine.

Method

Seven consecutive patients admitted during a period of nine months were treated with Vadrine and have now been observed for periods of 9-18 months. Five had had no previous treatment, one had been treated with dapsone (DDS) from 1947 to 1954, and one had been taking dapsone for 9 months immediately prior to admission to the Jordan Hospital. All seven patients were proved to be suffering from the lepromatous type of leprosy and had no atypical features clinically or histologically. Bacilli were very numerous in all.

Vadrine was supplied in the form of tasteless yellow tablets of 200 mg., and we decided to commence with one tablet daily, to increase by one tablet every 6 days up to a maximum dosage of 40 mg./kg. of body weight, and to continue at this level. Five patients have completed one year's treatment or more, the remaining two having had treatment for only 9 months.

Results

This paper is mainly concerned with the results of treatment during the first year, since only 3 patients have exceeded one year's treatment and one of these has had a restricted dosage owing to *erythema nodosum leprosum.*

Clinical Observations. Patient No. 1 is a Eurasian (Anglo-Indian) female, aged 46, who gave an 18 months' history of skin lesions. At the time of admission she was found to have large

numbers of erythematous macules and infiltrated lesions on face, buttocks and limbs, the face appeared puffy, the nose was broadened and the nasal septum was ulcerated. Improvement has taken place steadily with disappearance of all lesions by the end of one year leaving light brown marks on the skin, and there has been no clinical deterioration during the ensuing 6 months. Nasal ulceration healed after 2 months' treatment. Early changes of keratitis developed in the eyes during the first 6 months and have remained unchanged. Mild, non-febrile *erythema nodosum leprosum* commenced 7 months after commencement of the trial and has recurred ever since. This has not called for any special treatment, nor has it necessitated any reduction in dosage of Vadrine.

Patient No. 2 is an Italian female, aged 24, and is the only one in the series who has had known contact with leprosy; her father was treated for lepromatous leprosy when she was a child. She says that she noticed her first skin lesions at the time of the birth of her baby one year prior to admission here. On admission there were many erythematous macules, infiltrated lesions, papules and nodules on face, arms, buttocks and thighs, she had early keratitis in both eyes, and the nasal septum was ulcerated. A number of new lesions appeared on both legs about 3 months after commencing treatment, and during the following 9 months there was slight but definite clinical improvement. The appearance of eyes and nose remained unchanged. Between 12 and 15 months her lesions began to look active again, the nasal mucosa looked worse and the eyes developed more obvious corneal changes.

Patient No. 3 is a Eurasian (Anglo-Burmese) male, aged 32, who noticed his first leprosy lesions one year prior to admission here and commenced sulphone therapy in Burma 3 months later. Dapsone was stopped prior to commencing treatment with Vadrine, and examination revealed many macules, papules, nodules and infiltrated lesions. Slight but definite clinical improvement has occurred but has been somewhat masked by severe *erythema nodosum leprosum* which commenced 3 months after commencing Vadrine. It recurred in bouts for the next 6 months and has been continuous after that. Large doses of prednisone have been required to keep the reaction under control, and the dosage of Vadrine has been reduced.

Patient No. 4 is a German lady, aged 49, whose first lesions appeared 6 months previously. On admission here she had very large numbers of erythematous macules and infiltrated lesions over face, trunk, buttocks and limbs, the face was puffy and the eyes showed early changes of keratitis. After 6 months' treatment all the macules disappeared, the infiltrated lesions had flattened, and there was no longer any oedema of face. By the end of one year the skin had become completely normal in appearance and the keratitis had much improved. There has been no clinical deterioration during the

ensuing 3 months. Her gall-bladder was removed for calculi 9 months after commencing the trial, and Vadrine was continued without interruption.

Patient No. 5 is a Euro-African male from British Guiana, aged 24, who gave a two years' history of skin lesions and increasing numbness of hands and feet. On admission he had leonine facies, infiltrated lesions on limbs and buttocks, nasal ulceration, early keratitis, and anaesthesia of all four limbs. By the end of one year the thickening of the face has improved and the lesions on the rest of the body have flattened, but nasal ulceration is still present. Keratitis has remained unaltered.

Patient No. 6 is a Eurasian (Anglo-Indian) male, aged 27, who noticed skin lesions 6 months prior to admission here. He was found to have multiple small erythematous macules and infiltrated lesions on buttocks and limbs, and the eyes showed early changes of keratitis. He has completed 9 months' treatment and all the skin skin lesions have flattened and become purple-brown in colour. The eye changes have not altered. Treatment for intestinal amoebiasis was successfully carried out concurrently with the trial, and no ill-effects were encountered.

Patient No. 7 is a Eurasian (Anglo-Indian) female, aged 57, who was treated for leprosy in India with sulphones from 1947 to 1954. Treatment then ceased, and 3 years later fresh lesions appeared. When she was examined here she had enormous numbers of erythematous nodules and infiltrated lesions over back, abdomen, buttocks and limbs, the skin of the face and nose was diffusely thickened, the ear lobes were pendulous, the eyes showed changes of keratitis and there was anaesthesia over all four limbs. Between the 1st and 24th week of treatment with Vadrine many of the more prominent nodules became necrotic and ulcerated, followed by healing. After 9 months' treatment the skin of the face has become markedly less thickened and many of the skin lesions have become flatter. The keratitis has not changed.

If clinical observations during the first year of treatment with Vadrine are compared with the results we would have expected from sulphones, it can be said that results with patient No. 4 have been considerably better, with No. 1 slightly better, with Nos. 3, 6 and 7 on a par, and with Nos. 2 and 5 slightly worse. The failure of nasal ulceration to heal in patients 2 and 5 is significant.

The development of early keratitis in patient No. 1 and the persistence of keratitis during the first year of treatment in Nos. 2, 5, 6 and 7, are in keeping with what we would expect from sulphone therapy at this hospital. Similarly, the ulcerating nodules in patient No. 7 during the early stages of treatment and the onset of *erythema nodosum leprosum* in No. 3 are developments which might have occurred with sulphone therapy.

Apart from slight anaemia occurring in patient No. 1 six weeks after commencing treatment, which responded to iron, the absence of side-effects has been striking.

Bacteriological Progress. Bacteriological progress was assessed at 3-monthly intervals from the bacterial index of skin smears and also from skin biopsies (Ridley, 1958). No significant alteration was to be expected in the bacterial index of smears, and none was seen; this index seldom alters in lepromatous patients of European or Eurasian origin during the first year of treatment with sulphones. The biopsy index did not alter significantly during the first 3 months, but at the end of 6 months the mean value for the 7 patients had fallen by 23%, and by the end of 12 months (4 cases only) it had fallen by a further 31%. The mean fall throughout the year was 26% per period of 6 months, compared with 25% which was the figure obtained from a larger series of similar cases on sulphones. The method of calculating these results was given in the earlier paper (Ridley).

The period of treatment under review, one year, is too short to obtain an accurate assessment of the progress of each individual patient since there is considerable random variation between biopsies, but in general the results agree with clinical impressions. In patient No. 4 who responded very well clinically, the index fell at twice the average rate; in patients 2 and 5 who showed a rather poor clinical response, the index in No. 2 fell at the usual rate up to the end of the year, only to rise again at the end of 15 months' treatment when solid-staining forms of bacilli reappeared in the skin lesions, and in No. 5 the index did not alter significantly during the year and the bacilli never became properly granular. These two patients therefore must be considered to have responded poorly. In all the other patients the bacilli became granular after 3 months' treatment.

Of other laboratory tests, the serum globulin level was raised (over 3.0 g./100 ml.) in five of the seven patients on admission, and in three of them it had returned to normal (2.5 g./100 ml. or lower) at the end of one year's treatment. In the other two patients (Nos. 1 and 5) both total globulin and gamma globulin levels remained high. The erythrocyte sedimentation rate appeared to be of no value. Other tests failed to detect any leucopenia or any diminution of hepatic or renal function which could be ascribed to the drug. In one patient the haemoglobin percentage dropped slowly from 86% to 72% during the early stages of treatment, but gradually returned to the pre-treatment level, without interrupting treatment, with the addition of oral iron.

Conclusions

As far as can be judged from a small series of cases, Vadrine appears to be a non-toxic drug, which during the first year of treatment, has a potency equal to that of sulphones. Not all patients

responded equally, however, and whereas one responded exceptionally well, in two it was thought advisable to discontinue the drug at the end of one year or 15 months. It is not yet possible to say whether these failures indicate an individual variation in the response to Vadrine or whether they are part of a general pattern of drug resistance developing towards the end of a year. A further analysis of the results will be made on completion of the trial.

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REFERENCES

BRODHAGE, H., and WILDER SMITH, A. E. (1955). Br. J. Tuberc. and Dis. Chest, **49,** 185.
RIDLEY, D. S. (1958). Leprosy Review, **29,** 45.
WILDER SMITH, A. E. (1954). Science, **119,** 514.