SOME OBSERVATIONS ON THE ROLE OF METHISAZONE ('MARBORAN') IN THE PROPHYLAXIS OF SMALLPOX IN A RURAL AREA*

DUNCAN L. FERGUSON, M.B., CH.B.(EDIN.), D.P.H.(RAND), *Acting Medical Officer of Health, Port Elizabeth Divisional Council.*

During the first half of 1964 an outbreak of smallpox occurred in the Eastern Cape Province, South Africa. The areas controlled by several local authorities were eventually involved, including that of the Port Elizabeth Divisional Council, where 11 definite cases of the disease were reported, with 3 deaths representing a case mortality rate of 27%. The infection could thus be considered as a virulent type.

All these cases were admitted to the emergency smallpox isolation hospital set up by the Port Elizabeth Municipality under the control of its Medical Officer of Health and his staff, assisted by the Medical Officer of Health of Walmer. Doubtless a full report will be published on their findings in due course.

Contacts were divided into 3 categories:

1. Household contacts, namely persons who ate and slept in the same premises as the patient.
2. Close contacts, namely persons living in dwellings contiguous to those occupied by a patient.
3. Social contacts, namely persons who visited and talked casually to members of the patient's family or who worked with the patient at the time of the onset of the disease and during the period before hospitalization.

Household and close contacts were placed in quarantine for 21 days. Social contacts were kept under surveillance.

In 1953 Thompson *et al.*[1] demonstrated the antiviral activity of certain drugs in mice infected with vaccinia virus. Subsequently Bauer *et al.*[2] reported on the use of compound 33T57 'marboran' in a field experiment in Madras, India as follows: 'The drug exerted its prophylactic effect regardless of the vaccination status of the contacts and was much more effective than vaccination or revaccination in protecting persons who had been in contact with smallpox infection.'

From a public-health point of view this was a finding of the utmost importance. It was therefore decided to test this claim, if conditions made this possible, during the outbreak in the area where I was responsible for prophylactic measures. Fortunately the circumstances surrounding 3 of the 11 cases enabled a well-controlled investigation, albeit on a small scale, to be carried out.

The following points of similarity in the 3 cases were significant:

1. All were Bantu male adults.
2. None had definite old or recent vaccination scars.
3. All lived in dwellings of almost identical structure.
4. All gave a history of contact with previously known cases.
5. All were first isolated after the appearance of the rash.
6. In all, recent movements were accurately verified.

*Refer to Editorial article on p. 855 of this issue of the *Journal*.

Case 1: J.M., of Coega Brickfields.

This patient had 5 household contacts and 370 social contacts. He was isolated in hospital about 4½ days after the initial febrile onset.

A team of vaccinators had been in the area a few days previously but the percentage of takes was low; so everybody was again vaccinated within 24 hours except those in whom recent successful vaccination was observed. Daily inspections were carried out, and where unsatisfactory reactions were noted vaccination was immediately repeated. The presence of old big vaccination scars appeared to modify the reaction to subsequent vaccination; in fact in some cases as many as 6 attempts failed to produce any appreciable reaction.

Infected premises and fomites were disinfected with formalin.

Marboran was not administered.

In this group of 375 contacts no secondary case occurred.

Case 2: S.K., of Pullen's round, Veeplaats.

This patient had 3 household contacts and 200 social contacts. He was isolated about 4½ days after the febrile onset of the disease. He eventually died.

Vaccination had also been carried out in this area previously, but here again there was a considerable percentage of non-takes. Revaccination was done immediately wherever necessary. The household contacts included a woman aged 19 with her baby aged 10 months and a 12-year-old sister. The sister had excellent healing vaccination scars on her left deltoid. The woman and her baby had no scars of previous successful vaccination and accordingly were vaccinated immediately after the patient had been removed to hospital. It was noteworthy that all these last scarifications in both the woman and her baby produced excellent reactions.

Premises and fomites were disinfected with formalin.

Marboran was not administered.

In this group of 3 household contacts and 200 social contacts no secondary case of smallpox occurred.

Case 3: E.K., of Kleinskool.

This patient was admitted to hospital on 20 May 1964 suffering from a severe type of smallpox. He had been ill for about 8 days before admission. He held religious views against vaccination and doctors generally, and there had thus been undue delay in reporting the case to the health authorities.

There were 7 household contacts and 36 close contacts. All were placed in quarantine for a period of 21 days calculated from the appearance of the last case among the quarantined individuals, viz. 3 June.

Vaccination had been carried out in the area of Kleinskool shortly before and a large percentage of the 43 persons concerned showed old and/or recent vaccination scars. Every contact was vaccinated or revaccinated on 21 May.

In addition marboran was administered to these 43 contacts.

The procedure adopted is clearly set out in a report by Clinic Sister Joan Bands reading as follows:

'I personally supervised the giving of valoid tablets and marboran capsules to smallpox contacts from the afternoon of 21 May until the morning of 23 May (for 48-hour treatment), at Kleinskool near Mr. Ferreira's shop.

Total number of patients: 43.

Number of adults (i.e. 10 years and over): 23. Dosage: One valoid tablet given half-an-hour before marboran. Two marboran capsules given *b.d.* (8 capsules in 48 hours). Biscuits given with marboran capsules.

Number of children (i.e. 18 months to 9 years): 15. Dosage: Half a valoid tablet given half-an-hour before marboran. One marboran capsule given *b.d.* (4 capsules in 48 hours). Biscuits given with marboran capsules.

Number of babies (under 18 months): 5. Dosage: Quarter of a valoid tablet given half-an-hour before marboran. Half a marboran capsule given *b.d.* (2 capsules in 48 hours). Babies given feeds.'

50-mg. valoid tablets and 1·5-G. capsules of marboran were used. The author was present on two of the four occasions when marboran was being given. The method of administra-

tion described above seemed to minimize the side-effects of marboran in that vomiting and nausea were not excessive.

Of this group of contacts 4 persons contracted smallpox, one being fatal. A short history of each secondary case follows:

Secondary Case (*case* 4): Elsie K.

Wife of case 3 (E.K.), she was admitted from quarantine to isolation hospital on 27 May in labour. Vaccinated successfully on 21 May. Given marboran capsules during 21—23 May. Delivered of an infant on 28 May. Temperature rose during labour and subsequent events proved that she was then in the pre-rash stage of virulent smallpox. Death took place on 8 June.

Secondary Case (*case* 5): L.K.

Bantu male aged 4 years, child of Elsie K. and E.K. No earlier vaccination marks. Given marboran during 21—23 May and vaccinated on 21 May (followed by moderate reactions). Became febrile on 29 May and transferred from quarantine to the isolation hospital on 30 May suffering from smallpox. Good recovery.

Secondary Case (*case* 6): K.K.

Bantu female aged 2 years, child of Elsie K. and E.K. No earlier vaccination marks. Given marboran during 21—23 May and vaccinated on 21 May (followed by moderate reactions). Became febrile on 29 May and transferred from quarantine to the isolation hospital on 30 May suffering from smallpox. Good recovery.

Secondary Case (*case* 7): E.M.

Bantu female aged 20 years. Old vaccination scars doubtful. Vaccinated successfully on 21 May. Given marboran during 21—23 May. Transferred to the isolation hospital from quarantine on 3 June. Good recovery.

The above 4 secondary cases (cases 4, 5, 6 and 7) were all household contacts of case 3 (E.K.).

Other findings of an individual nature are worth recording:

J.K., Bantu male aged 10 years, successfully vaccinated about March 1964. Given marboran during 21—23 May. No reaction to several vaccinations while in quarantine. Child of Elsie K. and E.K. and an intimate household contact. Escaped smallpox.

W.M., Bantu male adult. Had old vaccination scars. Vaccinated unsuccessfully while in quarantine. Given marboran during 21—23 May. Escaped smallpox although a household contact of E.K., L.K., K.K., and E.M.

B.M., Bantu male adult. No old scars visible. Vaccinated unsuccessfully while in quarantine. Given marboran during 21—23 May. Face shows old pock-marks clinically typical of previous attack of smallpox-like condition. Escaped smallpox although a household contact of E.K., L.K., K.K., and E.M.

DISCUSSION

Two household contacts of case 2 (S.K.), who were successfully vaccinated 4—5 days after S.K. sickened, escaped contracting the disease. There was no evidence of previous successful primary vaccination in these individuals.

The same statement applies to 2 of the 5 household contacts of case 1 (J.M.).

The 4 household contacts of case 3 (E.K.), namely Elsie K., K.K., L.K. and E.M., who subsequently developed smallpox were all successfully vaccinated after having been exposed to infection for at least 8 days. Of these, Elsie K., K.K., and L.K. developed the typical smallpox rash approximately 9 days after having received the first capsule of marboran. E.M. exhibited the typical rash 13 days after having received the first capsule of marboran although satisfactory vaccination lesions were present. Vaccination was performed 13 days previously.

Among the 8 household contacts together with 570 known social contacts of cases 1 and 2 — 578 in all — no secondary case of smallpox occurred. Here reliance was solely on vaccination and revaccination. No marboran given.

Among the 7 household contacts and 36 close social contacts of case 3 — 43 in all — 4 persons developed typical smallpox, including one fatal case. These persons were vaccinated, revaccinated and in addition were given marboran.

CONCLUSIONS

Successful primary vaccination without marboran within the first 5 days of exposure to infection protected all known contacts, including household contacts.

Successful primary vaccination together with marboran after 8 days of exposure to infection failed to prevent the disease in 4 of my cases. Three of these patients received marboran 9 days, and the fourth 13 days, before the appearance of smallpox rash.

Pre-outbreak primary vaccination and/or recent pre-contact vaccination, as evidenced by satisfactory typical scars, protected all contacts, including intimate household contacts, without marboran.

Clinically those contacts who did *not* receive marboran showed a more satisfactory reaction to vaccination than those who did.

Strict isolation in hospital of all known cases of smallpox is an essential part of prophylaxis.

Marboran in the circumstances described was disappointing. The results of the Madras experiment reported by Bauer *et al.*[2] were not confirmed in this instance.

Marboran may allegedly,[2] by modifying the reaction to vaccination, lower the degree of immunity of the individual exposed to infection and may thus even be harmful. This aspect requires investigation.[3]

Experience in this outbreak has demonstrated the efficacy of vaccination in the control of smallpox. Much more work will have to be undertaken in the search for a reliable chemical prophylactic agent against smallpox before vaccination is replaced as the sheet-anchor of prophylaxis. The high potency of the South African vaccine is important from a practical point of view, for it is often vital that the first attempt at vaccination should be successful, particularly if the individual concerned has already been exposed to infection; time is the essence of prevention in such circumstances. The ideal, of course, is for everybody to have been successfully vaccinated before there is any question of an outbreak.

The vaccine used was manufactured in the Republic of South Africa at the Government Vaccine Institute in Cape Town.

The marboran and valoid used were supplied by Messrs. Burroughs Wellcome and made available through the good offices of the Port Elizabeth Municipal Medical Officer of Health, Dr. J. Lewis, to whom I offer my thanks.

I wish to express appreciation also for the encouragement given to me by colleagues in the State Health Department, especially those of the Cape Town Regional Office, and also by the District Surgeon of Port Elizabeth, Dr. B. Tucker. The medical and senior nursing staff of the Smallpox Emergency Hospital have been most helpful.

REFERENCES

1. Thompson, R. L., Minton, S. A., Officer, J. E., Hitchings, G. H. (1953): J. Immunol., **70**, 229.
2. Bauer, D. J., St. Vincent, L., Kempe, C. H., Downie, A. W. (1963): Lancet, **2**, 494.
3. Leading article (1963): *Ibid.*, **2**, 501.