required any treatment and the oedema is not progressive. It is probably secondary to fibrotic changes in the nodes following the gold injection.

Discussion

The treatment of malignant melanoma, particularly in cases where there is no clinical evidence of metastasis—what might be termed "stage I" cases—has been difficult to plan in the past. Fortner *et al.* (1964) have performed routine block dissection of regional lymph nodes after removing the primary. They found that 38% of these patients had microscopical evidence of node involvement. Others have hesitated to perform routine prophylactic block dissections in the absence of clinical evidence of involvement. Wound-healing is poor after block dissection and the incidence of wound sepsis is high. There is inevitable deformity and scarring and very often severe lymphoedema. Indeed, many patients decline to have such an operation. An alternative plan of management is to excise the primary and wait to see if nodes become clinically involved before performing block dissection. This avoids a proportion of unnecessary operations but almost certainly leads to poorer results in the patients who do develop node metastases.

Another disadvantage of surgical treatment is the difficulty of dealing with the possible growth of secondaries in the lymphatics intervening between the primary lesion and the regional nodes, for it is only occasionally possible to excise primary and nodes in a single block. Irradiation of this block of tissue by conventional external methods only, even by supervoltage *x*-ray or cobalt gamma-ray, to the high dosage required for destruction of these malignant cells, is often impossible without the risk of widespread radiation morbidity. This might require extensive surgical excision to repair. This complication does not occur in endolymphatic therapy; the high dose is concentrated in the lymphatics, and, as has been shown, radionecrosis, should it occur, is localized and presents a relatively minor surgical problem.

It will be seen, therefore, that an alternative to block dissection would be very desirable if an effective one could be found. Endolymphatic therapy on the principle described here seems to offer such an alternative. The clinical results in this small group of patients seem sufficiently promising to warrant a larger scale trial on a statistical basis. This is particularly so as there have been considerable improvements in technique since this trial started five years ago.

Endolymphatic therapeutic injections may be combined with surgery or external irradiation in various ways, particularly for more advanced cases, but discussion of this is outside the scope of the present review.

Conclusions

Thirteen patients with malignant melanoma have been treated by excision of the primary and subsequent injection of radioactive gold particles into the lymphatics of the region.

The aim of the endolymphatic injection has been to treat possible metastases in the draining lymph vessels and in the regional nodes.

A review of these patients followed up to five years after treatment is encouraging and warrants further trial of endolymphatic therapy.

We wish to thank Dr. J. A. Fleming for his help and advice in this work. Four patients were treated while one of us (G. H. J.) worked in the Surgical Unit, St. Mary's Hospital, and we thank Professors C. G. Rob and W. T. Irvine for help with these. We are indebted to Dr. T. Gimlette and to the Radioisotope Departments of St. Thomas's Hospital and of St. Mary's Hospital for help with physical measurements. We would also like to thank Dr. W. F. Clapham for his help, particularly with the dosimetry.

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Eczema Vaccinatum

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When generalized vaccinia occurs in a patient with eczema the disorder is known as *eczema vaccinatum*, a grave and sometimes fatal illness. The characteristic rash of profuse vaccinial lesions, particularly dense in eczematous areas, is sometimes known as Kaposi's varicelliform eruption. Since, however, a clinically indistinguishable eruption and illness may be caused by herpes simplex in an eczematous subject, the terms eczema vaccinatum and eczema herpeticum are more exact.

Eczema vaccinatum is usually distinguishable from eczema herpeticum by the history, although for diagnosis virological studies may be necessary. In generalized vaccinia in non-eczematous subjects the systemic upset is usually less severe and the eruption is more scattered. The variolas, modified smallpox, varicella, and erythema multiforme occasionally mimic eczema vaccinatum.

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We report a study of eczema vaccinatum based on records made in the first few months of 1962 during the mass smallpox vaccination in England and Wales. Of chief interest were the incidence and mortality of the disease in relation to the following: age and sex; source of infection, whether accidental or intended; type and activity of the underlying eczema. Other matters for inquiry were whether the infection followed primary vaccination or revaccination, virulence of specific batches of vaccine, and value of antivaccinial gamma-globulin and other treatments.

Our information came mainly from three sources. First, a questionary was sent to all consultant dermatologists in England and Wales; nearly all replied. Second, the Ministry of Health, from information supplied by medical officers of health, smallpox consultants, general practitioners, and other sources, made available to us 50 eczema vaccinatum case histories, including

those of all patients who had died. Third, the Public Health Laboratory, Colindale, gave us information about 50 patients for whom help had been sought for virus studies and supply of antivaccinial gamma-globulin.

A retrospective inquiry of this nature is subject to a number of errors. We believe that we have avoided some of these, since in many instances we were able to cross-check our information. Certainly not all cases of eczema vaccinatum have come to our notice. The disease may have gone unrecognized and cases were not always reported to the Ministry of Health. In other instances the records were incomplete or were lost. The type of eczema was sometimes in doubt and also the degree of activity at the time of vaccination. Virological proof was available in less than a third of patients, but we accepted presumptive evidence of vaccinial infection. We have complete records of all patients who died and most of those admitted to hospital. In South Wales 35 patients, whose records form part of our findings, were studied prospectively, with virological culture when necessary, by Dr. Eric Waddington, a dermatologist with special experience of smallpox. The findings (Waddington *et al.*, 1964) in this intensively studied group tally with those from the 150 other patients.

Findings

Incidence and Mortality.—We have records of 185 patients with eczema vaccinatum in England and Wales during the early months of 1962 ; of these 11 died (approximately 6%). A minimum of three and a quarter million patients received intended primary vaccination during this period (Ministry of Health, 1963) and about the same number were revaccinated. The number of accidental primary vaccinations is unknown. We have full details of the incidence and mortality in relation to age, sex, and source of infection in 137 patients (see Table).

Age, Sex, Mortality, and Source of Infection in 137 Patients with Eczema Vaccinatum in England and Wales

Age in Years	Total No. of Patients	Sex (Figures in Brackets Indicate Deaths)		No. of Accidental Vaccinations	Attack Rate*
		Males	Females		
0–1	25	17 (1)	8 (1)	19	6/410
1–5	42	26 (4)	16 (1)	29	13/420
5–10	24	14	10	19	
10–20	13	9 (1)	4	5	29/2,400
20+	33	21 (1)	12 (1)	17	
Total	137	87 (8)	50 (3)	89	48/3,230

* Number of patients receiving intended primary vaccination in relation to estimated minimum total in thousands of primary intended vaccinations. (Ministry of Health, 1963 : Smallpox vaccination ; Summary of returns made to the Ministry of Health for the year ended 31 December 1962.)

Age and Sex.—Out of the 137 patients with eczema vaccinatum, 67, including 8 of the 11 who died, were under the age of 5 years—25 of them being under the age of 1 year. Eczema vaccinatum occurred twice as commonly in males as in females ; 8 of the 11 deaths were in male patients.

Source of Infection.—Vaccination was accidental in 89 patients and intended in 48. Seven of the 11 deaths were from accidental vaccination. Of the 89 patients with accidental eczema vaccinatum 74 acquired the infection from some other member of the family, often a sibling. Children were not the only victims of accidental eczema vaccinatum ; 17 patients were over the age of 20. Four adults acquired the infection from their newly vaccinated infants. Of those who were not infected by a member of the family, in only five was the source of the virus untraced. The contacts were usually close associates—for example, school friends or, as in the three patients undergoing hospital treatment for eczema, a newly admitted and recently vaccinated patient.

Type of Eczema.—Of the 185 patients, 148 had atopic eczema, 8 had seborrhoeic eczema, and 29 were not definitely classified. Atopic eczema usually begins in infancy or childhood, has a characteristic morphology and distribution, and is genetically linked with asthma and hay-fever. Sometimes distinction between the eczemas, particularly in infancy, may be difficult, and more than one type may be present in the same patient.

Activity of Eczema.—The findings, in answer to a separate questionary sent mainly to dermatologists, refer to 123 patients in England and Wales. These patients tended to be those more seriously ill and included all who died ; we have complete data on them. Nearly all are among those included in the Table. An attempt was made to classify the state of the eczema at the time of vaccination as "active," "quiescent," and "latent"—namely, no active eczema but with a positive past history. The distinction between latent and quiescent proved difficult, and, as no great precision could be claimed, we have grouped these two together and classified the state of eczema at the time of vaccination as (1) active and obvious, and (2) inactive. Since vaccination often seemed to reactivate eczema, the possibility of overlooking minor skin change will have been lessened and reports will have favoured "active and obvious" rather than "inactive." Indeed we have well-authenticated records of reactivation of eczema complicated by eczema vaccinatum in patients who had been free of eczema for many years, including a patient of Dr. Scovell's in whom the interval was 10 years.

Two-thirds of those with eczema vaccinatum, including seven who died, did not have active and obvious eczema at the time of vaccination.

Primary Vaccination and Revaccination.—We have only one record of eczema vaccinatum following revaccination: a child aged 2 seen by Dr. R. E. Bowers who developed eczema vaccinatum following revaccination after a successful primary vaccination 18 months previously.

Virulence of Specific Batches of Vaccine.—Insufficient data to assess virulence were collected.

Treatment.—Many gravely ill patients were treated with hyperimmune antivaccinal gamma-globulin, systemic antibiotics, systemic corticosteroids, intravenous infusions, and a variety of local treatments.

Miscellaneous.—Three patients with Darier's disease were victims of accidental primary vaccination followed by the clinical features of eczema vaccinatum. A boy aged 15 (a patient of Dr. F. J. V. Jenner's) was infected by his brother or sister ; in another family (both were Dr. C. W. Mackenzie's patients) the father was infected from an unknown source and later transmitted the infection to his adult daughter. These cases have not been included in our series of eczema vaccinatum.

Discussion

Although Kaposi (1895) is generally credited with the first description of the varicelliform eruption in eczema vaccinatum, priority should go to Martin (1882), who reported three cases, one in great detail. Kaposi thought that the eruption was probably caused by a fungus, but Martin correctly attributed it to smallpox vaccination then carried out by the calf-to-arm method. Monckton Copeman (1911), the originator of the method of vaccination with glycerinated lymph used in this country since 1898, was aware of the reports of eczema vaccinatum with this preparation. That herpes simplex could cause a similar eruption and illness in association with eczema was not recognized until Esser and Seidenberg (quoted by Lynch and Steves, 1947) isolated and identified it during a small epidemic of such cases in an infants' ward in 1941.

Most authorities believe that successful vaccination is followed by a viraemia (Ellis, 1935 ; Dixon, 1962), although Kempe (1959) states that no recent virological studies are available in support of this. In primary vaccinia, virus multiplies locally at the site of inoculation, enters the blood, and then disappears from the circulation as virus-neutralizing antibody

appears towards the end of the first week. In generalized vaccinia an extension of this process occurs. The demonstrable viraemia (J. A. Dudgeon, personal communication, 1963) disseminates the virus widely. It multiplies and gives rise to the secondary vaccinial eruption which, in eczema vaccinatum, appears simultaneously not only in the areas of eczema but also on normal skin and occasionally on mucous membranes.

The resistance of normal unbroken skin to vaccinial inoculation (Waddington *et al.*, 1964) and the many reports which we have received of eczema vaccinatum in patients with covered vaccination sites appear further to discountenance the belief that auto-inoculation is of major importance in eczema vaccinatum.

We know of 185 patients with eczema vaccinatum during the period studied ; an estimated incidence of 1 in 20,000 primary vaccinations. The relevance of this figure to the risk of vaccination of a patient with atopic eczema is doubtful. There are several reasons for this:

1. The incidence of atopic eczema in the population is unknown, though this may be 3–4% (Walker and Warin, 1956 ; Lowenthal, 1958). Therefore among 20,000 persons there might be about 750 at risk with eczema.

2. The denominator—that is, the number of primary intended vaccinations performed—is unknown. The official figures are minimum figures and probably greatly underestimate the true number of persons vaccinated.

3. Accidental (primary) vaccination accounted for more cases of eczema vaccinatum than intended (primary) vaccination.

4. On medical advice many with atopic eczema were not vaccinated.

5. Host-resistance to the virus is probably important. Most patients with atopic eczema, even when in an active state, had no ill effects from vaccination. In one family, seen by Dr. W. Beach, all three siblings developed eczema vaccinatum following accidental vaccination ; but in another family of three siblings with eczema, seen by Dr. A. Bigham, none had eczema vaccinatum following intended vaccination. Dr. G. C. Wells and Dr. C. F. H. Vickers saw three siblings with eczema vaccinatum in one week after intended vaccination of one of them.

6. Preparations of lymph may vary in their infectivity.

The preponderance of males in all age-groups with eczema vaccinatum is unexplained. The sex incidence of atopic eczema shows no such disproportion (Calvert, 1963 ; Roth and Kierland, 1964). The mortality in both sexes was about 6%. Studying benign generalized vaccinia, E. T. Conybeare (personal communication, 1963) found that in 45 infants aged less than 3 months there were three times more males than females with the disease, but over this age the sex incidence was equal ; a finding substantiated in 160 recent cases (Ministry of Health, 1963).

That eczema vaccinatum is more common after accidental than after intended vaccination is emphasized by many authors and may be explained, in part, by reluctance to vaccinate patients with eczema. Several patients with eczema vaccinatum, including one who died, had deliberately not been vaccinated "because of the eczema" yet acquired the virus from other members of the family.

Eczema vaccinatum occurs predominantly in patients with atopic eczema. Some reports of eczema vaccinatum in other forms of eczema may be due to difficulties in diagnosis or to coexistence of more than one form of eczema.

Patients with Darier's disease also appear to be unduly susceptible to vaccinia (Gerstein and Shelley, 1960).

The precise value of hyperimmune antivaccinial gamma-globulin cannot be stated in the absence of a control series, but many experienced clinicians believe it to be life-saving. Systemic antibiotics are probably of value in the control of secondary infection.

More recently, antivaccinial gamma-globulin has been recommended for prophylactic use if vaccination of an eczematous subject is essential. It may be given either at the time of vaccination (Ministry of Health, 1962) or about a week later at the time of the expected viraemia.

The incidence and treatment of eczema vaccinatum may be greatly changed by recent advances such as the introduction of a non-infectious killed vaccinia virus preparation (Kaplan, 1962) and oral synthetic chemical prophylactic agents (Bauer *et al.*, 1963).

Conclusions

From the findings in this series and from information which has since become available, our conclusions about prophylaxis and treatment may be summarized thus: (1) Before vaccination, specific inquiries should be made about eczema both in the patient and in potential contacts. (2) Atopic eczema, even if quiescent, is an absolute contraindication to vaccination except when the patient is a contact of a known or suspected case of smallpox or is going to an area where smallpox is endemic. (3) Eczematous subjects, particularly in childhood, and even if the eczema is quiescent, should be isolated strictly from the recently vaccinated. The risk of accidental vaccination should be emphasized. (4) Hyperimmune antivaccinial gamma-globulin should be given to any patient seriously ill with eczema vaccinatum. It should be given prophylactically if vaccination of an eczematous subject is essential. (5) These conclusions probably apply to Darier's disease.

Summary

In the 1962 mass smallpox vaccination in England and Wales 185 patients had eczema vaccinatum, an estimated incidence of 1 in 20,000 intended primary vaccinations. There were 11 deaths ; a mortality of approximately 6%.

About half of the patients, including 8 of the 11 who died, were under the age of 5 years. Eczema vaccinatum was twice as common in males as in females.

Vaccination was accidental in 89 (65%) of 137 patients.

The eczema at the time of vaccination was reported as inactive in two-thirds of the patients. It was predominantly of the atopic variety.

Recommendations for prophylaxis and treatment are given.

We wish to acknowledge our indebtedness to our dermatological colleagues, to Sir George Godber (Ministry of Health), and to Sir Graham Wilson (Public Health Laboratory Service) for allowing us access to their records. We owe much to Dr. D. H. D. Burbridge of the Ministry of Health, for his most helpful and time-consuming researches on our behalf. Dr. Eric Waddington (Cardiff Royal Infirmary) and Dr. David Miller (Public Health Laboratory Service, Colindale) have also given us invaluable assistance, as has Dr. G. C. Wells.

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