here 24/5/45: A.S.P., 58 units. Skiagram: "Irregular sclerosis left pelvis; maybe early secondaries. *Nil* in skull, dorsal or lumbar spine." Inguinal glands enlarged. Perurethral resection, 24/5/45, removing small obstructing nodule near external sphincter, proved on section to be malignant. Residual urine reduced to 1/2 oz. (14 ml.), with complete relief of urinary symptoms. Given 30 mg. dienoestrol daily. A.S.P. (alternate days), 65, 76, 88, 105, 72 units. Home against advice. Returned three weeks later with liver hard and enlarged to umbilicus; inguinal glands larger; A.S.P., 80 units. Bilateral orchidectomy, 8/8/45. A.S.P. still 80 units (28/8/45), with no clinical improvement. Home against advice and died two days later.

Oestrogen Therapy

1. *Dosage.*—"The correct dosage of an endocrine preparation is not a subject for generalization but rather for individualization" (Cameron, 1945). The truth of this statement is shown by at least two case histories. In Case 24 (Muir 3, previously described) the development of sciatic pain, raised acid serum phosphatase, and spinal metastases followed the reduction of stilboestrol from 30 mg. daily to 5 mg. daily. Reverting to the original dose of 30 mg. daily relieved the pain and lowered the acid serum phosphatase to normal. This case also illustrates the disastrous results that may follow continuing treatment on a lowered maintenance dose—a practice often advocated—even when the dose is reduced at a time when the malignant process appears, both clinically and pathologically, to be under control. In the second case severe lumbo-sacral and sciatic pain, intense enough to confine the patient to bed, was completely relieved by changing from stilboestrol 30 mg. daily to dienoestrol 30 mg. daily. (Dienoestrol is stated to be three times as active oestrogenically as stilboestrol.) In the first case 30 mg. of stilboestrol daily proved to be an adequate dose; in the second case it was inadequate.

These cases demonstrate clearly that an apparent stilboestrol failure may be due to an actual error in dosage. The impression gained from the literature, especially American, is that the dosage of stilboestrol administered has been too low. One author states that he found castration alone more effective than oestrogen alone. The explanation of this anomaly he himself provides by stating that the dose of stilboestrol given was "one or more milligrams daily." I believe the dose of stilboestrol should be large, that it should never be lowered in group 3 cases, that it is wiser not to lower it in group 2, and that it is safe, subject to the results of repeated examinations, to lower it in group 1. My practice in the later cases of this series has been to begin treatment on 30 mg. stilboestrol daily.

2. *Cardiac Complications.*—Four patients have developed cardiac complications while on stilboestrol. This has been accepted as a disquieting incidence, although in this advanced age group the association of degenerative changes with any form of treatment may be more apparent than real. In three cases acute congestive heart failure developed—in the first after three weeks on stilboestrol 20 mg. daily by mouth, in the second after six weeks on stilboestrol 5 mg. daily by intramuscular injection, in the third after two years on 15 mg. daily for the first year and 10 mg. daily for the second. Two cases had extensive spinal metastases, and in one of these definite evidence of myocardial degeneration was present before stilboestrol was started. The third case, a patient weighing 22 st. (140 kg.), also had signs of initial myocardial degeneration. The connexion between stilboestrol therapy and cardiac complications was, at any rate, beyond dispute in the fourth case. This patient, an intelligent man under close observation in the follow-up clinic, while on stilboestrol 10 mg. daily developed pain across the front of the lower chest on exertion, increasing in intensity until, after a period of three months, it was induced in a severe form by such mild exertion as getting out of bed. Changing from stilboestrol to dienoestrol relieved this pain. The development of nausea in four cases necessitated a change from stilboestrol. Dienoestrol was substituted in each instance with complete relief. In view of these experiences it is proposed to treat all future cases with dienoestrol in preference to stilboestrol.

3. *Relation to Prostatic Obstruction.*—The early relief of a major degree of prostatic obstruction by stilboestrol in adequate doses has proved a complete failure in the two cases in which it was attempted. Furthermore, a third patient, while in hospital on stilboestrol 20 mg. daily, developed an acute retention with a bladder distension to 1 in. (2.5 cm.) from the umbilicus eleven days after the beginning of treatment. The stilboestrol had in the meantime completely relieved his pain from spinal metastases. Three cases—two with acute retention and one with prostatic dysuria, all subsequently proved to be group 1—were relieved of symptoms by catheterization without stilboestrol for periods of one month, four years, and twelve months respectively. These latter experiences demonstrate clearly that the factors responsible for urinary retention or dysuria may be of a temporary nature even in malignant prostates and that early or immediate relief of such symptoms, if occurring while the patient is on stilboestrol, may be erroneously attributed to it. Reports of immediate or early relief of retention by stilboestrol should be viewed with considerable scepticism.

Orchidectomy.—The two cases in which orchidectomy was carried out after stilboestrol or dienoestrol, in adequate doses, failed to show any improvement either clinically or in reduction of acid serum phosphatase.

Summary

Suprapubic cystostomy and suprapubic resection as methods of relieving malignant prostatic retention are unjustifiable survivals of pre-endoscopic days. Normal micturition can and should be restored by perurethral resection.

The importance of pathological grading in assessing survival periods and of giving and continuing to give oestrogen in adequate doses has been stressed.

Reasons for a proposed change from stilboestrol to dienoestrol have been given.

Observations on the acid serum phosphatase in the blood have been made.

I should like to thank Dr. J. M. Greenwood, medical superintendent, for facilities for treating these patients.

REFERENCES

Barnes, R. W. (1942). *Endoscopic Prostatic Surgery*, p. 223, Henry Kimpton, London.
Cameron, A. T. (1945). *Recent Advances in Endocrinology*, Introduction, p. 3, London.
Caulk, J. R. (1937). *J. Urol.*, **37**, 832.
Cox, H. T. (1945). *Lancet*, **1**, 138.
Huggins, C., and Hodges, C. V. (1941). *Cancer Research*, **1**, 293.
—— Scott, W. W., and Hodges, C. V. (1941). *J. Urol.*, **46**, 997.
Muir, E. G. (1934). *Lancet*, **1**, 667.

THE OUTBREAK OF SMALLPOX IN MIDDLESEX, 1944

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A case of variola major in a large hospital in Middlesex in 1944 was followed by 10 further cases, three of them fatal. The outbreak is thought to be of interest in that the diagnosis was not made in the primary case until the patient was ambulant in hospital, by which time six other persons had been infected—three nurses and a patient in the hospital, a nurse on leave at home, and a visitor. The diagnosis of smallpox in the nurse on leave drew attention to the outbreak. After the isolation of these secondary cases four others occurred.

Case Histories

Case 1.—L. C., a soldier aged 23, had arrived in convoy from Gibraltar on Feb. 6, and had been admitted direct to the hospital on account of an anxiety state. He had slight fever on admission, which became more pronounced on succeeding days. On Feb. 10 an erythematous rash appeared and his temperature rose to 103° F. (39.4° C.). A rubella-like eruption the next day was followed two days later by lesions suggesting chickenpox, so that on Feb. 13 the diagnosis of chickenpox with rubella was made and the patient barrier-nursed in a four-bedded ward until Feb. 24. Later the patient was up and about, and subsequently visited other parts of the hospital. A barber visiting the hospital cut his hair in company with that of a number of other patients.

When seen on March 2, the soldier had a few faint scars on the forehead, a number of seeds in the soles of the feet, one seed under a finger-nail, and a few scabs on the dorsa of the feet. He bore good vaccination marks from infancy, and a single scar from revaccination dated in his Army pay-book Sept. 17, 1942. Nevertheless, the condition from which he had been suffering appeared without doubt to be smallpox.

Case 2.—Nurse E. H., aged 24, unvaccinated, at home in Finchley on leave, became unwell on Feb. 22 with a bilious attack and vomiting. On Feb. 24 she developed a morbilliform rash, and on Feb. 28 vesicular lesions appeared on the hands and fingers. The following day the rash was profuse, and smallpox was suspected by the medical officer of health. This diagnosis was confirmed next day, when the patient showed a confluent early pustular rash on the face, upper chest, and back, with discrete but copious late vesicular lesions on the feet and legs. Many of the papules were haemorrhagic, and the vesicles showed central bluish haemorrhage. Death occurred on March 3.

A history of contact with a case diagnosed as rubella and chickenpox led to a visit to the hospital, with the discovery there of Case 1 and the four cases next described.

Case 3.—Nurse N. P., aged 22, who had nursed Case 1 at night, fell ill on Feb. 22 and reported sick on the 25th. She was admitted to the hospital sick bay that day, and transferred later the same day to a cubicle in the isolation ward as a chickenpox suspect. On March 2 a discrete modified pustular rash of scanty but typical smallpox distribution was present. She had been vaccinated at the age of 3 or 4 years.

Case 4.—Another contact, Nurse M. G., aged 20, vaccinated successfully in infancy, reported sick on the 25th, having been first unwell on Feb. 22. She was admitted to a cubicle in the isolation ward, where chickenpox was diagnosed on the 27th. On March 2 this nurse showed a moderately profuse papular rash of typical smallpox distribution, which (seen later) evolved rapidly with much modification of individual lesions.

Case 5.—Nurse N. B., aged 34, vaccinated successfully in infancy, had also nursed Case 1. This nurse lived at home. She felt unwell on Feb. 26 and went to bed at home, where a diagnosis of chickenpox was revised to smallpox on March 3. When seen later many of the lesions were aborting in all stages of evolution.

Case 6.—This patient, aged 51, suffered from carcinoma of the breast in a ward on the same corridor as Case 1, but separated from him by an intervening ward. The nursing staff, however, were common to the two wards. On Feb. 29 this patient had a temperature of 101° F. (38.3° C.), which rose to 105° F. (40.6° C.) on March 2. Seen the next day, she presented a very profuse bluish purple papular rash of typical smallpox distribution. On the face the lesions were so close as to appear as a uniform coloration of the skin. They were suggestive of a toxic haemorrhagic attack, and this proved to be the case, the patient dying on March 6 with a confluent haemorrhagic eruption little beyond the papular stage. Haematuria, melaena, and metrorrhagia preceded death. The marks of vaccination in infancy were present.

Case 7.—On March 3 it was learned that an unvaccinated woman (M. C.), who on Feb. 12 had visited another officer in the same ward as Case 1, had been taken ill in Bedford on Feb. 22, took to her bed on the 24th, two days before a rash appeared on Feb. 26, and died on March 2. When first seen this patient had a temperature of 103° F. (39.4° C.), and was thought to have measles. Two days later there was a profuse papular eruption of general distribution, but most marked in the flexures, on a dusky red background. There were petechial haemorrhages, giving an appearance of erythema multiforme plus purpura. Oedema of the face and eyelids was marked, as were conjunctival haemorrhages. She died with her case undiagnosed, but it was undoubtedly haemorrhagic smallpox. This completed the secondary cases.

Cases 8 and 9.—On March 9 and 10 F. H. and I. H., two sisters of Case 2, one of whom had nursed her at home for eight days, fell ill and developed a rash, diagnosed as smallpox, on March 12 and 13 respectively. They had been successfully vaccinated on March 2. The eruption in the sister who had acted as nurse was profuse; the other was less so, and she was reported to have had no actual physical contact with Case 2. Both girls recovered.

Case 10.—M. H., an unvaccinated youth aged 17, who had been admitted from another hospital on Feb. 18, was transferred to a cubicle in the isolation ward on Feb. 24 with chickenpox. His cubicle was in the same corridor as that to which Cases 3 and 4 had been moved, all three patients being nursed by the same staff. There was no evidence of any direct contact with the nurse-patients (Cases 3 and 4). When seen on March 2 he had a very profuse chickenpox rash with an abnormally high incidence of lesions on the face and forearms. Despite this, no doubt was entertained that the condition was chickenpox. He was primarily vaccinated that evening, and vaccination developed typically into a large pustule with extensive erythema and some adenitis. On the 10th the boy developed slight fever which rose to 105° F. (40.6° C.) on March 12. On the 13th there was a discrete profuse macular rash, contrasting vividly with the scars of the almost faded chickenpox rash. He developed modified smallpox.

Case 11.—The only other case to occur was that of an ambulance driver (F. T.) who removed Case 5 in the early hours of March 3. He was not revaccinated until March 6, and developed a rash on March 15. He had been successfully vaccinated in infancy and during the 1914–18 war. Vaccination was stated to have failed to take three times before March 6.

These cases are set out in the accompanying Table.

Table of Principal Clinical Features and Relevant Dates

Case	Age	Successful Vaccination	Source of Infection	Probable Date of Infection	Date of Onset of Symptoms	Date of Efflorescence of Rash	Type	First Day of Exposure to Infection	Remarks
L. C. 1	23	Infancy and 17/9/42	Mediterranean port	27/1/44	7/2/44	10/2/44	Discrete, modified	?	? Prodromal erythema, "chickenpox" lesions on 12/2/44. *Primary case*
E. H. 2	24	None	L. C.	10/2/44	22/2/44	24/2/44	Confluent, haemorrhagic	7/2/44	Died on 3/3/44
N. P. 3	22	Infancy	L. C.	13/2/44	25/2/44	26/2/44	Discrete, modified	7/2/44	? Prodromal erythema. Chickenpox spots noticed on 28/2/44
M. G. 4	20	Infancy	L. C.	13/2/44	25/2/44	28/2/44	Discrete, modified	7/2/44	
N. B. 5	34	Infancy	L. C.	14/2/44	26/2/44	28/2/44	Discrete, modified; scanty rash	7/2/44	First seen with vesicular rash 3/3/44
M. L. 6	51	Infancy	L. C.; fomites	17/2/44	29/2/44	2/3/44	Confluent, haemorrhagic	7/2/44	Died on 5/3/44
M. C. 7	36	None	L. C.	10/2/44	22/2/44	27/2/44	? Purpura haemorrhagica variolosa	5/2/44	Died, undiagnosed, on March 2, 1944. Labelled erythema multiforme
F. H. 8	32	Primary 2/3/44	E. H.	27/2/44	9/3/44	11/3/44	Discrete, modified	22/2/44	Sister to E. H.; vaccinated successfully 9 days after exposure
I. H. 9	19	Primary 2/3/44	E. H.	28/2/44	10/3/44	12/3/44	Discrete, v. modified; scanty rash	22/2/44	Sister to E. H.; vaccinated successfully 9 days after exposure
M. H. 10	17	Primary 2/3/44	N. P. or M. G.	28/2/44	10/3/44	13/3/44	Discrete, profuse	25/2/44	Suffering from varicella. Contracted variola subsequently
F. T. 11	56	Infancy and 6/3/44	N. B.	3/3/44	? 13/3/44	15/3/44	Discrete, profuse, modified	3/3/44	Ambulance driver; took N. B. to smallpox hospital. Successfully vaccinated 1914–18 war. "Failed to take" three times prior to March 6.

The numbers refer to the preceding clinical notes.

Transmission of Infection

Cases 2, 3, 4, 5, and 7 were all direct contacts of Case 1. Case 6 never made actual contact with Case 1, but was attended by the same nurses. Cases 8 and 9 were direct contacts of Case 2. Case 10 was infected from Cases 3 and 4, but without obvious contact. Case 11 was a direct contact of Case 5.

Action taken at the Hospital

The hospital was closed to further admissions; discharges were discontinued, and control measures—vaccination and surveillance of all close contacts—immediately applied. Since the infection had been present in the hospital for a relatively long period before detection, the number of possible contacts, both inside and outside the hospital, was large, and their identification a formidable task. Yet, so long as no unexplained case arose, it was felt that vaccination might be confined to persons

working at the hospital, possible contacts in the neighbourhood, and such visitors as investigation might show to have been possible contacts. Mass vaccination was not advised, but to allay local anxiety and to assist the Public Vaccinator, the medical officer of health of the local authority opened a vaccination clinic, at which those resident in the vicinity of the hospital could be vaccinated if they so wished.

By the evening of March 4 all patients and all members of the staff working at the hospital (approximately 1,100 persons) had been vaccinated, about 120 of them for the first time. On the same evening all members of the nursing, domestic, and laundry staff, etc., were inspected for rash on the head, neck, and arms, and all interrogated as to possible contact with any of the known sufferers. One or two girls who were not feeling well were kept under close observation, and the necessity for reporting sick at once if unwell was made clear to all.

The hospital consists of a main block (the original building) and a number of hutted wards erected as a wartime measure. The cases had occurred in the main block and in the isolation hut. These two buildings were placed out of bounds to all save the staff who worked there. Members of the staff were requested for the time being to limit their contacts and refrain from entering crowded places. For the observation of persons reporting sick arrangements were made to set aside one block containing a number of cubicles and two small wards. This proved extremely valuable for the observation of the numerous vaccinial rashes and reactions which appeared. All members of the staff, resident and non-resident, were kept under daily observation, and any non-resident members not attending for duty were reported to the medical officer of health of their place of residence. The laundry was dealt with in part at the hospital and in part at a public laundry in a near-by town. No infected laundry had gone outside, and arrangements were made that none should go.

Among the nurses who had been previously unvaccinated seven had had close contact with cases of smallpox. These were housed in a separate building in the grounds from March 8 to 16, and did not report for duty. Had smallpox developed in any of these nurses the contact would have been strictly limited to the medical officers observing them and one sister-in-charge. Although one nurse on the twelfth day after contact aroused some anxiety by reason of fever, headache, and backache, she did not develop smallpox.

Case 10 occurred in the isolation ward amongst a well-vaccinated community, and was removed to the smallpox hospital on March 13. From that date this ward was separated by physical barriers from the rest of the hospital. Arrangements were made for the nurses working in the isolation ward to sleep and feed in a nurses' hut next to that ward. No further cases developed from Case 10.

It became clear that the number of persons who might have been contacts was very considerable, and it was decided to notify medical officers of health of all patients discharged from the hospital between Feb. 6 and March 1 and of all visitors during that period. The patients were asked to prepare a list of their visitors between the dates mentioned. Names of visitors known to have entered smallpox wards were notified direct to the medical officer of health of their place of residence; all other visitors received a letter from patients, so worded that when the visitor took the letter as instructed to the medical officer of health it would be clear to the latter that this person was not thought to be in any appreciable danger. In this way it was hoped that the very large number who might possibly have been at risk would be brought under surveillance.

The hospital was freed from quarantine on March 17, with the exception of the main block, the isolation ward, and the ward used for observation cases. On March 20 the main block was freed for the admission of patients after cleansing had been carried out, and the other wards a week later.

Comment

The strain of variola major in this outbreak was of a high degree of virulence. Both the unvaccinated patients died from confluent haemorrhagic smallpox. Also, a modified attack occurred in Case 1; this patient, having been successfully vaccinated in infancy and 18 months previously, might have been expected to escape.

In spite of its virulence the disease was greatly modified by vaccination. The three nurses vaccinated in infancy—approximately 20 years previously—had mild modified attacks. Case 11, vaccinated in infancy and subsequently, was vaccinated four days after exposure and developed a profuse discrete but modified smallpox nine days later. Three previously unvaccinated persons (Cases 8, 9, and 10), vaccinated too late in the incubation period to afford complete protection, sustained modified attacks. The interval between vaccination and the appearance of the rash in those previously unvaccinated was 9, 10, and 11 days, suggesting that vaccination may have been performed on the fifth, fourth, and third days after the infection was contracted.

Wanklyn states that good marks of recent vaccination can be taken as evidence that an eruption is not smallpox. It would appear from Case 1 that this does not hold in the presence of a virulent strain. Nevertheless, the value of successful vaccination in mitigating the severity of an attack of smallpox even when, owing to lapse of time, it may not confer absolute protection, appears to be demonstrated by Cases 3, 4, and 5, whose vaccination dated back to infancy, some 20 years previously. The pronounced modification in Cases 8 and 9, whose sister died from a confluent haemorrhagic attack, appears to have been achieved by vaccination performed five and four days respectively after the infection had been contracted.

Case 1 was so much modified as to deceive competent medical opinion. In nearly all the vaccinated persons the lesions varied greatly in size, a large proportion aborting in the papular or vesicular stage. These lesions, together with the tendency for the rash to run a more rapid course, produced a picture simulating chickenpox, which, associated with the concurrent prevalence of the latter disease in the hospital, added to the difficulties of diagnosis.

After the isolation of the primary case and those infected by that patient, and the complete vaccination of the hospital population and outside contacts, there was no extension of the outbreak in the hospital apart from Case 10. The cases which did occur after the institution of these measures— Nos. 8, 9, and 11—acquired their infection outside the hospital.

Considering the opportunities for spreading the disease afforded by the primary case, by the number of unvaccinated persons in the hospital population, and by the virulence of the virus, the persons infected were remarkably few.

Conclusion

The experience of this outbreak suggests that control was achieved by the careful ascertainment, vaccination, and surveillance of contacts without embarking on the vaccination of the population generally. Of the seven nurses kept under close supervision because they were unvaccinated at the time of intimate exposure to infection, none developed smallpox. Nevertheless, one, as has been described, did develop headache, fever, and backache, and in four well-vaccinated nurses who had handled smallpox patients unexplained pyrexia without rash occurred under circumstances suggesting that they were reacting to the variola virus (Downie, 1946). There was serological evidence for this statement, and undoubtedly the virus was available in the hospital for the infection of nurses and patients. The failure of the disease to spread is attributed to vaccination.

At the present time importation of smallpox by returning Service men is a frequent occurrence. In these men the disease is modified, and may be misdiagnosed. It would therefore seem to be a wise precaution to employ only well-vaccinated persons in general hospitals, as well as in infectious disease hospitals.

REFERENCE

Downie, A. W. (1946). *Mon. Bull. Min. Hlth., and Emer. P.H. Lab. Serv.*, **5**, 114.

With a view to securing a more constructive type of legislation the National Smoke Abatement Society (Chandos House, Buckingham Gate, London, S.W.1) is putting forward for discussion preliminary proposals for extensions of the Public Health Acts by means of which local authorities could obtain bylaws that will help to prevent smoke and will directly enourage fuel efficiency and coal conservation. Three sets of bylaws are proposed. Details may be had from the society.