39.4° C.) and rash continued for 22 days. Jaundice appeared 35 days (September 30) after starting phenindione treatment. During the next week the jaundice, fever, and rash subsided rapidly. Liver-function tests (see Table, No. 8) suggested cholestatic jaundice. The blood count was normal. Three months later the blood count, serum proteins, and liver-function tests were repeated and found normal.

Case 3.—A man aged 62 started treatment with phenindione on January 10, 1957, after his second myocardial infarction. Three weeks later he developed a rash on the arms and legs, and nicoumalone was substituted. On February 15 he felt unwell and had developed anorexia. A week later he had epigastric pain and two days after this became jaundiced, 46 days after treatment with phenindione was started. Throughout his illness he remained apyrexial with a bradycardia of 55–60 a minute. Initially the liver was just palpable and slightly tender. Liver-function tests (see Table, No. 9) suggested cholestatic jaundice. The blood count was normal. He improved slowly, but was still jaundiced two months later (on April 25 the serum bilirubin was 1.2 mg./100 ml.), and it was not until towards the end of the third month that he was well and his serum bilirubin returned to normal (0.6 mg. on May 23). Anticoagulants were stopped when the jaundice developed, and were not used again. He was symptom-free when last seen (January, 1961).

Discussion

Selected details from the previously recorded cases and of the three described here are given in the Table, and the Diagram shows the chronology of phenindione hepatitis.

The dose of phenindione associated with hepatitis was within the usual therapeutic range except in one case (Makous and Veer, 1954). Jaundice never appeared within 25 days of the beginning of phenindione therapy, and never lasted more than three months. A.C.T.H. or steroids were used in the first five cases reported, but there is no evidence that this treatment influenced the duration of jaundice. In the three cases reported here, as in the six already in the literature, jaundice was not the first symptom but appeared 3 to 25 days after the initial toxic manifestation. Jones (1960), however, found bilirubin in the urine of his patient within 24 hours of the onset of fever, three days before the appearance of jaundice. Routine liver-function tests might therefore reveal subclinical hepatitis in some patients who never become icteric.

The type of jaundice is uncertain from the reported investigations, which do not include liver biopsy. Burns and Desmond (1958) suggested that in their case it was "mildly obstructive" and of "chlorpromazine type," and Jones (1960) pointed out the resemblance of this form of hepatitis to that produced by chlorpromazine and methyltestosterone. On the present evidence and by analogy with chlorpromazine jaundice it is reasonable to regard phenindione hepatitis as a sensitivity reaction and therefore associated with intrahepatic obstructive or cholestatic jaundice. Liver-cell damage also occurs, as indicated by the abnormal flocculation tests (Table, Nos. 1 and 3), and by the raised serum transaminase (No. 7). In chlorpromazine jaundice Zelman (1959) correlated the raised serum transaminase levels with biopsy studies, which showed centrilobular and periportal necrosis.

Summary

Three cases of hepatitis due to phenindione are described and compared with the six previously reported. The evidence suggests that hepatitis is an unusual complication of phenindione therapy, and that the

jaundice produced is mainly cholestatic in type, although liver-cell damage may occur.

Case 1 was under the care of Dr. Richard Asher at the Central Middlesex Hospital, and Cases 2 and 3 were under the care of Dr. Paul Wood, at the Brompton and National Heart Hospitals respectively. We are most grateful to these physicians for their help and permission to publish their cases.

REFERENCES

- Bingle, J., and Shine, I. (1959). *Lancet*, **2**, 377.
 Brooks, R. H., and Calleja, H. B. (1960). *Ann. intern. Med.*, **52**, 706.
 Burns, C., and Desmond, F. B. (1958). *N.Z. med. J.*, **57**, 283.
 East, E. N., and Beamish, R. E. (1957). *Canad. med. Ass. J.*, **77**, 1028.
 Jones, N. L. (1960). *Brit. med. J.*, **2**, 504.
 Kirkeby, K. (1954). *Lancet*, **2**, 580.
 Makous, N., and Veer, J. B. V. (1954). *J. Amer. med. Ass.*, **155**, 739.
 Soulier, J. P., and Gueguen, J. (1947). *C.R. Soc. Biol. (Paris)*, **141**, 1007.
 Zelman, S. (1959). *Amer. J. Med.*, **27**, 708.

EPIDEMIC OF TUBERCULOSIS IN A PRIMARY SCHOOL

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It has been demonstrated repeatedly that a pupil can have open pulmonary tuberculosis without causing an outbreak of tuberculous disease among his or her classmates (Ivar Lundius, 1928–9; Anderson and Grenville-Mathers, 1952). Most outbreaks reported in these islands have been traced to a member of the teaching or non-teaching staff. The epidemic here reported is of interest not only because the probable source was a pupil, but because the pupil in question had a routine contact x-ray examination at the time she was probably spreading infection and her film was not thought to show a significant lesion.

On March 5, 1960, a girl aged 13 was admitted to Daisy Hill Hospital, Newry, County Down, with erythema nodosum, which had been present for one week. Her x-ray film showed a primary tuberculous complex in the right lung. She volunteered the information that several other children sharing the same classrooms at school had a similar rash, and on investigation nine further cases were found. These children were all radiographed, disclosing four more cases of primary pulmonary tuberculosis, and making a full investigation of the school necessary. It was a church school, consisting of three classrooms, in a small seaside town. The classroom where the outbreak occurred was 29½ ft. (9 m.) long, by 22½ ft. (6.8 m.) wide, by 15 ft. (4.6 m.) high, well lighted and ventilated, but overcrowded. New classrooms were in process of erection at the time. There were 71 girls, aged 9 to 15 years, in this room, which was separated from a smaller classroom by a glass partition. The total number of pupils attending the school was 153.

Investigations

All the teaching and non-teaching staff, including the man who delivered milk (pasteurized), were radio-

graphed. None showed evidence of pulmonary tuberculosis. Next, all the pupils who had not already been investigated, with the exception of five whose parents refused consent, were Heaf-tested. Thirty-five more positive reactors were discovered, bringing the total to 45, of whom 37 were taught in the classroom where the outbreak of erythema nodosum occurred. These figures give a 52.1% reactor rate in the affected classroom, compared with a 10.4% reactor rate for the rest of the school. These 35 positive reactors were radiographed in the local chest clinic, bringing to light one case of miliary tuberculosis, one pleural effusion, one case of post-primary pulmonary tuberculosis, and nine further cases of primary tuberculosis. One of these cases came from the infants' classroom, 10 from the room primarily involved, and one from the adjacent room.

From May 23 to 30 the mobile mass radiography unit x-rayed 1,331 of the population of the town and district over the age of 5. This figure represented 75% of the population and included 300 schoolchildren, of whom 112 attended the church school. As a result of the survey two cases of active primary tuberculosis were found in pupils from the classroom where the outbreak started, but no case of active tuberculosis was detected in the adult population or in the children attending other schools. Of the two cases mentioned one had been Heaf-negative in March, while the other, although positive, had a normal radiograph.

A month later all the pupils who had been Heaf-negative in March and April were retested and eight, all from the affected classroom, were found to have converted, bringing the total number of positive reactors in the classroom to 45 and the total in the school to 53. This figure includes nine children who had been B.C.G.-vaccinated prior to the epidemic. The reactor rate in the classroom where the outbreak started had now risen to 63.4%. When the converters were radiographed one was found to have a primary lesion, bringing the total number with radiological lesions to 20. All negative reactors were advised to have B.C.G. vaccination, and 79 accepted.

For purposes of comparison the pupils attending the other two schools in the town were Heaf-tested. In a small mixed school 35 children were tested and 4 (11.4%) were found to be positive. All of these had been B.C.G.-vaccinated previously. In the second school—a boys' school—55 were tested and 13 (23.6%) were found to be positive, of whom two had had previous B.C.G. vaccination.

Disposal

Those who would accept hospitalization were admitted to Crawfordsburn Hospital, 14 in all. The remaining six have been treated at home. The 27 positive reactors in the affected classroom with no radiological evidence of disease were divided into two groups: 13 were treated with P.A.S. and isoniazid or with isoniazid alone for periods varying from two to six months; and 14 were given no treatment. This last group included four children who had been B.C.G.-vaccinated before the epidemic occurred. All these pupils were kept under observation and at the time of writing no lesions had developed in the treated children, but in the untreated group a small pleural effusion occurred in two children and a pulmonary lesion in one

child. The effusions were detected in August and September, 1960, and the pulmonary lesion in April, 1961.

No connexion was demonstrated between the strength of tuberculin reaction and the subsequent development of disease in the untreated reactors. Some children with strongly positive Heaf tests remained well, while others with lesser reactions developed lesions.

Cases Admitted to Hospital

Case 1.—Aged 13. Enlarged right hilar and paratracheal glands with pulmonary focus; erythema nodosum; gastric juice cultures negative; progress slow. Lesions gradually increased for four months after treatment started. Glands still enlarged eight months later.

Case 2.—Aged 13. Enlarged left hilum; erythema nodosum; gastric juice cultures negative; progress uneventful.

Case 3.—Aged 10. Enlarged left hilum; erythema nodosum; gastric juice cultures negative; progress uneventful.

Case 4.—Aged 11. Enlarged right hilum and pulmonary infiltration; symptomless; gastric juice cultures positive; progress uneventful.

Case 5.—Aged 12. Enlarged left hilum with infiltration left upper zone; symptomless; gastric juice cultures negative; progress slow. Deteriorated radiologically four months after treatment started. Still has gland mass at left hilum.

Case 6.—Aged 12. Left pleural effusion; headache and fever; gastric juice cultures positive; progress uneventful.

Case 7.—Aged 10. Miliary lesions both lungs, with enlarged right hilum; erythema nodosum; gastric juice cultures positive; progress good. Developed transient segmental atelectasis of the middle lobe.

Case 8.—Aged 14. Infiltration throughout right upper lobe; severe cough; gastric juice cultures positive; progress uneventful.

Case 9.—Aged 14. Enlarged left hilum; symptomless; gastric juice cultures negative; progress uneventful.

Case 10.—Aged 12. Glands right hilum with pulmonary focus; erythema nodosum; gastric juice cultures negative; progress uneventful.

Case 11.—Aged 9. Enlarged right hilum with pulmonary focus; symptomless; gastric juice cultures positive; progress slow. Developed transient segmental atelectasis right upper lobe.

Case 12.—Aged 10. Enlarged left hilum; symptomless; gastric juice cultures negative; progress uneventful.

Case 13.—Aged 13. Enlarged right hilum with pulmonary focus; symptomless; gastric juice cultures negative; progress uneventful.

Case 14.—Aged 11. Enlarged right hilum; stiff neck and cough; gastric juice culture positive; progress uneventful.

Cases Treated at Home

Case A.—Aged 10. Enlarged right paratracheal glands; erythema nodosum; developed infiltration in right lower zone 13 months after treatment commenced. It was discovered that she had not been taking her treatment regularly.

Case B.—Aged 15. Enlarged left hilum with pulmonary focus; symptomless; progress uneventful.

Case C.—Aged 6. Enlarged right hilum; symptomless; progress uneventful.

Case D.—Aged 9. Enlarged right hilum with pulmonary focus; symptomless; progress uneventful.

Case E.—Aged 13. Gland right hilum; symptomless; progress uneventful.

Case F.—Aged 13. Focus first right interspace; symptomless; progress uneventful.

Case G.—Aged 12. Small pleural effusion right base; symptomless; progress uneventful.

Case H.—Aged 15. Trace of fluid left base; pain left lumbar region; progress slow. The fluid had increased after two months' treatment with streptomycin, P.A.S., and isoniazid, but had cleared six weeks later.

Case I.—Aged 14. Lesion second left interspace without hilar enlargement; symptomless.

Discussion

Many school epidemics of tuberculosis have been reported in the literature. Sometimes the source has been found easily (Bevan *et al.*, 1951; Anderson, 1954), while sometimes the source could not be found (Roe and Dick, 1949; Mande *et al.*, 1958).

In the present investigation 75% of the population of the town and district, including most of the home contacts of the children with lesions, were radiographed by the mass radiography unit without discovering a single case of active tuberculosis, and all the teaching and auxiliary staff of the school involved were radiographed with negative results. It appears obvious that the source of infection was one of the pupils. The first case of erythema nodosum occurred on February 26, 1960. Assuming that the incubation period for erythema nodosum is three to eight weeks, then infection occurred between January 1 and February 5.

The only pupil known to have had a cough at this time was a girl aged 14, who had been under radiographic observation since June, 1958, when an elder sister was admitted to hospital with a pleural effusion. She was Heaf-positive when first radiographed as a contact. Her last film prior to the outbreak was taken on January 21, 1960, when it was noted that the lung markings in the second right interspace appeared more pronounced than in her previous film, and continued observation was advised. When next seen in April she had infiltration throughout the right upper lobe. She had a severe cough on admission to hospital and three gastric juice cultures were positive. It is thought that this child is the most likely source of infection and that her sputum was probably heavily positive about the time she was radiographed in January, although the source of the heavily infected material is not obvious in her x-ray film. It could possibly have come from a gland, not visualized in her film, rupturing into a bronchus or from a bronchial lesion. All the cases of erythema nodosum occurred within a period of five weeks, so it is just possible that they were all infected on the same day.

The question arises why did so many children become diseased. The most likely contributory factors were age and overcrowding at school. There is no evidence that they were undernourished; their home conditions were satisfactory, and there had been no outbreak of an infectious disease in the school in the six months preceding the epidemic.

It is interesting to note that 5 of the 14 children admitted to hospital started menstruating either before admission or before discharge and that four of these had parenchymal lesions. Two of these cases deteriorated initially while under treatment, but only one

of the nine pre-adolescent children deteriorated in hospital.

Hyge (1947) in his classical work on a school epidemic in Scandinavia produced convincing evidence of the protection given by B.C.G. vaccination. In the epidemic reported here, all of the nine vaccinated children have remained well, giving an incidence of disease in the vaccinated children of 0% compared with 16% in the non-vaccinated.

Summary and Conclusions

After the discovery of 10 cases of erythema nodosum in one classroom in a primary school, full investigation and follow-up uncovered 23 cases of tuberculosis in the school. Twenty-one of these cases were in the one classroom. There were 17 primary cases, 2 post-primary, 1 miliary case, and 3 cases of pleural effusions. The reactor rate in the classroom where the outbreak occurred was 63.4% compared with 10.4% for the rest of the school.

The source of infection was thought to be a pupil who had been under "contact observation" for two years.

Children, especially girls, should be B.C.G.-vaccinated before puberty rather than at 13.

All positive reactors known to have been exposed to recent infection should receive a prophylactic course of chemotherapy.

If treatment is started within four months of first infection, chemotherapy for four or even two months may be sufficient to prevent lesions developing.

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REFERENCES

- Anderson, A. W., and Grenville-Mathers, R. (1952). *Lancet*, 2, 330.
 Anderson, C. E. (1954). *N.Z. med. J.*, 53, 35.
 Bevan, R. T., Bray, P. T., and Hanly, J. F. (1951). *Brit. med. J.*, 2, 828.
 Hyge, T. V. (1947). *Acta tuberc. scand.*, 31, 1.
 Lundius, I. (1928-9). *Ibid.*, 4, 275.
 Mande, R., Herrault, A., Loubry, P., and Bouchet, C. (1958). *Sem. Hôp. Paris*, 34, 1837.
 Roe, J. T. N., and Dick, W. P. (1949). *Tubercle (Lond.)*, 30, 39.

"The Bourton-on-the-Water and Cotswold Village Hospital was founded by Dr. John Moore, and opened on March 11, 1861. It was the third cottage hospital in England; literally in a cottage rented for £12 a year. Dr. Moore was the Medical Officer—the establishment consisted of 'a regular nurse, who shall have occasional assistance'; and the disbursements during 1861, including repairs, alterations and the wages of the nurse, totalled £130 9s. 2½d. Wine, spirits and linen were supplied chiefly by private munificence. The accounts showed a balance of £30 14s. 7½d., from which the Committee hoped to supply a bath and such other necessities as they hesitated to purchase in the first year of experiment. By the end of the year, 22 in-patients and 208 out-patients had been treated. Of the former, twelve were discharged cured, one improved, four discharged to out-patients, and one died from 'innutrition' after discharge: but a girl aged nine years, who was admitted on July 22nd, was 'Discharged July 27th, for bad conduct.' The Annual Report states that the Hospital was limited to three in-patients, one extra bed being reserved for emergencies." (Centenary of the Bourton-on-the-Water Cottage Hospital, 1861-1961.)