

Summary

Twenty-seven cases of basal-cell carcinomata (rodent ulcers) are described occurring in sites other than the face and scalp.

The clinical varieties of rodent ulcer, the multiplicity of lesions, and their site are discussed.

Treatment by surgical excision and that by irradiation are compared and contrasted.

Surgical excision of all rodent ulcers is recommended.

We wish to express our thanks to the late Dr. ff. Creed, lately Director of Pathology, King's College Hospital, to Dr. H. A. Lucas, and to Professor H. A. Magnus, Professor of Pathology in King's College Hospital, for their assistance with the histology of these tumours. We wish to acknowledge the assistance of Mr. W. Smith, of the department of photography, King's College Hospital, who prepared the photomicrographs.

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STREPTOMYCIN TREATMENT OF TUBERCULOUS BRONCHOPNEUMONIA IN CHILDHOOD

BY

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[WITH PHOTOGRAVURE PLATE]

This report is concerned with the use of streptomycin for tuberculous bronchopneumonia in childhood, and is based upon the treatment of eight patients admitted between January, 1947, and April, 1948, to the streptomycin centres under the auspices of the Medical Research Council at Alder Hey Children's Hospital, Liverpool (7 cases), and the Royal Hospital for Sick Children, Glasgow (1 case). Two of the patients died, and the six survivors have been followed up for periods of between 6 and 22 months subsequent to admission.

Diagnosis

Tuberculous bronchopneumonia simulates other types of bronchopneumonia closely, the main clinical differences being the insidious onset, steady progress of symptoms, increasing pallor, flabbiness, and weakness, and the progressive character of the abnormal pulmonary signs in tuberculous bronchopneumonia (Naish, 1933). The evidence

upon which the diagnosis was based in our cases was as follows.

History of Contact.—The tuberculosis officer of the local authority co-operated with us closely during this investigation, and in seven cases a history of contact with a proved case of pulmonary tuberculosis was obtained (Table I).

History of Illness.—A period of ill-health varying from 27 to 90 days before admission to hospital was a feature,

TABLE I.—Contact History

Case No.	Contact	Site	X-ray Film	Sputum	Details of Contact
1	Stepfather	Lungs	Active tuberculosis	Positive	Living in same house: has had sanatorium treatment
	Stepfather's sister	Lungs	—	—	Living in same house until death from pulmonary tuberculosis two years ago
2	Mother Brother (18 years)	Lungs	Quiescent	Negative	Living in same house and nursing the child for one month before entering sanatorium
		Lungs	Active	Positive	
3	Grand-mother	Lungs	Active	Positive	Living in same house for first 15 months of child's life
4	Father	Lungs	—	—	Living in same house. Died of pulmonary tuberculosis, July, 1948
5	Father	Lungs	—	Positive	Living in same house
6	No known contact				
7	Mother	Lungs	Quiescent	Negative	" "
		Glands in neck			
8	Brother (3 years)	Lungs	Active	Negative	" "
		Brother			
8	Brother (8 years)	Lungs	Active	Positive (Guinea-pig)	Lived in same house until death, at age of 15, from pulmonary tuberculosis, 1945
		Cervical glands; dactylitis			
8	Sister (7 years)	Lungs	Quiescent	—	Lived in same house, but now in hospital with pulmonary tuberculosis
	Mother—refused examination				Living in same house

and in two cases the illness followed an attack of measles. All the patients had shortness of breath severe enough for the parents to remark upon it; cough of several weeks' duration was present in seven cases, sputum was noted in one case, and loss of weight had been observed in half the cases.

Clinical Signs.—The most striking signs were pallor (7 cases), variable degrees of dyspnoea (7 cases), cough (7 cases) accompanied by vomiting (2 cases), and poor nutritional state (3 cases). The pulmonary signs were those of bronchitis (4 cases), consolidation (3 cases), and collapse of the left lower lobe (1 case). (See Table II.)

Radiography.—Radiographs of the chest showed patchy shadowing of the lung fields in all patients: in Case 4 it was

TABLE II.—General Clinical Signs on Admission of Cases to Hospital

Case No.	Nutrition	Colour	Dyspnoea	Clubbing	Glands in Neck	Cough	Sputum	Chest Signs
1	Poor; very emaciated	Pale; no cyanosis	Slight	Fingers and toes	Small	Moderate	—	Consolidation both bases. Cavitation right upper lobe anteriorly
2	Poor	Pale; slight cyanosis	"	Absent	"	Severe, with vomiting	Yellow	Consolidation left lung anteriorly; bronchitic signs right side
3	Fair	Pale; no cyanosis	Stridor	"	None	Absent	—	Bilateral bronchitic signs
4	Good	Very pale	Slight	"	Enlarged and bilateral	Moderate	Swallowed	Consolidation upper two-thirds left lung
5	Poor	Pale	Marked	"	None	Severe	—	Generalized bronchitic signs
6	Fair	No cyanosis	Slight	"	Small	Moderate	—	Generalized bronchitic signs
7	"	Pale	"	"	"	Severe, with vomiting	—	Bronchitic signs at both bases
8	"	"	Absent	"	Marked enlargement, with discharging sinuses	Slight	Swallowed	Clinical evidence of collapse of left lower lobe; bronchitic signs in other lung fields

associated with massive consolidation of the left lung, in Case 8 with collapse of the left lower lobe, and in Case 2 with partial collapse of the left lung and compensatory emphysema. In Cases 3, 7, and 8 enlarged hilar glands were visible. A fine miliary type of mottling in addition to the coarse patchy shadowing was present in Case 5. (See Table III.)

Isolation of Organism.—*Mycobacterium tuberculosis* was obtained from stomach washings or sputum in all cases, was seen on direct film examination (Cases 1, 2, 5, and 6), and was isolated by culture (Cases 3, 4, and 8) or by guinea-pig inoculation (Cases 4 and 7). The tubercle bacilli were of the human variety in seven cases and bovine in Case 3.

Tuberculin Reaction.—In five cases strong positive reactions to 1 in 10,000 old tuberculin were obtained; in two cases a dilution of 1 in 1,000 was positive; and in one case the test was negative at 1 in 10,000 but was not tested with higher concentrations.

Course of Illness After Admission to Hospital and Before Starting Streptomycin

Case 2 received streptomycin from the day of admission to hospital, but the remaining seven cases were observed for

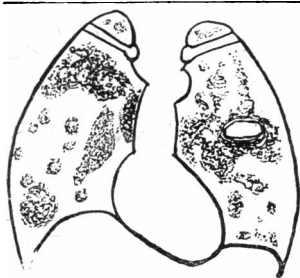
periods varying from 17 to 102 days before streptomycin administration was started. An assessment of the clinical condition during this period before streptomycin treatment has been made in Table IV.

Case 3 was admitted for the treatment of suppurative otitis media, and initially no abnormal chest signs were noted. Bronchitis first developed on the 48th day of observation. Fever was minimal except on the 97th day, when a temperature of 104° F. (40° C.) was recorded. No obvious deterioration in general condition was observed. In contrast, the course in Case 1 was progressively downhill: this patient lost 1½ lb. (570 g.) in 17 days, his temperature reached 102° F. (38.9° C.) daily, and the respiratory signs increased in severity. Similar evidence of increasing consolidation was noted in Case 4 and the temperature was raised to 102° F. daily, but this patient's general condition was fairly satisfactory throughout. In the remaining four cases weight was stationary, appetite was fairly good, temperature was normal except for an occasional rise to 100° F. (37.8° C.), and no alteration in the chest signs was observed.

Streptomycin Administration

The streptomycin used was in the form of the hydrochloride, obtained from America (Merck), and the dosage

TABLE III.—Details of X-ray Findings on Admission to Hospital (Radiologist's Report)



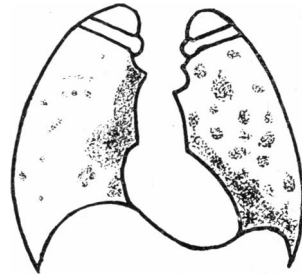
Case 1.—Gross changes in both lung fields typical of tuberculous bronchopneumonia, with cavitation on the left.



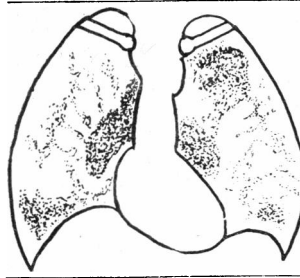
Case 5.—Diffuse bronchopneumonic tuberculous infiltration with finer miliary mottling.



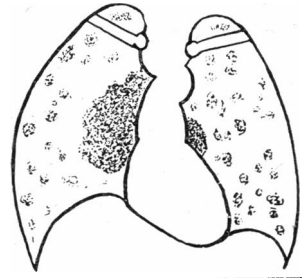
Case 2.—Consolidation and partial collapse of left lung with compensatory emphysema. Bronchopneumonic changes in the right lung.



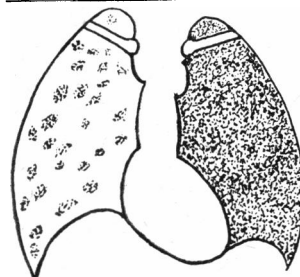
Case 6.—Bronchopneumonic changes in both lungs, but especially the left. Some de-aeration of left lower lobe. ? Tuberculous.



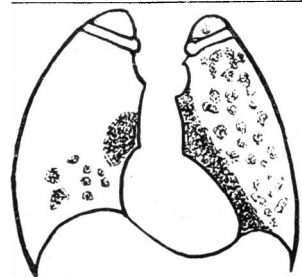
Case 3.—Opacity in left upper lobe and in right lower lobe due to consolidation of bronchopneumonic type; well-marked peripheral hyperaemia in all areas due to bronchopneumonic congestion. Both hilar shadows enlarged.



Case 7.—Bronchopneumonic consolidation of both lungs. Enlarged right mediastinal shadow.



Case 4.—Mediastinum enlarged to the left; areas of consolidation in right lung and massive consolidation of left lung.



Case 8.—Enlarged right hilar gland with infiltration at right base. Collapse of left lower lobe and bronchopneumonic shadowing in left upper lobe.

TABLE IV.—Clinical Course of Patients from Day of Admission until Start of Streptomycin Therapy

Case No.	Period of Observation	General Observations	Temperature	Weight	Appetite	Chest Signs
1	17 days	Lethargic and apathetic. Frequent bouts of coughing. Increasing pallor. Progressive loss of flesh	Up to 102° F. (38.9° C.) daily	Loss of 1½ lb. (570 g.)	Good	Evidence of consolidation with cavitation
2	Treatment started on day of admission					
3	102 days	Superficial skin sepsis. Right suppurative otitis media. Measles. Occasional bouts of sweating. Cough and dyspnoea from 48th day; later became cyanosed. Inspiratory stridor noted on 72nd day	Up to 99° F. (37.2° C.) daily, 104° F. (40° C.) on 97th day	—	Poor	Developed bronchitic signs on 48th day
4	21 days	Fair general condition. Loose cough. Dyspnoea. No cyanosis	Up to 102° F. (38.9° C.) daily	—	Poor	Signs of increasing consolidation
5	41 days	Admitted as whooping-cough (17/7/47) but not confirmed. On 1/8/47 developed marked cervical adenitis. (No local cause in throat)	99–100° F. (37.2–37.8° C.)	Stationary	Poor	Bronchitic signs. (Radiograph on 1/6/47 showed primary complex)
6	20 days	Quiet—resents examination. Occasional dry cough. No cyanosis. No dyspnoea	Normal	..	Good	Bronchitic signs
7	42 days	Pallor. Fair general condition. No dyspnoea. No cyanosis. Fretful	99 to 100° F., with occasional spikes to 101° F. (38.3° C.)	..	Fairly good	" "
8	48 days	Discharging sinuses in neck and axilla. Bouts of coughing. Dyspnoeic. No cyanosis	Normal	..	" "	Collapse of left lower lobe

TABLE V

Case No.	STREPTOMYCIN			TUBERCLE BACILLI		Sensitivity <i>in Vitro</i> (units/ml.)	Weeks after starting Streptomycin
	Daily Dose and Route	Duration	Total Dose	Source	Date Isolated		
1	0.8 g. i.m. 1.0 g. i.m. 1.0 g. i.m. 0.1 g. i.m.	22/8/47–3/9/47 4/9/47–15/10/47 25/10/47–21/1/48 30/10/47–28/11/47	130 g.	Gastric lavage Sputum " " " " " "	6/8/47 10/8/47 29/1/48 30/1/48 31/1/48 2/4/48 26/4/48 27/4/48	1 ½ 6½ 6½ 6½ 25 50 50	— 23 23 23 32 35 35
2	0.3 g. i.m. 0.5 g. i.m.	22/1/48–1/4/48 2/4/48–12/4/48	27 g.	Gastric lavage " "	20/2/48 29/2/48 2/3/48	½ 1 1	4 5½ 6
4	1.0 g. i.m. 0.5 g. i.m. 0.4 g. i.m. 1.0 g. i.m.	21/1/47–24/3/47 26/3/47–21/4/47 27/6/47–25/7/47 23/1/48–20/2/48	112.5 g.	Gastric lavage " " "	17/1/47 22/1/47 14/5/47 27/6/47	0.25 0.25 0.125 0.125	— — 16 22
8	1.0 g. i.m.	2/4/48–26/6/48	84 g.	Sputum "	25/2/48 16/7/48	0.125 0.125	— 15

adopted was 0.02 g. per lb. (454 g.) body weight every 24 hours, intramuscularly. The drug was dissolved in distilled water and was given in divided doses six-hourly. This regime was continued for a period ranging between 12 and 22 weeks, making a total dosage of 27 to 130 g. of streptomycin. Three patients showed evidence of mild sensitivity to streptomycin. In Cases 1 and 7 a maculo-papular rash was present on the limbs, face, and trunk. In Case 4 albumin, red cells, white cells, and hyaline casts were present in the urine, and in Case 1 albumin and pus cells were found; these reactions quickly disappeared when the drug was suspended temporarily. Eosinophilia was not a feature, and no effects on the vestibular apparatus were observed. Local soreness, erythema, and induration at the site of injection occurred in one case.

Sensitivity of *M. Tuberculosis* to Streptomycin

The method of testing was that used in two investigations undertaken by the Medical Research Council (1948) in which the sensitivity was compared with that of the standard culture H37Rv. In half the cases tubercle bacilli were not isolated after treatment with streptomycin had started. In three of the remainder (Cases 2, 4, and 8) the tubercle bacilli showed no increased resistance to the action of streptomycin, but in Case 1 increased resistance was observed. The details of the sensitivity tests are recorded in Table V.

Clinical Course

(a) Fatal Cases (2)

CASE 1

A boy aged 5 years 4 months had a history of measles 26 days before admission, followed by anorexia, loss of weight, apathy, and refusal to play. Unproductive cough continued from the time of the measles. The child's father, suffering from active pulmonary tuberculosis, was living in the same house. On clinical examination, nutrition was poor and loss of weight was obvious. The axillary and inguinal glands were enlarged and clubbing of fingers and toes was present. There was flattening and diminished movement of the right side of the chest, and dullness to percussion at both bases with rales. Cavernous breathing was noted at the right apex anteriorly.

Tubercle bacilli were seen in direct films (and later cultured) from stomach washings. Chest radiographs showed "gross changes in both lung fields typical of bronchopneumonia, with cavitation on the left side." The cerebrospinal fluid showed no abnormality (total protein 30 mg. per 100 ml., sugar normal, cells 2 per c.mm.). Intramuscular streptomycin treatment in a dosage of 0.02 g. per lb. body weight per day (0.8 g.) was started. His condition deteriorated, and 23 days after the beginning of treatment a generalized erythematous rash was observed, albumin appeared in the urine, and treatment was temporarily suspended. One month later tuberculous dactylitis of the left fifth metacarpal bone was noted and his general condition had deteriorated. Two weeks later routine lumbar puncture revealed changes typical of tuberculous meningitis, although there was no suspicion of neck rigidity or other abnormal neurological signs. Total protein, 200 mg. per

100 ml.; globulin, positive; chloride, 670 mg. per 100 ml.; sugar, reduced; leucocytes, 26 per c.mm. (90% mononuclears); tubercle bacilli present.

Intrathecal streptomycin treatment was started with 0.1 g. daily for 29 days. Improvement in the general condition followed and he began to gain weight, but chest signs and x-ray findings were little changed. After 19 weeks in hospital streptomycin treatment was discontinued—a total of 130 g. having been given. He had gained 4 lb. (1.81 kg.) in weight during this period. Repeated stomach washings were positive for tubercle bacilli (on culture) and x-ray films of the chest showed little change.

His general condition continued to improve, and during the succeeding three months he gained a further 4 lb. in weight. He was then transferred to a convalescent hospital, but three weeks later was readmitted because of loss of weight (3 lb.: 1.36 kg.), severe cough, pyrexia, and occasional vomiting. Chest signs had altered little, sputum was positive for tubercle bacilli, and he had purulent conjunctivitis, blepharitis, and rhinitis, which improved slowly. There were no abnormal signs in his nervous system, and lumbar puncture produced a clear, colourless fluid containing: total protein, 60 mg. per 100 ml.; globulin, positive; sugar, normal; chlorides, 740 mg. per 100 ml.; leucocytes, 10 per c.mm. (80% mononuclears). No tubercle bacilli were found.

His general condition now deteriorated rapidly, chest signs became more pronounced, with increase of cavitation, and x-ray films indicated a progressive "adult" type of phthisis of the left lung. Death occurred two months after his re-admission. Permission for post-mortem examination was refused.

CASE 2

A girl aged 5 months; said to be healthy until one month before admission, when she contracted a cold and cough, which became severe and spasmodic and was accompanied by vomiting. There was considerable loss of weight, and on admission she weighed 12 lb. 4 oz. (5.46 kg.) (birth weight, 8 lb. 14 oz. (4.02 kg.)). The child's brother had active pulmonary tuberculosis, and had been in close contact with the patient for one month.

On examination the only abnormal signs were in the chest, where movement of the left side was diminished, the percussion note was dull, and crepitations were heard. Radiography of the chest revealed bronchopneumonic shadowing of the right lung, consolidation and partial collapse of the left lung, and an area of compensatory emphysema. Radiologically the lesion was more extensive than was expected in view of the child's general condition.

Tubercle bacilli were isolated in large numbers from gastric washings, and the Mantoux reaction (1 in 10,000) was positive at 48 hours (8 by 12 mm.). Streptomycin, 0.02 g. per lb. body weight per day (0.3 g.), was given intramuscularly in divided doses six-hourly, and was later increased to 0.5 g. daily. Subsequently her general condition deteriorated; anorexia and vomiting began, the liver became progressively larger, and the abnormal chest signs and radiological changes persisted.

Throughout the illness there were no neurological signs or changes in the cerebrospinal fluid. Death occurred twelve weeks after admission, when a total of 27 g. of streptomycin had been given.

Post-mortem Examination.—Wasted infant. Skull and brain normal; no evidence of meningitis. Neck: Large caseous lymph gland in right anterior cervical triangle; several other glands affected to a smaller degree. Lungs: Left upper lobe: extensive caseating confluent tuberculous bronchopneumonia with multiple cavities. Left lower lobe: several caseating foci as well as miliary tubercles. Right lung: multiple tuberculous foci with caseation and miliary tubercles. The mediastinal glands were caseous. Liver grossly enlarged, with miliary tubercles throughout. Spleen slightly enlarged, with widely scattered miliary tubercles. Other viscera normal.

Histology

Lung, Right Lower Lobe.—The material sectioned lay immediately beneath the pleura and included part of a cavity approximately 4 mm. in diameter. The cavity wall consisted of an

irregular layer of necrotic consolidated lung surrounded by a zone of spreading bronchopneumonia with an alveolar fibrinous exudate and a predominantly mononuclear cytology. The alveoli showed necrosis of their lining cells and of the exudate contained within them. There was no indication of peripheral fibroblastic activity or of giant-cell formation. Tubercle bacilli were numerous both in the cavity wall and in the surrounding alveolar septa and spaces. Scattered irregularly throughout the remainder of the section were smaller areas of similar nature though without central cavitation; some of these would appear to have arisen by bronchiolar aspiration, while others were probably haematogenous in origin. The intervening lung showed patchy areas of atelectasis and alveolar emphysema. Scanty foci of mononuclear cells, surrounded by a hyaline zone of radiating collagen fibres, with a narrow peripheral layer of concentrically arranged fibroblasts and newly formed capillaries, were also present, representing healing of older haematogenous lesions.

Liver.—This organ showed a moderate degree of fatty infiltration, principally at the periphery of lobules. The parenchymal pattern and the portal tracts were normal. There were numerous foci of necrosis up to 0.5 mm. in diameter, similar to those in the lungs and containing numerous tubercle bacilli; and, especially in places in relation to portal tracts, there were small areas composed of loosely arranged hyaline connective tissue with scanty mononuclear cells, representing healing tubercles. Very scanty lesions of this type, but rather more cellular, showed giant cells.

Spleen.—Large numbers of caseous tubercles, similar to those in the liver, were present. There was no indication of healing.

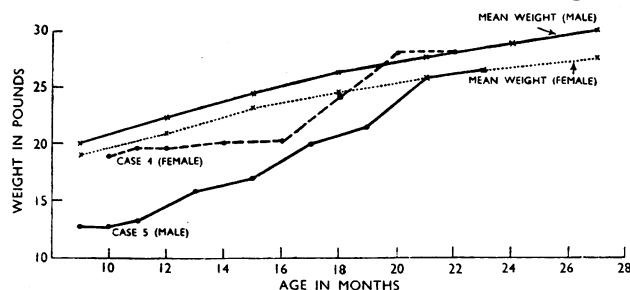
Conclusions.—The microscopical appearances indicate an early military dissemination with partial healing, followed at a later date by a massive haematogenous infection. The bronchopneumonic areas in the right lower lobe could be due either to direct aspiration of infected material into this lobe or possibly to intrabronchial rupture of caseous tubercles within the lobe.

(b) Cases (5) Making Good Progress

In these cases progress has been satisfactory as judged by clinical and radiological examination made 16, 15, 10, 8, and 4 months after cessation of streptomycin therapy. This statement is based on the following observations:

General Condition.—On admission the patients were in subnormal health, as evidenced by pallor, dyspnoea, skin sepsis, flabby musculature, apathy, and disinterestedness. After treatment they had a fresh colour, nutrition was good, muscle tone was normal, and they were happy and contented. In the case records appeared such statements as: "Fat, fit, and rosy-looking; very good general condition"; "Happy, smiling, playing normally, very interested in all that is going on"; "Pink colour, happy and contented."

Weight.—All the patients had gained weight (see Table VI), and in Cases 4 and 5, treatment of which began at



Graph showing gain in weight in Cases 4 and 5. (Mean weight curves are taken from Mitchell-Nelson's *Textbook of Pediatrics*, 4th edition.)

10 months and 9 months of age respectively, the gain was striking (see Graph). Case 4 was 1 lb. (453 g.) under mean weight at the beginning of treatment, and 10 months later she was 4½ lb. (2.04 kg.) above the mean weight. Case 5 was 7 lb. (3.175 kg.) below the mean weight when treatment was begun, and 14 months later was only 2 lb. (0.9 kg.)

TABLE VI

Case	Age when Streptomycin was Started	Duration of Illness Before Starting Streptomycin	Streptomycin		Weight at Start of Treatment	Change of Weight (Compared with Initial Weight) During and After Treatment								Months After Cessation of Streptomycin to Oct., 1948	X-ray Report, General Remarks, etc., October, 1948
			Daily Dose (g.)	Duration, with Date of Initial and Final Injection		Total Dose (g.)	1 Mth	2 Mths	4 Mths	6 Mths	8 Mths	10 Mths	12 Mths		
1	5 years 4 mths	28 days	0.8 later 1.0	19 weeks 22/8/47-21/1/48	25 lb. 14 oz. (11.74 kg.)	+2½ lb. (1.13 kg.)	-1 lb. 1 oz. (482 g.)	+1 lb. 7 oz. (652 g.)	+7 lb. 6 oz. (3.34 kg.)	+5 lb. 13 oz. (2.64 kg.)	+4 lb. 3 oz. (1.9 kg.)			16	No abnormal signs. Appetite good. Gaining weight. Radiograph shows calcification left hilar region. No evidence of activity of primary focus in right lower lobe. Slight broadening of mediastinum, otherwise clear.
2	5 mths	28 days	0.3 later 0.5	12 weeks 22/1/48-12/4/48	12 lb. 4 oz. (5.46 kg.)	-4 oz. (113 g.)	-2½ lb. (1.25 kg.)	+1 lb. 5 oz. (595 g.)	+2½ lb. (1.13 kg.)	+4½ lb. (2.15 kg.)	+6 lb. (2.72 kg.)			16	No abnormal signs. Appetite good. Gaining weight. Radiograph shows calcification left hilar region. No evidence of activity of primary focus in right lower lobe. Slight broadening of mediastinum, otherwise clear.
3	14 mths	54 days	0.75	18 weeks 14/3/47-19/7/47	20 lb. (9.07 kg.)	+8 oz. (227 g.)	-2½ lb. (1.25 kg.)	+1 lb. 5 oz. (595 g.)	+1 lb. 7 oz. (652 g.)	+5 lb. 5 oz. (2.41 kg.)	+9 lb. 5 oz. (4.2 kg.)			15	No abnormal signs. Good appetite. Gaining weight. Radiograph shows calcification starting in right hilum.
4	10 mths	51 days	1.5 later 0.75 1.0	(1) 18 weeks; 21/1/47-25/7/47 (2) 4 weeks; 23/1/48-20/2/48	19 lb. 2 oz. (8.67 kg.)	+10 oz. (284 g.)	+11 oz. (312 g.)	+1 lb. 1 oz. (482 g.)	+4 lb. 3 oz. (1.93 kg.)	+7 lb. 7 oz. (3.37 kg.)	+9 lb. 5 oz. (4.2 kg.)			10	No abnormal signs. Good appetite. Gaining weight. Radiograph shows calcification starting in right hilum.
5	9 mths	90 days	0.5	16 weeks 28/8/47-16/12/47	12 lb. 13 oz. (5.81 kg.)	+1 oz. (28 g.)	+9 oz. (255 g.)	+3 lb. 2 oz. (1.41 kg.)	+4 lb. 3 oz. (1.93 kg.)	+7 lb. 7 oz. (3.37 kg.)	+9 lb. 5 oz. (4.2 kg.)			8	No abnormal signs. Good appetite. Gaining weight. Radiograph: right lower lobe calcification or fibrosis.
6	1 year 9 mths	27 days	0.5	12 weeks 22/10/47-25/2/48	17 lb. 14 oz. (8.11 kg.)	+1 lb. 5 oz. (595 g.)	+1 lb. 6 oz. (624 g.)	+1 lb. 14 oz. (0.85 kg.)	+5 lb. 2 oz. (2.32 kg.)	+4 lb. 9 oz. (2.07 kg.)	+4 lb. 10 oz. (2.1 kg.)			4	No abnormal signs. Good appetite. Gaining weight. Radiograph: some resolution left base and considerable re-aeration right base, but changes still extensive.
7	1 year 8 mths	58 days	0.5	12 weeks 12/3/48-4/6/48	18 lb. 12 oz. (8.5 kg.)	+1½ lb. (680 g.)	+1½ lb. (680 g.)	+1 lb. 14 oz. (1.3 kg.)	+5 lb. 2 oz. (2.32 kg.)	+4 lb. 9 oz. (2.07 kg.)	+4 lb. 10 oz. (2.1 kg.)			4	General condition deteriorating. Radiograph still shows collapse of left lower lobe.
8	11½ years	48 days	1.0	12 weeks 2/4/48-26/6/48	50 lb. 8 oz. (22.9 kg.)	+4 lb. (1.8 kg.)	+8 oz. (227 g.)	+2½ lb. (1.13 kg.)	+4 lb. 3 oz. (1.93 kg.)	+7 lb. 7 oz. (3.37 kg.)	+9 lb. 5 oz. (4.2 kg.)			4	No abnormal signs. Good appetite. Gaining weight. Radiograph shows calcification starting in right hilum.

below the mean weight, his weight having doubled in this period.

Clinical Signs in Chest.—When treatment with streptomycin was started there was clinical evidence of consolidation of the left lung in Case 4, and bronchitic signs were present in the other four patients. These abnormal chest signs could not be detected after 10 months (Case 4) and after three months in the other patients.

X-ray Examination.—In Cases 3, 5, and 6 (illustrated in Plate) calcification had appeared; in Case 4 there was broadening of the mediastinal shadow, but the radiograph was otherwise clear; and in Case 7, although resolution had occurred in the right lung field, changes were still extensive on the left side.

The clinical record of Case 5 is summarized here as it is representative of the progress of this group of five cases.

CASE 5

Boy aged 9 months. Well until 6 months old, when he developed a cough. Radiography of the chest revealed a primary tuberculous complex. One month later he was admitted to a fever hospital with "whooping-cough"; but this diagnosis was not confirmed, and his condition was ascribed to pressure of tuberculous mediastinal glands. Subsequently the radiological appearances were those of bronchopneumonia, and tubercle bacilli were isolated from gastric washings. The boy had been in close contact with his father, who was suffering from active pulmonary tuberculosis.

On admission the child was extremely ill. There was pallor, cyanosis, dyspnoea, and obvious loss of weight. Weight, 12 lb. 13 oz. (5.8 kg.), or 7 lb. (3.175 kg.) below the expected weight. Temperature, 101° F. (38.3° C.). The cervical glands were much enlarged; moist sounds were present in all lung fields and the tip of the spleen was palpable. No abnormal nervous signs. Radiography of the chest showed "diffuse bronchopneumonic tuberculous infiltration with fine miliary mottling" (Plate, Fig. 4).

His general condition improved within two weeks of starting streptomycin. There was no dyspnoea, the hoarse cry had disappeared, temperature remained below 99° F. (37.2° C.), and feeds were taken well from the bottle. The chest signs had not improved, however, and the neck glands had not diminished in size. During the next two months the improvement was maintained; the child was lively and was playing with his toys. A gain in weight of 9 oz. (255 g.) had occurred, temperature was normal, and the neck glands were slightly smaller. Chest signs had not altered. During this stage weaning had been successfully undertaken.

Four months after treatment had started there was a marked improvement in his general condition; he was happy and contented, appetite was good, his face was visibly fatter, and he had gained 3 lb. (1.36 kg.) above his admission weight. No small gland was palpable on each side of his neck. No abnormal chest signs were detected and an x-ray film (Plate, Fig. 5) showed considerable improvement. Subsequent progress, as judged by general condition, clinical signs, and radiological appearances (Plate, Fig. 6), was very satisfactory. His gain in weight (see Graph) may be taken as representative of his general progress.

(c) Case Showing Temporary Improvement

Case 8, girl aged 11½ years. History of cervical adenitis of 12 months' duration with caseation of glands and sinus formation. Three other members of the family were proved cases of active chest tuberculosis.

The child was pale and thin, with no cyanosis and no dyspnoea at rest. Her fundi were normal, there was no neck resistance, Kernig's sign was negative, and abnormal nervous signs were absent. A discharging sinus was present in the right submandibular area, with scars of previous sinuses on both sides of the neck; there was also a discharging sinus in the left axilla. The left lower lobe was collapsed, and crepitations were heard over the whole of the left chest. The tip of the spleen was palpable. Sputum contained tubercle bacilli. A radiograph showed collapse of the left lower lobe

and bronchopneumonic shadowing in the left upper lobe. The cerebrospinal fluid was normal. The Mantoux reaction (1 in 10,000) was positive (12 by 15 mm.).

Streptomycin treatment was started (1 g. daily in divided doses six-hourly), and after six weeks of treatment all the sinuses in neck and axilla had healed. There was a marked improvement in the general condition and appetite was good, but the chest signs were unchanged. After twelve weeks streptomycin was discontinued; the sputum still contained tubercle bacilli.

The patient was sent to a convalescent hospital. Her sputum has remained positive, and x-ray films of the chest show little change. Since streptomycin treatment has been discontinued there have been bouts of pyrexia up to 103° F. (39.4° C.) and her general condition has slightly deteriorated.

Discussion

1. The *diagnosis* of tuberculous bronchopneumonia presents difficulties because the clinical signs and radiological appearances may closely resemble those of non-tuberculous bronchopneumonia. In one of our cases, for instance, the radiographs were suggestive of staphylococcal pneumonia, and the correct diagnosis was reached by isolating tubercle bacilli from gastric washings after a prolonged course of sulphathiazole had produced no obvious radiological improvement. Patchy areas of atelectasis associated with bronchopneumonia or with allergic conditions may present similar radiological shadows.

In addition to areas of bronchopneumonia of varying size, the finely mottled appearance of miliary tuberculosis may also be apparent on the x-ray film, as in Case 5. The experience of Blacklock (1932) was similar. In his study of 148 tuberculous children who came to necropsy 58 showed mixed miliary and bronchopneumonic lesions. Macroscopically there was often much difficulty in distinguishing between an early bronchopneumonic lesion and a subacute miliary one, and histological examination was frequently essential for differentiation. This same difficulty was found in the radiological assessment and diagnosis of our cases.

Scattered bronchopneumonic areas with cavitation are occasionally observed radiologically in the shadowed area surrounding a primary focus. These areas may progress to extensive pulmonary destruction (Caffey, 1945), and thus may be confused with the cavitation of tuberculous bronchopneumonia—a condition in which dissemination of the infection has occurred to parts of the same lung or the opposite lung through rupture of a caseous lymph node into a bronchus.

2. As to *prognosis*, it is generally considered that recovery is improbable, and the usual course is a progressive deterioration (Nelson, 1946). The seven cases studied at Alder Hey Hospital during these trials were the only examples of tuberculous bronchopneumonia admitted in this period, and they were all treated with streptomycin. The only controls that we can offer, therefore, were similar cases in the hospital during the two years preceding the trials.

(a) *Duration of Survival and Mortality Rate.*—During the two years (1945 and 1946) preceding this trial eight proved cases of tuberculous bronchopneumonia were admitted to Alder Hey Hospital. The length of stay in hospital and results of treatment were as follows:

	Sex	Age	Stay in Hospital	Result
T.D.	Male	8 months	4 weeks	Died
J.W.	"	11 months	9 days	"
J.N.	"	1 year 3 months	4 weeks	"
D.H.	"	1 year 8 months	7 days	"
M.M.	Female	1 year 9 months	8 weeks	Taken home against advice
F.R.	Male	1 year 10 months	4 "	Died
B.B.	Female	5 years 9 months	2 "	"
M.D.	"	6 years 5 months	4 "	"

Seven of these eight patients died in hospital after a stay of seven days to four weeks, and the remaining case was taken home in poor general condition after eight weeks.

The results of streptomycin treatment of our patients compare favourably with these figures, both in the duration of life and in the more favourable outcome. The two fatal cases survived for 12 weeks and 9½ months respectively after the beginning of streptomycin therapy. The five cases making good progress have survived 16, 15, 10, 8, and 4 months after cessation of streptomycin therapy.

(b) *Change in Weight.*—Gain in weight is considered a reliable guide in assessing improvement in these cases. The details of increase in weight are recorded in Table VI.

(c) *Isolation of Tubercle Bacilli.*—Gastric lavage was performed at regular intervals both during and after streptomycin therapy. In the two fatal cases tubercle bacilli were isolated on every occasion. In Case 8, which showed temporary improvement, tubercle bacilli reappeared after two months of streptomycin therapy. In only one of the five cases showing marked clinical improvement were tubercle bacilli isolated from gastric washings after streptomycin therapy had begun; this was Case 4, in which tubercle bacilli were isolated 16 and 22 weeks after the starting of streptomycin therapy.

(d) *Radiography.*—Radiographs taken at regular intervals during the trials showed a gradual clearing of the bronchopneumonic areas over a period of months (see Plate). In Cases 3, 5, and 6 calcification appeared 14, 13½, and 12 months after treatment was begun.

(e) *Pyrexia.*—The temperature records were of little value in assessing progress of the cases. In Cases 5, 6, 7, and 8 temperature was normal during and after streptomycin administration. In Case 4 the temperature was normal during treatment except on five isolated occasions. In Case 3 temperature was normal during the first eight days of streptomycin therapy, and then figures of 101° F. (38.3° C.) were recorded daily. Clinically, otitis media and tonsillitis had developed, and the temperature remained raised until these conditions had subsided. Three days later the temperature again rose to 101° F., and clinically the general condition of the patient had deteriorated and there was an increase in the chest signs. A transfusion of 300 ml. of fresh blood was given; thereafter the temperature remained normal. In Case 1 the temperature at 6 a.m. and 6 p.m. was above 100° F. (37.8° C.) for the first 25 days and often as high as 102° F. (38.9° C.). During the next 80 days it rose to 100° F. on three or four occasions each week; subsequently, normal temperatures were recorded. In Case 2 the temperature was normal except during the first three days of treatment and for the three days preceding death.

3. *Tuberculous meningitis* developed in one of our cases, and was diagnosed by routine examination of cerebrospinal fluid before any abnormal neurological signs were present. It is suggested that the cerebrospinal fluid of all cases of tuberculous bronchopneumonia under treatment with streptomycin should be examined at two-weekly intervals during the first two months of treatment and at monthly intervals thereafter to detect early spread of disease to the meninges.

Summary

Streptomycin has been given to eight children suffering from tuberculous bronchopneumonia. Their ages at the beginning of treatment varied from 5 months to 12 years.

Two of these patients have died, and the six survivors have been under observation for periods of from 6 to 22 months.

The diagnosis of tuberculous bronchopneumonia presents difficulties because it closely simulates non-tuberculous bronchopneumonia, patchy collapse of the lung, and confluent miliary tuberculosis.

Gain in weight and radiological improvement in the lung fields are the two most valuable means of assessing progress.

In one child tuberculous meningitis developed during treatment and the organism became resistant to streptomycin.

This investigation was carried out under the auspices of the Medical Research Council Streptomycin in Tuberculosis Trials Committee (chairman, Dr. Geoffrey Marshall) at the centres at Alder Hey Children's Hospital, Liverpool, and the Royal Hospital for Sick Children, Glasgow. These two centres were under the charge of

R. McLAREN TODD : STREPTOMYCIN TREATMENT OF TUBERCULOUS BRONCHOPNEUMONIA IN CHILDHOOD

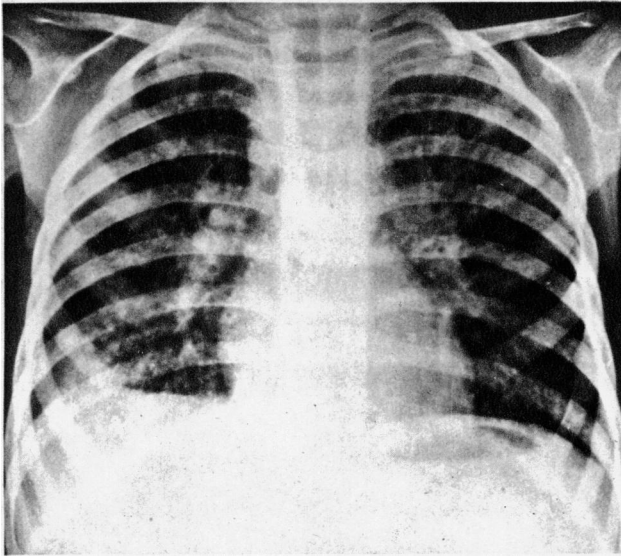


FIG. 1.—Case 3. Feb. 10, 1947. Bilateral hilar shadows: bronchopneumonic consolidation in left upper and right lower lobes.

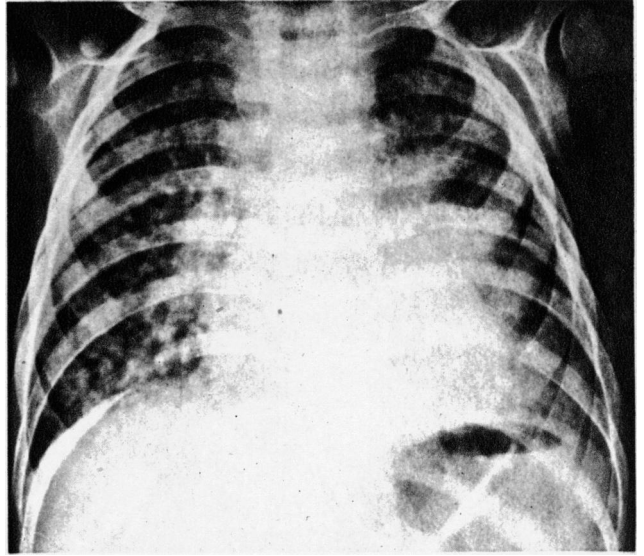


FIG. 4.—Case 5. Aug. 27, 1947. Diffuse bronchopneumonic infiltration.

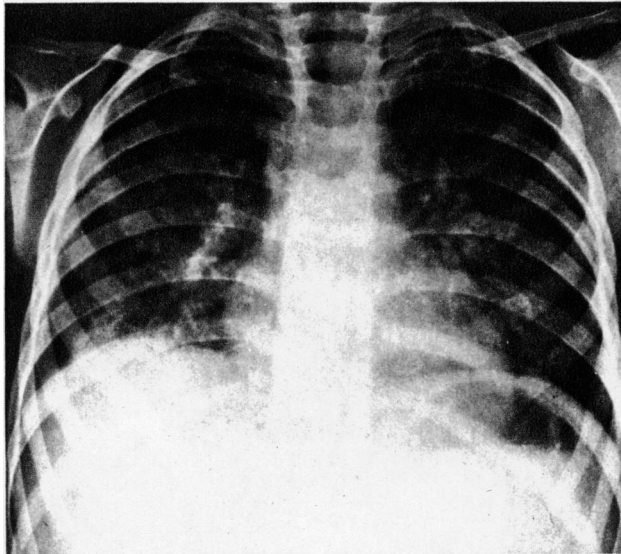


FIG. 2.—Case 3. Aug. 1, 1947. Marked improvement in right lower lobe.

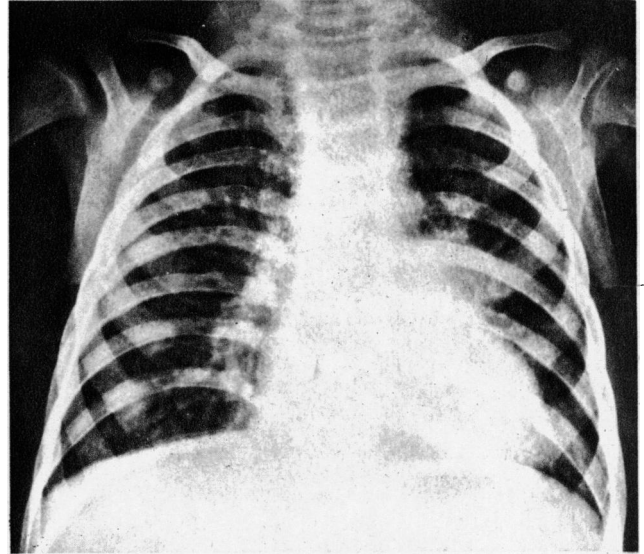


FIG. 5.—Case 5. Jan. 1, 1948. Considerable improvement in periphery of lung fields.

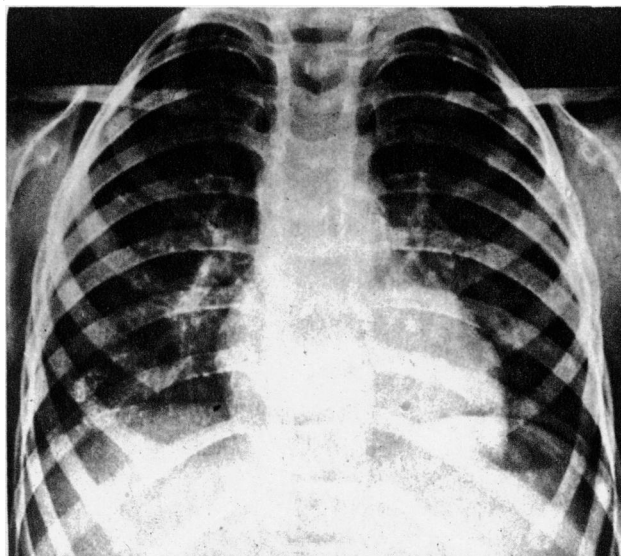


FIG. 3.—Case 3. Oct. 15, 1948. Areas of calcification, especially at right apex, right midzone, and left apex: calcification at right base, probably site of primary focus.

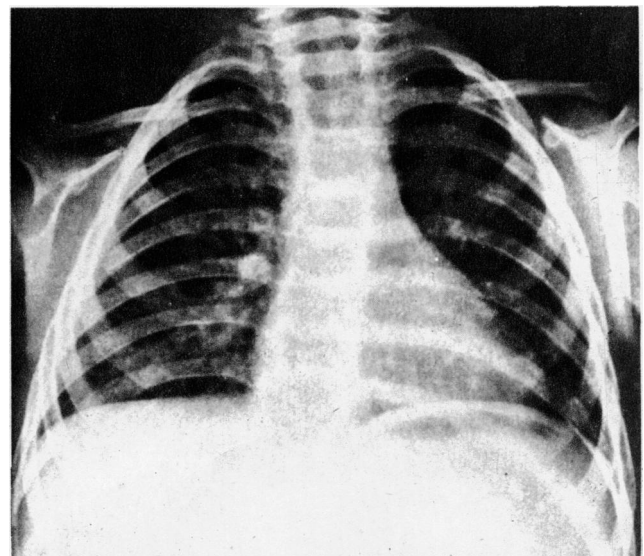


FIG. 6.—Case 5. Oct. 11, 1948. Calcification right base (probably site of primary focus) and right hilar glands.

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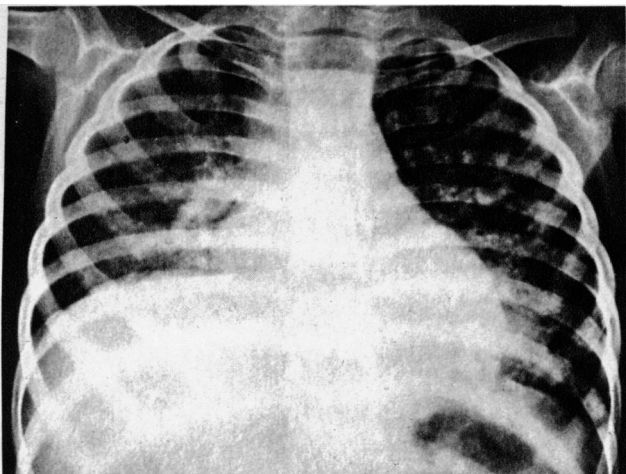


FIG. 7.—Case 6. Oct. 15, 1947. Bronchopneumonic changes in both lungs, more marked on left.

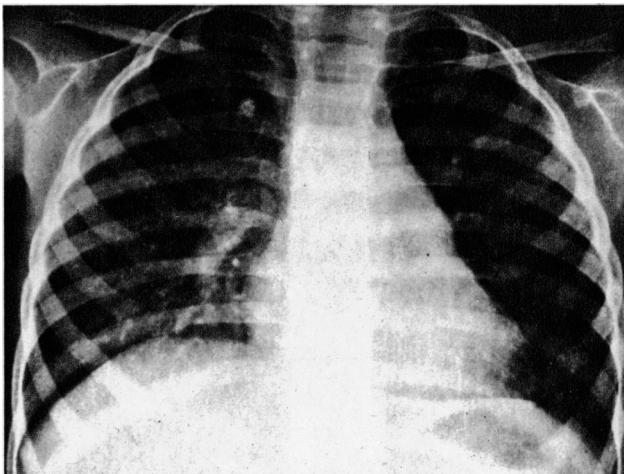


FIG. 8.—Case 6. April 12, 1948. Showing considerable improvement.

SIR CECIL WAKELEY AND PETER CHILDS : RODENT ULCER

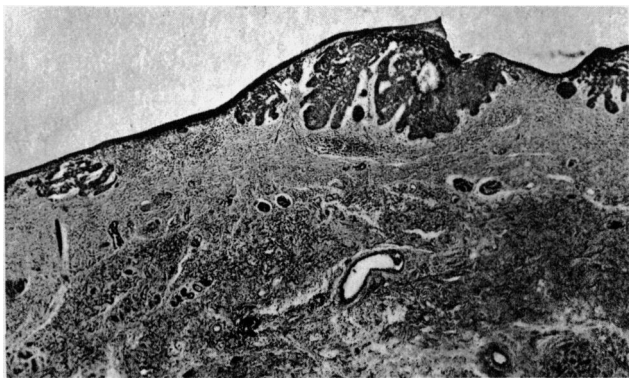


FIG. 1.—Case 5. Low-power view ($\times 23$) of recurrent superficial rodent ulcer found on anterior chest wall, showing multi-centric origin of recurrence.

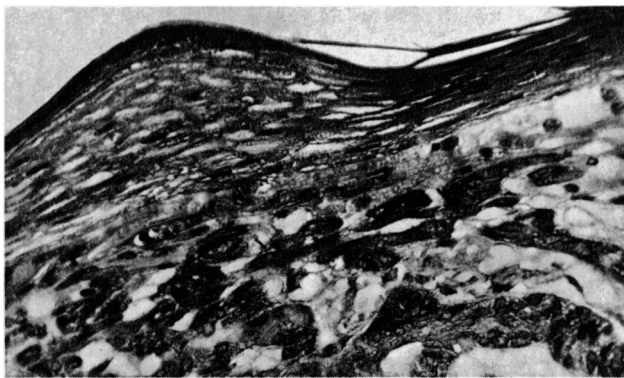


FIG. 2.—Case 5. High-power view ($\times 260$) of section shown in Fig. 1.

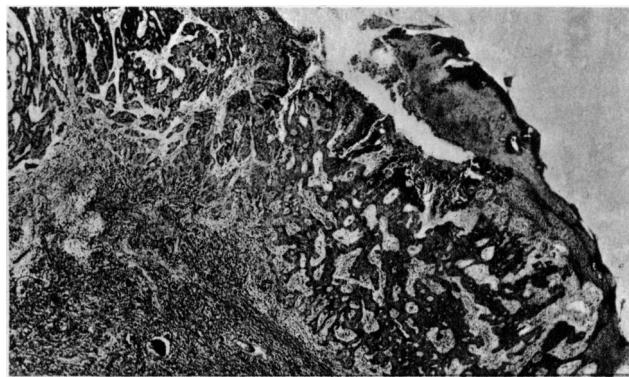


FIG. 3.—Case 6. Low-power view ($\times 23$) of the lesion illustrated in FIG. D (in text). Typical rodent ulcer showing superficial ulceration, and deep penetration of corium on left.

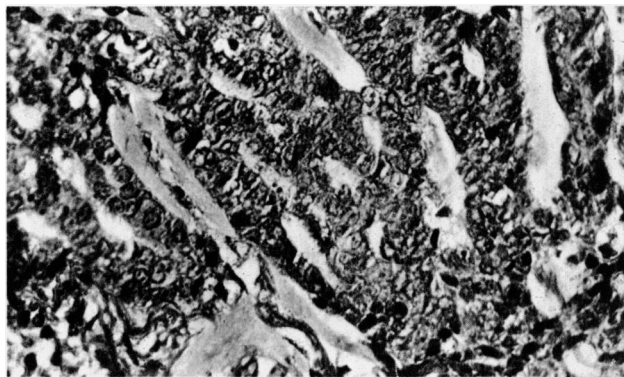


FIG. 4.—Case 6. High-power view ($\times 260$) of the lesion illustrated in Fig. 3.

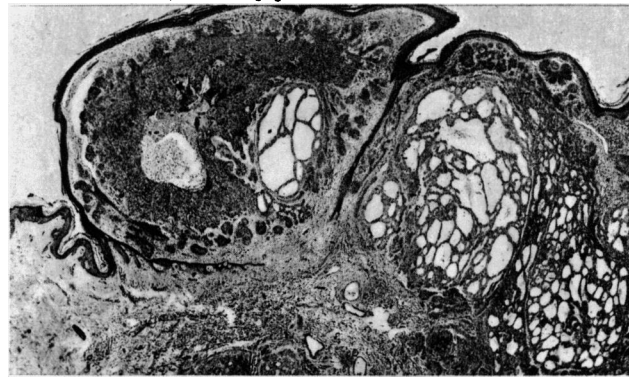


FIG. 5.—Case 14. Low-power view ($\times 23$) of rodent ulcer showing cystic degeneration.

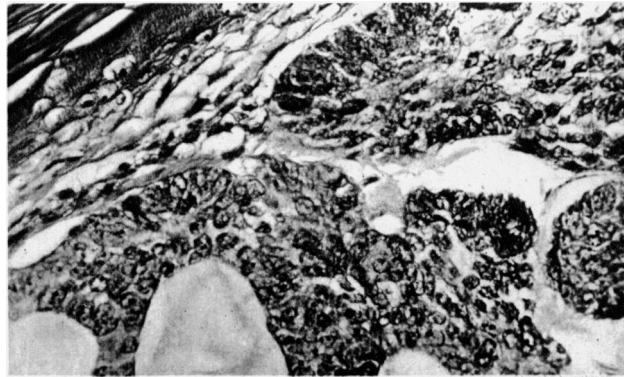


FIG. 6.—Case 14. High-power view ($\times 260$) of rodent ulcer shown in Fig. 5.

Professor Norman B. Capon and Professor Stanley Graham respectively.

I wish to express my gratitude to all who have been associated with this work, especially the medical staffs of these hospitals.

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SOME PRACTICAL PROBLEMS OF TUBERCULOSIS IN CHILDHOOD*

BY

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It is strange to learn that while Aristotle realized that tuberculosis was an infectious disease Laennec believed it was not contagious, and Koch held that bovine tuberculosis could not be communicated to man. Now it is generally accepted that the majority of infants and children, particularly those living in urban civilized communities, are infected early and develop a high degree of immunity; otherwise few would survive under the housing conditions we have inherited from the industrial revolution of the nineteenth century. It has been long recognized that good ventilation, general cleanliness, and the proper disposal of sputum diminish the risk of repeated massive doses of infection and reduce the incidence of primary infection and reinfection. A health commission sitting in Florence in 1754 reported that "phthisical patients who lived in large airy rooms did not require more than that their rooms should be well cleaned and always purified by widely opened windows; but that stuffy rooms with still air increased the danger to others" (Burrell, 1933).

Susceptibility of Infants

The infant and child are more susceptible than adults, and the younger the patient the greater the risk. Newsholme (1926) says one of the most important problems is how to minimize the risks of infection in the first five years, and especially in the first two years. Kayne (1935) points out that both infection and mortality are greater where the contact is with a parent than with a more distant relative; and with the mother more than with the father. This is obviously explained by the more frequent and intimate association with the mother than with any other member of the household, an exception being the tragic event in which a healthy mother leaves the care of her infant mainly to a "nannie" or nurse who unknowingly is infective. The infant lives strictly within the family, whereas older children share their time at school, out-of-doors, and at home; so that if a parent become infectious he or she may or may not infect the older children, but the toddlers are more likely to be infected, and the infant almost certainly will be.

Infection is known to occur at all ages. My youngest case was diagnosed at 8 weeks (and died three days later), another case at 3 months, and recently one at 7 months. Lemaire (1925) found that if contagion arose before 1 year the mortality was 57%, if between 1 and 2½ years it was 1.66%. Nassau and Zweig (1925) found that of twenty

*Address given to the Nottingham Medico-Chirurgical Society on Nov. 17, 1948.

infants infected during the first three months all died; of sixteen infected during the second three months 18.75% died, and of thirteen infected between six and twelve months 3.8% died. Asserson (1927) states that of those infected under 12 months 15% died, and of those between 1 and 2 years 2.6% died. These figures show in general that tuberculosis in young infants carries a heavy mortality, but the chances of survival increase rapidly thereafter.

Mode of Infection

It is now generally accepted that the majority of cases of childhood tuberculosis are the result of human contact. It is certain that almost every case of intrathoracic tuberculosis is of the human type, and all but a few of the cases of abdominal, bone, and joint disease are of bovine origin.

Human Contacts

Infection of infants and children may arise as a consequence of the intimacy of the home environment. In the case of the child diagnosed at 8 weeks the post-mortem examination showed the condition to have been tuberculosis with extensive caseation of the tracheo-bronchial glands. The contact was proved to be the grandmother, who had come into the household to assist her daughter during her confinement by undertaking her household duties and "looking after" the newborn infant. The grandmother was found to have fibroid phthisis with a positive sputum. You will in this connexion remember that Madame Curie (1938) never understood as a child why her mother would never kiss her; she realized afterwards that her mother was consumptive and later appreciated to the full the loving restraint exercised.

Blacklock (1947), in a series of 144 cases of tuberculous meningitis, showed that the source of infection was most often the mother: mother 44%, father 22%, sister 21%, brother 20%, aunt 12%, uncle 6%, grandmother 2%, grandfather 6%, others 11%. What is true of tuberculous meningitis applies to other forms. It is inadequately realized that tuberculous meningitis arises just as effectively from a focus in the chest as from one in the abdomen, and, as there is much more intrathoracic tuberculous infection than abdominal, the majority of cases of tuberculous meningitis are found to be of human origin. McMurray (1944) showed in my series of 24 cases that 72% were human type organisms.

The explanation of the tuberculous mother's complicity is that the infant is exposed by its close contact during nursing, fondling, dressing, etc., to the risk of inhaling a massive dose of bacilli and to repeated infections. Where the mother's position is superseded or supplanted by a grandmother, an aunt, or a domestic who is infectious, the risk is obviously an equal one. In the case of older infants and young children it should be remembered that school-teachers—not forgetting nursery-school and kindergarten teachers—who are the victims of the disease may infect their pupils. The Report of the Children's Committee of the Joint Tuberculosis Council (1948) gives the example of a sputum-positive schoolmaster in whose class two children died of tuberculous meningitis and 45% of the children were found to be tuberculin-positive: in another instance a teacher with positive sputum was probably responsible for two deaths from meningitis. I have a number of records where the domestic servant (and in one case a children's nurse) was entirely unsuspected of having phthisis until tuberculosis was diagnosed in a child in the family and the unsuspected disease discovered.

Indirect infection of children from the inhalation of dust containing dried tuberculous sputum, due to the careless disposal of this highly infectious material, is difficult to prove. But it behoves the infected adult to be considerate of others,