he had fully recovered. Since that date he had been well except for occasional conjunctivitis and a very slight urethral discharge. There was no previous history of dysentery or venereal disease other than the above.

On Aug. 13 he sought advice on account of a slight urethral discharge of one week's duration. A smear showed pus cells but no gonococci; he was given sulphathiazole 5 g. daily for five days. On the following day he fell and injured his left knee. When he returned on Aug. 20 he showed an improvement in the urethral discharge, but a marked effusion was present in the left knee; moreover, there was a severe bilateral conjunctivitis of two days' and a balanitis of six weeks' duration.

He was admitted to hospital and given 200.000 units of penicillin in five three-hourly doses of 40,000 units. On the 21st his urethral smear continued to show many pus cells, while the urine was hazy in two glasses. The blood Wassermann and Kahn tests and the gonococcal complement-fixation test were negative; blood count: haemoglobin, 115%; red cells, 5,490,000; white cells, 10,600; polymorphs 61%, lymphocytes 35%, mononuclears 4%; urine: albumin, sugar, ketones, bile negative; stool: no pathogens found in culture; blood sedimentation rate, 6 mm. in 1 hour. A skiagram of the knee revealed no bone injury.

On the following day urethral and conjunctival smears were taken for special examination and the left knee was aspirated. Gold therapy with myocrisin was then begun. Temperature recordings, daily urine examination for albumin, and skin inspection and blood counts twice a week did not reveal any toxic reactions. The dates and amounts of the myocrisin, together with the relevant sedimentation rates, are as follows:

Date	B.S.R.	Myocrisin
Aug. 22	12 mm. in 1 hour	0·01 g.
„ 28	„ —	0·02 g.
Sept. 2	—	0·02 g.
„ 7	3 mm. in 1 hour	0·025 g.
„ 13	4 „ „	0·025 g.
„ 19	5 „ „	0·05 g.
„ 25	—	0·05 g.
	Total in 5 weeks:	0·2 g.

The eyes were treated locally with saline washes and resolution was rapid, both becoming normal within 72 hours. The balanitis showed steady improvement and had quite gone by Sept. 2. The urine cleared within three days, but a morning urethral discharge persisted for three and a half weeks. The knee filled up again after the initial tapping, but had begun to subside when a second aspiration was performed on Sept. 18, after which time it did not refill.

On the 19th Flexner vaccine was instilled into the right eye without result (see below). The patient was discharged to duty on Sept. 25. There was no improvement with penicillin, though with gold therapy it was steady and maintained.

The Eye Test

The possible dysenteric origin of some cases of Reiter's syndrome has recently received considerable attention. Wood (1946) states that he succeeded in reproducing the sterile conjunctivitis in three cases by instilling a drop of Flexner vaccine into the eye. It was decided to apply this test to these cases. Flexner bacteria (mixed I–VI) were killed by heat at 55° C., and a suspension of 3,000 million organisms per ml. was kindly prepared by Lieut.-Col. Archer, R.A.M.C., to whom due acknowledgment is given. It produced no reaction in three rabbits or in two human controls.

A drop of this material was placed in the right eye in the above two cases and in a third case which had previously shown polyarthritis, urethritis, and conjunctivitis and had apparently recovered. No reaction was noted in any of these cases. None of these patients' sera showed any agglutination with strains of dysentery bacilli of the Shiga type. It may be of interest to note that cases of non-specific urethritis, arthritis, and conjunctivitis are not uncommon in West Africans among whom Shiga dysentery is exceptionally rare.

Discussion

Although the hypertherm is probably the most satisfactory treatment for patients with Reiter's syndrome, gold salts appear capable of producing a satisfactory cure. It is, however, unwise to assume from the therapeutic action of a particular drug in different diseases that the causative organisms of these diseases are necessarily related. Antimony salts, for instance, have a curative action in schistosomiasis and in infections due to *Leishmania* and trypanosomes. Penicillin is known to be valueless in diseases due to pleuropneumonia-like organisms, but as streptomycin has been found to be curative in rodent arthritis due to similar organisms (Powell *et al.*, 1946) its action in patients with Reiter's syndrome would be of interest. Further investigation of patients with Reiter's syndrome for the presence of pleuropneumonia-like organisms is desirable.

Conclusions

Apart from the production of arthritis in a single mouse by the injection of joint fluid from one patient, an investigation of two patients with Reiter's syndrome was negative for the presence of pleuropneumonia-like organisms.

Gold salts were curative in two patients with Reiter's syndrome not associated with bacillary dysentery, while penicillin and sulphonamides were of little value.

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SCRUB TYPHUS VACCINE

ITS EFFECT ON SIXTEEN CASES INCUBATING THE DISEASE

BY

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On account of the high incidence of scrub typhus in Mandalay during the autumn of 1945 the D.M.S., Twelfth Army, decided that all troops in that area should receive scrub typhus prophylactic vaccine. Seven and a half litres of the special vaccine prepared in "Operation Tyburn" at the Wellcome Veterinary Research Station, Frant, Sussex (Buckland *et al.*, 1945), was employed in 1-ml. doses. on three occasions at weekly intervals. All the inoculations were given during November, 1945, and, since this was the month of peak incidence of scrub typhus, local commanding officers were glad to co-operate in arranging inoculation parades.

Initially the intention was to inoculate half of each company so that the remainder would serve as controls in the evaluation of the efficacy of the vaccine, but the increased incidence and the commanding officers' suspicion that it was something of an experiment resulted in a fresh instruction that all troops should be inoculated. Inoculation produced a slight local tingling lasting five minutes due to the formalin vehicle, but no immediate constitutional reaction resulted, though fever was reported in some cases, and these are included among the 16 cases which form the basis of this report. In all 2,500 troops were inoculated with prophylactic vaccine.

It had been suggested that the bite of a mite could produce an eschar whether the trombiculid was infected with rickettsiae or not, so this mass-inoculation programme was made use of to carry out a routine skin examination, in which search was made at the time of the first inoculation for eschar-like sores in all troops. It seems worth recording that, apart from cases which were subsequently shown to be incubating the disease, the presence of an eschar in an otherwise healthy man was not reported.

This paper is concerned solely with the immediate effect of the inoculation upon the course of the disease in 16 men who were inoculated fortuitously during their period of incubation of scrub typhus; the question of its prophylactic efficacy in respect of the remainder of the 2,500 inoculated had to be left to a successor.

Post-inoculation Cases of Scrub Typhus

All 16 cases had received one or more inoculations of the prophylactic vaccine between Nov. 10 and 18, 1945, and were received into hospital between Nov. 12 and 20. Eight had come from one unit and four from another unit in an adjacent site at Fort Dufferin, Mandalay. These 12 cases, arising apparently out of their inoculation a few days previously, not unnaturally gave rise to some alarm among the officers and other ranks (who totalled 450). Among the victims were the commanding officer and the second-in-command of the unit most seriously affected. Careful examination of the cases showed that 14 of the 16 had typical eschars with lymphadenitis of related glands. This was most fortunate for me, for anxious and irate senior officers had to be faced with a very definite opinion as to whether any blame might attach to the inoculations which all area troops were in process of receiving. A reasoned explanation was accepted and the inoculation scheme proceeded with. All the cases were subsequently proved by Weil-Felix agglutination tests.

Of the 16 cases, 12 had received one inoculation of 1 ml. of prophylactic vaccine before the development of symptoms, two had received two weekly injections of 1 ml., and two had, during and overlapping the incubation period, received three injections of 1 ml. of the vaccine.

Classification into Four Groups

For descriptive purposes the cases have been divided arbitrarily into four groups, according to the number of doses of vaccine administered and the length of interval between the administration and the development of symptoms, since these two factors appeared to modify the illness. Group I cases received 1 ml. of vaccine less than three days before onset of symptoms; Group II cases received 1 ml. three or more days before onset of symptoms; Group III cases received two 1-ml. doses during or overlapping their incubation period; and Group IV cases three 1-ml. doses during or overlapping the incubation period. A sample case history is given for each group, and particulars of the others will be found in the Tables.

Group I: Case 1

A British officer aged 34 was admitted on Nov. 18, 1945, complaining of not feeling fit since inoculation with scrub typhus vaccine on Nov. 12, and expressing indignation that he should have thus been made ill. Only slight headache had been felt and he had worked until the 17th. He was unwilling at this point to go to hospital, but was finally persuaded to do so.

On examination an eschar was found on the scrotum, with enlarged, tender, rubbery left inguinal glands. The eschar was known to have been present since Nov. 14, and was the only physical sign of disease. The blood pressure was 125/75 mm. Hg. The white blood cells numbered 5,000 per c.mm. (polymorphs, 52%; lymphocytes, 44%; monocytes, 4%; eosinophils, nil).

During the first week of illness he remained bright, ate well, and read technical literature; he was slightly peevish, and had

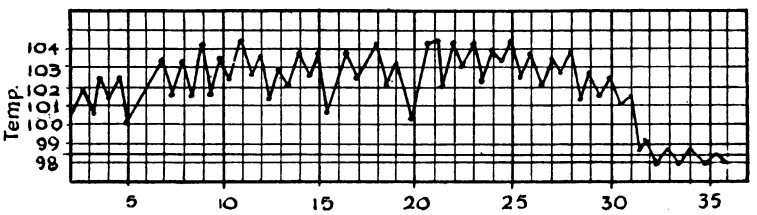

FIG. 1.—Group I, Case 1.

a gently swinging temperature of 101°–102° F. (38.3°–38.9° C.) daily. No further sign appeared. On the seventh day the OX K titre was 1:80 and the blood pressure 100/60 mm. Hg. In the second week the general condition remained good, he continued to sit up to eat and read; a few basal rhonchi and a slight cough appeared. Fever was now maintained at 102°–104° F. (38.9°–40° C.), and the OX K titre was 1:320. The spleen was one fingerbreadth increased, the liver was just palpable, and cerebration was normal. The third week brought no detectable change in his condition, apart from an appearance of tiredness, though the fever continued to swing between 101° and 104° F. (38.3° and 40° C.) daily. Slight insomnia was added to the headache and cough, the OX K titre was 1:1,280, and the blood pressure was 120/70 mm. Hg. Deep reflexes were absent and superficial reflexes feebly present. The white cells numbered 4,200 per c.mm. (polymorphs, 65%; lymphocytes, 23%; eosinophils, 12%). The spleen was one fingerbreadth increased and the liver just palpable.

Between the 22nd and 26th days of illness a few toxic signs appeared—ashen pallor with the smallest degree of cyanosis, extrasystoles, and irritability. He continued to sit up in bed and enjoyed his meals, though he found that he could read only "light" literature. There was no loss in weight, and even after all this time he stated on questioning that he felt quite well, though he looked a shade anxious. This mild course was maintained until fever settled by lysis on the thirty-second day of illness. On the 24th day a small degree of tympanites was noted, and this persisted for three days. At the conclusion of the fever the spleen and the liver were one fingerbreadth increased. The respiratory, gastro-intestinal, and genito-urinary systems were normal. Deep reflexes were increased and the circulatory system was normal. Two months' convalescence was granted, and this passed without incident.

Group II: Case 9

An African aged 25 was admitted on Nov. 19, 1945, giving a history of not feeling fit since Nov. 17. He had been inoculated with 1 ml. of scrub typhus vaccine on Nov. 10. He complained of severe headache, retro-orbital and retrosternal pain, and had a slight cough with mucopurulent sputum.

On examination the throat was injected, the eyes were suffused, and a few rales and rhonchi were heard in the upper zones of both lungs. The blood pressure was 100/70 mm. Hg. There was slight epigastric tenderness. An eschar was noted

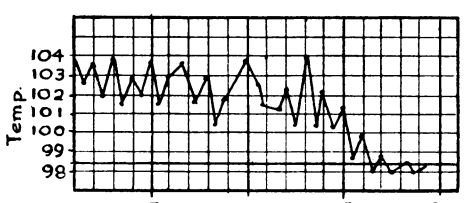

FIG. 2.—Group II, Case 9.

on the anterior wall of the left axilla, and the related lymphatic glands were greatly enlarged, rubbery, and tender. Other lymph nodes, especially the posterior cervical, were also enlarged and tender. The spleen was one fingerbreadth increased; the liver was one fingerbreadth increased and tender. No rash

was seen. Fever rose within 48 hours to 104° F. (40° C.) daily, never falling to normal at any time. Deep and superficial reflexes were normal. The urine was normal. The patient lay quietly in bed and had none of the usual buoyancy of the West African. The white cell count was 5,600 (polymorphs 58% ; lymphocytes, 38% ; monocytes, 2% ; eosinophils, 2%).

During the first week all the above-mentioned signs and symptoms increased in intensity. Bronchitis became severe and headache most intense. The blood pressure remained at 100/70 mm. Hg, and the pulse rate did not exceed 110. He lay quietly in bed obviously frightened. On the seventh day of illness his OX K titre was 1:40, his deep reflexes were abolished, and he was complaining of mid-abdominal pain. In the second week the fever continued unabated with continuation of headache and bronchitic signs. To these was now added dyspnoea with a respiratory rate of 46 per minute. The blood pressure dropped to 95/50 mm. Hg. The urinary chlorides fell to 3 g. per litre. By now the spleen was increased 2½ and the liver 1½ fingerbreadths. Further complaints were of pain in the right elbow-joint and pain with swelling in both knee-joints. Acute laryngitis with complete aphonia developed, and some slight delirium with maniacal behaviour occurred ; this had to be treated with intramuscular paraldehyde. The OX K titre was now 1 : 80. On the 15th day resolution started and fever settled by lysis, with sudden cessation of symptoms and gradual clearing of all physical signs. Deep reflexes returned and became exaggerated, the blood pressure rose to 110/70 mm. Hg, the white cell count was 6,500 (polymorphs, 46% ; lymphocytes, 48% ; monocytes, 4%; and eosinophils, 2%). The spleen and liver were palpable and two fingerbreadths increased ; the OX K titre had risen to 1: 320. Recovery was very rapid and he was fit for transfer to another hospital on the 18th day of illness.

TABLE I.—*General Clinical Findings*

Case No.		Race	Date of Inoculation	Date of Onset	Site of Eschar	Glands Involved	Rash	Respiratory	Abdominal	Deafness	Days of Fever
Group I	1	B.O.	12th	12th	Scrotum	Inguinal	Nil	Bronchitis	Tympanites (21)	Slight late	32
	2	I.O.	12th	14th	Penis	,,	Morbilliform	Bronchopneumonia	,, ,,	Late marked	34
	3	I.	14th	14th	Rt. lumbar	,,	Nil	Nil	Nil	Nil	17
	4	B.	12th	14th	Lt. flank	,,	Morbilliform	Mild bronchitis	Tumid	Slight	26
	7	I.	14th	16th	Nil	General	Nil	,,	Tympanites (7)	,,	12
	11	A.	10th	10th	Scrotum	Inguinal	,,	Bronchitis	Slight tympanites (14)	Nil	14
	12	A.	10th	8th	Lt. shoulder	Axilla	,,	,,	Tympanites (19)	,,	18
Group II	5	I.	12th	16th	Rt. ear	Cervical	,,	Slight bronchopneumonia	,, (11)	,,	15
	6	I.	14th	19th	Nil	General	,,	Slight bronchitis	,, (10)	,,	12
	8	I.	14th	19th	Rt. flank	Inguinal	,,	Bronchitis	Slight tympanites (14)	,,	17
	9	A.	10th	17th	Lt. axilla	Axilla	,,	Nil	Nil	,,	16
	10	A.	10th	16th	Rt. axilla	,,	,,	Slight bronchitis	,,	Slight	13
Group III	13	I.	14th, 21st	21st	Penis	Inguinal	,,	Nil	,,	Nil	12
	14	I.	18th, 25th	23rd	Scrotum	,,	,,	,,	Slight tympanites	,,	30
Group IV	15	I.	6th, 13th, 20th	22nd	Rt. axilla	Axilla	,,	,,	Nil	,,	10
	16	I.	12th, 19th, 26th	26th	Rt. groin	Inguinal	,,	,,	,,	,,	9

B = British. O = Officer. I = Indian. A = African. No. in parentheses = Day of onset of tympanites.

TABLE II.—*Agglutinations—OX K*

Case No.		7th Day	14th Day	21st Day	Fever in Days	Eschar	Toxicity
Group I	1 ..	80	320	1,280	32	+	Late, mild
	2 ..	Nil	40	1,280	34	+	Late, severe
	3 ..	40	80	320	17	+	Slight
	4 ..	Nil	80	1,280	26	+	,,
	7 ..	40	160	320	12	−	Toxic, early
	11 ..	Nil	80	160	14	+	Moderate, early
	12 ..	40	160	320	18	+	,,
Group II	5 ..	40	80	640	15	+	Moderate
	6 ..	80	1,280	—	12	−	,,
	8 ..	40	80	320	17	+	Slight
	9 ..	40	80	320	16	+	Toxic, early
	10 ..	40	80	640	13	+	Slight
Group III	13 ..	40	80	Lost	12	+	Very slight
	14 ..	40	80	,,	30	+	,,
Group IV	15 ..	40	80	,,	10	+	Absent
	16 ..	40	160	—	9	+	,,

Group III : Case 13

An Indian aged 30 was admitted on Nov. 28. 1945, complaining of slight headache and chilliness since Nov. 21. He had been inoculated with 1 ml. of scrub typhus vaccine on Nov. 14 and 21. On examination on the seventh day of disease the only abnormalities noted were an eschar on the ventral surface of the penis, with related groin lymphadenitis, and slight injection of the fauces. No rash was seen. The blood pressure was 110/70 mm. Hg. Deep and superficial reflexes were all present and normal. The spleen was increased two fingerbreadths, the liver was just palpable. The white cell count was 6,200 (polymorphs, 65%; lymphocytes, 32%; and monocytes, 3%). The OX K titre on the seventh day was 1:40. The fever swung between 101° and 103° F. (38.3° and 39.4° C.) daily. Throughout the illness he ate well, slept well, and sat up in bed to read, making very little complaint of discomfort. On the 12th day of illness lysis occurred with cessation of all symptoms. On the 14th day the spleen and liver were increased one fingerbreadth, but on the 21st day the spleen was just palpable and the liver was still one fingerbreadth increased. The blood pressure on the 12th day was 100/65 mm., on the 16th day 110/70 mm., and on the 21st day 115/80 mm. Hg. Deep reflexes were feeble on the 12th but were brisk by the 21st day. By the 14th day the OX K titre was 1:80. (Further results were lost in a laboratory fire.) On the 14th day the white cell count was 4,500 (polymorphs, 50%; lymphocytes, 45%; monocytes, 2%; and eosinophils, 3%). Full recovery was rapid.

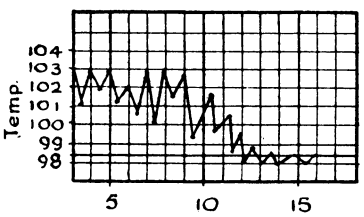

FIG. 3.—Group III, Case 13.

Group IV : Case 16

An Indian Viceroy's commissioned officer aged 25 was admitted on Nov. 30, 1945, complaining of slight fever and frontal headache of four days' duration. Inoculations had been given on Nov. 12, 19, and 26. On examination an eschar was found in the right groin, with accompanying lymphadenitis. No rash was seen. The temperature on admission was swinging between 102° and 104° F. (38.9° and 40° C.), but immediately thereafter dropped to 99°–102° F. (37.2°–38.9° C.) for the next three days, followed by resolution by lysis starting by the ninth

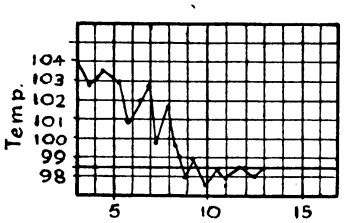

FIG. 4.—Group IV, Case 16.

and completely normal by the tenth day. This was the shortest fever of all 16 inoculated cases and also the shortest fever of the entire series of 130 cases. The eyes were slightly suffused, the spleen was just palpable, the liver was not palpable on the sixth day, and both were unchanged on the tenth day. All other systems were found to be normal.

On the seventh day the blood pressure was 90/65 mm. and on the tenth day 95/70 mm. Hg. The deep reflexes were unaltered throughout. The white cell count on the seventh day was 7,000 (polymorphs, 52%; lymphocytes, 40%; monocytes, 8%). It was difficult to persuade the patient to remain in bed, since he maintained throughout that he felt perfectly fit; he ate and slept well. The Weil-Felix reaction was as follows:

7th day	...	OX K,	1:40	...	OX 19,	1:80	...	OX 2, nil
10th „	...	„	1:80	...	„	1:80	...	„ nil
14th „	...	„	1:160	...	„	1:40	...	„ nil

The blood pressure rose on the 14th day to 105/75 mm. Hg. All fever, signs, and symptoms had cleared by the 12th day of illness, and the patient, at his own urgent request, was not sent to convalescence, as was the normal procedure, but was returned to his unit on the 14th day, with recommendation for 10 days' "excused duty."

Comment

Group I.—The outstanding modifications of the usual course of the disease appeared to be: (1) A considerable lengthening of the fever (average 21.5 days, as against an average for the complete series of 17.38 days and for Group II of 14.5 days). (2) A delay in the development of toxicity in some cases and its relative diminution in others. This latter was a remarkable feature in view of the long fevers (32 days in Case 1, 34 days in Case 2, and 26 days in Case 4) and the relatively high temperature reached daily—103°–104° F. (39.4°–40° C.). It was odd to see all but Case 2 able to sit up in bed to read and to enjoy meals, and to find that, with the same exception, headache, retro-orbital pain, and respiratory signs, when present, were minimal. Of the 16 patients, No. 2 alone showed loss of weight, and he and No. 7 both had a circulatory collapse, the former on the 21st and the latter on the 12th day. The fever was prolonged in Case 12 by a coincident amoebic hepatitis.

Group II.—These cases seemed to be less affected in their general course than those of other groups. It did seem, however, that the course of the illness was probably shortened. The average length of fever in this group was 14.5 days, as against 17.38 days for the entire series of 130 cases and 21.5 days in Group I. All five cases were moderately toxic; four of them showed eschars.

Group III.—These two cases shared the common feature that neither patient was really ill; both sat up in bed to read and eat, and neither had any complications.

Group IV.—The two cases of this group were so mild that had there not been eschars and lymphadenitis to confirm the diagnosis it would have been in doubt, especially so since the final agglutinations were lost by fire and Case 15 reached only a titre of OX K 1 : 80 and Case 16 1 : 160. Neither of these patients really felt ill at all, the fever subsiding in 10 and 9 days respectively, the former being sent to convalescence on the 16th and the latter to his unit on the 14th day.

Summary

The effect is reported of scrub typhus prophylactic vaccine on 16 men who were at that time in the process of incubating the disease.

Of these only one (Case 2) became seriously ill; four others became slightly toxic at some stage of the disease. This compares most favourably with the mortality rate of 7% for the entire series of 130 uninoculated cases and the fact that of these quite 50% were severely toxic.

Inoculation of 1 ml. of scrub typhus prophylactic vaccine seemed to have the effect of lengthening the fever very considerably while materially reducing and delaying the onset of toxicity.

Inoculation of two doses of 1 ml. produced yet milder cases, and inoculation of three 1-ml. doses gave the mildest of all cases seen.

The presence of an eschar in the high proportion of 14 out of 16 cases was most helpful in diagnosis.

The general clinical features are set out in tabular form.

I wish to thank Brig. Harris and Brig. Macnamara, Twelfth Army, for their encouragement and for permission to publish findings; also Lieut.-Col. C. E. Moorhead and Lieut.-Col. P. O'Shea, R.A.M.C., my commanding officers.

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PROGNOSIS OF PRIMARY PLEURISY WITH EFFUSION

BY

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Pleurisy with effusion, when its cause is otherwise in doubt, is now usually believed to be of tuberculous aetiology. It is sometimes followed by frank tuberculosis in the lungs or other organs, but the incidence of such secondary disease has never been statistically established. Published figures range from 5% (Helms, 1934) to 66% (Borelius, 1933), and a recent review by Robson (1944) shows that this wide divergence is due to three factors: (1) A clear definition is not always made between whether parenchymal tuberculosis was or was not already in evidence at the time of the initial pleurisy; indeed, many studies do not include satisfactory *x*-ray diagnosis. (2) Though examination of a group of patients after a period of years may show a certain proportion to have developed phthisis, it cannot establish the date of onset of such disease. This method, on which most investigators have relied, must also miss a proportion of the lesions which arise and resolve spontaneously during the intervening period. (3) Patients lost sight of must be statistically evalued; they vitiate the results in proportion to their number, and this has generally been high.

The present study is based on 233 patients, the sum-total of all cases referred to the Ealing Chest Clinic in the years 1937–44 on account of primary pleurisy with effusion. Of these, 43 were judged to have *x*-ray evidence of parenchymal pulmonary tuberculosis at the outset and are therefore excluded. The remaining 190 were kept under constant observation at this clinic, with regular *x*-ray examination, for maximum periods up to the end of 1945, with the following exceptions: one patient was lost sight of after two and a half years; eight ceased to attend after one year and five after two years owing to removal from the district, etc., but were known to be alive, well, and at work at the end of the maximum observation period. Of these 190 patients 40 have so far developed secondary tuberculosis, and six have died.

It is clear from Table I that the relative incidence of secondary tuberculosis was approximately the same in each age group and that case-fatality rates were also evenly distributed. Of the 40 patients 18 were male and 22 female. It was possible to date within a few weeks the onset of the earliest radiological evidence of a pulmonary