TREATMENT OF PRIMARY PULMONARY TUBERCULOSIS WITH P.A.S.*

BY

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Lehmann (1946) was the first to use *para*-aminosalicylic acid (P.A.S.) in the treatment of patients suffering from tuberculosis, and during the succeeding six years many workers have employed this drug in a variety of tuberculous conditions. P.A.S., combined with streptomycin, has been used successfully in miliary tuberculosis and tuberculous meningitis, conditions which result from dissemination of tubercle bacilli from a primary tuberculous complex, but as yet there have been few reports of the treatment of primary tuberculosis with P.A.S. Scarzella (1949) used it in eight children suffering from primary tuberculosis. Debré *et al.* (1950) treated two children aged 14 months and 11½ years, Lesné *et al.* (1951) 28 children aged 2 to 6 years, and Haggemüller (1951) 72 children aged 2 to 15 years. These workers claimed that P.A.S. seemed to be of value when judged by the return of temperature and sedimentation rate to normal, by gain in weight, and by improvement in the radiological appearances. It is, however, the experience of workers in this field that when children suffering from primary tuberculosis are removed from contact with adults who have open pulmonary tuberculosis and are given adequate rest and a suitable diet, progress is usually satisfactory. The assertion that P.A.S. is of value in primary tuberculosis may be justifiably questioned because in none of the above-mentioned papers was a control group of children of the same age and with identical hospital care studied.

The present investigation was planned to assess more critically the value of P.A.S. in primary tuberculosis. The children were seen during 1951 in Liverpool, where the mortality rate for tuberculosis is higher than the average for England and Wales, and the incidence of primary tuberculosis provides a large enough number of cases to be studied in one centre.

Plan of Investigation

Most of the children were admitted to Alder Hey Children's Hospital, Liverpool, where they were at rest in bed for a period of three months and received a diet adequate in protein, calories, and vitamins. On admission the following investigations were undertaken: tuberculin test, gastric lavage, full blood count, sedimentation rate, x-ray film of the chest, lumbar puncture, and weight. Subsequently the white-cell count and sedimentation rate were evaluated every two weeks, and lumbar puncture was performed at fortnightly intervals during the first six weeks and monthly thereafter. X-ray films of the chest were taken every month, and the children were weighed at weekly intervals.

Sixty-nine patients were studied, and for the purpose of this investigation they were divided into four age groups (see Table I). Alternate patients (trial group) in each age

TABLE I.—Age Grouping of 69 Patients with Primary Tuberculosis

Age Group	Trial Group	Control Group
Under 1 year	5	5
1 and 2 years	9	8
3 to 6	14	15
7 to 15	7	6
Total	35	34

group received 1 g. of P.A.S.* per lb. (2.2 g. per kg.) weight daily in divided doses two-hourly, for 12 weeks, while the remaining cases were given no specific chemotherapy (control group).

Table II records the clinical details of the trial and control groups, and shows that in most respects the two groups are comparable, though tubercle bacilli were isolated on gastric lavage from rather more patients in the control group.

In Table III the estimated duration of the tuberculous process is set out, and this shows that most of the patients had suffered from the disease for three months or less. This

TABLE II.—Diagnostic Features in 69 Patients with Pulmonary Tuberculosis

	Trial Group (35)	Control Group (34)
Contact history	25 (70%)	24 (70%)
Mantoux 1 in 10,000	20	14
Mantoux 1 in 1,000	13	18
Jelly test	2	2
Radiograph:		
Focus in L.U.L.	4	3
" L.L.L.	7	10
Left hilar gland	1	—
" R.U.L.	4	6
" R.M.L.	3	2
" R.L.L.	15	12
Right hilar gland	1	1
Positive gastric lavage ..	13 (37%)	17 (50%)

TABLE III.—Estimated Age of Primary Focus

	Trial Group (35)	Control Group (34)
1 month	12	14
2 months	6	6
3	7	7
4	3	3
5	1	—
6	1	—
Unknown	5	4

assessment was made on the time of appearance of erythema nodosum, phlyctenular conjunctivitis, and Mantoux conversion, and by a detailed investigation of the contact history.

Assessment of Progress

The progress of these cases cannot be estimated by any one test, and in this investigation six criteria were used—namely, clinical impression (based on appetite, vitality, temperature, pulse rate), serial blood counts, serial sedimentation rates, weight gain, serial chest x-ray films, and incidence of complications.

The clinical impression was that progress was equally satisfactory in both trial and control groups. In the majority of patients the temperature was normal throughout or it returned to normal within two weeks of admission. Appetite was good in most patients, and persistent tachycardia was not recorded.

White-cell counts and sedimentation rates were estimated on admission and at fortnightly intervals thereafter. The

*The preparation of P.A.S. used throughout this investigation was "paramisan sodium," kindly supplied by Herts Pharmaceuticals Ltd. It was given in the following mixture:

P.A.S.	1 g.
Liquid extract of liquorice or syrup of	
orange	5 minims (0.3 ml.)
Water	ad 1 dr. (3.5 ml.)

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general trend in all cases was towards normal figures, and, although there was a wide degree of scatter, no significant difference was found in the control and trial groups. The children were weighed on admission and at weekly intervals, and the percentage weight gain above the admission weight in each of the four age divisions was compared in the control and trial groups. No significant difference was shown. The x-ray appearances in the trial and control groups were compared one, two, three, and six months after admission to hospital (see Chart). Decrease in the

Radiological appearances after one, two, three, and six months.
T, Trial group; C, Control group

TABLE IV.—Complications

Age	Trial Group	Control Group
Under 1 year	1 patient: stridor, associated with collapse R.U.L. and emphysema R.L.L. 1 patient: vomiting after PAS 1 patient: D. and V.	1 patient: tuberculous meningitis at 4 months → death at 6 months 1 patient: tonsillitis 1 patient: D. and V.
1 to 2 years	1 patient: glandular pressure → collapse R.L.L. 1 patient: renal tuberculosis at 4 months	1 patient: tuberculous meningitis at 4 months → death at 7 months 1 patient: extension of primary focus following measles and whooping-cough 1 patient: Sonne dysentery
3 to 6 years	1 patient: collapse of R.M.L. 1 patient: ascitic tuberculous peritonitis at 3 months 1 patient: PAS sensitivity—rash, oedema	1 patient: miliary spread at 1 month
7 to 15 years	1 patient: collapse R.M.L. 1 patient: occasional vomiting with PAS	

x-ray shadow is indicated by plus 1, 2, or 3 (plus 3 indicates complete radiological resolution); when the shadow remained unchanged it is recorded as 0, and the extent of increase in size of the shadow is indicated by minus one, two, or three. There appeared to be no difference in radiological progress of trial and control cases using this method of assessment.

Table IV shows the complications encountered. These were of three main types: (1) complications of the tuberculous process, both local in the lung and generalized; (2) those resulting from P.A.S.; and (3) those, such as gastroenteritis, due to hospital cross-infection.

Local lung complications were more common in the trial group. Spread of the disease to the meninges occurred in

two children in the control group, and in spite of treatment with streptomycin and P.A.S. they died. One patient in the control group who developed miliary tuberculosis responded satisfactorily to these drugs. Renal tuberculosis and ascitic tuberculous peritonitis developed in two patients who had received P.A.S. for three months, and both subsequently recovered when streptomycin was given. One child in the trial group developed a generalized scarlatiniform rash and oedema of face, hands, and legs, but these toxic manifestations quickly subsided when P.A.S. was discontinued. In almost all patients the drug was well tolerated, and in only two patients were nausea and vomiting troublesome.

Discussion

There is general agreement with Wallgren (1945) that the mortality rate from tuberculosis is higher in infants and young children. In his series the mortality rate was 35.9% in the age group 0 to 1 year, 15.6% in the group 1 to 3 years, 4.4% in children from 3 to 7 years, and 0.8% in those aged 7 to 16 years.

Furthermore, the serious complications such as tuberculous meningitis usually arise within three months of the development of the primary complex. It is therefore not surprising that the two patients in the present investigation who died from tuberculous meningitis were under 3 years of age. In the children under the age of 3 years there was no obvious difference in the course of the disease in the trial and control groups when judged by clinical response, white-cell count, sedimentation rate, weight gain, and serial chest x-ray films. The serious complications, however, did arise in the control group, but even in the trial group one child developed renal tuberculosis and one developed tuberculous peritonitis.

Debré (1951) considers that, because primary tuberculosis in children under 2 years of age is likely to be severe, since early detection of general dissemination is difficult, and because tuberculous meningitis has a bad prognosis, streptomycin and P.A.S. should be given to all patients with primary tuberculosis in this age group. There is no doubt that as a general principle young children with primary tuberculosis should be under strict observation, and that early detection of complications may be possible by regular examination of the optic fundi for choroidal tubercles, routine lumbar punctures at intervals of not more than two weeks, and frequent x-ray films of the chest. Streptomycin may then be reserved for the treatment of these complications. A further controlled investigation is being carried out at the present time to assess the value of P.A.S. combined with streptomycin in children under the age of 3 years, but the number of cases so far treated is too few to assess the value of combined therapy.

The dosage of P.A.S. used in this investigation (0.5 g. per lb. (1.1 g. per kg.) per day) is higher than that given by Debré *et al.* (1950), Haggemüller (1951), and Lesné *et al.* (1951); their patients received approximately 0.3 g. per lb. (0.66 g. per kg.) per day, and it may be thought that the dosage used in the present cases was excessive, but the intention was to maintain a minimum blood level of about 8 mg. of P.A.S. per 100 ml. Lehmann (1946) recommended a level of up to 7 mg. per 100 ml., and Dempsey and Logg (1947) suggested 10 mg. per 100 ml. Blood P.A.S. levels were estimated in all our cases half an hour and two hours after the ingestion of the drug, and wide variations were found in the same patient on different occasions, but the average blood level at half an hour was 12.5 mg. per 100 ml. and at two hours (immediately before the next dose of P.A.S. was given) 7.5 mg. per 100 ml. Almost all the 35 patients tolerated this dosage, and in only one child did a generalized rash and oedema arise.

Electrocardiograms were taken on a number of patients, but no evidence of potassium deficiency (Cayley, 1950) was found. No other toxic manifestation such as bone-marrow depression, hypothrombinaemia, liver damage, or renal damage were observed in this series.

Summary and Conclusions

Sixty-nine children with primary tuberculosis were studied in Liverpool during 1951. Of these, 35 were given P.A.S. for a period of three months, and 34 were given the same general treatment but without P.A.S. When judged by clinical progress, white-cell count, sedimentation rate, weight gain, and serial chest x-ray films, there seemed to be no benefit from P.A.S. therapy. The severe complications occurred in children under the age of 4 years who did not receive P.A.S. Treatment with streptomycin and P.A.S. of young children with primary tuberculosis is discussed.

P.A.S. seems to be most useful in acute exudative tuberculosis (Marsh, 1952), and its value is limited in fibrous and caseous disease. In primary tuberculosis the most striking pathological feature is caseation in the regional lymphatic glands, and the primary focus in the lung is often small. It is therefore not surprising that P.A.S. has not caused a dramatic improvement in patients with primary tuberculosis.

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INCIDENCE OF BLACK TONGUE IN ANTIBIOTIC TREATMENT

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Black tongue (brown tongue, glossophytia, melanoglossia, nigrities linguae) has been described by many authors, but its aetiology is so far unknown. It is usually associated with hypertrophy of the filiform papillae. In cases of extreme hypertrophy there is an accumulation of matted hair-like processes on the surface of the tongue, and the condition is known as black hairy tongue. Heavy smoking, dyspepsia, irradiation, various inflammatory lesions, washing the mouth with hydrogen peroxide, boric acid, silver nitrate, or chromic acid, and the use of certain tooth pastes have been rightly or wrongly blamed for the production of black tongue.

With the introduction of antibiotics into therapeutics black tongue is seen much more often, and is now regarded as one of the side-effects of antibiotic treatment. It was first reported in connexion with treatment with penicillin lozenges (Bedford, 1946; Ellinger and Shattock, 1946b; Ackers, 1947; Cross, 1949; Wolfson, 1949), but it has also been reported after parenteral penicillin therapy (Lahiri, 1947). It was soon noticed that systemic treatment with other antibiotics—for example, aureomycin and chloramphenicol—also pro-

duced this syndrome (Harris, 1950; Phillips, 1950; Wilhelms, 1950; Tomaszewski, 1951a, 1951b).

In this paper an account is given of clinical observations and direct microscopical examination of the tongue scrapings in cases of black tongue associated with antibiotic therapy and in cases of idiopathic black tongue. Very few histological examinations of this condition have so far been reported (Heidingsfeld, 1910; Swinburne, 1939). An attempt was made to ascertain whether there was a common bacterial or fungal factor in these two types of the condition which might be of aetiological significance. The use of antibiotics in the treatment of a few cases of idiopathic black tongue is also described.

Material and Method

Investigations were made in various wards of the Royal Infirmary, Edinburgh, in cases of idiopathic black tongue; patients treated systemically with aureomycin, chloramphenicol, and penicillin; and in healthy volunteers who sucked penicillin, aureomycin, chloramphenicol, and streptomycin lozenges. Scrapings of the surface of the tongue from as far back as possible were taken with a sterile slide, and the material was pressed with another slide in order to obtain an even film. The scrapings were made at intervals of one to three days before, during, and after treatment. The films were examined unstained and after staining with Gram. For the unstained films phase-contrast microscopy was found to be particularly useful.

Black Tongue Occurring During Systemic Treatment with Chloramphenicol, Aureomycin, and Penicillin

In all, 21 cases of black tongue produced by oral administration of chloramphenicol and aureomycin in capsule form were examined. They comprised about 10% of a group of patients treated with these antibiotics. The incidence of black tongue was approximately the same with either treatment. Two cases appearing after the intramuscular administration of penicillin were also studied. The results of the investigations are given in Table I.

TABLE I.—*Microscopical Examination of Black Tongue which Developed in 23 Patients Receiving Systemic Treatment with Antibiotics*

Antibiotic	No. of Cases	Days of Treatment Before Discoloration	Onset of Discoloration		Blochy Cells	Leucocytes
			Absence of Bacterial Flora	Presence of Fungi		
Aureomycin ..	9	5–21 (8)	4	6	5	1
Chloramphenicol ..	12	5–14 (7)	6	7	6	2
Penicillin ..	2	14–18 (16)	—	1	1	1

Figures in parentheses—average.

In most patients no subjective symptoms accompanied the discoloration, which was often first noticed by the doctor. Some patients, however, complained of a feeling of some foreign body or a tickling sensation on the tongue. The discoloration usually appeared after a few days' treatment (average about one week). In one-third of the cases the change in colour was associated with some degree of hypertrophy of the papillae, but in the remainder the papillae were normal or atrophied. In a few cases the number of leucocytes in the scrapings increased. Staining with Gram revealed a few peculiarly marked epithelial cells, the so-called "blochy" cells, in about half of the cases.

These antibiotics exerted a pronounced influence on the bacterial flora of the tongue. In about 40% of cases bacteria were absent when the discoloration appeared. In the others the bacteria were greatly decreased in number and changed in character; but the development of the discoloration was not associated with the presence of any particular type of bacterial flora. Fungi were present in about 60% when the discoloration first appeared, and were invariably monilia.