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

BY

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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		Blotchy 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 "blotchy" 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.

Black Tongue Following the Local Use of Antibiotics in the Mouth

In order to study more closely the action of antibiotics in the causation of black tongue, investigations were also made by applying them direct to the surface of the tongue. Lozenges were used containing penicillin (500 units), aureomycin (5–15 mg.), chloramphenicol (10 mg.), and streptomycin (50 mg.). As a routine 10 lozenges daily were administered for at least one week. In a number of patients dummy lozenges were used in order to determine whether any constituent of the lozenge other than the antibiotic could be responsible for the brown discoloration. In none of the persons taking dummy lozenges was black tongue produced after one week of administration.

Penicillin was mostly used in lozenge form (500 units), but in three cases five drops of a strong aqueous penicillin solution (100,000 units in 1 ml.) were put on the tongue every half to one hour. All three developed black tongue. In one of these three cases discoloration appeared within 24 hours. The details of this part of the investigation are shown in Table II. In most of the cases which followed the

TABLE II.—*Microscopical Examination of Black Tongue which Developed in 18 Patients Receiving Local Treatment with Antibiotics in the Mouth*

Antibiotic	No. of Cases	Days of Treatment Before Discoloration	Onset of Discoloration		Blotchy Cells	Leucocytes
			Absence of Bacterial Flora	Presence of Fungi		
Penicillin	9	1–7 (4)	3	1	3	5
Aureomycin	6	1–4 (3)	6	2	3	4
Chloramphenicol	1	4	1	—	1	1
Streptomycin	2	2–8 (5)	—	1	1	1

Figures in parentheses = average.

local application of these antibiotics, atrophy of the filiform papillae was found. This effect was most noticeable in patients treated with aureomycin. In some the discoloration and shortening of the papillae was only a stage in the development of a red smooth tongue.

The number of leucocytes increased in about half of the cases. "Blotchy" epithelial cells were present in eight cases, but in much greater numbers than were found in the patients treated systemically. As a rule, the brown discoloration appeared after three to five days—rather earlier than in those treated systemically. It started on the back or on the side of the tongue and spread gradually to the front or to the other side. The edges and the tip invariably remained clear. After cessation of treatment the pigmentation disappeared spontaneously in one to three weeks. Its removal could be hastened by vigorous scraping or by painting the tongue with 10% salicylic acid or a weak solution of trichloroacetic acid.

The oral bacterial flora disappeared completely in all patients treated with aureomycin and chloramphenicol and in one-third of those treated with penicillin. Where bacteria persisted they were scanty and changed in character; but no special type of bacteria was common to all. Yeast cells were found in only one-quarter of the cases when discoloration was first noticed.

Investigations on Idiopathic Black Tongue

Investigations of black tongue of antibiotic origin would not be complete without comparison with the idiopathic condition. A group of 16 patients (14 men and 2 women) with idiopathic black tongue were investigated by the method described for the antibiotic group. The majority had marked hypertrophy of the filiform papillae (the so-called black hairy tongue). In three patients brown pigmentation was associated with normal papillae and one case with some degree of atrophy. The colour of these tongues varied from light to dark brown. The discoloration had lasted from a few months to several years.

Idiopathic black tongue was not associated with any particular type of bacterial flora, but a prolific growth of various bacteria could usually be demonstrated. Fungi were present in about 60% of the cases and were invariably monilia. An increased number of leucocytes in the scrapings was noted in four cases. Scanty "blotchy" epithelial cells were seen in two cases only. Idiopathic black tongue differed from that produced by antibiotics by the presence of a comparatively rich bacterial flora and by the hypertrophic condition of the filiform papillae. The more frequent occurrence of fungi in idiopathic black tongue is probably due to the fact that hypertrophied papillae provide an excellent breeding-place for all kinds of microflora.

The results of the histological examination of the material scraped from the tongue will be published elsewhere.

Action of Antibiotics on Idiopathic Black Tongue

It is known from previous investigations (Tomaszewski, 1951a, 1951b) that in the majority of persons antibiotics cause a rapid desquamation of the epithelial cells in the tongue and shortening of the papillae, which leads to denudation, redness, and smoothness of the organ. The present investigation demonstrated that the prolonged local application of antibiotics to the normal tongue could produce first a black tongue and later, with the continuation of treatment, a complete disappearance of the black coating, rendering the tongue red, smooth, and tender. It was therefore thought that antibiotics used locally might diminish the hypertrophic state of the idiopathic black hairy tongue. Experiments were made in six typical cases: in five of them aureomycin lozenges (10 daily) were given for one to three weeks, and in one case penicillin lozenges (12 daily) were given for one week.

By scraping the untreated "hairy tongue" with a slide some portions of the long "hairs" can be removed with difficulty, but it is impossible to scrape off these long filaments entirely. In all six cases after one to three weeks' treatment the brown felt-like overgrowth from the surface of the tongue could be easily scraped off, to the surprise of the patients who had previously tried all kinds of treatment without success. The exposed dorsum of the tongue was red and somewhat tender. It was also noted that the intensity of the brown discoloration increased significantly during the first few days of treatment.

In four cases the therapeutic effect was seemingly permanent, as the hypertrophy and discoloration have not recurred after one year. In two cases (one treated with penicillin lozenges) some hypertrophy of the papillae and slight pigmentation returned after a few weeks.

Discussion

Since the first description of black tongue (Rayer, 1835) a "parasitic" fungus aetiology has been postulated by a number of authors, the culprits being respectively identified as a non-sporulating yeast or torula (Alvarez, 1926), as a streptothrix (Weidman, 1928), as an actinomyces (Thompson and Montgomery, 1929), as a monilia-type yeast (Kennedy and Howles, 1940), as *Penicillium mucor niger* (cit. after Thoma, 1950), and as *Mucor rhizopodiformis* (cit. after Prinz and Greenbaum, 1939). However, an equally large number of investigators have maintained that the presence of spores and mycelium is accidental rather than aetiological (Heidingsfeld, 1910; Price, 1937; Swinburne, 1939; and others). Inoculation experiments have been unsuccessful, and spores similar to those found in black hairy tongue have been found on the normal tongue.

This investigation showed that no special type of bacterial flora was associated with the syndrome of black tongue, whether occurring spontaneously or during antibiotic therapy. Furthermore, the discoloration could develop in the complete absence of bacteria and fungi, as in the cases which followed local application of antibiotics.

As for fungi, these were found only in about 50% of cases at the onset of discoloration, and were all of monilia type. This type could also be seen in patients treated with

antibiotics who had no brown discoloration of the tongue. The results suggest that the so-called "parasitic" theory of black tongue is untenable. They indicate also that the presence of bacteria or fungi is incidental and of no aetiological significance.

It is well known that nicotinic acid deficiency produces the syndrome of black tongue in dogs. A nicotinic acid deficiency following antibiotic treatment has also been suggested as the cause of the discoloration in man (Ellinger and Shattock, 1946b), the deficiency being due to the destructive action of the antibiotics on the intestinal bacterial flora which normally produce nicotinic acid. Cross (1949) showed, however, that nicotinic acid given simultaneously with penicillin does not prevent the occurrence of black tongue. The rapid development of the discoloration also renders the deficiency theory improbable.

So far nothing is known about the nature of this pigment and about the mechanism of its production, and it is difficult to explain how four antibiotics which are chemically distinct can produce the same effect. It remains to be seen whether the new antibiotics (terramycin, bacitracin, etc.) will exert the same action on the tongue. It is noteworthy that black tongue has also been found in persons treated with sulphanilamide (Burgheim, 1939; Ellinger and Shattock, 1946a).

Treatment of the idiopathic black hairy tongue is of interest. Strange as it may seem at first, the antibiotics which produce black tongue can also cure it. This phenomenon has also been observed by other investigators who used aureomycin lozenges (Cornbleet, Cohen, and Musgrave, 1951). Parenterally administered penicillin had no effect (Kleinert, 1946). Antibiotics do not remove the pigmentation; on the contrary, in the first few days of treatment the brown discoloration deepens appreciably. The "curing" effect of antibiotics is produced by their facilitating the total removal of the "hairs." The disappearance of the growth in a case of black hairy tongue treated with x rays (Gandy, 1952) can probably be explained by the same mechanism.

Summary and Conclusions

Clinical observations and microscopical examinations of the lingual scrapings were made in 57 cases of black tongue: in 23 patients treated systemically with antibiotics; in 18 using antibiotics (penicillin, aureomycin, chloramphenicol, and streptomycin) locally in the mouth; and in 16 suffering from idiopathic black tongue.

Discoloration of the tongue occurred in about 10% of cases treated systemically with chloramphenicol and aureomycin, and generally appeared after one week's treatment.

Local application of antibiotics gave rise to discoloration of the tongue in 40% of persons; it usually appeared in the first three to five days of treatment, in rare instances even in twenty-four hours.

No evidence was found that any special type of bacteria or fungi is of significance in the aetiology of black tongue, whether occurring spontaneously or in response to treatment with antibiotics.

Locally applied antibiotics were used to treat six cases of idiopathic black hairy tongue, with good results. The mechanism of this therapeutic action is discussed.

ADDENDUM.—After the paper was submitted for publication, investigations were carried out with large amounts of terramycin oral drops applied locally. The terramycin was kindly supplied by C. Pfizer and Co., New York. Two out of four healthy volunteers developed black tongue with complete absence of bacteria and fungi.

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RENAL TUMOURS

BY

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This communication is based on a review of the case records of all patients with tumours of the kidney seen at the Postgraduate Medical School, Hammersmith Hospital, in the 12-year period 1939–50. We have accepted the simple classification (Willis, 1948) of (1) epithelial tumours arising in the kidney parenchyma, (2) epithelial tumours arising in the kidney pelvis, and (3) embryonal tumours. In our opinion no useful purpose is served by attempting to distinguish between the hypernephroma of Grawitz (1884) and the renal carcinoma of Ewing (1940).

Incidence

Fifty-one patients with tumours of the kidney were seen in the 12-year period—38 (21 males, 17 females) had carcinoma of the renal parenchyma, 10 (7 males, 3 females) had tumours of the renal pelvis, and 3 (1 male, 2 females) had embryonal tumours. With the exception of six carcinomas of the renal parenchyma all the tumours were examined histologically.

Tumours of the kidney are comparatively rare. In our 700-bed general hospital the average annual incidence of all tumours of the kidney has been roughly four, which is somewhat less than that of carcinoma of the bladder (Shackman, 1947). The relative incidence of the three