increased dosage of digitalis is required for uncontrolled auricular fibrillation, such treatment may be disastrous in the presence of the toxic arrhythmia. Even electrocardiographic analysis may be difficult. Well-defined P waves are helpful, and should be sought in all leads. Oesophageal leads may be necessary (Brown, 1936). Our patients were thought to have auricular fibrillation in the first instance. Cuttings from appropriate leads showing P waves were selected for the figures. An isoelectric interval between successive P waves helps to differentiate paroxysmal auricular tachycardia with auriculo-ventricular block from auricular flutter. Such electrocardiographic diagnoses as "impure flutter" and "impure fibrillation" should be regarded with suspicion, especially if the patient is receiving digitalis. It is doubtful if they have any fundamental meaning, and they may conceal the serious disturbance of auricular rhythm under review. In our cases the auricular rate varied between 195 and 230 a minute.

Our cases were receiving digitalis when they developed paroxysmal auricular tachycardia with auriculo-ventricular block. The response to potassium treatment supports the view that digitalis was the causative agent (Cases 1, 2, and 3; Lown and Levine, 1955). An excessive dose of the drug may cause the arrhythmia, but it is important to realize that it may occur when the heart muscle is sensitized to digitalis by potassium loss (Lown, Salzberg, Enselberg, and Weston, 1951). Thus in intractable heart failure prolonged diuresis may render a therapeutic dose of digitalis a toxic dose, and thereby cause paroxysmal auricular tachycardia with auriculo-ventricular block.

Prompt treatment is essential in paroxysmal auricular tachycardia with auriculo-ventricular block due to digitalis toxicity. The drug, of course, must be stopped, and diuresis, paracentesis, and other measures aimed at diminishing the load on the heart must be suspended, to conserve body potassium. Potassium is the specific remedy (Lown and Levine, 1955). In urgent cases it may be given intravenously. We used oral therapy in Cases 1, 2, and 3—5 g. of potassium chloride being given daily in divided doses under continual electrocardiographic control until sinus rhythm was restored. Lown and Levine (1955) note that auriculo-ventricular block is abolished before the ectopic auricular centre is suppressed by potassium. Thus the ventricular rate increases before the sudden restoration of sinus rhythm. Procaine amide is also effective (Case 1). We prefer the intramuscular route, 0.5 g. of the drug twelve-hourly, until sinus rhythm is restored. Two of our cases had fresh myocardial infarction (Cases 3 and 4). One of them recovered with potassium treatment; the other, who received no specific treatment, died. The digitalis treatment of fresh myocardial infarction requires special care with regard to its toxic action causing this serious disturbance of auricular rhythm.

Finally, more rarely, paroxysmal auricular tachycardia with auriculo-ventricular block may occur spontaneously—in the absence of digitalis administration (Lown and Levine, 1955; Friedberg, 1949). It appears to be a benign condition, and, paradoxically, digitalis is the treatment of choice.

Summary

Paroxysmal auricular tachycardia with auriculo-ventricular block is a serious complication of digitalis toxicity that cannot be differentiated clinically from auricular fibrillation. Four cases are described; the importance of diagnosis depends upon the identification of well-defined P waves in any appropriate lead separated by isoelectric intervals.

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TWO CASES OF ALKAPTONURIA

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Alkaptonuria results from an inherited inability to metabolize homogentisic acid, a breakdown product of tyrosine, which undergoes oxidation in alkaline urine to form pigments, giving the urine its characteristic brown or black appearance. The condition is relatively rare; only about 200 cases have been described (Martin *et al.*, 1952). Hogben *et al.* (1932) calculated the incidence of the condition to be about one in ten million.

Apart from constituting an interesting metabolic disorder, alkaptonuria is important in that cases may be misdiagnosed. Thus the presence of a reducing substance (homogentisic acid) in the urine may lead to a diagnosis of diabetes mellitus, whilst the complication of ochronotic arthritis may be diagnosed as some other arthritic condition.

For this reason we are prompted to describe two new and apparently unrelated cases which illustrate diagnostic pitfalls.

Case 1

A 12-year-old schoolgirl was admitted to the professorial surgical wards of the Royal Infirmary, Edinburgh, on May 4, 1956, for the investigation of intermittent attacks of lower abdominal pain. When several months old she had been admitted to another hospital for the investigation of a red coloration of the urine; a diagnosis of pyelonephritis was made, although there is no record of bacteriological examination of the urine or the presence of red cells on microscopy. During the whole of the patient's childhood the mother had often observed brown staining of the diapers and undergarments.

The child was normally developed and no abnormalities were detected on physical examination apart from a generalized brown pigmentation of the skin. Barium-meal and x-ray examination of the skeletal system failed to reveal anything abnormal. The Wassermann and Mantoux reactions were negative. Her urine when freshly voided was acid and usually a normal colour, although occasionally there was a faint red coloration; on standing exposed to the air for several days, however, the urine became alkaline and gradually turned a deep brown colour. Tests for homogentisic acid were positive (see below). Over a seven-day period the excretion of homogentisic acid averaged 2.4 g. in 24 hours.

A diagnosis of alkaptonuria associated with non-specific mesenteric adenitis was made. When seen four months after discharge from hospital she was asymptomatic. A search for other cases of alkaptonuria among relatives was unsuccessful.

Case 2

A coal-miner aged 53 was seen at the Industrial Chest Unit, Bangour Hospital, on July 25, 1956, complaining of breathlessness on exertion. In 1938 he had been admitted to another hospital for the investigation of intermittent lower back pain. At that time there were no abnormalities on physical examination, but an x-ray film of the lumbar

spine was reported as showing "atypical arthritic changes of the spondylitis type with commencing ossification of the ligaments." The urine was noticed to darken on standing and it reduced Benedict's solution. The fasting blood-sugar level was normal. No firm diagnosis was made of the urinary abnormality.

Subsequently he received physiotherapy on several occasions for what was described as osteoarthritis of the spine, shoulders, and knees. Shortly before being seen at Bangour he had attended the out-patient department of another hospital with a pain in the chest which was at first thought to be related to coronary insufficiency. However, his electrocardiogram was normal. His urine was again found to reduce Benedict's solution and to darken on standing: indicanuria was diagnosed.

On admission he was found to be well nourished, with a slight stoop and with mild bronchitis and emphysema. A soft, localized systolic murmur was heard in the mitral area

FIG. 1.—Eye (Case 2) showing characteristic pigmentation of sclera.

and the B.P. was 200/115. Some diminution of movement was noted in both shoulders and in the lumbar spine. The most striking feature, however, was the presence of two patches of slate-grey pigmentation on the sclera of both eyes to each side of the corneal limbus (Fig. 1). There was thickening of the auricular cartilages with a bluish discoloration. The affected cartilages were opaque. X-ray examination of the spine showed the intervertebral disks to be thin and densely calcified (Fig. 2). Calcification was also present in the tendons in relation to the shoulders, pelvis, and knees (Fig. 3). The Kahn reaction was negative.

FIG. 2.—X-ray film of spine (Case 2), showing thinning and calcification of intervertebral disks.

FIG. 3.—X-ray film of pelvis (Case 2), showing calcification of tendons arising from the ischium.

The urine was straw-coloured when voided, but became the colour of nut-brown ale when allowed to stand for two or three days. It never became black even after standing for three weeks. The urine contained a reducing substance which was not fermented by yeast. This was identified as homogentisic acid. The daily excretion of homogentisic acid was measured for two days on a normal hospital diet and was 3.6 g. and 3.8 g. respectively.

Identification of Urinary Homogentisic Acid

Many tests have been described for the detection of homogentisic acid in the urine (Harrison, 1947), but most of the simple tests are not specific.

Colour.—Except rarely in Case 1, the urines were of normal colour when freshly voided. On standing exposed to the air, however, the urines in the course of a few days became dark but not black in colour. While such a finding is of value in arousing a suspicion of alkaptonuria, false-positive results occur; darkening may be observed in urines containing melanogen, indican, urobilinogen, porphyrins, and phenols, including gentisic acid, a metabolic product of salicylates.

Colour on Alkalinization.—Both urines darkened from above downwards on being made alkaline. However, we have observed that urines containing gentisic acid derived from ingested salicylate behave similarly.

Reduction of Copper Salts.—With Benedict's solution the urines gave, on boiling, a black solution with, subsequently, the formation of a yellow precipitate. The urines gave also positive results with "clinitest" but negative results with glucose oxidase tests ("clinitix" and "tes-tape"), which are specific for glucose (Hunt *et al.*, 1956; Tunbridge *et al.*, 1956).

Reduction of Silver Nitrate.—The addition to each urine of an equal volume of silver nitrate solution produced a black precipitate within 10 seconds. Ascorbic acid also reduces silver nitrate; chlorides give a precipitate of silver chloride which turns black slowly on exposure to light.

Reduction of Ammoniacal Silver Nitrate.—The addition to each of the urines of an equal volume of ammoniacal silver nitrate produced an immediate black precipitate. Ascorbic acid and uric acid also reduced ammoniacal silver nitrate in the cold.

Ferric Chloride Test.—In our hands this test gave inconsistent results. Ferric chloride added drop by drop to urine is said to give an evanescent blue colour. However, this reagent gives colours with various other phenolic substances.

Chromatography.—This was performed using the solvent N-butanol, acetic acid, and water (4:1:5 v/v), with ammoniacal silver nitrate as reagent. Homogentisic acid has an R_f of approximately 0.8 in this solvent, and gave an immediate brown or black spot with ammoniacal silver nitrate. Of

normal constituents ascorbic acid ($R_F=0.2$) also gives an immediate brown colour; uric acid ($R_F=0.4$) gives an orange colour slowly, while chloride and other inorganic ions ($R_F=0.1-0.2$) form spots which turn blue on exposure to light. An immediate brown or black spot is also given by gentisic acid ($R_F=0.9$), and other unidentified substances (R_F less than 0.5) present in the urine of patients receiving large doses of salicylates. Neuberger *et al.* (1947), using chromatography, noted, in the urine of a relative of a patient with alkaptonuria, the presence of an unidentified substance which reduced the silver reagent. Fig. 4 shows a chromato-

FIG. 4.—Chromatogram of urines confirming the presence of homogentisic acid.

gram on which has been run urine from both cases along with pure homogentisic acid, homogentisic acid isolated from the urine of Case 1, and gentisic acid. The position of the spots confirmed the presence of homogentisic acid in both urines.

Isolation of Homogentisic Acid.—The acid was isolated from the urine in Case 1; this was carried out according to the method of Neuberger *et al.* (1947). The melting-point of the free acid was found to be 144°C .; Neuberger *et al.* give the result as $144-145^{\circ}\text{C}$. This melting-point was not depressed by admixture with a pure sample of homogentisic acid.

Discussion

It is not at all surprising that a condition as rare as alkaptonuria should sometimes go undiagnosed. In the past the condition has often been confused with diabetes mellitus (Osler, 1904). In the two cases described here the colour of the urine was the cause of diagnostic errors; in Case 1 the pink colour in the urine led to a diagnosis of pyelonephritis, whilst in Case 2 darkening on standing was attributed to indicanuria. The typical ochronotic arthritis in Case 2 was not recognized and was treated for many years as arthritis of unknown aetiology.

Whilst the diagnosis of the fully developed case presents no serious difficulty, in patients without ochronosis or arthritis the diagnosis is more elusive. The tests for homogentisic acid commonly employed are not entirely reliable,

and Janney (1918) has pointed out that alkaptonuria can be diagnosed with certainty only by the isolation of homogentisic acid from the urine. We suggest that chromatography, which is a more simple procedure than the isolation of homogentisic acid, should be used as a confirmatory test.

Typically, alkaptonuria does not manifest itself, except by the urinary abnormality, until the third decade or later, when ochronosis appears and arthritic changes cause symptoms. The present two cases demonstrate this very well, as the first showed no evidence of ochronosis or arthritis, whilst the second patient developed arthritic symptoms at the age of 35 and had characteristic changes in the sclera and auricular cartilages when seen at the age of 53.

The actual nature of ochronotic pigment is unknown. Chemically it resembles melanin and is believed to be formed from homogentisic acid. The deposition of pigment takes place mainly in cartilage and tendons, and is followed by calcification in these sites; in joints this gives rise to arthritic changes. Pomeranz *et al.* (1941) have described cutaneous pigmentation, and it may be that the skin pigmentation noted in Case 1 was the first manifestation of developing ochronosis. The sclera is often affected. It is of interest that an identical appearance is produced in sclera and cartilage by the prolonged application of phenol (carbolic acid) to wounds (Reid *et al.*, 1908), while a somewhat similar appearance in the eye has been reported in workers engaged in the manufacture of hydroquinone (Anderson, 1947).

The mode of inheritance of the condition has been a subject of dispute. Garrod (1923) thought that transmission was by means of a simple autosomal recessive gene, but Hogben *et al.* (1932), in reviewing the pedigree of 45 alkaptonuric families, found the character to be dominant in three families and recessive in the others. Pieter (1925) has described a case in which inheritance was by means of a Mendelian dominant. Milch (1955) has summed up the position by suggesting that the disease is inherited by a pair of coexistent and incompletely penetrant dominant factors.

Many of the reported cases have occurred as a result of consanguineous marriages. However, in the present cases the parents were not related except by marriage. We have investigated 16 relatives of Case 1 and 8 relatives of Case 2 without finding another case of alkaptonuria, and can therefore add nothing to knowledge on the transmission of the condition.

Summary

Two apparently unrelated cases of alkaptonuria are described.

Tests for the detection of urinary homogentisic acid, including chromatography, are discussed and evaluated.

Attention is drawn to alkaptonuria as a condition to be considered in the investigation of patients with reducing substances in the urine, or with arthritis.

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