ALKAPTONURIA

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The occurrence of alkaptonuria is sufficiently rare to justify the publication of the following case. Only nine of the seventy or so recorded cases of alkaptonuria have been reported occurring in the states.

As the exact cause of this condition is still unknown and as relatively few cases have been reported, it seemed well to add this record to those which have been published, with the findings and result of treatment. Fromherz has recently expressed the opinion that many alkaptonurics remained unnoticed, and he calls attention to the fact that forty-five of the seventy cases have been reported within the last fifteen years.

The term alkaptone (from *alkali* and *κάπτειν*, "to absorb greedily") was first ascribed by Bödeker in 1857 to a substance found in the urine of a patient, which possessed two chief characteristics: first, the power to reduce alkaline copper solutions, and secondly, the property of absorbing oxygen from the atmosphere in the presence of alkali, and as a result turning to a brown-black color.

The urine may be clear and of normal color when passed, but later becomes of a dark brown and finally black color on exposure to the air. This condition may be present in cases of ochronosis, but is not a necessary accompaniment of this affection. Gouget has found a number of references in the literature of the past to cases of melanuria which were probably instances of alkaptonuria. Thus, Scribonius (1584), Zacutus and Lusitanus (1649) describe cases of young children in apparent health who passed black urine; and Scheneck (1609) reports the case of a Monk who presented the same urinary anomaly during his whole life.

In 1875 Ebstein and Müller obtained a substance from the urine of an alkaptonuric patient by treating the urine with alcohol-ether, which formed the reactions given by pyrocatechin. This observation was of interest because it was the first case in which the opinion had been expressed as to what the reactions in alkaptonuria were. Fleischer next observed a urine which gave similar reactions with those of Fürbinger in which he was able to demonstrate small quantities of pyrocatechin. Bödeker in a communication to Fürbinger expresses the view that his alkaptone bodies might be similar to pyrocatechin.

* Submitted for publication April 9, 1918.

About this date Baumann reported that pyrocatechin is a normal constituent of horses' urine, and that frequently, if not regularly, is present in varying amounts in human urine.

An excess of excretion of the normal constituent of pyrocatechin in the urine led many to the belief that it was identical with alkaptonuria. This view was expressed by Salkowski and Leube, who said: "Apparently identical with pyrocatechin is the alkaptone of Bödeker and Furbinger." The opinion has been expressed of late that homogentisic acid (hydroquinon-acetic acid), which is apparently derived from tyrosin, is a normal intermediary product in the destruction of tyrosin and phenylalanin, that its formation represents an oxidation which precedes the breaking up of the benzene ring, and that its appearance in the urine is an expression of metabolic insufficiency which renders the destruction of the benzene ring impossible..

In 1886 and 1889 Kirk made a further contribution to our knowledge regarding alkaptonuria. The report is of interest chiefly because it is the first instance recorded in which the urine of more than one member of a family presented the characteristics of alkaptonuria. The opinion was conveyed that the condition may be congenital and occur in the offspring of consanguineous marriages. To Baumann and Wolkow we are indebted for the most exhaustive study of the subject of alkaptonuria. They were able to obtain the "alkaptone" in pure form, to ascertain its constitution, and to determine its derivation as a product of tissue metabolism. From the urine they isolated in pure form homogentisic acid, which has the following formula.

It crystallizes in the form of large, transparent, prismatic crystals, which melt at 146.5 to 147 C. and become yellow when free from water. They are not hygroscopic, and are soluble in water, ether, chloroform, benzene and in toluol. The authors draw comparisons

between homogentisic acid and the glycosuric acid of Marshall and the urolenticic acid of Kirk, showing the marked similarity in constitution.

Embsen studied another case of alkaptonuria and concludes as a result of his work, first, that we know nothing definite as to the etiology or place of formation of the homogentisic acid, and secondly, that the evidence that homogentisic acid is derived from tyrosin in the intestine as a result of the action of micro-organisms is rather against than for this view.

As to treatment, there is nothing to be done, as the condition is of no pathologic significance. Alkaptonuria is of importance, however, owing to the liability of its being mistaken for glycosuria. The negative results with bismuth ferrocyanid and the polariscopic tests should at once rule out glycosuria.

REPORT OF CASE

History.—The case here recorded occurred in a male patient, aged 32, married, the father of two healthy children (the urine of these were normal). There was no history of alkaptonuria in the family. The patient was a civil engineer, but was employed as a chemist for the previous two years.

Present Illness.—Complained of passing black urine, with periodic attacks of urticaria.

Previous Illness.—Had herpes zoster fifteen years prior to this consultation. He denied all genito-urinary infection.

Examination.—The patient was a well developed, muscular, white man, height, 5 feet 8 inches; weight, 162 pounds.

Eyes: Reflexes normal; ophthalmoscopic examination negative; no abnormal pigmentation of retina.

Heart and chest and abdomen were normal.

The physical findings were negative except for the passage of a brown-black urine.

The Wassermann reaction before treatment was negative; after administration of large doses of potassium iodid (40 to 60 grains three times a day) there was a four plus reaction.

The Urine: Physical Properties.—Appearance: When fresh, the urine was a light brown color, at times clear and free from sediment.

Color: On standing the urine perceptibly darkened, and this change was the more pronounced the longer the urine was exposed to the air, until it became of an inky black color. Fleischer says it is at first, almost black; later brown by reflected light. This condition was not determined.

Odor: There was a peculiar and slightly aromatic odor when freshly voided.

Volume: From the statements of other writers many alkaptonurics excrete either an excessive or deficient quantity of urine. Some of the patients had other maladies; for this reason, perhaps, these divergencies from the normal are of no particular significance as far as alkaptonuria is concerned. In the following instances the quantity of urine was less than 1,000 c.c.: Fürbringer's case, quantity small; average 600 c.c.; Brunne's, 900 c.c.; Ogden's, 974 c.c., and Moraczewski's, 500 to 1,200 c.c., and later 200 to 400 c.c.; Stier's, 360 to 1,030 c.c.; Hirsch's 700 c.c.; Garrod's, scanty and highly concentrated. On the other hand, the following observers have reported quantities exceeding 2,000 c.c., namely, Garner and Voirin, 2,000 to 4,000 c.c.; Stange, 1,000 to 4,000 c.c. However, more instances of deficient than excessive quantities seem to have been recorded. In my case 1,400 c.c. was the average.

Specific Gravity: The specific gravity of alkaptonuric urine in several instances appears to have been high. Urines ranging from 1.020 to 1.025 have been recorded by Fürbringer, Armstrong, Smith, Brune, Noccioli and Donsencci and Hammarstein and Schumm. In my case there was a specific gravity of 1.021.

Chemical Properties.—**Acidity:** I did not attempt to determine the acidity of the urine quantitatively, but merely tested each sample with litmus paper and found it to be decidedly acid. Alkaptonuric urine seems to retain its acidity for a considerable time on standing.

Fermentation, sugar, albumin, blood and blood pigments were absent.

Copper Tests: Alkaptonuric urine will reduce Fehling's solution only on being heated, but to no extent with a cold solution. Supernated alkali solution on the urine produced a black zone but no precipitate (sodium hydroxid 10 per cent.).

Spectroscopic examination was negative for bands due to iron.

Clinical Analysis.—Alkaptonuria must be differentiated from the hemoglobinurias due to drugs (phenols) and diseases (malaria, etc.) by the presence of hemoglobin in the urine; from the melanurias and hematorporphyrinurias, and especially from the condition known as "paroxysmal hemoglobinuria frigore," by chemical and spectroscopic tests for the pigments.

As no treatment has been indicated in the various textbooks, at the suggestion of Dr. Schultz I attempted to unite the benzene ring of alkaptone with the benzoates, but with negative results. After continued failure to relieve the patient of his black urine, and in spite of a negative Wassermann I administered large doses of potassium iodid (from 40 to 80 grains, increasing to 100 grains three times a day). At the end of three days the patient had a severe iodid rash, and at the end of two weeks' treatment (modified) the urine became normal in physical appearance and in its chemical composition. Another blood test was made which showed a strongly positive Wassermann (4+). I doubted the specificity and accuracy of the test and two specimens of blood were submitted to Dr. Benjamin Gruskin of the Medical Research Laboratory and to Dr. Fischer. Reports of four plus Wassermann were returned for each specimen. I then administered 10 grains of tyrosin and twenty-four hours later submitted new specimens. The reports from these two laboratories and my own test showed a negative Wassermann. Therefore, the patient twenty-four hours after the administration of 10 grains of tyrosin turned a fully four plus Wassermann reaction into a fully negative one.

In a hasty review of the literature on the Wassermann reaction I found a somewhat similar condition reported by Söderbergh in which a strongly positive Wassermann reaction was converted by the administration of sodium bicarbonate and tyrosin into a negative test.

A further note on this phase will be published in a separate communication.

I had delayed the report of this case until the present time in the hope that a more complete study could be made, but in view of the fact that I am on active service with the colors in France and no opportunity for continued work along this line is possible at present, I wish to make this preliminary report.

I beg to acknowledge my indebtedness to Dr. Solomon Strauss for confirmation of my chemical findings and to Dr. Schultz of the Michael Reese Research Institute for many helpful suggestions in this study.