ABOUT ALKAPTONURIA

BY

ARCHIBALD E. GARROD, M.A., M.D.

Received October 21st—Read November 26th, 1901

In a paper read before this Society in 1899, the present writer gave the results of the examination of the urine in five cases of alkaptonuria not previously recorded, and a summary of the then state of our knowledge of this rare and interesting urinary abnormality.

The object of the present communication is to call attention to certain facts, and to record some observations, which tend to throw fresh light upon its nature and causation.

1. *The Relation of Alkaptonuria to Consanguinity of Parents.*

That alkaptonuria may be met with in several members of a family was first pointed out by Kirk in 1886, and of the cases since recorded a considerable number have served to emphasise this fact. However, although brothers and sisters share this peculiarity, there is, as yet, no known instance of its transmission from one generation to another, nor is anything known as to the urine of children of alkaptonuric individuals.

On the other hand I am able to bring forward evidence which seems to point, in no uncertain manner, to a very special liability of alkaptonuria to occur in the children of first cousins. The information available relates to four families, including no less than eleven alkaptonuric members, or more than a quarter of the recorded examples of the condition.

I have recently learnt that the parents of my own patient, Thomas P—, and of an infant brother, born in the present year, who also is alkaptonuric, are first cousins, their mothers being sisters.

Again, in the notes which were kindly furnished to me by Dr. Pavy of a family of fourteen, referred to in my previous paper, of whom four were alkaptonuric, it is mentioned that in this instance also the parents were first cousins.

I am also greatly indebted to Dr. Robert Kirk for kindly making inquiries from the father of the three children whose cases were so thoroughly investigated by him some years ago, inquiries which brought to light the fact that their parents also were first cousins, the children of sisters. Dr. Kirk adds that the mother is dead, that the father has married again, and that his only child by his second wife, who is not a blood relation, is not alkaptonuric.

Against this may be set the fact that the parents of the patient studied by Dr. Walter Smith in 1882, and of a younger brother whose urine I examined, were not blood relations.

The children of first cousins form so small a section of the community, and the number of alkaptonuric persons is so very small, that the association in no less than three out of four families can hardly be ascribed to chance, and further evidence bearing upon this point would be of great interest.

In a recent paper by Erich Meyer it is mentioned that the parents of his patient were related, but the exact degree of relationship is not stated. Elsewhere the litera-

ture is silent upon this matter, a silence which counts for little, seeing that the information is not usually forthcoming unless asked for, as Dr. Kirk's experience and my own show.

There are some indications that the younger members of a family are more liable than the elder ones. Thus the alkaptonuric members of the family observed by Dr. Pavy, were the ninth, eleventh, thirteenth, and fourteenth. Thomas P— and his alkaptonuric brother are the fourth and fifth children, and in the family observed by Dr. Kirk, the second, third, and fourth children showed the peculiarity.

The facts here brought forward lend support to the view that alkaptonuria is what may be described as a "freak" of metabolism, a chemical abnormality more or less analogous to structural malformations. They can hardly be reconciled with the theory that it results from a special form of infection of the alimentary canal. There is here no question of the intensification of family tendencies by intermarriage, for in no instance were the parents themselves alkaptonuric, and, as has been already mentioned, there is, up to now, no recorded instance of alkaptonuria in two generations of a family.

2. *The Onset of Alkaptonuria in a New-born Infant.*

That alkaptonuria may persist through life without any apparent detriment to health, and may date from earliest infancy, has long been known, but there have hitherto been wanting observations bearing upon the exact period of its onset in congenital cases. This deficiency I am now able to supply to some extent.

The fifth child (a male) of the parents of Thomas P— and the second alkaptonuric member of the family, was born at 6 a.m. on March 1st, 1901. The mother was tended after her confinement by a district nurse, and both she and the nurse were fully alive to the possibility that the child might show the same peculiarity as its elder brother, and were on the look-out for any indication that

this was the case. The information which follows was given to me by the nurse within a few days of the infant's birth.

During the first day of life the child was put to the breast, and was given a teaspoonful of butter and sugar, according to a practice common among the poorer classes. The napkins were first changed at 9 p.m. on March 1st (when the child was fifteen hours old), and it was specially noted that, although urine had been passed freely, there was no indication whatever of the staining which was so familiar in the case of the elder child.

When the napkins were next changed, at 11 a.m. on March 2nd, the nurse noticed a slight staining, and at 10.30 a.m. on March 3rd (fifty-two hours after birth), and on all subsequent occasions, the napkins were deeply stained in the characteristic manner.

The child had been put to the breast during the previous night, and on the morning of March 3rd the nurse found that the mother's breasts contained milk, but were not full. The mother was not conscious of the "draught" until a later hour on March 3rd.

Some urine collected during the eighth to eleventh days of life reduced Fehling's solution, and had all the ordinary properties of alkapton urine.

The above facts, carefully recorded by one who was wholly without bias in favour of any theory of the nature of alkaptonuria, or knowledge of the questions at issue, nevertheless agree completely with what was to be expected on theoretical grounds.

The evidence available points to tyrosin, formed as a product of pancreatic digestion, as the parent substance of the homogentisic acid which imparts to alkapton urine its peculiar properties, and we should anticipate that the peculiarity of metabolism would first manifest itself after the entry of proteid food into the alimentary canal. As, moreover, the human tissues appear to be able to destroy a certain amount of homogentisic acid, this substance would not be excreted until this destructive power was overtaxed.

The observations on the new-born infant appear to be most readily explained on the assumption that the development of alkaptonuria resulted from feeding, but as the child was suckled, the exact time when food began to enter the alimentary canal cannot be fixed with any degree of certainty.

When the elder child was first seen by me the mother stated that in his case her attention had been first called to the staining of the napkins on the day after his birth, thus in both instances the condition may be fairly described as congenital. In this connection a most interesting case recently recorded by Winternitz may be referred to. He had under observation a family of three alkaptonuric children, a boy aged twelve, a girl aged ten, and another girl aged six. The mother, who stated that the urine of the two elder children had stained the napkins from the first days after their birth, added that this had only been the case with the youngest child during the last year. This recalls Maguire's case in which the condition was said to have dated from the age of twenty-seven, the intermittent case recorded by Stange, and the still more puzzling cases of temporary alkaptonuria.

3. *The Relation in Time of the Output of Homogentisic Acid to a Proteid Meal.*

In a quite recent paper, which embodies many other observations of much interest, Mittelbach gives the results of the estimation of the reducing power of the samples of urine passed by his patient at different periods of a twelve-hour day, which show the maximum excretion of homogentisic acid following within the first two or three hours after the chief meal, and not, as is the case with the ordinary products of metabolism, appearing in the urine in the largest quantities from five to seven hours after a meal.

This result was so unexpected, and seemed so difficult to reconcile with the view that tyrosin is the parent substance of homogentisic acid in these cases, that further observations upon the point appeared desirable. I accord-

ingly estimated the reducing power of the several specimens of urine passed by Thomas P— (aged four) during three periods of twenty-four hours each, and the results are embodied in the following tables. The estimations were made by Baumann's silver method, but, owing to the small bulk of many of the specimens, 5 instead of 10 c.c. of urine were used for each testing, and it was not attempted to secure estimations within 0·5 c.c. of $\frac{N}{10}$ silver nitrate solution.

The urine of the child is always rich in homogentisic acid, and the daily output approaches that of some of the adult patients. At the age of three the average daily excretion during seven days was 2·6 grms. of homogentisic acid, and that of Meyer's patient of about the same age was 3·24. The figures for adults vary between 3 and 6 grms. per twenty-four hours.

Day 1.—On this day the patient was taking the ordinary hospital diet for children of his age. The first meal was at 5 a.m : dinner consisting of minced meat and rice pudding at 12 noon; tea including an egg at 3.45; supper consisting of milk and bread and butter at 6 p.m.

Hour of day.	Quantity of urine passed in c.c.	No. of c.c. $\frac{N}{10}$ silver nitrate solution reduced by 5 c.c. urine.	No. of c.c. $\frac{N}{10}$ silver solution reducible by total urine.	Corresponding to a reducing power per hour of—
A.M. 9.30	60	10	120	—
P.M. 12.30	53	10·5	111·3	37 c.c.
4	46	13	119·6	34·2
5.55	27	16	86·4	45
9.30	55	11	121	33·7
A.M. 12.45	35	9	63	19·3
3.45	28	5·5	30·8	10·2
6	25	5·5	27·5	12·2
Totals	329 c.c.		679·6 c.c. (corresponding to 2·79 grammes of homogentisic acid)	

Here the maximum excretion per hour was between 4 and 5.55 p.m., *i. e.* four to six hours after the chief meal,

but the results are somewhat obscured by the overlapping of the effects of several meals rich in proteid.

Day 2.—On this day the diet was so arranged that the articles richest in proteids were given at the chief meal, which, as before, was at 12 noon, and hourly specimens of urine were fortunately obtained from 4 to 9 p.m. inclusive. It is clearly seen that although there is a conspicuous rise in the specimen passed at 1·30 p.m., the maximum excretion was between 3 and 7 p.m.

Hour of day.	Quantity of urine passed in c.c.	No. of c.c. $\frac{N}{10}$ silver nitrate solution reduced by 5 c.c. urine.	No. of c.c. $\frac{N}{10}$ silver solution reducible by total urine.	Corresponding to a reducing power per hour of—
A.M. 9.55	26	6	31·2	—
11.40	43	5·5	47·3	27 c.c.
P.M. 1.30	25	16	80	43·6
2.50	30	10	60	45
4	30	14·5	87	84·5
5	32	15	96	96
6	20	15	60	60
7	31	14	86·8	86·8
8	25	10	50	50
9	24	8·5	40·8	40·8
10.55	65	3	39	20·3
A.M. 12.55	27	6	32·4	16·2
2	5	6 or 7	8·4?	7·7
4.40	16	7	22·4	8·4
8	41	8	65·6	19·6
Totals	440 c.c.		806·9 c.c. (corresponding to 3·327 grammes of homogentisic acid)	

The total excretion of homogentisic acid was increased, owing to some increase of the proteid food, partly in the form of Plasmon. The effect of the early breakfast at 5 a.m. is still clearly marked.

Day 3.—On this day the meal richest in proteid was given at 9 a.m. instead of at noon, and the maximum output of reducing substance per hour was also three hours earlier, viz. between 12.15 and 4.25 p.m. The rise during the hours immediately following the meal is again very

noticeable. The total reducing power of the twenty-four hours' urine was on this day somewhat larger still.

Hour of day.	Quantity of urine passed in c.c.	No. of c.c. $\frac{N}{10}$ silver nitrate solution reduced by 5 c.c. urine.	No. of c.c. $\frac{N}{10}$ silver solution reducible by total urine.	Corresponding to a reducing power per hour of—
A.M. 6	32	6	38·4	—
8	30	?	?	—
9.25	26	5	26	18·3 c.c.
11.15	46	8	73·6	40·1
P.M. 12.15	29	9	52·2	52·2
4.25	99	14	277·2	66·5
6	46	8·5	78·2	49·3
9.30	95	6·5	123·5	35·3
11.45	31	7·5	46·5	20·6
A.M. 2.50	35	6	42	13·6
4.45	41	4·5	36·9	19·2
Totals .	510 c.c.			

It will be at once apparent that these results do not bear out Dr. Mittelbach's observation that the reducing power of the urine reaches its maximum within two or three hours of a proteid meal, but show, on the other hand, that in the case of my patient, although such a meal is quickly followed by a much increased excretion of homogentisic acid, a still larger amount is excreted during the second period of four hours than during the four hours immediately following the meal. In a word, they tend to support the view that the change from tyrosin to homogentisic acid takes place in the tissues after the absorption of the former, rather than the alternative view that the change in question is brought about in the alimentary canal.

Since the publication of the previous paper in 1899, cases of alkaptonuria have been recorded by Winternitz (three children in one family), E. Meyer (one child), and Mittelbach (an adult male); and these with the infant above described raise the total of recorded examples to thirty-seven.

The following additions may also be made to the bibliography there given:

HUPPERT, H.—Ueber die Homogentisinsäure. Deutsches Archiv f. klin. Medicin, 1899, lxiv (Festschrift), p. 129.

WINTERNITZ.—Münchener med. Wochenschr., 1899, xlvi, p. 749.

ORTON, K. J. P., and GARROD, A. E.—The Benzoylation of Alkapton Urine. Journal of Physiology, 1901, xxvii, p. 89.

MEYER, ERICH.—Ueber Alkaptonurie. Deutsches Archiv f. klin. Med., 1901, lxx, p. 443.

MITTELBACH, F.—Ein Beitrag zur Kenntniss der Alkaptonurie. Deutsches Archiv f. klin. Med., 1901, lxxi, p. 50.

DISCUSSION.

The CHAIRMAN (Dr. C. THEODORE WILLIAMS) expressed regret that more papers on chemical pathology were not communicated to the Society. It was along these lines that the greatest advance in medicine had been made. After alluding to the importance of being able to recognise the presence of alkapton in the urine in examination for life insurance, he asked by what test it could be distinguished from sugar in the urine.

Dr. W. A. OSBORNE mentioned the case of a man who was rejected for life assurance because his urine reduced Fehling's solution, which he had found to be due to alkapton. A second and a third brother were similarly affected, and their parents were first cousins. These were the three cases that had been described by Dr. Pavy. Homogentisic acid was present in the urine as a salt. If homogentisic acid was derived, as was suggested, from tyrosin, then a person the subject of alkaptonuria if fed on a tyrosin-free diet should cease to pass alkapton in the urine. Such a diet might consist of sugar, fat, and gelatine. It was very difficult to understand on chemical grounds how tyrosin could become changed into homogentisic acid. He suggested that it might be a good plan to give an alkaptonuric patient some of the intermediate substances between tyrosin and homogentisic acid, and observe the effect on the excretion of alkapton in the urine.

Dr. GARROD, in reply, said that it would be difficult to give a tyrosin-free diet in his case, as the patient was a child of four years. The experiment had been tried abroad by Mittelbach, whose adult patient had consented to take only tea and brandy for three days. Mittelbach found that after such fasting the homogentisic acid excretion fell to about one third of the usual amount, but that the acid did not completely disappear from the urine.