current in this manner but I have seen steady improvement take place under its continued use.

In many cases no special diet is necessary. When there is any emaciation a liberal diet is required which may be supplemented by two extra pints of milk in the day. If there is great emaciation forced feeding may be necessary.

In a large number of cases, and especially in those which are seen in hospital out-patient practice, we can unfortunately carry out little more than medicinal treatment and often in circumstances which are not at all favourable to recovery. Belladonna was frequently prescribed and was useful in some cases but I have often been disappointed in the results of its use. To be of service in exophthalmic goitre any line of treatment should be steadily maintained for some weeks or even months and patients often dislike to continue taking belladonna in sufficient doses to produce physiological effects. Convallaria has proved useful in cases in which the frequency of the pulse has been very high and is more effectual in lowering the pulse-rate than other cardiac tonics. Bromides are useful in cases in which there are marked nervousness and tremors. Arsenic is useful in nearly all cases and may be combined with other drugs with advantage. The best results are obtained by giving small doses of three or four minims of Fowler's solution three times a day for a month or two or for the first three weeks of each month for five or six months. Of the animal extracts thymus and suprarenal tablets have both been of service. Thyroid extract is harmful, as it often exaggerates the symptoms, and should not be given in exophthalmic goitre. Special measures are frequently required for the treatment of urgent symptoms. The sudden attacks of diarrhœa were readily controlled by laudanum and dilute sulphuric acid. Severe attacks of palpitation with very rapid pulse yielded to the application of an ice-bag to the præcordial area. Persistent vomiting in acute cases is difficult to treat. On the whole rectal feeding and the administration of morphia, either subcutaneously or by the rectum, gave better results than other lines of treatment.

Newcastle-on-Tyne.

THE INCIDENCE OF ALKAPTONURIA: A STUDY IN CHEMICAL INDIVIDUALITY.

BY ARCHIBALD E. GARROD, M.A., M.D. OXON., F.R.C.P. LOND.

PHYSICIAN TO THE HOSPITAL FOR SICK CHILDREN, GREAT ORMOND-STREET; DEMONSTRATOR OF CHEMICAL PATHOLOGY AT ST. BARTHOLOMEW'S HOSPITAL.

ALL the more recent work on alkaptonuria has tended to show that the constant feature of that condition is the excretion of homogentisic acid, to the presence of which substance the special properties of alkapton urine, the darkening with alkalies and on exposure to air, the power of staining fabrics deeply, and that of reducing metallic salts, are alike due. In every case which has been fully investigated since Wolkow and Baumann[1] first isolated and described this acid its presence has been demonstrated and re-examination of the material from some of the earlier cases also has led to its detection. The second allied alkapton acid, uroleucic, has hitherto only been found in the cases investigated by Kirk and in them in association with larger amounts of homogentisic acid.[2] By the kindness of Dr R. Kirk I have recently been enabled to examine fresh specimens of the urines of his patients who have now reached manhood and was able to satisfy myself that at the present time even they are no longer excreting uroleucic acid. After as much of the homogentisic acid as possible had been allowed to separate out as the lead salt the small residue of alkapton acid was converted into the ethyl ester by a method recently described by Erich Meyer[3] and the crystalline product obtained had the melting-point of ethyl homogentisate (120° C.). Further observations, and especially those of Mittelbach,[4] have also strengthened the belief that the homogentisic acid excreted is derived from tyrosin, but why alkaptonuric individuals pass the benzene ring of their tyrosin unbroken and how and where the peculiar chemical change from tyrosin to homogentisic acid is brought about, remain unsolved problems.

There are good reasons for thinking that alkaptonuria is not the manifestation of a disease but is rather of the nature of an alternative course of metabolism, harmless and usually congenital and lifelong. Witness is borne to its harmlessness by those who have manifested the peculiarity without any apparent detriment to health from infancy on into adult and even advanced life, as also by the observations of Erich Meyer who has shown that in the quantities ordinarily excreted by such persons homogentisic acid neither acts as an aromatic poison nor causes acid intoxication, for it is not excreted as an aromatic sulphate as aromatic poisons are, nor is its presence in the urine attended by any excessive output of ammonia. However, regarded as an alternative course of metabolism the alkaptonuric must be looked upon as somewhat inferior to the ordinary plan, inasmuch as the excretion of homogentisic acid in place of the ordinary end products involves a certain slight waste of potential energy. In this connexion it is also interesting to note that, as far as our knowledge goes, an individual is either frankly alkaptonuric or conforms to the normal type, that is to say, excretes several grammes of homogentisic acid per diem or none at all. Its appearance in traces, or in gradually increasing or diminishing quantities, has never yet been observed, even in the few recorded temporary or intermittent cases. In cases in which estimations have been carried out the daily output has been found to lie within limits which, considering the great influence of proteid food upon the excretion of homogentisic acid and allowing for differences of sex and age, may be described as narrow. This is well illustrated by Table I., in which the cases are arranged in order of age:—

TABLE I.—*Showing the Average Excretion of Homogentisic Acid.*

No.	Sex.	Age.	Average excretion of homogentisic acid per 24 hours on ordinary mixed diet.	Names of observers.
1	M.	2½ years.	3·2 grammes.	Erich Meyer.
2	M.	3½ ,,	2·6 ,,	A. E. Garrod.
3	M.	8 ,,	2·7 ,,	Ewald Stier.
4	M.	18 ,,	5·9 ,,	P. Stange.
5	M.	44 ,,	4·6 ,,	Mittelbach.
6	M.	45 ,,	4·7 ,,	H. Ogden.
7	M.	60 ,,	5·3 ,,	Hammarsten.
8	F.	60 ,,	3·2 ,,	H. Embden.
9	M.	66 ,,	4·3 ,,	Wolkow and Baumann.

The information available as to the incidence of alkaptonuria is of great interest in connexion with the above view of its nature. That the peculiarity is in the great majority of instances congenital cannot be doubted. The staining property of the urine allows of its being readily traced back to early infancy. This has been repeatedly done and in one of my cases[5] the staining of the napkins was conspicuous 57 hours after the birth of the child. The abnormality is apt to make its appearance in two or more brothers and sisters whose parents are normal and among whose forefathers there is no record of its having occurred, a peculiar mode of incidence which is well known in connexion with some other conditions. Thus of 32 known examples, which were presumably congenital, no less than 19 have occurred in seven families. One family contained four alkaptonurics, three others contained three, and the remaining three two each. The proportion of alkaptonuric to normal members is of some interest and Table II. embodies such definite knowledge upon this point as is at present available regarding congenital cases.

[1] Wolkow and Baumann: Zeitschrift für physiologische Chemie, 1891, Band xv., p. 228.

[2] R. Kirk: Journal of Anatomy and Physiology, 1899, vol. xxiii., p. 69. Huppert: Zeitschrift für Physiologische Chemie, 1897, Band xxiii., p. 342.

[3] E. Meyer: Deutsches Archiv für Klinische Medicin, 1901, Band lxx., p. 435.

[4] Mittelbach: Ibid., 1901, Band lxxi., p. 50.

[5] A. E. Garrod: THE LANCET, Nov. 30th, 1901, p. 1484; Transactions of the Royal Medical and Chirurgical Society, 1902, vol. lxxxv., p. 89.

TABLE II.—*Showing the Proportion of Alkaptonuric Members to Normal Members in 9 Families.*

No.	Total number of family (brothers and sisters).	Number of alkaptonuric members.	Number of normal members.	Observers.
1	14	4	10	Pavy.
2	4	3	1	Kirk.
3	7	3	4	Winternitz.
4	2	1	1	Ewald Stier.
5	2	2	0	Baumann, Embden.
6	1	1	0	Erich Meyer.
7	10	1	9	Noccioli and Domenici.
8	5	2	3	A. E. Garrod.
9	3	2	1	W. Smith, Garrod.
Totals	43	19	29	—

The preponderance of males is very conspicuous. Thus, of the 40 subjects whose cases have hitherto been recorded 29 have been males and only 11 females.

In a paper read before the Royal Medical and Chirurgical Society in 1901 the present writer pointed out that of four British families in which were 11 congenitally alkaptonuric members no less than three were the offspring of marriages of first cousins who did not themselves exhibit this anomaly. This fact has such interesting bearings upon the etiology of alkaptonuria that it seemed desirable to obtain further information about as many as possible of the other recorded cases and especially of those which were presumably congenital. My inquiries of a number of investigators who have recorded such cases met with a most kindly response, and although the number of examples about which information could still be obtained proved to be very limited, some valuable facts previously unknown have been brought to light and indications are afforded of points which may be inquired into with advantage regarding cases which may come under observation in the future. In a number of instances the patients have been lost sight of, or for various reasons information can no longer be obtained concerning them. To those who have tried to help me with regard to such cases, and have in some instances been at great trouble in vain, my hearty thanks are no less due than to those who have been able to furnish fresh information.[6]

The following is a brief summary of the fresh information collected. Dr. Erich Meyer,[7] who mentioned in his paper that the parents of his patient were related, informs me that as a matter of fact they are first cousins. Dr. H. Ogden[8] states that his patient is the seventh of a family of eight members and that his parents were first cousins. The three eldest children died in infancy; the fifth, a female, has three children, but neither is she nor are they alkaptonuric. There is no record of any other examples in the family. The patient, whose wife is not a blood relation, has three children none of whom are alkaptonuric. Professor Hammarsten[9] states that the parents of an alkaptonuric man, whose case he recently described, were first cousins. The patient, aged 61 years, has three brothers and the only brother whose urine has been seen is not alkaptonuric. I have learned from Professor Noccioli[10] that the parents of the woman whose case he investigated with Dr. Domenici were not blood relations. The patient, a twin, who is one of two survivors of a family of ten, states that none of her relations have exhibited the condition. Dr. Ewald Stier[11] informs me that the parents of his patient were not related and it is mentioned in his paper that they were not alkaptonuric. Professor Ebstein[12] states that the parents of the child with "pyrocatechinuria" whose case was investigated by him in conjunction with Dr. Müller in 1875 were not related, but I gather that he would not regard this as an ordinary case of alkaptonuria, the abnormal substance in the urine having been identified as pyrocatechin. Lastly, Professor Osler supplies the very interesting information that of two sons of the alkaptonuric man previously described by Dr. Futcher[13] one is alkaptonuric. This is the first known instance of direct transmission of the peculiarity. The parents of the father, who has an alkaptonuric brother whose case was recorded by Marshall,[14] were not blood relations. The above particulars are embodied with those of the congenital British cases previously recorded in the following tabular epitome (Table III.).

TABLE III.—*Showing the large Proportion of Alkaptonurics who are the Offspring of Marriage of First Cousins.*

A.

Families the offspring of marriages of first cousins.

No.	Total number of family.	Number of known alkaptonuric members.	Observers.
1	14	4	Pavy.
2	4	3	R. Kirk.
3	5	2	A. E. Garrod.
4	1	1	Erich Meyer.
5	8	1	H. Ogden.
6	4	1	Hammarsten.
Total	36	12	—

B.

Families whose parents were not related and not alkaptonuric.

No.	Total number of family.	Number of known alkaptonuric members.	Observers.
1	3	2	Armstrong, Walter Smith, and Garrod.
2	2	1	Ewald Stier.
3	10	1	Noccioli and Domenici.
4*	?	2	Marshall and Futcher.
Total ...		6	—

C.

Family in which alkaptonuria was directly inherited from a parent.

No.	Total number of family.	Number of known alkaptonuric members.	Observers.
1*	?	2	Osler and Futcher.
Total ...	—	2	

* B 4 and C 1 refer to two generations of one family. No information is forthcoming as to the absence of alkaptonuria in previous generations. Ebstein and Müller's case, which is not included in the table for reasons given above, would raise the number of families in list B to 5.

It will be seen that the results of further inquiries on the continent of Europe and in America confirm the impression derived from the British cases that of alkaptonuric individuals a very large proportion are children of first cousins. The above table includes 19 cases in all out of a total of 40 recorded examples of the condition, and there is

[6] To Hofrath Professor Huppert and to Professor Osler my very special thanks are due for invaluable aid in collecting information, and I would also express my most sincere gratitude to Professor Hammarsten, Geheimrath Professor Ebstein, Geheimrath Professor Fürbringer, Geheimrath Professor Erb, Professor Noccioli, and Professor Denigès, as also to Dr. F. W. Pavy, Dr. Kirk, Dr. Maguire, Dr. Futcher, Dr. Erich Meyer, Dr. H. Ogden, Dr. H. Embden, Dr. Mittelbach, Dr. Ewald Stier, Dr. Grassi, Dr. Carl Hirsch, and Dr. Winternitz, all of whom have been kind enough to help the inquiry in various ways.

[7] E. Meyer, loc. cit.

[8] H. Ogden: Zeitschrift für physiologische Chemie, 1895, Band xx., p. 25.

[9] Hammarsten: Upsala Läkareförenings Förhandlingar, 1901, vol. vii., p. 26.

[10] Noccioli e Domenici: Gazetta degli Ospedale, 1898, vol. xix., p. 303.

[11] Ewald Stier: Berliner Klinische Wochenschrift, 1898, Band xxxv., p. 165.

[12] Ebstein and Müller: Virchow's Archiv, 1875, Band lxii., p. 564.

[13] Futcher: New York Medical Journal, 1898, vol. lxvii., p. 69.

[14] Marshall: Medical News, Philadelphia, 1887, vol. l., p. 35.

little chance of obtaining any further information on the point until fresh cases shall come under observation. It will be noticed that among the families of parents who do not themselves exhibit the anomaly a proportion corresponding to 60 per cent. are the offspring of marriages of first cousins. In order to appreciate how high this proportion is it is necessary to form some idea of the total proportion of the children of such unions to the community at large. Professor G. Darwin,[15] as the outcome of an elaborate statistical investigation, arrived at the conclusion that in England some 4 per cent. of all marriages among the aristocracy and gentry are between first cousins; that in the country and smaller towns the proportion is between 2 and 3 per cent., whereas in London it is perhaps as low as 1·5 per cent. He suggests 3 per cent. as a probable superior limit for the whole population. Assuming, although this is, perhaps, not the case, that the same proportion of these as of all marriages are fruitful, similar percentages will hold good for families, and assuming further that the average number of children results from such marriages they will hold good for individuals also. A very limited number of observations which I have made among hospital patients in London gave results which are quite compatible with the above figures. Thus, among 50 patients simultaneously inmates of St. Bartholomew's Hospital there was one whose parents were first cousins. On another occasion one such was found among 100 patients, and there was one child of first cousins among 100 children admitted to my ward at the Hospital for Sick Children. It is evident, on the one hand, that the proportion of alkaptonuric families and individuals who are the offspring of first cousins is remarkably high, and, on the other hand, it is equally clear that only a minute proportion of the children of such unions are alkaptonuric. Even if such persons form only 1 per cent. of the community their numbers in London alone should exceed 50,000, and of this multitude only six are known to be alkaptonuric. Doubtless there are others, but that the peculiarity is extremely rare is hardly open to question. A careful look-out maintained for several years at two large hospitals has convinced me of this, and although the subject has recently attracted much more attention than formerly the roll of recorded examples increases but slowly.

The question of the liability of children of consanguineous marriages to exhibit certain abnormalities or to develop certain diseases has been much discussed, but seldom in a strictly scientific spirit. Those who have written on the subject have too often aimed at demonstrating the deleterious results of such unions on the one hand, or their harmlessness on the other, questions which do not here concern us at all. There is no reason to suppose that mere consanguinity of parents can originate such a condition as alkaptonuria in their offspring, and we must rather seek an explanation in some peculiarity of the parents, which may remain latent for generations, but which has the best chance of asserting itself in the offspring of the union of two members of a family in which it is transmitted. This applies equally to other examples of that peculiar form of heredity which has long been a puzzle to investigators of such subjects, which results in the appearance in several collateral members of a family of a peculiarity which has not been manifested at least in recent preceding generations.

It has recently been pointed out by Bateson[16] that the law of heredity discovered by Mendel offers a reasonable account of such phenomena. It asserts that as regards two mutually exclusive characters, one of which tends to be dominant and the other recessive, cross-bred organisms will produce germinal cells (gametes) each of which, as regards the characters in question, conforms to one or other of the pure ancestral types and is therefore incapable of transmitting the opposite character. When a recessive gamete meets one of the dominant type the resulting organism (the zygote) will usually exhibit the dominant character, whereas when two recessive gametes meet the recessive character will necessarily be manifested in the zygote. In the case of a rare recessive characteristic we may easily imagine that many generations may pass before the union of two recessive gametes takes place. The application of this to the case in question is further pointed out by Bateson, who, commenting upon the above observations on the incidence of alkaptonuria, writes as follows:[17] "Now there may be other accounts possible, but we note that the mating of first cousins gives exactly the conditions most likely to enable a rare, and usually recessive, character to show itself. If the bearer of such a gamete mate with individuals not bearing it the character will hardly ever be seen; but first cousins will frequently be the bearers of similar gametes, which may in such unions meet each other and thus lead to the manifestation of the peculiar recessive characters in the zygote." Such an explanation removes the question altogether out of the range of prejudice, for if it be the true account of the matter it is not the mating of first cousins in general but of those who come of particular stocks that tends to induce the development of alkaptonuria in the offspring. For example, if a man inherit the tendency on his father's side his union with one of his maternal first cousins will be no more liable to result in alkaptonuric offspring than his marriage with one who is in no way related to him by blood. On the other hand, if members of two families who both inherit the strain should intermarry the liability to alkaptonuria in the offspring will be as great as from the union of two members of either family, and it is only to be expected that the peculiarity will also manifest itself in the children of parents who are not related. Whether the Mendelian explanation be the true one or no there seems to be little room for doubt that the peculiarities of the incidence of alkaptonuria and of conditions which appear in a similar way are best explained by supposing that, leaving aside exceptional cases in which the character, usually recessive, assumes dominance, a peculiarity of the gametes of *both* parents is necessary for its production.

Hitherto nothing has been recorded about the children of alkaptonuric parents, and the information supplied by Professor Osler and Dr. Ogden on this point has therefore a very special interest. Whereas Professor Osler's case shows that the condition may be directly inherited from a parent Dr. Ogden's case demonstrates that none of the children of such a parent need share his peculiarity. As the matter now stands, of five children of two alkaptonuric fathers whose condition is known only one is himself alkaptonuric. It will be interesting to learn whether this low proportion is maintained when larger numbers of cases shall be available. That it will be so is rendered highly probable by the undoubted fact that a very small proportion of alkaptonurics are the offspring of parents either of whom exhibits the anomaly. It would also be extremely interesting to have further examples of second marriages of the parents of alkaptonurics. In the case of the family observed by Dr. Kirk the only child of the second marriage of the father, not consanguineous, is a girl who does not exhibit the abnormality. The only other available example is recorded by Embden. The two alkaptonurics studied by Professor Baumann and himself were a brother and sister born out of wedlock, and as far as could be ascertained the condition was not present in the children of the subsequent marriages which both parents contracted. The patient of Noccioli and Domenici was a twin, and I gather from Professor Noccioli's kind letter that the other twin was also a female, did not survive, and was not alkaptonuric. Further particulars are wanting, and the information was derived from the patient herself, who is described as a woman of limited intelligence but who was aware that in her own case the condition had existed from infancy. It is difficult to imagine that of twins developed from a single ovum one should be alkaptonuric and the other normal, but this does not necessarily apply to twins developed from separate ova.

It may be objected to the view that alkaptonuria is merely an alternative mode of metabolism and not a morbid condition, that in a few instances, not included in the above tables, it appears not to have been congenital and continuous but temporary or intermittent. In some of the cases referred to the evidence available is not altogether conclusive, and it is obvious that for the proof of a point of so much importance to the theory of alkaptonuria nothing can be regarded as wholly satisfactory which falls short of a complete demonstration of the presence of homogentisic acid in the urine at one time and its absence at another. The degree and rate of darkening of the urine vary at different periods apart from any conspicuous fluctuations in the quantity of homogentisic acid which it contains. The staining of linen in infancy is a much more reliable indication, especially if the mother of the child has had previous experience of alkaptonuric staining. In Geyger's case[18] of a diabetic man the

[15] G. Darwin: Journal of the Statistical Society, 1875, vol. xxxviii., p. 153.

[16] W. Bateson: Mendel's Principles of Heredity, Cambridge, 1902.

[17] W. Bateson and Miss E. R. Saunders: Report to the Evolution Committee of the Royal Society, No. 1, 1902, p. 133, note.

[18] A. Geyger: Pharmaceutische Zeitung, 1892, p. 488.

intermittent appearance in the urine of an acid which he identified with the glycosuric acid of Marshall was established beyond all doubt, and the melting-point and proportion of lead in the lead salt render it almost certain that he was dealing with homogentisic acid. In Carl Hirsch's case[17] a girl, aged 17 years, with febrile gastro-intestinal catarrh, passed dark urine which gave the indican reaction for three days. Professor Siegfried extracted by shaking with ether an acid which gave the reactions of homogentisic acid and formed a sparingly soluble lead salt. Neither the melting-point of the acid nor any analytical figures are given. After three days the urine resumed its natural colour and reactions.

Von Moraczewski[20] also records a case of a woman, aged 43 years, who shortly before her death passed increasingly dark urine, rich in indican, from which he extracted an acid which had the melting-point and reactions of homogentisic acid. Such increasing darkening of the urine as was here observed not infrequently occurs with urines rich in indoxyl-sulphate, as Baumann and Brieger first pointed out, and this was probably a contributory factor in the production of the colour which first called attention to the condition. Stange[21] has described a case in which the presence of homogentisic acid was very fully established, but he clearly does not regard the mother's evidence as to the intermittent character of the condition as conclusive. Zimnicki's[29] case of intermittent excretion of homogentisic acid by a man with hypertrophic biliary cirrhosis is published in a Russian journal which is inaccessible to me, and having only seen abstracts of his paper I am unacquainted with the details. Of hearsay evidence the most convincing is afforded in Winternitz's cases.[23] The mother of seven children, three of whom are alkaptonuric, was convinced that whereas two of her children had been alkaptonuric from the earliest days of life this had not been so with the youngest child in whom she had only noticed the peculiarity from the age of five years. This is specially interesting as supplying a link between the temporary and congenital cases. In a somewhat similar case described by Maguire[24] the evidence of a late onset is not so conclusive. Slosse's case[25] in which, as in von Moraczewski's, the condition apparently developed in the last stages of a fatal illness, completes the list of those falling into the temporary class. Evidently we have still much to learn about temporary or intermittent alkaptonuria, but it appears reasonable to suppose that those who exhibit the phenomenon are in a state of unstable equilibrium in this respect, and that they excrete homogentisic acid under the influence of causes which do not bring about this result in normal individuals. There is reason to believe that a similar instability plays a not unimportant part in determining the incidence of certain forms of *disease* in which derangements of metabolism are the most conspicuous features. Thus von Noorden,[26] after mentioning that diabetes occasionally develops at an early age in brothers and sisters and comparatively seldom occurs in the children of diabetic parents, adds that in three instances he has met with this disease in the offspring of marriages of first cousins. In one such family two out of six children, in another two out of three, and in the third the only two children became diabetic at ages between one and four years.

The view that alkaptonuria is a "sport" or an alternative mode of metabolism will obviously gain considerably in weight if it can be shown that it is not an isolated example of such a chemical abnormality, but that there are other conditions which may reasonably be placed in the same category. In the phenomenon of albinism we have an abnormality which may be looked upon as chemical in its basis, being due rather to a failure to produce the pigments of the melanin group which play so conspicuous a part in animal colouration than to any defect of development of the parts in which in normal individuals such pigments are laid down. When we study the incidence of albinism in man we find that it shows a striking resemblance to that of alkaptonuria. It, too, is commoner in males than in females, and tends to occur in brothers and sisters of families in which it has not previously appeared, at least in recent generations. Moreover, there is reason to believe that an undue proportion of albinos are the offspring of marriages of first cousins. Albinism is mentioned by most authors who have discussed the effects of such marriages and Arcoleo,[27] who gives some statistics of albinism in Sicily, states that of 24 families in which there were 62 albino members five were the offspring of parents related to each other in the second canonical degree. On the other hand, Bemiss[28] found that of 191 children of 34 marriages of first or second cousins five were albinos. In a remarkable instance recorded by Devay[29] two brothers married two sisters, their first cousins. There were no known instances of albinism in their families, but the two children of the one marriage and the five children of the other were all albinos. After the death of his wife the father of the second family married again and none of the four children of his second marriage were albinos. Again, albinism is occasionally directly inherited from a parent, as in one instance quoted by Arcoleo, but this appears to be an exceptional occurrence. The resemblance between the modes of incidence of the two conditions is so striking that it is hardly possible to doubt that whatever laws control the incidence of the one control that of the other also.

A third condition which suggests itself as being probably another chemical "sport" is cystinuria. Our knowledge of its incidence is far more incomplete and at first sight direct inheritance appears to play here a more prominent part. However, when more information is forthcoming it may turn out that it is controlled by similar laws. In this connexion a most interesting family described by Pfeiffer[30] is very suggestive. Both parents were normal, but all their four children, two daughters and two sons, were cystinuric. The elder daughter had two children neither of whom was cystinuric. A number of other examples of cystinuria in brothers and sisters are recorded, but information about the parents is wanting, except in the cases of direct transmission. In some of the earlier cases such transmission through three generations was thought to be probable, but the presence of cystin in the urine of parent and child has only been actually demonstrated in two instances. In Joel's[31] often-quoted case it was only shown that the mother's urine contained excess of neutral sulphur. E. Pfeiffer[32] found cystin in the urine of a father and son and in a family observed by Cohn[33] the mother and six of her children shared the peculiarity. As more than 100 cases are on record the proportion of cases of direct inheritance has not hitherto been shown to be at all high and Pfeiffer's first case shows that, as with alkaptonuria, the children of a cystinuric parent may escape. A large majority of the recorded cystinurics have been males. There is as yet no evidence of any influence of consanguinity of parents and in the only two cases about which I have information the parents were not related. Neither has it yet been shown that cystinuria is a congenital anomaly, although in one case, at any rate, it has been traced back to the first year of life. Observations upon children of cystinuric parents from their earliest infancy or upon newly-born brothers or sisters of cystinurics would be of great interest and should in time settle this question. Lastly, it seems certain that, like alkaptonuria, this peculiarity of metabolism is occasionally temporary or intermittent. The so frequent association with cystinuria of the excretion of cadaverine and putrescine adds to the difficulty of the problem of its nature and upon it is based the infective theory of its causation. However, it is possible that, as C. E. Simon[34] has suggested, these diamines may themselves be products of abnormal metabolism. Unlike alkaptonuria and albinism cystinuria is a distinctly harmful condition, but its ill effects are secondary to its deposition in crystalline form and the readiness with

[17] C. Hirsch: Berliner Klinische Wochenschrift, 1897, Band xxxiv., p. 566.
[20] W. von Moraczewski: Centralblatt für die Innere Medicin, 1896, Band xvii., p. 177.
[21] P. Stange: Virchow's Archiv, 1896, Band cxlvi., p. 66.
[22] Zimnicki: Jescheneteluik, 1900, No. 4. Abstract, Centralblatt für Stoffwechsel und Verdauungs-Krankheiten, 1900, Band i., p. 343.
[23] Winternitz: Münchener Medicinische Wochenschrift, 1899, Band xlvi., p. 749.
[24] R. Maguire: Brit. Med. Jour., 1884, vol. ii., p. 308.
[25] A. Slosse: Annales de la Société Royale des Sciences Médicales et Naturelles, Bruxelles, 1895, tome iv., p. 89.
[26] Von Noorden: Die Zuckerkrankheit, 3. Aufgabe, 1901, p. 47.
[27] G. Arcoleo: Sull' Albinismo in Sicilia. See notice in Archivio per l'Anthropologia, 1871, vol. i., p. 367.
[28] Bemiss: Journal of Psychological Medicine, 1857, vol. x., 368.
[29] Devay: Du Danger des Mariages Consanguins, &c., Paris, 1857.
[30] E. Pfeiffer: Centralblatt für Krankheiten der Harn- und Sexual-Organe, 1894, Band v., p. 187.
[31] Joel: Annalen der Chemie und Pharmacologie, 1855, p. 247.
[32] E. Pfeiffer: Centralblatt für Krankheiten der Harn- und Sexual-Organe, 1897, Band viii., p. 173.
[33] J. Cohn: Berliner Klinische Wochenschrift, 1899, Band xxxvi., p. 503.
[34] C. E. Simon: American Journal of the Medical Sciences, 1890 vol. cxlx., p. 39.

which it forms concretions. Its appearance in the urine is not associated with any primary morbid symptoms. All three conditions above referred to are extremely rare and all tend to advertise their presence in conspicuous manners. An albino cannot escape observation; the staining of clothing and the colour of the urine of alkaptonurics seldom fail to attract attention, and the calculous troubles and the cystitis to which cystinurics are so liable usually bring them under observation sooner or later. May it not well be that there are other such chemical abnormalities which are attended by no obvious peculiarities and which could only be revealed by chemical analysis? If such exist and are equally rare with the above they may well have wholly eluded notice up till now. A deliberate search for such, without some guiding indications, appears as hopeless an undertaking as the proverbial search for a needle in a haystack.

If it be, indeed, the case that in alkaptonuria and the other conditions mentioned we are dealing with individualities of metabolism and not with the results of morbid processes the thought naturally presents itself that these are merely extreme examples of variations of chemical behaviour which are probably everywhere present in minor degrees and that just as no two individuals of a species are absolutely identical in bodily structure neither are their chemical processes carried out on exactly the same lines. Such minor chemical differences will obviously be far more subtle than those of form, for whereas the latter are evident to any careful observer the former will only be revealed by elaborate chemical methods, including painstaking comparisons of the intake and output of the organism. This view that there is no rigid uniformity of chemical processes in the individual members of a species, probable as it is *a priori*, may also be arrived at by a wholly different line of argument. There can be no question that between the families, genera and species both of the animal and vegetable kingdoms, differences exist both of chemical composition and of metabolic processes. The evidences for this are admirably set forth in a most suggestive address delivered by Professor Huppert[35] in 1895. In it he points out that we find evidence of chemical specificity of important constituents of the body, such as the haemoglobins of different animals, as well as in their secretory and excretory products such as the bile acids and the cynuric acid of the urine of dogs. Again, in their behaviour to different drugs and infecting organisms the members of the various genera and species manifest peculiarities which presumably have a chemical basis, as the more recent researches of Ehrlich tend still further to show. To the above examples may be added the results of F. G. Hopkins's[36] well-known researches on the pigments of the pieridæ and the recent observations of the precipitation of the blood proteids of one kind of animal by the serum of another. From the vegetable kingdom examples of such generic and specific chemical differences might be multiplied to an almost indefinite extent. Nor are instances wanting of the influence of natural selection upon chemical processes, as for example, in the production of such protective materials as the sepia of the cuttle-fish and the odorous secretion of the skunk, not to mention the innumerable modifications of surface pigmentation. If, then, the several genera and species thus differ in their chemistry we can hardly imagine that within the species, when once it is established, a rigid chemical uniformity exists. Such a conception is at variance with all that is known of the origin of species. Nor are direct evidences wanting of such minor chemical diversities as we have supposed to exist within the species. Such slight peculiarities of metabolism will necessarily be hard to trace by methods of direct analysis and will readily be masked by the influences of diet and of disease, but the results of observations on metabolism reveal differences which are apparently independent of such causes, as for example, in the excretion of uric acid by different human individuals. The phenomena of obesity and the various tints of hair, skin, and eyes point in the same direction, and if we pass to differences presumably chemical in their basis idiosyncrasies as regards drugs and the various degrees of natural immunity against infections are only less marked in individual human beings and in the several races of mankind than in distinct genera and species of animals.

If it be a correct inference from the available facts that the individuals of a species do not conform to an absolutely rigid standard of metabolism, but differ slightly in their chemistry as they do in their structure, it is no more surprising that they should occasionally exhibit conspicuous deviations from the specific type of metabolism than that we should meet with such wide departures from the structural uniformity of the species as the presence of supernumerary digits or transposition of the viscera.

Chandos-street, W.

[35] Hupp: Ueber die Erhaltung der Arteigenschaften, Prague, 1896.
[36] F. G. Hopkins: Philosophical Transactions of the Royal Society, 1895, vol. clxxxvi, B., p. 661.

ABLATION OF THE CRYSTALLINE LENS TO RECTIFY HIGH MYOPIA.

BY SIR WILLIAM J. COLLINS, M.S., M.D. LOND., F.R.C.S. ENG.,
SURGEON TO THE ROYAL EYE HOSPITAL; OPHTHALMIC SURGEON TO THE NORTH-WEST LONDON HOSPITAL.

SOME seven years ago my friend, Mr. C. Wray, who was then assisting in my clinique at the Royal Eye Hospital, made a collection of cases of myopia having more than 10 dioptres of error with a view to ascertain the liability to visual degeneration, choroidal change, and retinal detachment to which such myopes were exposed as age advanced. The results of these observations were embodied in a communication to the Ophthalmological Society by Mr. Wray on Jan. 31st, 1895, entitled "The Extraction of Transparent Lenses in High Myopia." It appeared that while nearly a fourth of these cases of highly myopic eyes had a visual acuity of less than $\frac{6}{36}$ (corrected) the vast majority of such cases owed their visual defect to retino-choroidal degeneration and very few indeed to retinal detachment. The discussion which followed the paper indicated that in 1895 the operation of di-cission of clear lenses for myopia was almost unknown or very little practised in this country.

When the question was again brought before the Ophthalmological Society on June 9th, 1899, in an able and comprehensive paper by Mr. F. R. Cross, it was clear that the operation practised by A. Weber, condemned by von Graefe and Donders, and revived by Fukala, was passing out of the experimental stage and was taking a recognised place in ophthalmic surgery. It was also clear that caution and judgment were required in deciding in each particular case as to whether operation was advisable or not. It therefore seems desirable that all cases of ablation of the lens with a view to rectify high myopia should be carefully noted and published. The following are all the cases in which I had performed this operation up to the end of 1901.

CASE 1.—A young woman, aged 23 years, had never worn glasses until four years previously. Since then she had worn −10 D. for each eye but the sight was getting shorter. The vision in the right eye was $\frac{6}{9}$ c. − 23 D. = $\frac{6}{24}$ partly and J. 10 only; in the left eye it was $\frac{6}{9}$ c. − 21 D. = $\frac{6}{18}$ and J. 1 very close. On March 21st, 1900, the right lens was needled. On April 2nd some pain and tension were present. The temperature was 99° F. Lens matter was evacuated. On the 19th more lens matter had come well forward into the anterior chamber; this was again evacuated. On May 1st the vision in the right eye without a glass was $\frac{6}{12}$ and J. 10, c. + 2 D. J. 4. On the 4th she could read J. 1 with the operated eye with a + 2·50 D. On the 10th while dusting in the ward the patient noticed that her vision was misty and said that she could not count fingers. Ophthalmoscopically nothing abnormal could be seen. She was kept in bed for a few days and when discharged she could read J. 1 with the operated eye and her distant vision from having been $\frac{6}{9}$ before operation was improved to $\frac{6}{12}$. On Sept. 8th, 1902, she again reported herself. The vision of the operated eye was the same and that of the other eye was only $\frac{6}{9}$ with a glass and J. 2 at four inches. The patient begged to have the other eye operated on as she found so great benefit from the improvement effected in the operated eye.

CASE 2.—A girl, aged 11 years, very fair and rather small for her age, had been attending my clinique at the Royal Eye Hospital from March 15th, 1899. Her note showed that she then had myopia of about nine dioptres. On May 29th it was noted that there were "thinning of choroids and posterior staphylomata." She had been ordered iodide of potassium and iodide of iron. On July 26th there was found to be myopia (with some astigmatism) of between 12 D. and 15 D. Vision = less than $\frac{6}{36}$ with either eye. On Jan. 15th, 1900, the right eye showed − 16 D in the horizontal meridian and − 20 D. in the vertical, and the left eye showed − 15 D. in the horizontal meridian and rather