CHAPTER II

THE INCIDENCE AND HEREDITY OF INBORN ERRORS OF METABOLISM

All the known inborn errors of metabolism are extremely rare, and it is probable that the rarity of albinism in man, of which each of us is able to judge from personal observation, is no greater than that of the other anomalies. Statistics collected in Italy indicate that, in that country, about 1 individual in 20,000 is an albino. It has seemed to me that cystinuria is the least rare of the six, but C. E. Simon met with only one cystin sediment among some 15,000 urines examined, and Primavera 1 in 20,000 urines. Striking testimony to the rarity of alcaptonuria is supplied by the frequency with which any one interested in the subject hears of the same case over and over again from fresh quarters, but very rarely of a new case. Pentosuria may well be less uncommon than the number of recorded cases suggests, whereas the very scanty records of cases of congenital haematoporphyrin, despite its far more conspicuous signs and effects, point to the exceptional rarity of that anomaly. Of the frequency of the occurrence of congenital steatorrhoea it is too soon to speak; up to now only three cases have been recorded.

All six anomalies are wont to occur in several members of a family, most often in brothers and sisters whose parents do not share their peculiarity, and whose children, also, are usually immune.

All are much commoner in males than in females, and
the following figures show a resemblance so remarkable as to suggest some underlying law:

<table>
<thead>
<tr>
<th></th>
<th>No. of cases</th>
<th>Males</th>
<th>Per cent.</th>
<th>Females</th>
<th>Per cent.</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Albinism</td>
<td>1,000</td>
<td>566</td>
<td>56.6</td>
<td>434</td>
<td>43.4</td>
</tr>
<tr>
<td>Alcaptonuria</td>
<td>112</td>
<td>74</td>
<td>66.07</td>
<td>38</td>
<td>33.03</td>
</tr>
<tr>
<td>Cystinuria</td>
<td>150</td>
<td>103</td>
<td>68.60</td>
<td>47</td>
<td>31.34</td>
</tr>
<tr>
<td>Porphyrinuria</td>
<td>18</td>
<td>13</td>
<td>72.22</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Steatorrhoea</td>
<td>3</td>
<td>3</td>
<td>100.00</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pentosuria</td>
<td>44</td>
<td>33</td>
<td></td>
<td>11</td>
<td></td>
</tr>
</tbody>
</table>

There is no such preponderance of males among the subjects of structural malformations, as far as can be judged from figures collected from the records of two large hospitals; and it is a remarkable fact that in the majority of reputed cases of temporary alcaptonuria the subjects have been females, and that toxic porphyrinuria, due to sulphonial, is almost confined to women.

To the students of heredity the inborn errors of metabolism offer a promising field of investigation, but their adequate study from this point of view is beset with many difficulties. Save in the case of albinism one is driven to rely upon the casual mating of human beings, and the conclusions based thereon cannot be checked by experimental breeding of animals. It is true that cystinuria is known to occur in dogs. A calculus obtained from a dog was described by Lassaigne\(^1\) in 1823, and other examples have since been recorded,\(^2\) but hitherto the diagnosis has only been made after the death of the animal, and no

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* The figures for albinism are extracted from the pedigrees published by Pearson, Nettleship, and Usher in their *Monograph of Albinism in Man*; those for alcaptonuria embrace all the recorded cases except a few in which the sex is not stated, or which have not been accessible; those for cystinuria are compiled from the tables of Desmoulière and Link, and the remainder from recorded cases.

1 *Annales de Chimie*, 1823, 2\(^{e}\) s., xxiii. 328.
opportunity has presented itself of utilizing this fact for
the advancement of the study of that anomaly. The
so-called ochronosis of lower animals, in which the bones
are deeply stained by deposition in them of a pigment of
the porphyrin group, bears witness to the occurrence of
porphyrinuria in them, but here again we have no know-
ledge of the clinical aspects of the condition.

Again, it is naturally far more difficult to collect information
as to the occurrence of chemical than of structural anomalies
in past generations of a family, save in the case of albinism
and possibly, of acaptonuria and hæmatoporphyrina. Even
as regards the relative numbers of normal and abnormal
members, a knowledge of which is so important in con-
exion with questions of heredity, the information available
is scanty and unreliable unless based upon personal examina-
tion. However, one point which stands out clearly is the
remarkable similarity of the modes of incidence of acapto-
uria and albinism, which suggests that the manifestation
of both is governed by the same laws. Both are apt to occur
in several brothers and sisters of a family whose parents
do not exhibit the anomaly, and direct transmission of
either from parent to child is very rare. It has been
repeatedly stated that a considerable proportion of human
albinos are the offspring of consanguineous marriages.
Thus Ascolco found that of 24 families which included
60 albino members 5 were the offspring of the mating of
first cousins. In only two instances was albinism directly
transmitted from parent to child.

Of 500 sibships (to adopt the term used by Karl Pearson
for families of children of the same parents and correspond-
ing to the German 'Geschwister') which I extracted from
the pedigrees of albinism in man, 110 were the offspring of
consanguineous marriages; the parents of 174 were not
blood relations, and concerning 216 no information on this
point is forthcoming. Such information is seldom given
unless asked for, and we certainly are not justified in assuming that where the point is not mentioned there was no consanguinity. The inquiries which I made some twenty years ago into recorded cases of alcaptonuria showed how fallacious such an assumption would be. Accordingly if we take only those families about which we have definite information, we find that of 284 sibships 110, or 38.73 per cent., were the offspring of consanguineous unions of various degrees.

Of 73 sibships, containing more than 100 alcaptonuric members in all, 12 were the offspring of unions of first cousins, the parents of 29 were not akin, and in the records of the remaining 32 the point is not mentioned. This corresponds to a percentage of 29.27, of the families concerning which such information is forthcoming.*

There appears to be a close connexion between the occurrence of an anomaly in several children of normal parents and consanguinity of the parents, a connexion which has been emphasized by Feer. No one would suggest nowadays that the mere fact that the parents are of one blood would cause an anomaly to appear de novo in their children, but it is obvious that the reappearance of a latent character which both parents tend to transmit is likely to be favoured by the mating of members of certain families.

The statistics as to the proportion of first-cousin marriages in this country are very scanty. Sir George Darwin calculated that less than 3 per cent. of all marriages

* These figures for alcaptonuria rest, in part, upon supplementary information kindly furnished by authors of papers, which does not appear in the published records. The families with consanguinity have been recorded by Kirk, Pavy, Erich Meyer, Ogden, Hammarsten, Rutgers, and Hijmans van den Bergh, Cronvall, Poulsen, Kolaczek, Debenedetti, Cuthbert, and myself.

* Jahrbuch für Kinderheilkunde, 1907, lxvi. 188.

* Journal of the Statistical Society, 1875, xxxviii. 153.
are of this class, and Professor Karl Pearson\(^5\) has collected some figures which give a percentage of 4·9 first-cousin marriages among the professional classes, a figure which, for reasons which he states, he regards as probably somewhat too high, and of 0·86 among the classes from which patients in London hospitals are drawn. The percentages of consanguineous marriages of all degrees in the two classes were 7·76 and 1·3 respectively. Hence it is obvious that the proportion of such marriages among the parents of alcaptonuric families is altogether abnormal. On the other hand, the proportion of alcaptonurics among children of such marriages must be very small indeed. Only some 120 cases of alcaptonuria have been recorded in Europe and America, whereas in London alone there are probably many thousands of children of first cousins.

It was pointed out by Bateson,\(^6\) and has been emphasized by Punnett,\(^7\) that the mode of incidence of alcaptonuria finds a ready explanation if the anomaly in question be regarded as a rare recessive character in the Mendelian sense. Mendel's law asserts that as regards two mutually exclusive characters one of which tends to be dominant and the other recessive, cross-bred individuals will tend to manifest the dominant character, but when they inter-breed the offspring of the hybrids will exhibit one or other of the characters and will consist of dominants and recessives in definite proportions. Mendel's theory explains this by the supposition that the germinal cells or gametes of each generation are pure as regards the qualities in question, and accounts for the numerical results observed by the production of dominant and recessive gametes in equal numbers. Of the offspring of two hybrids, one

\(^4\) Brit. Med. Jour., 1908, i. 1396.
\(^6\) Proceedings of the Royal Society of Medicine, 1908, vol. i, Epidemiological Section, p. 148.
quarter will result from the union of two dominant gametes and will produce such gametes only; another quarter will result from the union of recessive gametes and will produce only recessive gametes. The remaining half will themselves manifest the dominant character, but will be hybrids like their parents and will produce gametes of both varieties. Only when two recessive gametes meet in fertilization will the resulting individual show the recessive character. This is conveniently expressed by designating the union of the hybrids as DR × DR, and the offspring of such a union as 1 DD – 2 DR – 1 RR.

If the recessive character be a rare one many generations may elapse before the union of two such gametes occurs, for the families in which they are produced will be few in number and the chance that in any given marriage both parents will contribute both R and D gametes will be very small. When, however, intermarriage occurs between two members of such a family the chance will be much greater, and of the offspring of such a marriage several are likely to exhibit the peculiarity. The rarer the anomaly the more conspicuous should be the influence of consanguinity. When a recessive individual mates with an apparent dominant, who produces both R and D gametes, a larger proportion of the offspring (viz. ½) will be recessives, and we should expect that recessive children of a recessive parent, but whose other parent is apparently normal, will occasionally be met with. Of such direct transmission of alkaptonuria from parent to child, the other parent not being alkaptonuric, several examples are known. One of these was observed by Osler. An alcaptonuric father whose brother also showed the anomaly had an alcaptonuric son. The second case, which was recorded by Orsi, was that of a mother and her son and daughter, all alcap-

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* See Garrod, The Lancet, 1902, ii. 1617.
* Gazzetta Medica Lombarda, 1889, xlviii. 115.
tonuric, a third by Umber and Bürger,\textsuperscript{10} that of an alcaptonuric father who begat four alcaptonuric sons.\textsuperscript{11} Lastly, when recessive mates with recessive all the offspring should manifest the recessive character, and cases are recorded in the statistics of human albinism; but no such marriage of alcaptonurics is known to have occurred. Whereas in animals, such as mice, which produce a numerous progeny the proportions of dominants and recessives among their offspring can be readily observed, the results of the chance matings of human beings, who are so much less prolific, are far less demonstrative.

It must be confessed, indeed, that as regards human characteristics the relative numbers of dominant and recessive offspring have often departed widely from those required by Mendel's law, but a number of sources of error will tend to vitiate such results. Experience has shown that the information supplied as to the normality or otherwise of other members of a patient's family can seldom be relied upon, and this is especially the case with chemical anomalies. An individual in middle life seldom knows much about his brothers and sisters who died in infancy. Miscarriages must be taken into account, and again the figures supplied may relate to incomplete families and may be profoundly modified by subsequent births. As regards the figures available for alcaptonuria they do not depart more widely from Mendelian requirements than do those for human albinism,\textsuperscript{12} although in selective breeding of lower animals albinism behaves as a recessive character.\textsuperscript{13} One fact stands out clearly, that in any collection of families,

\textsuperscript{10} \textit{Deutsche med. Wochenschr.}, 1913, xxxix. 2337.

\textsuperscript{11} In Fromherz' family the mother appears to be an intermittent alcaptonuric, but he was not able to satisfy himself fully that this was the case.

\textsuperscript{12} Castle and Allen, \textit{Proceedings of the American Academy of Arts and Sciences}, 1903, xxxviii. 603.

\textsuperscript{13} \textit{Brit. Med. Jour.}, 1908, i. 1252.
and in most individual families, the normal considerably outnumber the alcaptonuric members. Thus in 13 recorded families of 5 or more collaterals there were 100 members, of whom 68 were normal DD or DR and 32 alcaptonuric RR, not 25 as required by Mendel's law. Fifty such sibships, with five or more members, extracted from Pearson's pedigrees of albinism, contained 449 individuals, of whom 306 were normal and 143 albinotic, a proportion of DD + DR 68·15 and RR 31·85 amongst 100 individuals, figures almost identical with those for alcaptonuria.

Toenniessen, in a recent paper, quotes three sibships which include 31 members of whom 23 were normal and 8 alcaptonuric, numbers which agree closely with those to be expected from the crossing of DR with DR, and in the first edition of this book I pointed out that the recorded sibships with five or more members, at that time nine in number, yielded the following figures: Total 76 members, DD + DR 57, RR 19, but the inclusion of families since recorded raised the RR figure from 25 to 32 per cent. It is obvious that by including only the larger families we reduce the source of error.

Toenniessen also quotes the pedigree published by Umber and Bürger of a family in which of the eight children of an alcaptonuric father and a normal mother four were alcaptonuric. These figures are in strict accord with Mendelian requirement, for a union of RR × DR should yield equal numbers of recessives and apparent dominants.

As an alternative Toenniessen considers the possibility that alcaptonuria may be the product of two dominant factors, but considers this to be excluded by the known fact that, as a rule the offspring of the union of an alcaptonuric with a normal individual are all normal, whilst in one at least of the very rare instances of direct transmission of

\[\text{Zeitschrift f. induktive Abstammungs- und Vererbungslehre, 1922, xxix. 26.}\]
the anomaly the proportion of alcaptonurics to normal individuals was 1:1, not 3:1 as that hypothesis demands.

The known alcaptonuric families supply five examples of twin births. In three cases the twins were of different sexes; in two instances one twin was certainly, and in the remaining three was probably, normal; and in three cases the normal twin died whereas the alcaptonuric survived.

In the albino pedigrees referred to I find 29 records of twins one or both albinotic. In 11 pairs both were albinos and in 18 one twin was normal. In 20 cases the twins were of the same sex and in seven of different sexes; the sex of two pairs is not stated. Ten pairs with both albinotic were of the same sex.

The available evidence regarding the inheritance of cystinuria is much more scanty than that relating to alcaptonuria. This is largely due to the less obvious character of the anomaly, for it is only by careful examination of the urine of each member of a family that any certainty can be reached as to the numbers of cystinuric and normal members. A cystinuric does not necessarily form calculi, and at any given time his urine may deposit no crystals, nor are the statements of patients as to other members of their families of any value in this connexion, save that a history of several cases of 'stone' may be suggestive. Such information as is forthcoming points to a greater frequency of direct transmission from parent to child than is met in connexion with the other metabolic errors, and in more than one instance cystinuria has been traced with certainty in three successive generations. Thus in the family investigated by Abderhalden the

paternal grandfather and father were cystinuric, whereas the mother was normal. Of five children, one had died with symptoms of inanition at twenty-one months, and deposits of cystin were found in its tissues; two others had died with like symptoms at nine and seventeen months respectively, but were not known to excrete cystin. The surviving children, aged five and a half years and fourteen months respectively, were both cystinuric. Such large proportion of cystinuric members as was here met with has been observed in other families. In one which Cohn described a cystinuric mother and a normal father had twelve children. The urine of two of them could not be obtained, but of the remaining ten no less than seven excreted cystin. Again, Pfeiffer records four children of normal parents who were, as he has informed me, first cousins, all of whom were cystinuric. The two children of one of the affected daughters were normal. In another family which has come under my notice, in which two out of six children were cystinuric, the parents were the children of half-brothers.

Pfeiffer's example of a family in which all the members of a sibship were affected does not stand alone, and I have myself had under observation a family of three children, of normal parents who were not related in blood, all of whom were cystinuric. One brother had passed several cystin calculi, but his brother and sister had not suffered in any way, and the abundant cystin crystals in their urine were only found in the course of a routine examination of the members of the family.

In a family described by Cohn there were twin boys, both cystinuric, and there was a similar pair of male twins with cystinuria in that described by Krotschmer.  

16 Berliner klinische Wochenschrift, 1899, xxxvi. 503.  
17 Centralblatt für Krankheiten der Harn- und Sexual-Organe, 1897, viii. 173.  
18 Berliner klinische Wochenschrift, 1899, xxxvi. 503.  
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I know of no instance in which all the members of a sibship exhibited any of the other metabolic errors, and this peculiarity of cystinuria, coupled with the greater frequency of its direct transmission, suggests that this anomaly is subject to different laws of heredity from those which control the incidence of albinism and alcaptonuria. Possibly, as Professor Punnett has suggested to me, two factors are concerned, both of which must be present to produce a cystinuric, but until more pedigrees are available, based upon systematic examination of all members of the families dealt with, we cannot hope to gain any better knowledge of the mode of transmission of this anomaly.

The heredity of pentosuria is especially difficult to trace. Only by systematic testing of the urine of all the members of a family can its distribution be made out, and even such slight help as is afforded by a history of urinary calculi in a cystinuric family is here lacking. In a sibship of five investigated by Bial\(^{20}\) one brother and two sisters were pentosuric, whereas the urine of the father, of the two remaining brothers, and of two children of the affected members contained no pentose. A pedigree given by af Klercker\(^{21}\) includes three generations of a Jewish family in which glycosuria also occurred. In the second generation the second and fifth members of a sibship of seven were pentosuric; the father and mother, who were not related, and two children of the eldest (normal) son did not excrete pentose. Other examples of pentosuria in brothers and sisters have been recorded by Brat\(^{22}\) and Janeway,\(^{23}\) and Cammidge and Howard\(^{24}\) met with this anomaly in a father and son of Greek descent and in a Jewish uncle and nephew,

\(^{20}\) *Berliner klinische Wochenschrift*, 1904, xli. 552.

\(^{21}\) *Nordiskt medicinskt Arkiv*, 1905, Afd. 2, Häft 1, p. 55.

\(^{22}\) *Zeitschrift f. klin. Medizin*, 1902, xlvi. 499.

\(^{23}\) *American Journal of Medical Sciences*, 1906, cxxxii. 423.

\(^{24}\) *British Medical Journal*, 1920, ii. 777.
the only cases in which it is known to have occurred in two generations.

It would seem that there is a special liability to this anomaly in the Jewish race, for among forty-four penta-
surics no less than ten are stated to have been Jews, and of the seven cases met with by Camidge and Howard, three were in members of that race.

Of congenital hæmatoporphyrria there are, as yet, less than twenty cases on record. McCall Anderson 25 met with it in two brothers, and further inquiry showed that they were the third and fourth members of a sibship of seven, and that a sister, who died at the age of 15, is reputed to have suffered from the same complaint. Ehrmann's 26 patient had a brother and sister with similar troubles, and the patients of Arzt and Hausmann 27 were brothers. The child investigated by Mackey and myself 28 is the youngest of five, and the only porphyrinic.

As regards consanguinity, all that is known up to now is that the parents of the patients of Arzt and Haus-
mann were first cousins, whereas those of the patients of Anderson, Günther, and Mackey and Garrod were not consanguineous.

Still more scanty, but of considerable interest, are the facts relating to congenital steatorrhœa. The first cases, described by Hurtley and myself, 29 were those of two brothers, the second and fifth of five children of a marriage of first cousins, whereas the only other case known is that recorded by R. Miller and H. Perkins 30 of a boy, the youngest of a family of three, whose parents were not consanguineous. As far as it goes the story recalls that of

25 British Journal of Dermatology, 1898, x. 1.
26 Archiv f. Dermatologie u. Syphilis, 1909, xxvii. 75.
27 Strahlentherapie, 1920, xi. 444.
28 Quarterly Journal of Medicine, 1922, xv. 310.
29 Ibid. 1913, vi. 242.
30 Ibid. 1920, xiv. 1
alcaptonuria, and suggests that the anomaly is a recessive characteristic.

It is to be regretted that so many observers of these anomalies have paid little or no attention to questions of their heredity, and that the materials for their study from that point of view are in consequence so sparse; but when the scraps of information available are pieced together there is revealed an underlying resemblance between them, which is specially evident in their sex-incidence, in their tendency to occur in several members of one generation of a family, and in the rarity of their direct transmission from parent to child. If the lack of a special enzyme be in each instance the underlying factor, it is to be expected that they should behave as Mendelian recessive characters.

Hitherto we have been considering these inborn errors of metabolism collectively, the points which they have in common, and the grounds for regarding them as constituting a distinct group of anomalies. But each one of them presents peculiar features of much interest which amply repay detailed consideration, if only on account of the light which their study throws upon the chemical processes at work in the normal human organism.