The Croonian Lectures

ON

INBORN ERRORS OF METABOLISM.

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LECTURE I.

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GENERAL AND INTRODUCTORY.

MR. PRESIDENT AND FELLOWS,—It is my first agreeable duty to offer my sincere thanks for the honour conferred upon me in the invitation to deliver the Croonian lectures of the current year before this College. I trust that the subject which I have selected will be found to conform closely to the instructions to the lecturer, for it is one which lies upon the very border-line of physiology and pathology and pertains to both sciences alike; nor is it without bearing upon the control and cure of disease, in so far as no study which helps to throw light upon the complex chemical processes which are carried out in the human organism can fail in the long run to strengthen our hands in the combat with the pathogenic influences which make for its destruction.

The differences of structure and form which serve to distinguish the various genera and species of animals and plants are among the most obvious facts of nature. For their detection no scientific training is needed, seeing that they cannot escape the notice of even the least cultivated intelligence. Yet with the growth of knowledge we have learned to recognise the uniformity which underlies this so apparent diversity and the genetic relationship of form to form. With regard to the chemical composition of the tissues of living organisms and the metabolic processes by which those tissues are built up and broken down, the advance of knowledge has been in the opposite direction, and the progress of chemical physiology is teaching us that behind a superficial uniformity there exists a diversity which is no less real than that of structure, although it is far less obvious. The differences of ultimate composition and crystalline form which distinguish the hæmoglobins of animals of distinct genera have long been known. That the fats of animals are not alike in composition is well recognised, as also are the differences of their bile acids, to quote only a few of the most conspicuous examples. As instances of distinctive end-products of metabolism may be mentioned kynurenic acid, which is present in the urine of animals of the canine tribe and which bears witness to a generic peculiarity in the manner of dealing with the tryptophane fraction of proteins, and the excretion by birds and reptiles of the bulk of their nitrogenous waste in the form of uric acid, whereas in the urine of mammals urea is the chief nitrogenous constituent.

A more extended study even by strictly chemical methods will doubtless serve to reveal innumerable minor differences, such as are foreshadowed by Przibram's[1] work on muscle proteins. The delicate ultra-chemical methods which the researches of recent years have brought to light, such as the precipitin test, reveal differences still more subtle, and teach the lesson that the members of each individual species are built up of their own specific proteins which resemble each other the more closely the more nearly the species are allied. Obviously it is among the highly complex proteins that such specific differences are to be looked for rather than in the simple end-products of their disintegration. The many amino-acids which enter into the structure of the protein molecules are capable of almost innumerable groupings and proportional representations, and each fresh grouping will produce a distinct protein; but all alike in their breaking down will yield the same simple end-products, urea, carbon dioxide, and others.

Nor can it be supposed that the diversity of chemical structure and process stops at the boundary of the species, and that within that boundary, which has no real finality, rigid uniformity reigns. Such a conception is at variance with any evolutionary conception of the nature and origin of species. The existence of chemical individuality follows of necessity from that of chemical specificity, but we should expect the differences between individuals to be still more subtle and difficult of detection. Indications of their existence are seen, even in man, in the various tints of skin, hair, and eyes, and in the quantitative differences in those portions of the end-products of metabolism which are endogenous and are not affected by diet, such as recent researches have revealed in increasing numbers. Even those idiosyncrasies with regard to drugs and articles of food which are summed up in the proverbial saying that what is one man's meat is another man's poison presumably have a chemical basis.

Upon chemical as upon structural variations the factors which make for evolution have worked and are working. Evidences of this are to be detected in many directions, as, for example, in the delicate selective power of the kidneys, in virtue of which they are enabled to hold back in the circulation the essential proteins of the blood but at the same time allow free passage to other proteins which are foreign to the plasma, such as hæmoglobin, egg albumin, and the Bence-Jones protein, when these are present in any but quite small amounts. The working of these factors is also seen in the various protective mechanisms against chemical poisons, such as that which averts the depletion of the fixed alkalies of the organism by the neutralisation of abnormal supplies of acids by ammonia. This mechanism is well developed in the carnivora and in man, but in vegetivorous animals which from the nature of their diet are little exposed to acidosis it appears to be wanting.

Even in the normal metabolic processes the working of such influences may be traced, as in the power which the organism possesses of destroying the benzene ring of those aromatic amino-acids which enter into the composition of proteins and cannot therefore be regarded as substances foreign to the body; whereas the benzene ring of foreign aromatic compounds, with very few exceptions, are left intact, and such compounds require to be rendered innocuous by being combined with sulphuric acid to form aromatic sulphates, or with glycocoll to form the acids of the hippuric group and so combined are excreted in the urine and got rid of. The few exceptions referred to are compounds which so closely resemble the protein fractions in their structure that they fall victims with these to the normal destructive processes.

The great strides which recent years have witnessed in the sciences of chemical physiology and pathology, the newly-acquired knowledge of the constitution of proteins and of the part played by enzymes in connexion with the chemical changes brought about within the organism, have profoundly modified our conceptions of the nature of the metabolic processes and have made it easier to understand how these changes may differ in the various genera and species. It was formerly widely held that many derangements of metabolism which result from disease were due to a general slackening of the process of oxidation in the tissues. The whole series of catabolic changes was looked upon as a simple combustion and according as the metabolic fires burnt brightly or burnt low the destruction of the products of the breaking down of food and tissues was supposed to be complete or imperfect. A very clear setting forth of such views will be found in the lectures of Bence Jones[2] on Diseases of Suboxidation, delivered and published in 1855, but the thesis in question is chiefly associated with the name of Bouchard,[3] who expounded it in his well-known lectures on Maladies par Ralentissement de la Nutrition, published in 1882. The so frequent clinical association of such maladies as gout, obesity, and diabetes was involved in its support, nor was it regarded as a serious obstacle to the acceptance of such views that there is but scanty evidence to show that failure to burn any particular metabolic product, such as glucose, is associated with inability to deal with others.

Nowadays, very different ideas are in the ascendant. The conception of metabolism in block is giving place to that of metabolism in compartments. The view is daily gaining ground that each successive step in the building up and

[1] Hofmeister's Beiträge, 1902, Band ii., p. 143.

[2] Medical Times and Gazette, 1865, vol. ii., pp. 29–83.

[3] Maladies par Ralentissement de la Nutrition, Paris, 1882.

breaking down, not merely of proteins, carbohydrates, and fats in general, but even of individual fractions of proteins and of individual sugars, is the work of special enzymes set apart for each particular purpose. Thus the notion of general suboxidation is reduced to very narrow limits, to the recognition of a controlling influence exercised by certain glandular organs, such as the thyroid, upon metabolism as a whole. For example, it is known that lævulose is not dealt with in the human organism in the same way as dextrose is but follows its own path. A patient whose power of burning dextrose is seriously impaired may yet utilise lævulose in the normal manner. Again, there is evidence to show that the several fractions of proteins, tyrosin, cystin, tryptophane, and the rest, do not merely serve as fuel for a common furnace but are dealt with each in a special manner and in successive stages.

It may well be that the intermediate products formed at the several stages have only momentary existence as such, being subjected to further change almost as soon as they are formed; and that the course of metabolism along any particular path should be pictured as in continuous movement rather than as series of distinct steps. If any one step in the process fail the intermediate product in being at the point of arrest will escape further change, just as when the film of a biograph is brought to a standstill the moving figures are left foot in air. All that is known of the course of catabolism tends to show that in such circumstances the intermediate product in being is wont to be excreted as such, rather than that it is further dealt with along abnormal lines. Indeed, it is an arguable question whether, under abnormal conditions, the metabolic processes are ever thrown out of their ordinary lines into entirely fresh ones, with the result that products are formed which have no place in the normal body chemistry. It is commonly assumed that this happens, but if the conception of metabolism in compartments, under the influence of enzymes, be a correct one, it is unlikely, *a priori*, that alternative paths are provided which may be followed when for any reason the normal paths are blocked. It is far easier to suppose that in such circumstances normal intermediate products are excreted without further change and that processes which in health play but small parts in metabolism are called into unwonted activity.

This conception of the permanency of the metabolic paths is no new one, for it may be read between the lines in the writings of some physiologists of the last century, and especially in those of Claude Bernard,[4] from which the following passage is translated:—

> It used to be supposed that in diabetes wholly new conditions were developed in the economy, under the influence of the morbid state, and that there resulted therefrom a special morbid product—namely, glucose. But it is admitted nowadays that the observed phenomena are to be explained by an augmentation, pure and simple, of a normal function in virtue of which glucose is formed in all subjects, even in health. It is clear that the malady is nothing more than a physiological phenomenon perturbed and exaggerated.

Still more striking is the following passage[5]:—

> Et maintenant oserait on soutenir qu'il faut distinguer les lois de la vie à l'état pathologique des lois de la vie à l'état normal? Ce serait vouloir distinguer les lois de la mécanique dans une maison qui tombe, des lois de la mécanique dans une maison qui tient debout.

To prove the truth of the contention put forward it would be necessary to show that every abnormal product found in the tissues or in the excreta, und r morbid conditions, can be ascribed to other causes than the deflexion of the metabolic processes into new and unwonted paths. It must be admitted that this cannot yet be asserted of all such products. For example, we are still ignorant of the parent substance and mode of origin of the remarkable Bence Jones protein which is excreted in the urine of patients with multiple myeloma, nor is there any evidence as yet forthcoming that it is a normal intermediate product of protein metabolism. Nevertheless, when an endeavour is made to classify the unusual constituents which are occasionally present in that most important animal excretion, the urine, it is found that there are few of them which cannot be accounted for as intermediate products incompletely burnt, or as exaggeration of traces normally present; if we exclude such as are merely foreign substances absorbed from the alimentary canal or derivatives of these, or are products of bacterial life and action in the intestines or in the tissues.

A number of unusual constituents of urine, and of normal constituents also, are derived from the alimentary canal. Thus foreign substances administered in food or as drugs may be excreted unchanged or may undergo oxidation or reduction in the intestine or after absorption, or again may appear in the urine in combination with products of metabolism. These last compounds, which result from the working of the chemical protective mechanisms, cannot be regarded as abnormal excreta. Even in health some tenth part of the total sulphuric acid of the urine is in combination with aromatic substances as ethereal sulphates. Traces of compound glycuronates are also normally present, and the aromatic constituents of vegetable foods are in part excreted in combination with glycocoll as hippuric acid and its allies. When other harmful substances, with which these protective mechanisms are competent to deal, are introduced in abnormal quantities the protective processes are stimulated to unwonted activity.

It does not necessarily follow that the substances which are utilised for such combinations are themselves intermediate products of normal metabolism, for it may well happen that combination has preceded oxidation. Thus the glycuronic acid which is excreted in compound glycuronates may not represent an intermediate stage in the breaking down of glucose as it has been supposed to do, for, as Emil Fischer has pointed out, the oxidation of the alcohol grouping of dextrose, whilst the less stable aldehyde grouping remains intact, is more easily explained on the supposition that the primary combination of the foreign substance is with glucose itself, and that, the aldehyde group being thus protected from change, oxidation to glycuronic acid occurs as a subsequent event.

Some excreta are due to the action of bacteria in the alimentary canal upon the proteins of food or upon constituents of the bile. Thus urobilin is formed by the intestinal bacteria from bilirubin and is abundantly present in the fæces so long as bile enters the intestine. From the intestine some urobilin is absorbed and is excreted in part in the bile and in part in the urine, whilst some of it is probably destroyed in the tissues. Again, from the tryptophane of ingested proteins the intestinal bacteria form indol, which after absorption is oxidised to indoxyl and is excreted in the urine, mainly as indoxyl sulphate, but in part in combination with glycuronic acid. Disease of the actual organs of excretion has conspicuous effects upon the excreta. Thus diseased kidneys may hold back in part some constituents of the urine or, on the other hand, may allow passage to the normal proteins of the blood serum which it is their function to retain in the circulation. Again, by the blockage of a duct, as in jaundice, the products of glandular activity may be thrown back into the blood and appear in the urine, but the presence of such abnormal constituents is in no sense due to errors of metabolism.

Actual derangements of the metabolic processes follow almost any deviations from the normal health, but our interpretation of the urinary changes which result is in many instances greatly hampered by the scantiness of our knowledge of the intermediate steps of the paths of metabolism. Such knowledge as we have of these steps is derived from casual glimpses afforded when, as the outcome of one of Nature's experiments, some particular line is interfered with, and intermediate products are excreted incompletely burnt. Many of the substances which rank as abnormal constituents are present in traces in normal urine as by-products of the metabolic processes, and it may safely be assumed that we are not cognisant of all the traces which so occur. Exceptional methods will reveal traces previously unsuspected. Thus Dombrowski, working with enormous volumes of normal urine (100 litres), was able to demonstrate the presence of minute quantities of cadaverin; and that very delicate instrument the spectroscope reveals traces of hæmatoporphyrin in normal urine which would escape detection by rougher means. Only recently it has been shown that certain sulphur-containing acids, previously unknown, occur in no inconsiderable quantities in normal urine, and even now we do not know with any certainty all the constituents which go to make up the so-called neutral sulphur and residual nitrogen.

The effects of disease of the great laboratory glands, of which the liver is the chief, upon the chemical processes of which they are the seats, are less conspicuous than might be expected. This is perhaps due to the power of a small intact residue of an organ to carry on the functions of the whole,

[4] Pathologie Expérimentale, second edition, 1880, p. 15.
[5] Ibid., p. 568.

nor must it be forgotten that any very grave interference with the metabolic activities of the liver is incompatible with life. On the other hand, the phenomena of exophthalmic goitre and of myxœdema bear witness to the profound effects of atrophy or disease of a gland which exerts a controlling influence over the metabolic processes as a whole. Some abnormal constituents of urine are believed to be products of undue breaking down of tissues, of autolysis *intra vitam*. Such an origin is now usually ascribed to the tyrosin and leucin excreted in acute yellow atrophy of the liver, and to the albumoses met with in urine.

There is a group of maladies in which metabolic disturbances are by far the most conspicuous features, whereas the structural changes behind them are scanty or even inappreciable. Of such "diseases of metabolism," diabetes, gout, and obesity are the most important. It is still uncertain how far the accumulation of uric acid in the blood and the deposition of sodium biurate in the tissues which are the characteristic features of gout, are actually due to derangement of metabolism, as distinct from a mere excretory defect. In diabetes mellitus, under which name we probably include more than one morbid condition attended by persistent glycosuria, the metabolic derangements, primary and secondary, dominate the clinical picture. At the outset sugar may be excreted in very small quantity and only after a meal rich in carbohydrates; at a later stage the glycosuria tends to become continuous and the percentage of glucose in the urine rises until, in grave cases, the excretion almost ceases to be controlled by diet and the tissue proteins are called upon to supply sugar. By the destruction of fats and proteins the acetone bodies and especially β-oxybutyric acid are formed in increasing amounts, and to them the fatal ending is commonly attributed at the present day, although the accumulation of unburnt glucose in the blood is itself productive of serious evils. The liability to develop diabetes or gout is often inherited but the diseases themselves are not inherited, for they are never congenital. Developing at any period of life, the mischief, once begun, tends to become aggravated as time goes on, but the rate of aggravation differs widely in individual cases and is often conspicuously controlled by appropriate treatment.

Quite unlike that of the above metabolic diseases is the course of the anomalies of which I propose to treat in these lectures and which may be classed together as inborn errors of metabolism. Some of them are certainly, and all of them are probably, present from birth. The chemical error pursues an even course and shows no tendency to become aggravated as time goes on. With one exception they bring in their train no serious morbid effects, do not call for treatment, and are little likely to be influenced by any therapeutic measures at our disposal. Yet they are characterised by wide departures from the normal of the species far more conspicuous than any ordinary individual variations, and one is tempted to regard them as metabolic sports, the chemical analogues of structural malformations. It is interesting to note that as far back as the earlier years of the nineteenth century, one of them, albinism, was classed by Mansfeld[6] and by Meckel[7] as a "Hemmungsmissbildung" or malformation by arrest.

It may be pointed out that the epithets inborn and congenital are by no means synonymous. Structural abnormalities may be present at birth which owe their origin to intra-uterine disease or intra-uterine injury and are in no sense developmental errors. Again, an infective disease may be congenital but cannot be inborn. It has merely been acquired in utero. Even true developmental errors are of several distinct kinds. In some there is malposition or transposition of organs, partial or complete; in others doubling of parts or inclusion of twin structures. Some structural anomalies are malformations by excess such as polydactyly, and some are malformations by defect, such as absence of the middle phalanx of each digit. In one large class, the so-called malformations by arrest, the process of development meets with a check and some portion of the body is left unfinished. To this group belong such abnormalities as hare lip, cleft palate, and spina bifida. Speaking of such arrests Professor J. A. Thomson writes:[8] "These abnormalities occasionally recur repeatedly in a family tree, but it seems probable that what is really inherited is a deficiency in 'developmental vigour' accentuated by nutritive defects on the parts of the mothers during the period of gestation." No extraneous causes, such as intra-uterine injury or disease, can be assigned to the metabolic errors which are under discussion. As far as our present knowledge of them enables us to judge they apparently result from failure of some step or other in the series of chemical changes which constitute metabolism, and are in this respect most nearly analogous to what are known as malformations by defect. It is not only in the field of metabolism that inborn derangements of function are met with, and Daltonism and night-blindness may be quoted as examples of such anomalies having no obvious chemical basis.

At first sight there appears to be little in common between inborn derangements of function and structural defects, but on further consideration the difference is seen to be rather apparent than real. Almost any structural defect will entail some disorder of function; sometimes this is almost inappreciable, but, on the other hand, the resulting functional disorder may be so conspicuous that it completely overshadows the defect to which it is due. Very slight structural changes may lead to profound functional derangements, as witness the effects of atrophy of the thyroid gland, whether congenital or acquired in later life, and the stormy metabolic disorders which may ensue upon comparatively insignificant morbid changes in the pancreas. By selective breeding there has been produced a race of waltzing mice, but their bizarre dance is merely the functional manifestation of an inborn and hereditary malformation of the semicircular canals. In the same way beneath each chemical sport may well exist some abnormality of structure so slight that it has hitherto escaped detection. Among the complex metabolic processes of which the human body is the seat there is room for an almost countless variety of such sports, but the examples which can be adduced are very few in number. Indeed, up to now the only known anomalies which can, with any good show of reason, be assigned to this class are albinism, alkaptonuria, cystinuria, and pentosuria, and even as regards these the reasons for their inclusion in the group are not of equal cogency.

We should naturally expect that among such abnormalities those would earliest attract attention which advertise their presence in some conspicuous way, either by some strikingly unusual appearance of surface tissues or of excreta, by the excretion of some substance which responds to a test habitually applied in the routine of clinical work, or by giving rise to obvious morbid symptoms. Each of the known inborn errors of metabolism manifests itself in one or other of these ways, and this suggests that others, equally rare, which do not so advertise their presence, may well have escaped notice until now. One man in 20,000 whose urine of 24 hours habitually contained a few grammes of aspartic acid might well be overlooked. Theoretically any anomaly which claims a place in the group should be present from birth and should persist throughout life, but it must be confessed at the outset that this cannot as yet be definitely asserted of all the four metabolic errors which I have mentioned. Some of them produce no obvious effects which compel attention, and may only be accidentally detected in adult life, and neither the evidence of the patient himself nor that of his parents can be of any help in endeavouring to trace back the peculiarity to infancy.

That albinism is congenital and persists through life is self-evident and admits of no dispute, for the condition is as obvious as any structural malformation and much more so than many such. Its rarity in man is also evident, although by artificial selection it may be reproduced indefinitely in lower animals.

As regards alkaptonuria its lifelong persistence is equally well established, although it may be that this error, which is in the great majority of instances inborn, may occasionally occur as a temporary phenomenon in disease. The remarkable staining property of alkapton urine allows of its recognition at the very beginning of life, and I have been able to obtain reliable evidence with regard to two cases that the staining of clothing was noticed on the second day of life, and in one of these instances had an opportunity of examining some urine passed during the first ten days after birth.[9] On the other hand an individual who exhibits the anomaly may

[6] Archiv für Anatomie und Physiologie, 1826, p. 96.
[7] Handbuch der Pathologischen Anatomie, 1816, Band ii., 2, p. 3.
[8] Heredity, London, 1908, p. 289.

[9] THE LANCET, Nov. 30th, 1901, p. 1484; Transactions of the Royal Medical and Chirurgical Society, 1902, vol. lxxxv., p. 69.

reach adult life without being aware of any special peculiarity of his urine and the condition may only attract attention when he is an applicant for life insurance or comes under treatment on account of some illness. Winternitz [10] has recorded the interesting fact that the mother of seven children, three of whom were alkaptonuric, was convinced that whereas two of her children had passed alkapton urine from the earliest days of life, this had not been the case with the youngest child, in whom she had only noticed the peculiarity from the age of five years. Such information supplied by a mother familiar with the symptoms of alkaptonuria carries as much weight as any hearsay evidence can carry, but nothing short of actual chemical examination of the urine would suffice to prove a point of so much importance.

Turning now to cystinuria, the evidence of its congenital occurrence is much more difficult to obtain, for this anomaly is little likely to attract attention in a young infant. Seeing that cystinuria is not infrequently transmitted from parent to child, examination of the urine of the infant children of those who manifest the peculiarity offers the most likely means of settling the point. That it may be present in early childhood there is abundant evidence to show. The first cystin calculus ever examined [11] was taken from the bladder of a child of five years. Abderhalden [12] has placed on record the detection of cystinuria in two children of the same family at the ages of 21 months and 14 months respectively, and Ultzmann [13] the case of a child of two with a cystin calculus who had exhibited symptoms of stone from the age of 12 months. Not a few cases in older children have been described. As affording evidence of the long persistence of cystinuria a case which came under the observation of the late Sir Henry Thompson [14] may be quoted that of an old man, aged 81 years, for whom a cystin calculus was crushed, and who had passed a stone of the same nature 39 years previously. There is reason to believe that cystinuria, like alkaptonuria, is occasionally temporary or intermittent.

No direct evidence of the congenital occurrence of pentosuria, the latest discovered and least known member of the group, is yet forthcoming, and its inclusion is to be justified on other grounds. That it may persist unchanged for years is certain, but the youngest pentosuric yet observed was a boy aged 15 years.[15]

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 inborn errors. My belief is that cystinuria is decidedly the least rare of the four, but C. E. Simon [16] met with only one cystin sediment among some 15,000 urines examined, and Primavera [17] one in 20,000 urines. Another feature which all four anomalies share in common is their more frequent occurrence in males than in females. Of 38 cases of alkaptonuria, presumably congenital, 31 were in males and only seven in females. Of 93 cystinurics collected from the records by Simon 63 were males and 30 females. Of 26 pentosurics, 19 were males and seven females. That males preponderate among albinos has often been stated, but among the cases collected by Ascoleo [18] in Sicily the disparity was comparatively slight, the numbers being 34 males and 28 females. It does not appear that there is any such unequal liability of the sexes to structural malformations, as far as can be judged from figures collected from the records of two hospitals, and in the remarkable family described by Farabee [19] in which many members exhibited a curious malformation by defect—namely, absence of the middle phalanges—the majority of the affected members were females. In a similar family recorded by Drinkwater [20] male cases slightly preponderated.

To be harmless is no essential attribute of an inborn abnormality, but it stands to reason that an error of metabolism which persists from birth into adult and even into advanced life must needs be relatively innocuous. Albinism, although inconvenient, is certainly harmless, and the most serious direct result of alkaptonuria is the peculiar pigmentation, a variety of ochronosis, which some of its subjects develop in later life. Evidence is accumulating of the harmlessness of pentosuria, and that the excretion of a sugar with five carbon atoms in its molecule has none of the sinister significance of glycosuria. Only cystinuria can be classed as actually injurious, but even its ill-effects, serious as they often are, are not due to the deranged metabolism as such but are secondary, and result from the unsuitability of so sparingly soluble a substance as cystin for excretion by way of a urinary apparatus constructed upon the mammalian plan. Even in the single recorded instances in which death may possibly have resulted from cystinuria, apart from urinary complications, that of an infant aged 21 months, which Abderhalden describes, the deposition of cystin in the tissues was the conspicuous lesion found at the necropsy.

There remains to be mentioned yet another feature which the abnormalities under discussion possess in common—namely, the liability for each of them to occur in several members of a family, most often in collaterals of the same generation. In this respect, of course, they do not stand alone. In connexion with many actual diseases, as well as with structural malformations, hereditary influences come into play, and among diseases with none more strikingly than with such metabolic disorders as diabetes and gout. Only when taken in conjunction with all the other common features which have already been discussed can their mode of incidence be adduced in support of the view here taken of their nature.

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 [21] in 1823, and other examples have since been recorded,[22] but hitherto the diagnosis has only been made after the death of the animal and no opportunity has presented itself of utilising this fact for the advancement of the study of the anomaly. Whether alkaptonuria and pentosuria occur among lower animals is unknown. If they do they are little likely to be recognised.

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 alkaptonuria. Even as regards the relative numbers of normal and abnormal members, a knowledge of which is so important in connexion with questions of heredity, the information available is scanty and unreliable unless based upon personal examination. However, one point which stands out clearly is the remarkable similarity of the modes of incidence of alkaptonuria 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 Ascoleo found that of 24 families which included 60 albino members five were the offspring of the mating of first cousins. In only two instances was albinism directly transmitted from parent to child. Of the cases of alkaptonuria, concerning which the necessary information is forthcoming, a very large proportion have been in children of first cousin marriages. In a paper published in 1902 [23] I called attention to this point and more recent cases, although they have somewhat lowered the proportion, have borne out the fact, as will be seen from the following table, in which the more recent cases have been incorporated.

[10] Münchener Medicinische Wochenschrift, 1899, Band xlvi., p. 749.
[11] Philosophical Transactions of the Royal Society, 1810, vol. c., p. 223.
[12] Zeitschrift für physiologische Chemie, 1903, Band xxxviii., p. 557.
[13] Wiener Medicinische Wochenschrift, 1871, Band xxi., pp. 286, 307.
[14] Transactions of the Pathological Society, 1870, vol. xxi., p. 272.
[15] Chobola: Centralblatt für Innere Medicin (abstract), 1907, Band xxviii., p. 864.
[16] American Journal of the Medical Sciences, 1900, vol. cxix., p. 39.
[17] Quoted by Piccini e Conti, Lo Sperimentale, 1891, vol. xlv., p. 353.
[18] Archivio per l'Anthropologia, 1871, vol. i., p. 367.
[19] Papers of the Peabody Museum of American Archæology and Ethnology, Harvard, 1905.
[20] Proceedings of the Royal Society of Edinburgh, 1908, vol. xxviii., p. 35.
[21] Annales de Chimie, 1823, 2e s., tome xxiii., p. 328.
[22] Gross, S.W.: North American Medico-Chirurgical Review, 1861, vol. v., p. 311.
[23] THE LANCET, Dec. 13th, 1902, p. 1616.

Families the offspring of first cousins.

Names of observers.	Number of alkaptonuric members.
1. Pavy	4
2. R. Kirk	3
3. Garrod	2
4. Erich Meyer	1
5. Ogden	1
6. Hammarsten	2
7. Grutterink and van der Bergh	1
8. Cronvall	1
Number of families, 8.	15

Families of parents who were not blood relations.

Names of observers.	Number of alkaptonuric members.
1. W. Smith and Garrod	2
2. Ewald Stier	1
3. Noccioli and Domenici	1
4. Marshall and Futcher	3
5. Langstein and E. Meyer	1
6. Garrod and T. W. Clarke	1
7. Grutterink and van der Bergh	2
8. ,, ,,	4
9. Schumm	1
Number of families, 9.	16*

* In some instances private information has supplemented the published records. For some of the more recent cases the required information is not forthcoming. The new references will be found in the bibliography of Lecture II.

Thus of 17 families eight were the offspring of first cousins and nine were the children of parents who were not related, and of the total of 31 cases 15 fall into the first group. 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 emphasised by Feer [24] in a recent paper. 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 has calculated [25] that less than 3 per cent. of all marriages are of this class, and Professor Karl Pearson [26] has recently 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 0·86 among the classes from which patients in London hospitals are drawn. The totals of consanguineous marriages of all degrees in the two classes were 7·76 per cent. and 1·3 per cent. respectively. Hence it is obvious that the proportion of such marriages among the parents of alkaptonuric families is altogether abnormal. On the other hand, the proportion of alkaptonurics among children of such marriages must be very small indeed. Only some 50 to 60 cases of alkaptonuria 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,[27] and has recently been emphasised by Punnett,[28] that the mode of incidence of alkaptonuria 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 interbreed the offspring of the hybrids will exhibit one or other of the original 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 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 fertilisation will the resulting individual show the recessive character.

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 such 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 gametes of both kinds a larger proportion of the offspring 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, two examples are known. One of these was observed by Osler.[29] An alkaptonuric father whose brother also showed the anomaly had an alkaptonuric son. The second case, which was recorded by Ossi,[30] was that of a mother and her son and daughter, all alkaptonuric. Lastly, when recessive mates with recessive all the offspring should manifest the recessive character, but no such marriage of alkaptonurics 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 far 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 these 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. For the above reason little importance is to be attached to the figures available with regard to alkaptonuria, but those contained in the following table, which relate to 17 families, are given for what they are worth :—

—	Observers.	Total number in family.	Normal members.	Alkaptonuric members.
Family No. 1	F. W. Pavy.	14	10	4
,, 2	Noccioli e Domenici.	10	9	1
,, 3	Ogden.	8	7	1
,, 4	Zimper.	8	6	2
,, 5	Winternitz.	7	4	3
,, 6	Langstein and E. Meyer.	6	5	1
,, 7	Schumm.	6	4	2
,, 8	Garrod.	5	3	2
,, 9	R. Kirk.	4	1	3
,, 10	Bandel.	4	2	2
,, 11	Hammarsten.	4	2	2
,, 12	W. Smith and Garrod.	3	1	2
,, 13	Baumann and Embden.	2	0	2
,, 14	Ewald Stier.	2	1	1
,, 15	Erich Meyer.	1	0	1
,, 16	Garrod and Clarke.	1	0	1
,, 17	Cronvall.	1	0	1
Totals		86	55	31

Although the totals show that the normal members largely preponderate they do not approach the requirements of Mendel's law, according to which a recessive character should

[24] Jahrbuch für Kinderheilkunde, 1907, vol. lxvi., p. 188.
[25] G. Darwin: Journal of the Statistical Society, 1875, vol. xxxviii., p. 153.
[26] K. Pearson: Brit. Med. Jour., 1908, vol. i., p. 1395.
[27] Report of the Evolution Committee of the Royal Society, 1902, No. 1, p. 133, note.
[28] Proceedings of the Royal Society of Medicine, 1908, vol. i., p. 148.
[29] See Garrod, THE LANCET, Dec. 13th, 1902, p. 1617.
[30] Gazzetta Medica Lombarda, 1889, vol. xlviii., p. 115.

appear in one quarter of the offspring; the alkaptonurics should number 21 or 22 instead of 31. It is clear that the figures as they stand are not fair to Mendel, for in the last three families the affected members were only children, and in families 15 and 16 might be classed as first hildren. One would expect to obtain a more accurate estimate by confining our attention to the larger families, and it is noteworthy that if one takes families 1 to 8, each containing five or more children, the totals work out in strict conformity to Mendel's law, in the proportions 4 : 3 : 1. However, to draw the line at families of five and upwards is a purely arbitrary proceeding.

The patients of Baumann and Embden were a brother and sister born out of wedlock, but it is not quite clear from the record whether they were the only children of the union. Both parents subsequently married away and had children, none of whom were alkaptonuric. Two recorded alkaptonurics were twins and in one case the second twin was certainly and in the other was probably normal.[31] In each instance the normal twin died and the alkaptonuric survived. The twins were of the same sex in both cases.

It appears to me that the strongest argument which can be adduced in favour of this view that alkaptonuria is a Mendelian recessive character is afforded by the fact that albinism, which so closely resembles it in its mode of incidence in man, behaves as a recessive character in the experimental breeding of animals.[32] Nor do the figures quoted by Bateson[33] relating to the proportion of albino members in human families show any more close conformity to the requirements of Mendel's law than do those above quoted for alkaptonuric families.

Evidence is accumulating of the occurrence of pentosuria in brothers and sisters,[34] and no instance of its transmission from parent to child has yet been recorded. Of consanguinity of parents of the subjects of this abnormality nothing is yet known. There is some evidence of a special liability of the Jewish race.

The available evidence regarding the inheritance of cystinuria is much more scanty than that relating to alkaptonuria. 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 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 21 months and deposits of cystin were found in its tissues; two others had died with like symptoms at nine and 17 months respectively, but were not known to excrete cystin. The surviving children, aged five and a half years and 14 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[35] described a cystinuric mother and a normal father had 12 children. The urine of two of them could not be obtained, but of the remaining ten no less than seven excreted cystin. Again, Pfeiffer[36] 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. The frequency of direct inheritance and the large proportion of the offspring affected suggest that if cystinuria be transmitted on Mendelian lines it is probably a dominant rather than a recessive characteristic.

[31] Noccioli e Domenici: Gazzetta degli Ospedali, 1898, vol. xix., p. 303. D. Gerhardt: Münchener Medicinische Wochenschrift. 1904. Band li., p. 176.

[32] Castle and Allen: Proceedings of the American Academy of Arts and Sciences, 1903, vol. xxxviii., p. 603.

[33] Brit. Med. Jour, 1908, vol. i., p. 1252.

[34] Brat: Zeitschrift für Klinische Medicin, 1902, Band xlvii., p. 499. Bial: Berliner Klinische Wochenschrift, 1904, Band xli., p. 556, and others.

[35] Berliner Klinische Wochenschrift, 1899, Band xxxvi., p. 503.

[36] Centralblatt für Krankheiten der Harn- und Sexual-Organe, 1897, Band viii., p. 173.

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.

ALBINISM.

Of albinism I propose to speak very briefly, for its study from the chemical side has scarcely begun. In the fairly extensive literature of the subject much space is devoted to the ocular troubles which are connected with it; some authors have treated of its hereditary aspects; the question whether albinism carries with it any impairment of bodily or mental powers has been widely discussed but the actual nature of the anomaly has hardly been touched upon. Clearly it is an abnormality of a different kind from the others here under discussion which manifest themselves by errors of excretion. In albinism there is a defect of substances which are normal constituents of certain specialised tissues and which serve purposes of much utility to the organism. It is not necessary to enter upon any discussion of the question whether it should be classed as an error of anabolism or of catabolism. The work of F. G. Hopkins[37] upon the utilisation of excretory products in ornament, as exemplified in the employment of uric acid in the pigmentation of white butterflies of the genus Pieris, is of interest in this connexion, but it is probable that in insects, as in birds and reptiles, the excreted uric acid is largely formed by synthesis, as the breaking-down of nuclein does not provide an adequate source for the yield.

The essential phenomenon of albinism is the absence of the pigments of the melanin group which play the chief part in the colouration of man and lower animals and which serve the important function of rendering the eye a dark chamber. There are various kinds of melanins, but all alike are wanting in albinos, as witness the white hair, pink eyes, and unpigmented skin which characterise such individuals. Pigments of other kinds are not wanting, such as the lipochromes which impart their yellow tints to fats and blood serum, and hæmoglobin and its derivatives. In the urine of albinos I have found the same pigments as are ordinarily present. The fact that albinos of certain birds, such as the peacock, which are normally characterised by the brilliancy of the colouring of their plumage, are quite white, does not invalidate the truth of this statement. Their brilliant tints are interference colours, due to physical structure and not to pigmentation, and the absence of such colours is merely due to the lack of a dark background for their display, and such a background the melanins with their sombre hues provide. In the feathers of the albino peacock the iridescent tints are faintly visible in certain lights.

Our knowledge of the chemistry of melanins is still very imperfect. Their sulphur content varies widely; some contain iron, others do not. The presence of iron has been held to indicate an origin from hæmoglobin, but the trend of opinion at the present day is towards the view that they are derived from proteins in general, perhaps by the action of a tyrosinase upon tyrosin, and that the natural melanins are allied to the melanoid substances which are formed during the hydrolysis of proteins. If, as has been suggested, white hair contains a white chromogen and is pigmented and not merely devoid of colour; if also this is true of albino hair as well as that of white animals not albinos, we may suppose that the chromogen merely fails to be converted into the dark pigments in the ordinary way.

Three possible explanations of the phenomenon of albinism suggest themselves. We might suppose that the cells which usually contain pigment fail to take up melanins formed elsewhere; or that the albino has an unusual power of destroying these pigments; or again that he fails to form them. Some experiments of Kobert,[38] who injected solutions of melanin into rabbits, seem to negative the notion of an unusual destructive power. The animals excreted melanin, or rather its chromogen melanogen, in their urine. Kobert mentions that some of the animals injected were albinos, but

[37] Philosophical Transactions of the Royal Society, 1895, clxxxvi., B. p. 661.

[38] Ueber Melanine, Wiener Klinik, 1901, Band xxvii., p. 99.

does not say that they behaved any differently in this respect from the pigmented rabbits. The injection caused no pigmentation of the hair or eyes of albino rabbits, nor is it to be expected that it would do so whichever of the above hypotheses be correct. It is very unlikely that the melanin is conveyed to the pigmented cells and there deposited, for all the evidence available indicates that the pigment is formed *in situ*, probably by the action of intracellular enzymes. If the melanin were formed in albinos and merely not utilised we should expect it to be excreted by them in the urine, which is not the case. Only certain specialised cells appear to have the power of forming melanin, and in cases of melanotic sarcoma these are enormously multiplied, and there is a correspondingly increased production of pigment which may find its way into the blood and be excreted in the urine. Such an increase is only to be explained on the supposition that the pigment is actually formed in the tumour cells. In favour of this view is also the fact that melanotic tumours apparently originate only in structures in which melanins are normally present, such as the eye and skin, and possibly in the pineal gland, which as a vestigial remnant of the pineal eye of certainly lowly animal forms may retain some pigment forming power.

The hypothesis of local formation also supplies the easiest explanation of the phenomena of partial or local albinism, such as is seen in the Himalayan rabbit, which has the pink eyes of an albino but the hair of which is always pigmented at certain points. The partial albinism seen in man, in which the hair retains a certain amount of colour, and especially the rare form in which red hair is associated with pink eyes, a variety which has been met with in one albino of several in a family, the others conforming to the ordinary type,[39] is a phenomenon calling for careful investigation.

The ordinary physiological causes of pigmentation are not operative in albinos. In them exposure to the sun does not cause the usual tanning of the skin which is seen in normal individuals; a mere hyperæmia results. It has also been observed that in female subjects the pigmentation of the areolæ of the nipples and of other parts, which usually accompanies pregnancy, is not developed.[40] I know of no observations on the occurrence in albinos of tumours originating in the eye and running the course of melanotic sarcomata. One would expect that such growths, if they occur, would fail to be pigmented. Nor does there appear to be any record of Addison's disease occurring in such subjects which might throw important light upon the question whether the Addisonian pigment is a true melanin. Taking all the known facts into consideration, the theory that what the albino lacks is the power of forming melanin which is normally possessed by certain specialised cells is that which has most in its favour and is probably the true one. If so, an intracellular enzyme is probably wanting in the subjects of this anomaly, an explanation which, as we shall see later, brings albinism into line with some other inborn metabolic errors, of which a similar explanation is at least a possible one.

I must not omit to mention that there are indications that the differences between albinos and normal individuals are not confined to the absence or presence of melanins in the tissues. In animals differences have been observed in the matter of liability to certain infections, and clinical observations of the incidence of infective diseases upon human albinos would be of considerable interest. Halliburton, Brodie, and Pickering[41] found that intra-vascular injections of nucleo-proteins failed to produce in albino animals such clotting as they cause in pigmented ones. G. R. Mudge,[42] who has carried out a number of such experiments, found that all albinos do not behave alike in this respect. Differences were also observed between the results of the injection of nucleo-proteins derived from albino and pigmented animals respectively. He arrived at the conclusion that an albino animal requires a larger dose of nucleo-protein per kilogramme of body weight to cause death by intra-vascular clotting. Pickering's[43] remarkable observation that the Norway hare when in its winter coat behaves as an albino when injected with nucleo-protein, but in its summer coat as a pigmented animal, opens up the most interesting question of the relation, if any, of the change of coat in Arctic animals to albinism.

It will be clear from the above fragmentary sketch that even the lines along which the systematic study of albinism may profitably be directed are only beginning to indicate themselves. The carrying out of such a research remains as a task for future workers.

[39] Folker: THE LANCET, May 31st, 1879, p. 795. Nettleship: Transactions of the Ophthalmological Society, 1906, vol. xxvi., p. 244.
[40] B. W. Richardson: Dublin Hospital Gazette, 1856, vol. iii., p. 73.
[41] Journal of Physiology, 1894, vol. xvii., p. 148.
[42] Proceedings of the Royal Society, 1907, Series B., vol. lxxix., p. 103.
[43] Journal of Physiology, 1896, vol. xx., p. 310.

ON THORACOSTOMY IN HEART DISEASE.

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IN a paper published in THE LANCET of July 28th, 1906, and read before the Æsculapian Society of London on April 30th in the same year, I considered the circumstances of the normal growth and action of the heart and the manner in which hypertrophy of the organ is influenced by its adhesion to the pericardial sac and extraneous structures. I remarked in conclusion: "To return to our embryo, the growing organ requires a surplus of room to grow in; the overgrown organ requires more room to work in, and it may be that tethered by extraneous adhesion or not so restricted the hypermyotic heart may in the future, and in some cases, be provided with such by the genius and courage of some surgeon bold enough to undertake the task" (p. 212).

I was not aware until I read Professor Wenckebach's paper on Some Points in the Pathology and Treatment of Adherent Pericardium in the *British Medical Journal* of Jan. 12th, 1907, that Professor Brauer, at that time of Heidelberg, had induced Professor Petersen and Dr. Simon to perform an operation for the relief of cardiac motion in such cases with success so long ago as 1903,[1] and had termed his operation cardiolysis. Dr. William Mackenzie of Melbourne, unaware, like myself, of Brauer's work in cardiolysis, gave very definite instructions for a proposed operation for freeing the heart from costo-pericardial adhesions in the *Intercolonial Medical Journal* of Sept. 20th, 1906. Dr. Mackenzie even advocated removal of a portion of sternum as well as the ribs, a procedure which Dr. Simon adopted in two of Brauer's cases.

It is a subject which has long interested me and in my book on "Cardiac Failure," published in 1897, I had suggested the severing of pericardial adhesions for the relief of cor bovinum which, I stated, would be "an ideal triumph of modern surgery" (p. 88). A reviewer of my book remarked that I had in any case exhibited a "triumph of the imagination," but appeared to be of opinion that the safety of mankind would be consulted by my suggestion not being taken seriously. Since then there has, however, been a growing conviction in my mind that it was less the tethering of the heart than its *bulk* and force of systole which were the determining factors in the situation and that operation to afford room adequate for the free action of the enlarged organ was the primary consideration whether the organ itself were tethered or not. One has so often observed post mortem a large muscular heart usually associated with aortic valvular disease and without extraneous adhesion, succumb to the mechanical difficulty, while possessing apparently an amount of wholesome muscle which one would, *a priori*, have imagined should have contended with the obstacle in the circulation for a much longer period had it not been exhausted by some other cause.

Brauer's suggestion that the adhesions in adhesive pericarditis should be left alone and the incarcerated heart freed from bony encasement, together with the successful issue of the operations consequent on his suggestion, pointed the way to a wider application of his method. Whether the term "cardiolysis" would be the most appropriate one to designate an operation which had to do, not with loosening the heart from adhesion, but with providing the overgrown organ with more room, and saving it the shock of impact against bone, may be questioned. Thoracostomy is, perhaps, too general a term to indicate its special application to the relief of intra-thoracic pressure exerted upon the heart, or induced by a large and powerfully pulsating organ confined within the

[1] Archiv für Klinische Chirurgie, vol. lxxi.