CHAPTER I

THE CHEMISTRY OF THE SPECIES AND OF THE INDIVIDUAL

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 recognize the uniformity which underlies this so apparent diversity, and the genetic relationship of form to form. As regards 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 has been in the opposite direction, for the progress of bio-chemistry is teaching us that behind a superficial uniformity there exists a diversity which is no less real than that of structure, although 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 recognized, 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 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.[1]

A more extended study, even by strictly chemical methods, will doubtless serve to reveal innumerable minor differences, such as are foreshadowed by Przibram's [2] 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, such as urea and carbon dioxide.

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

[1] See Huppert, *Ueber die Erhaltung der Arteigenschaften*, Prag, 1896.

[2] Hofmeister's *Beiträge zur chem. Physiol. u. Pathologie*, 1902, ii. 143.

endogenous and are not affected by diet, such as recent researches have revealed in increasing numbers. The differences of type which are so important in the selection of a blood for transfusion, and the 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 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 neutralization by ammonia of acids present in excess. 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, is left intact. 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 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[3] on Diseases of Suboxidation, delivered and published in the year 1865, but the thesis in question is chiefly associated with the name of Bouchard,[4] 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 invoked 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.

[3] *Medical Times and Gazette*, 1865, ii. 29, 83, &c.

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

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 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 controlling influences 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 utilize 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 a continuous movement rather than as a 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 with 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 paths, 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 far easier to suppose that when, for any reason, the ordinary paths are blocked normal intermediate products are excreted without further change, or that secondary 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,[5] from which the following passage is taken :

'On supposait autrefois que chez les diabétiques des conditions entièrement nouvelles se développaient dans l'économie sous l'influence de l'état morbide, et qu'il en résultait un produit pathologique special, le sucre. Mais il faut admettre aujourd'hui que ces phénomènes s'expliquent par l'augmentation pure et simple d'une function normale, en vertu de laquelle du glucose est formé chez tous les sujets, même à l'état de santé. Il est donc évident que la maladie, en ce cas, n'est qu'un phénomène physiologique troublé ou exagéré.'

Still more striking is the following passage : [6]

'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, under morbid conditions, can be

[5] *Pathologie expérimentale*, second edition, 1880, p. 15.
[6] Ibid., p. 568.

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 utilized 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; for, as Emil Fischer has pointed out, the oxidation of the alcohol grouping of dextrose, whilst the less stable 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 products of 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 oxidized 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 of 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 cognizant 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 in normal urine traces of a pigment of the porphyrin group 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, 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 has been included more than one morbid condition attended by persistent glycosuria, the metabolic derangements, primary and secondary, dominate the clinical picture.

Quite unlike that of the above metabolic diseases is the course of the anomalies of which I propose to treat, 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, and they are little likely to be influenced by any therapeutic measures at our disposal. Yet they are characterized 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 Mansfeldt[7] and by Meckel[8] 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. 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 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. Nor is it only in the field of metabolism that inborn derangements of function are met with, for 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

[7] *Archiv für Anatomie und Physiologie*, 1826, p. 96.
[8] *Handbuch der pathologischen Anatomie*, 1816, ii. 2, p. 3.

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 there may possibly 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. 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 they are merely the most obvious members of a far larger group, and that not a few other such abnormalities which do not so advertise their presence may well have escaped notice hitherto. One man in 20,000 who habitually excreted a gramme or two of aspartic acid per diem might well be overlooked. Hence it

is not surprising that to the four metabolic errors which were discussed in the first edition of this book, namely albinism, alcaptonuria, cystinuria, and pentosuria, two others, congenital steatorrhœa and hæmatoporphyria congenita can already be added.

Any anomaly which claims a place in the series should be manifested from birth onwards, and although this cannot yet be asserted definitely of all the six metabolic errors mentioned, it is certainly true of most of them and probably of all.

That albinism is congenital and almost always persists throughout life is self-evident, but there are cases on record of albinos who have become pigmented. Its rarity in man is also evident, whereas, by selective breeding it can be reproduced indefinitely in lower animals.

The remarkable staining power of alcapton urine allows of its recognition at the very beginning of life. I have obtained evidence, as regards two cases, that the staining of napkins was noticed on the second day of life, and in a case reported by Scheltema it was observed on the third day, after milk had entered the alimentary canal. In one instance I was able to examine specimens of urine passed during the first ten days of life. On the other hand, an alcaptonuric may reach adult life without being aware of any special peculiarity of his urine, which may only be noticed when he is examined for life insurance or comes under medical care. Winternitz has recorded the interesting statement of the mother of seven children, three of whom were alcaptonuric, that whereas two of the children had passed alcapton urine from their earliest days, in the case of her youngest child she had only noticed the peculiarity when she was five years old. Such information, supplied by a mother familiar with the condition, cannot be lightly dismissed, but nothing less than chemical examinations of the urine would suffice to prove so important a point, although it would appear that this error,

which is in the great majority of cases inborn, is occasionally met with as a temporary sign of disease.

As regards cystinuria, the evidence of congenital occurrence is far more difficult to obtain, for this anomaly is much less likely to attract attention in a young infant. That it may be present at a very early age is shown by abundant evidence. The first cystin calculus ever examined was taken from the bladder of a child of five years, Ultzmann and Manby described such calculi from children of two years and one year respectively, and Kleinschmidt from an infant of ten and a half months. Abderhalden records cases of cystinuria in two children of the same family aged twenty-one and fourteen months. As affording evidence of the persistence of the condition a case may be quoted which came under the observation of Henry Thompson, that of a man aged 81 years for whom a cystin calculus was crushed, and who had passed a stone of the same kind thirty-nine years previously. There are grounds for the belief that cystinuria, like alcaptonuria, is occasionally temporary or intermittent.

Of the few known cases of congenital hæmatoporphyria the majority could be dated back to very early life, and the mother of a patient described by L. Mackey and myself was convinced that the very first urine which the child passed was red, and an eruption of hydroa appeared in the third month of life. But only a small proportion of cases of porphyrinuria belong to the congenital group, the majority being of toxic origin and due to the taking of sulphonal or allied drugs, or of an acute kind apart from the use of such drugs.

In all of the three recorded cases congenital steatorrhœa had been noticed in earliest infancy, and has persisted as long as the patients have been under observation. Acquired steatorrhœa, on the other hand, is a well-known sign of disease of the pancreas.

No direct evidence of the congenital occurrence of pentosuria is as yet forthcoming, and its inclusion in the group is to be justified on other grounds. It is far the least obvious of the six anomalies, and is only to be detected by testing the urine for sugar, and such tests are seldom carried out upon the urine of young infants. That it may persist for many years is certain. Alexander has described a case of pentosuria in an infant of eighteen months, but arrived at the conclusion that in this case the presence of pentose in the urine was directly due to the presence of milk in the child's diet. Aron has recorded a case of the more usual kind in a girl of five years.

To be harmless is no essential attribute of an inborn metabolic error, but it stands to reason that an abnormality which persists from birth into adult and even to advanced life must be relatively innocuous as such. The ill effects of cystinuria, which are sufficiently obvious, are not due to the derangement of the chemical processes, but result from the insolubility of cystin and its tendency to form urinary calculi. Even in the single recorded instance in which death may have resulted from cystinuria apart from urinary complications, that of an infant aged twenty-one months which Abderhalden described, the deposition of cystin in the tissues was the conspicuous lesion found at the necropsy.

In congenital hæmatoporphyria also, which is perhaps the most undesirable of the six anomalies in question, the evil effects are mainly due to the photo-sensitizing action of the pigment present in the tissues. Presumably a congenital porphyrinuric who spent his life in darkness or in a subdued light, would take no serious harm. Alcaptonuria is certainly less innocuous than used to be supposed. As age advances the subjects of this anomaly develop ochronosis, and have a special tendency to suffer from osteo-arthritic lesions. Of any ill effects of congenital steatorrhœa it is too soon to speak, and despite the frequency of functional nervous

symptoms in pentosurics, and the not infrequent association of pentosuria with glycosuria, we know little of any serious results of that anomaly.

Albinism causes impairment of vision and a consequent undue liability to accident, but the statements of some authors as to a special susceptibility of its subjects to infections require confirmation. However, Karl Pearson deduces from statistics that the expectation of life of albinos is below that of normal individuals.

When we come to discuss the several known inborn errors of metabolism in more detail it will be seen that in the case of each of them the most probable cause is the congenital lack of some particular enzyme, in the absence of which a step is missed, and some normal metabolic change fails to be brought about.