The basis of tissue evolution and pathogenesis / by Albert A. Gray.

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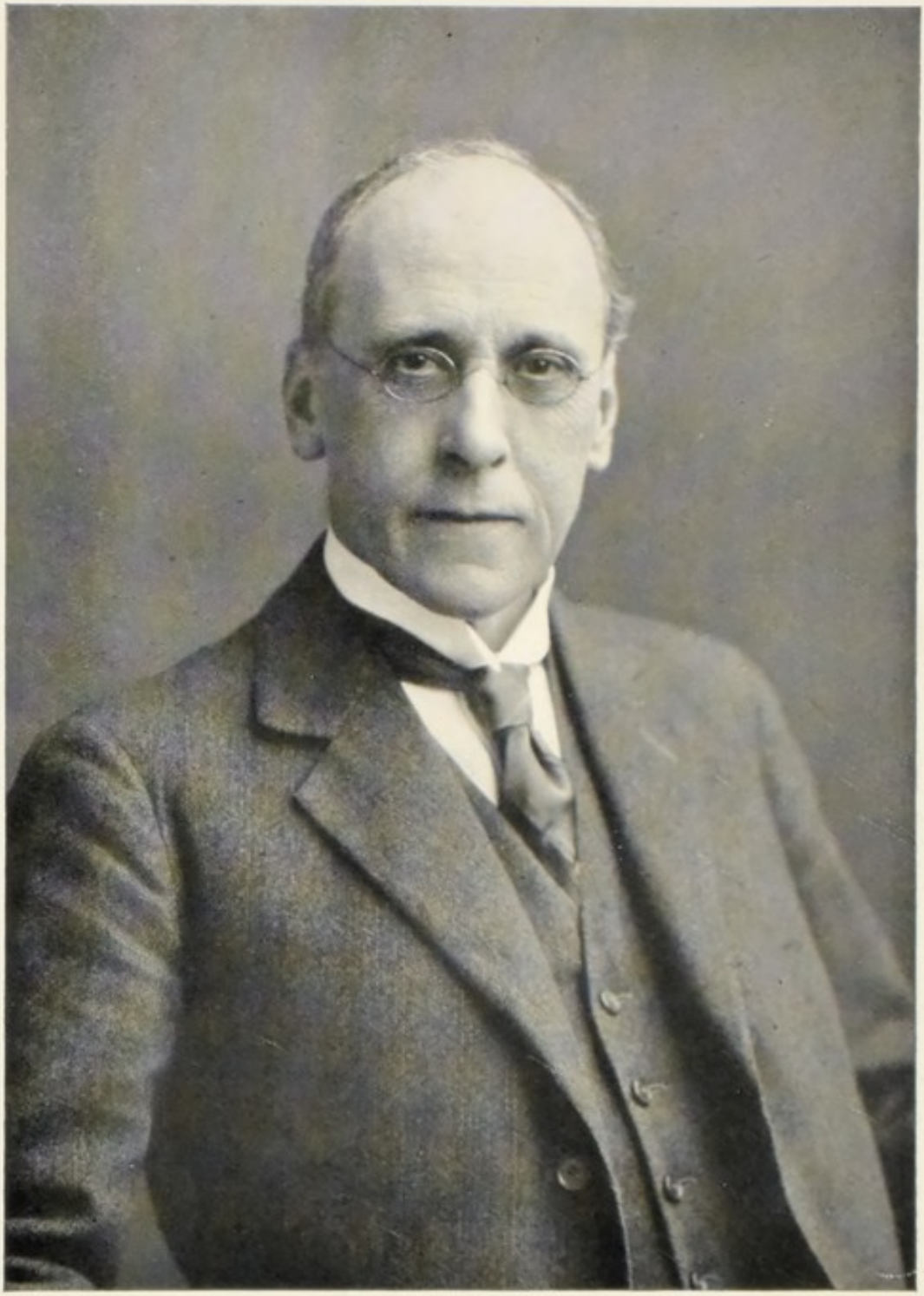

The Late ALBERT A. GRAY

THE BASIS OF TISSUE EVOLUTION AND PATHOGENESIS

BY

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CONTENTS

ILLUSTRATIONS

FOREWORD

It is important that those who set out to read through the pages of this book should be fully aware of the circumstances under which it was decided to present it for publication. In addition it would seem helpful to know something of the nature of the man who wrote it, of his methods and of the contributions which he made to science. Thereby the reader may gain some insight into the mind which formulated a simple explanation of the manner in which the structure of plants and animals may have evolved in direct relationship to environment.

Albert Alexander Gray died on January 4th, 1936, at the age of 67 in the full vigour of an active mind. Those who knew him fully recognised that he was singularly gifted—a man " sufficiently great unto himself and more than he appeared unto others."

Gray studied medicine at the University of Glasgow, where he finally obtained the degrees of M.B., C.M., in 1890 and M.D. in 1896, in both cases with commendation. As to the inspiration which he received as a student, he spoke in particular of the teaching of Professor Bower, Sir Hector Cameron and Sir William Gairdner. These amongst others helped to foster that keen enthusiasm which was one of his most noticeable characteristics, and which was preserved undiminished throughout his life. On many occasions he spoke of the example which Sir William Gairdner set in the methods which he employed in handling his clinical material and of his almost uncanny insight into the nature of disease.

For a short time, after he qualified, Gray was in general practice. He looked back upon this period as a major part of his education as a specialist. The human element, which enters so much into the healing art, was brought home to him as it only can be by contact with people in their own homes. He considered that without this the consultant was perhaps somewhat deficient.

The life of the general practitioner, however, affords little opportunity for scientific research. There is little leisure and the continual interruptions forbid his indulging in any other work requiring concentration and continued application. It was undoubtedly this which took Gray to Munich, there to study the diseases of the ear, nose and throat. He was by this time married, with an infant of less than one year old, and it must have required some courage on the part of both his wife and himself to make such a decision ; for he had no private means and was obliged to borrow in order to carry out his intentions. He recalled this part of his life with the happiest of memories ; for the days contained hours of congenial work, the evenings a delightful variety of intellectual and social interest and the whole was upheld by the companionship of his wife and the delight which each shared in the growing child. His cheerful optimism and confidence in his own ability sustained him—yet he cannot have been unaware of the difficulties which lay before him and of the disappointments which the fickleness of fortune might provide for him. It was at this time that he was much impressed by one of his teachers remarking that it would never be possible to dissect out the internal ear intact. It will be seen later how he overcame this difficulty and devised a most ingenious method whereby that delicate and beautiful structure could be completely divested of its bony surroundings and presented in its perfect entirety.

Returning to Glasgow in 1895 he put up his plate. He soon found that most of the hospital appointments had already been given to comparatively young men. Thus his chances of becoming known were considerably diminished. For some years his income was small and his anxieties proportionately great. Many have been placed in a similar situation. Gray went about the difficulty of building up a practice solely through patient endeavour in the laboratory and accurate clinical study. Such a method of making an appeal is only likely to bear fruit at the end of some years ; yet the tree so planted has its roots in the purest soil and will flourish in due course.

Finding ample leisure at his disposal he spent much of the time, after his return to Glasgow, in studying the mechanism of the cochlea, the anatomy of the ear and especially the comparative anatomy of the labyrinth. The latter structure happens to be surrounded by bone of exceeding density—in fact the densest in the body. Could such a feature be turned to useful account? The concept arose in his mind that, after removing the portion of the petrous bone containing the delicate semicircular canals and cochlea, paraffin wax could, given sufficient time, be made to percolate therein. After preliminary treatment the portion of bone was placed in the melted wax and kept at a temperature of 50°C. for a week or so. Thereafter the whole was allowed to cool—the wax was carefully scraped from the outer surface of the bone, which was eventually placed in very dilute hydrochloric acid. The experiment was justified, for, as the weeks went by, the dense bone, unaffected by the paraffin, bit by bit became dissolved away and the labyrinth, protected by its waxy content, freed itself. The paraffin was then cleared and the organ suspended in xylol. The whole process is, as a matter of fact, much more elaborate

than this and was only perfected at the sacrifice of much time and perseverance. It is, however, only necessary to point out the broad principle upon which it was based. It is doubtful if any portion of human anatomy is more beautifully shaped than the labyrinth. It makes an aesthetic as well as a scientific appeal. To Gray the result of his experiments opened up the possibility of the study of the comparative anatomy of the cochlea and the semicircular canals, for he was now able to display their structure with accuracy and ease. He received the most kindly encouragement from the late Professor J. G. McKendrick and through the help of other friends, who sent him specimens from every quarter of the globe, he was able to build up a unique collection, portions of which are preserved in the Hunterian Museum in Glasgow and in the Royal College of Surgeons in London. His first classic work *The Labyrinth of Animals* was published in 1908—the outcome of four years of the most painstaking industry. The merit of this work was quickly recognised both on the Continent and in America and as a direct result of it he received the Laureateship of the Lenval prize at the International Congress of Otology at Budapest in 1909.

Early in his career he began his attack on the problem of otosclerosis. From a purely clinical standpoint his contributions to the study of this disease must be considered as a great achievement, for he came to be recognised by many as, perhaps, the best authority on this common malady. Otosclerosis is probably the most frequent cause of adult deafness. It is one of the clearest examples of hereditary transmission. As a result of more than thirty years of work he had gradually formulated in his mind what he considered to be the fundamental defect. As in the rest of his original work, his views were formed

only after years of quiet contemplation and the accumulation of truly relevant facts. In 1935 he determined to apply his deductions in an attempt to help those many unfortunate individuals whose life is robbed of much of its enjoyment. As a result of the method which he introduced in 1935, some hope may be held out to these people. In particular is this true of the distressing symptom of " tinnitus " or ringing noises in the head—a feature often more distressing to the patient than the actual deafness. In certain selected cases the latter can also be improved, though rarely to a striking degree. It is wise to point out, however, that it will be many years before a just estimate of the value of this treatment can be given. Should the inception of this experimental therapeutic measure, with improvement in technique, provide a material boon to mankind we must honour this physician with the honour that is due unto him. At the same time, as one of his colleagues and friends pointed out, this was merely the fortunate and practical outcome of fundamental work which was infinitely greater in its conception. Part of the tragedy of his death lay in the fact that he was at the time engaged both in this and other important scientific problems.

At the age of forty Gray had sufficiently established an international reputation to make his future assured, and from that time his financial worries ceased to cause him anxiety. It might be remarked in passing, however, that he never wished to build up a lucrative practice. His desire was to provide enough to keep his family in comfort and give his two sons the best education available.

From his earliest days this quiet thinker pondered over the problems of evolution. His whole outlook on disease was merged in the wider concept that all pathological processes must have their biological significance and be

considered as such. It can be seen that this broad view influenced him in much of his work, for he endeavoured to trace it wherever it could be found. It is not known at what time the importance and significance of pathogenesis, as being part of the evolutionary process, occurred to him. It is probable that the idea arose in his mind in early middle life. It was continuously present during the last thirty years and it must have been about the year 1912 that he commenced writing on the subject. As in the case of the theory of the survival of the fittest, which had its inception in the minds of Darwin and Wallace as a sudden inspiration, so too, in this case, the idea arose apparently spontaneously and abruptly.

Allowing the subject to lie fallow in his mind for months at a time he would return to his hypothesis of evolutionary change, deleting and altering the manuscript until the whole became properly coherent only to himself.

In the meantime, having completed his investigation into the comparative anatomy of the internal ear he brought out a text-book on *The Ear and its Diseases* which was not only comprehensive in its appeal to both student and aurist but brought the problems to the reader in an original light. This was in 1910. In 1917 an authoritative book on otosclerosis was published. In this can be seen the accuracy and relevancy of his clinical observation and the attempt which he always made to correlate clinical facts with manifest pathological change. What may be described as his magnum opus was begun about the year 1918. The first volume of his *Atlas of Otology* was published in 1924. Anyone with any knowledge of the labour involved in the production of almost any single one of the photographic illustrations therein displayed must realise what patience and skill must have been required to produce them. The vast field which is covered required an

intricate and detailed knowledge of that which he sought to make clear—not so much through the laborious method of description as by means of the most exquisite photographs of the actual thing itself. Many of these are stereoscopic and are due to an ingenuity of technique which was entirely his own. The various processes through which he put the tissues in order to bring certain features into bold contrast were also quite original. Not the least impressive are the high-power magnifications which show a technical mastery which is unsurpassed.

In 1927 his life was robbed of much of its happiness by the death of his wife. Through the early days when the struggle was perhaps harder than has been depicted, the daily troubles and the anxieties over the future were shared by her, and it is questionable whether without the support which she gave him he would have been able to hold to his purpose. For there was a long period when there seemed little prospect of making an adequate means of livelihood. Those who remember her, recall a personality having great strength of character and charm—she provided just such help and devotion as were needed in these circumstances.

From this time his interest in consulting practice was relinquished and he decided to retire and live extremely quietly on a modest income. His pursuit in the scientific realm of his work continued, however, with increased vigour. Its interest kept his mind active and provided some solace for him in the remaining years of his life. In 1928 through the invitation of his friend and colleague Mr. F. J. Cleminson, he was made welcome at the Ferens Institute at the Middlesex Hospital. Nothing could have pleased him more. Here was provided most liberally the material and equipment wherewith to continue his congenial task. Here he spent the major portion of the

winter days and sometimes stayed late into the night so as to avoid the traffic vibrations which interfered with his delicate photography. Here he produced the second volume of the *Atlas of Otology* published in 1933—a larger companion to the first. The two together constitute a lasting monument to his industry, originality and skill.

The more significant honours which were bestowed upon him were the Lenval prize already mentioned—the gold medal of the American Academy of Ophthalmology and Otology in 1911—the Guyot Quadrennial Prize of Gröningen in 1929 and in 1933 the Dalby Memorial Award.

It was a curious feature of Gray's nature that he did not on many occasions seek advice. He could collaborate with others well and did so on many occasions with mutual benefit. Yet he much preferred to work entirely and absolutely alone, relying solely upon himself down to the minutest detail. This had both its advantage and its disadvantage. It meant that whatever he undertook reached a great perfection of achievement. On the other hand it entailed an immense sacrifice of time and thus tended to limit the field of his original work. Another interesting trait in his character was his extreme reluctance to discuss with others any project which he had in his mind until he had thought it out in his own way and decided to publish it. Thus his vessel was launched before anyone was aware that it was being built. It is remarkable how on almost all occasions his ship weathered the storms of criticism and usually reached its destined port. Latterly, owing to the esteem in which he was held, the voyage was less beset with contrary winds and became like sailing from Lima to Manila, when you can tie up the rudder and sleep before the wind.

He did, however, disclose something of what was in his

mind on most occasions to one who could, at any rate in broad outline, appreciate the principal theme of any work he had in hand. This was especially the case in regard to the pathogenesis of evolution and the theory of induced variation. When occasion permitted, the discussion was continued with mutual pleasure to both —the older bringing forward the evidence for his hypothesis, the younger offering support or criticism of particular points from his much more restricted knowledge. These talks, which ranged over every imaginable subject and only incidentally touched on the question of evolution when the drift of conversation so turned in that direction, gave to the younger an insight into the nature of the man and of the calibre of his mind, and increased an already deep affection and esteem as the years went by. For his knowledge was very considerable and ranged widely. At the same time he drank deep of the Pierian spring—tasting the essence of what was written with criticism and enjoying its truth or philosophy with discernment. One might say that his attitude towards the mystery of life was founded on his own observation of nature and in particular of human nature, together with all that science and philosophy brought to his notice. He held to the precept of no restricted creed but followed the instincts of his own conscience and good sense. Thus he walked through life humbly—much beloved by his fellow men.

It was known that Gray intended to make known his views and to publish a small book sometime during the year 1936. He stated that it would treat of the subject in a very broad way, leaving the reader to seek for and apply the general principle wherever nature gave a hint of the pathogenesis of evolutional change. Thus he intended to rely to a considerable extent on the reader's

ability to view a problem from a completely new standpoint ; for it is clear that no hypothesis can ever survive unless those who read of it do so with both insight and imagination. Again, many healthy seeds fall on barren ground. Gregor Mendel's simple yet precious discoveries found favour only many years after his death and Darwin's genius might never have borne fruit without the championship which Huxley gave it. Gray fully realised that his theory was unlikely to make any immediate and dramatic impression. Yet fortune is curious in this way in that she distributes her favours at random. Some may be impressed with a part or the whole of what they read. So the seed may fall on fertile soil.

One additional remark requires to be made. Since the subject matter was alone known to his younger son, the responsibility for publishing his father's work lay with him. It was known, however, that the author intended to submit his writings to two of his friends. The opportunity is here given me of thanking Sir Robert Muir for his kindly encouragement. He was emphatic in advising me to publish what he considered to be of great interest and of value. Professor Graham Kerr found time, when he was exceptionally busy, to read through my father's thesis. I must acknowledge with gratitude the very valuable help which he gave me in many ways. He, too, was in no doubt as to the wisdom of publishing. It is clear from his comments that he was impressed with the theory of Induced Variation and its relationship to pathogenesis and directional evolution. I should also like to thank Messrs. J. & J. Churchill for permission to reproduce eleven of my father's illustrations, which appeared in *The Labyrinth of Animals*, and Messrs. A. & C. Black for permission to reproduce the illustration appearing on page 12 taken from Ray Lankester's *Treatise on Zoology*.

As before hinted at, the manuscript is so written over, deleted and rearranged that it was at times difficult to render it in readable form. The first page, for instance, is so darkened with the passage of time that it is scarcely decipherable. So far as has been possible the minimum of alteration has been made. There is much repetition which, though a little tedious, still serves the purpose of emphasis. The subject matter is, however, clear—the broad principle frankly stated. No doubt there would have been much to add to, and much to subtract from, what is here published. Obvious mistakes and certain lapses in style must be condoned, and for these a measure of kindly indulgence can be expected.

O. G.

September 1937

THE BASIS OF TISSUE EVOLUTION AND PATHOGENESIS

The great advances made in recent years in pathology have for the most part been in the direction of ascertaining with increasing exactitude the agent, living or dead, which is in part responsible for the condition which we term disease. In other words, the advance has been made rather in the direction of increasing our knowledge of bacteria and their poisonous products than in comprehending the nature of the response which the living tissues make to these and other injurious agents. To this statement the important exception must be made in regard to the study of immunity. In this case the response of the tissue in one particular direction has been zealously studied with the most important results, such as vaccine prophylaxis and others which have been of the greatest value both from their purely scientific aspect, and from the relief which they have afforded to those suffering from disease.

But when all allowance has been made in this direction the physician, the surgeon and the pathologist, who have considered the subject deeply, must be painfully aware of the fact that the phenomena of pathogenic processes in many of their most interesting and important aspects remain untouched. It is only necessary to cite the cases of malignant disease, of arterio-sclerosis, of otosclerosis, of the numerous forms of disease of the central nervous system, together with many manifestations of pathological processes in the skin and other organs, in order to realize

how great is our ignorance of the biological conditions which are responsible for disease processes of various kinds. In all pathological processes there is present a soil and a seed. Of the seed, the injuring agent, a considerable amount of knowledge has been acquired as stated above, but of the soil, the injured living body, which makes the response to the injuring agent and which in reality gives the real characteristics to disease processes, very little is known.

A little consideration will show that there is a very good reason for this state of affairs. The injuring agent, whether it be of the nature of living organisms or toxins, can in many cases be isolated and studied outside the living body, and its behaviour observed. But in respect to the injured agent, the tissue cells, with the exception of those of the blood, either cannot be observed at all in their living state, or at the very most only in a very unsatisfactory manner. Knowledge of these responses which the fixed tissue cells make to the injuring agent can only be inferred indirectly from observations made by means of the microscope upon the dead tissues.

Nevertheless, it is incontestable that the pathologist, the physician and the surgeon must each make up his mind to have some conception as to the inherent qualities in the tissue cells which cause them to respond to injury in the manner in which they do, if the view of disease processes is to become a truly scientific biological study.

It is owing to this narrow view of pathogenesis that so much obscurity remains as to the aetiology of such conditions as were mentioned above: malignant disease, arterio-sclerosis, otosclerosis and many other conditions.

The truth of course is that disease processes are merely one manifestation of biological processes, and a great deal of misconception as to their nature arises from the fact that

we do not realize this sufficiently, but treat the subject as though the problem were something apart from the ordinary problems of biology.

Before we can pretend to understand the behaviour of the fixed tissues towards an injuring agent, it is necessary to have at least some conception of the processes through which these tissues have been evolved. The reason for this statement is that which has been mentioned above, namely that direct observation on the changes of the fixed tissue cells in diseased processes is impossible.

Now the time is past, by many millions of years, at which it might have been possible, by direct observation, to have studied the evolution of the normal tissues in the vertebrates. Indeed, on consideration, it will be seen that, properly speaking, such observation must be impossible at all times, since the process itself must extend over vast periods of time.

Unfortunately, therefore, we are compelled to speculate upon the method of evolution of the tissues, using as a basis the accumulated knowledge of biological and pathological processes, and particularly the process of repair in living tissues.

While, therefore, the problem presented as to the significance of pathological processes in this light is seen to be increased in difficulty, at the same time it acquires a far wider and deeper interest. For it becomes clear that the processes of the evolution of the tissues and, consequently, the origin of species in the animal and vegetable kingdom, as well as the changes which occur in disease and in the repair of living tissues, are different expressions of some general biological principle.

In order to realize the truth of this statement let the reader put to himself the question, " Why should repair or healing take place at all in a living body?" The bio-

logist of the present time cannot, of course, admit that it was originally teleological.

It is the object of the following pages to attempt to solve some part of these problems. From the very nature of such problems, some amount of speculation is absolutely necessary, but as far as is possible this will be avoided, and will be confined for the most part to that portion of the subject which deals with the evolution of the tissues, and even then it will be possible to bring considerable evidence from observed facts in support of the views advanced.

EVOLUTION OF THE TISSUES

It is a remarkable fact that the process of evolution by which the various tissues have arisen has had comparatively little consideration in proportion to the fundamental importance of the subject. It is true that an extremely important contribution to the subject was made by Roux as far back as 1881.[1] Weismann also has referred to it in his works.

The reasons for this neglect may be as follows. First that biologists may not have realized sufficiently that it is the fundamental factor in the earlier process of the differentiation of species ; and secondly, even those biologists who have really appreciated the great importance of the matter are at the same time aware of the fact, referred to above, that contributions to the study must inevitably be, in large part, speculative. Thirdly, pathologists have not realized that the explanation of the tissue changes, which occur in morbid conditions and in the process of repair, are fundamentally dependent upon the qualities which the various fixed tissues possess *as a result of the changes they have passed through during their evolution.*

The original differentiation of the tissues must have begun in the earliest stages of the evolution of the multicellular animal. Let us suppose that the multicellular animal began merely as a mass of contiguous unicellular organisms, some of which, instead of separating from one another at the time of the division of the mother-cells, remained in more or less close contact. This collection

[1]Wilhelm Roux, *Kampf der Theile im Organismus*, Leipzig, 1881.

of cells has the appearance, and is possessed, of qualities which are almost identical in each cell, but they are not absolutely identical, for no two living organisms ever can be. As a result of these minute differences in these cells, natural selection must at once begin to influence the character of the mass. Thus, certain of the cells may offer a slightly greater resistance than others to some possibly injurious constituent, chemical or physical, in the medium in which they live, and as a result, the outer layer of the mass will come ultimately to be composed of cells possessing this quality. Now supposing a portion of this conglomeration became separated from the main body, it would possess cells of both characters, those which offered a comparatively considerable resistance to external injurious agents and those which possessed this power in less degree. The raw surface, if we may so term it, would then be subjected to the same injurious external agencies, and would ultimately again come to be covered over with cells derived for the most part from the remains of that layer which possessed these qualities. In other words, the cells of the outer layer lining the edge of the raw surface would grow in, and cover that surface over. Incidentally, it may be remarked that this actually is the process by which a wound on an epithelial surface is actually healed in the human being, or other animal.

Without going further into this very important matter, at present, it may be said that, viewed in this light, the process of repair acquires a very real biological significance, quite apart from the usual teleological explanation (accepted by pathologists and surgeons), and which, of course, few biologists, if any, will admit. It is not the place here to enter into details of the processes of repair as they are known to the surgeon and to the pathologist : the subject will be discussed later (pp. 33-58). It is

important at present to emphasise the close relationship which exists, according to the view expressed in this paper, between the process of repair and the differentiation of the tissues in the course of their evolution.

At a certain stage, therefore, the multicellular animal consists of a mass of cells of two somewhat different types, all the different cells lying in comparatively loose contact with one another. It must be remembered, however, that neither of these types of cells has entirely lost its original characteristics and potentialities. Thus, the cells of the outer layer could still adapt themselves or at least give rise to daughter-cells which could adapt themselves in varying degrees to the comparatively secluded life of the cells of the deeper portion of the mass. And conversely the cells of the deeper parts could themselves give rise to daughter-cells which, in the course of a few generations, by adaptation or natural selection would be able to withstand the injurious influences acting on the outer surface of the mass as well as, or almost as well as, the original outer layer of cells.

This change in the character of a given tissue is termed metaplasia, and I hope that it can be shown that it is the basis of the evolution of species in the animal and vegetable kingdoms and is the fundamental factor in pathogenesis.

Thus it may be seen how, by the process of natural selection among the individual cells, the metazoa may have originated without any teleological explanation. The origin of an external layer of cells possessed of qualities which are resistant to the forces of disintegration which may be present in the medium surrounding the group of cells, is brought about by natural selection and not by any purposive act. The group of cells is thus kept together and the process of further differentiation among

the cells forming the group is rendered possible, and the evolution of the tissues has begun.

It has further been shown how, should any force break the original single group into several smaller ones, the torn surfaces may be covered by the multiplication of the cells lining the edge of the tear, because these cells are best able to live on the surface.

The daughter-cells derived from them will be better able to live on the surface than the daughter-cells derived from the exposed cells of the deeper layers. This covering over of the torn surfaces therefore is not purposive. It may be looked upon as the primitive process of repair of a surface and, as will be shown later, it is remarkable how closely it resembles the actual phenomena which occur in the healing of a wound of the skin or mucous surface in the human subject or other mammal.

But, as stated above, it must be borne in mind that this differentiation does not imply that either the cells of the outer layer or those of the inner layer have completely lost their original character. It only indicates that certain qualities have become predominant and other qualities have become less evident though still retained. And further, it must be emphasised that all the qualities potential or latent are transmitted in varying degrees to the offspring should the cells divide. Thus, for example, a cell from the outer layer might give rise to a large number of daughter-cells, and of these some would possess certain qualities of the mother-cell in even more pronounced degree than that cell itself, others would possess these qualities to the same degree as the mother-cell, and some would exhibit these qualities in lesser degree and in fact approach rather more closely in their characteristics to the cells of the inner layers. Hence it comes about that in the early simple forms of metazoa such as the cœlenter-

ates, there is an extraordinary degree of plasticity in the tissues. For example, the hydra may be turned inside out or macerated in various ways, and in spite of this the cells accommodate themselves to the new conditions by the latent potentialities which they possess.

Thus, the metaplasia of tissues may take place to an almost unlimited extent in the very simple and early forms of the metazoa. But even in this case it is probable that in order to bring it about there should be considerable reproductive activity among the cells of the tissues. That is to say, it is not so much the mother-cells that change their character, but the more plastic and more numerous daughter-, granddaughter-cells, etc., which bring about the change in the tissue because the qualities of the mother-cell are distributed among the daughter-cells in varying degree, and therefore a large number are offered for natural selection. In the more complex and highly evolved animals at any rate there is no doubt that reproductive cellular activity in the tissues is the chief factor in metaplasia.

One very important quality possessed in varying degree by the cellular elements of the metazoa is that of phagocytosis, and this faculty is of such vital necessity to the animal that some space must be devoted to its consideration.

In the simple unicellular protozoa each animal has the power of individual movement and lives by capturing for food such objects living or dead as come within its reach. Hence in this and other respects each cell or animal may be said to be equipollent. But even in certain of the protozoa, the choanoflagellate Proterospongia, the cells of the colony are divided into two classes, the choanocytes and the amœbocytes, which manifest different properties, even though one of these may develop into the other.[1]

[1] *Treatise on Zoology*, Ray Lankester, Introduction to Part I.

Such a colony of protozoa may therefore be considered as a stage in the direction of the production of the true metazoa. It fulfils one of the conditions of the conception of the metazoa; that is, it consists of a colony comprised of two different types of cells developed from a single ovum. It does not, however, fulfil one of the other supposed conditions—viz. that the cells of one tissue can only give rise to cells like themselves.

This last condition is one upon which great emphasis is laid by the zoologist, and it is not difficult to understand why it should have been accepted by them. But the pathologist knows that it is not an accurate statement. The zoologist studies the reproduction of the tissue cells under normal conditions, and in these circumstances the rule stated above may well be approximately true. But the pathologist looking at histogenesis under abnormal circumstances, sees frequent examples of tissue cells giving rise to cells very unlike the parents, and indeed occurrence of many diseased conditions depends upon this fact. The existence of cancer, for example, only becomes possible when the epithelial cells reproduce daughter-cells possessed of qualities in some respects very different from the parent.

It is remarkable how little attention the student of evolution has paid to the differentiation of the tissues. And this is the more remarkable when, as Shattock has pointed out, it is of far more fundamental importance in the evolution of the plant and animal kingdom than the ordinary mutations which are supposed to bring about the differentiation of species.

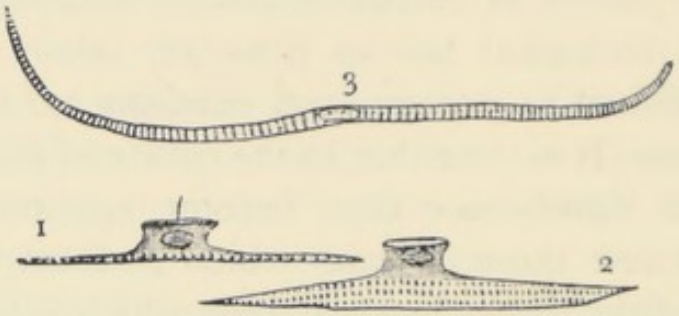
Were we able to solve, even if only approximately, these problems, then I venture to think the occurrence of variations and mutations would be to a certain extent understood. In other words, the real problem of evolution is

the differentiation of the tissues, and it is noteworthy that Shattock approaching the subject from a different standpoint has already reached the same conclusion. Further, when we understand the original meaning of the differentiation of normal tissues the significance of metaplasia and tissue changes under pathological conditions will fall into its natural biological relationship.

In the preceding pages an attempt has been made to illustrate the manner in which, from an undifferentiated colony of cells, an outer covering of epithelial cells might arise by a process of natural selection, without calling in any other biological law or principle other than those well established at present, and entailing no teleological significance. It is clear that in the course of generations a teleological significance does become apparently established, because those colonies which perform this differentiation of the tissues best are those which will survive as colonies, and by the law of inheritance give rise to colonies like themselves and therefore better able to survive. Thus a phenomenon, at first non-purposive, comes in the course of generations to be purposive, and the apparently contradictory points of view of those who believe in purposive evolution, and those who do not believe in it, become reconciled.

It is outside the scope of the present paper to suggest all the factors which may have played their part in the differentiation of all the tissues, as has been outlined in respect to the evolution of a specialised epidermal covering. It is of interest, however, to show an example of what has clearly been the evolution of muscle-fibres from epithelium. The accompanying illustration shows three different types in this evolution which is found in the cœlenterates. It is taken from Ray Lankester's *Treatise on Zoology*. The first illustration shows an epidermal

cell with a lateral prolongation at its base, and this prolongation shows some signs of striation. The second cut shows the condition in which the basal prolongation of a cell is much increased and striation more pronounced and the surface portion much diminished. The third cut shows a cell in which the surface portion has completely disappeared and only the striated muscular portion remains. In other words it is obvious that epithelial cells can in process of time become evolved into cells of a totally different character.



But although the illustration just given demonstrates the fact that a muscular tissue has been evolved from epithelial tissue, in the case of the cœlenterates, it does not explain how the process took place. And this is, I venture to think, the crux of the differentiation of tissues and therefore, ultimately, of the evolution of species, and the question requires careful consideration. The explanation which (it may be said) is usually accepted at present is that without any stimulus either a new quality has suddenly and spontaneously appeared in a cell or group of cells, or some quality already present has spontaneously become suddenly greatly increased in degree. Thus in the special case of the muscle fibre, its evolution from the epithelial cell is looked upon as being produced by a greater or less variation among one or more of the epithelial cells in the direction of rhythmic contractility. This spontaneous variation in the epithelial cell or cells gives

the animal or animals a greater chance of survival than those individuals who do not possess it, and therefore, by the process of natural selection, the former survive and the latter either perish or remain unspecialised in that particular direction. In other words the supply (*i.e.*, the variation) is offered before the demand (*i.e.*, the environment) is present.

It has for long appeared to the writer that this attitude of mind has led to a wrong conception of the evolution of tissues. It is, of course, true that the variations amongst the cells do exist, for no two cells are identical in their character. But what it is important to emphasise is that, according to the commonly accepted view, some quality *spontaneously* rises into importance in a cell or group of cells, and if it happens to give an advantage to the animal in its environment then that animal survives when the other animals perish, and hence a species arises with that particular quality anatomically and physiologically developed in special degree.

The reader will excuse the repetition of this argument in the last two paragraphs because it is of fundamental importance in understanding the difference between the point of view at present most accepted and that which the writer indicates in the following pages.

Put as tersely as possible the writer's hypothesis of the differentiation of the tissues is that the demand (that is, the environment) is made before the supply (that is, the new type of tissue) is evolved. As in the usually accepted point of view, so also in that now suggested, it is taken for granted that all the cells vary more or less in all their characters, that is to say no two cells are exactly alike. But from this point the two views differ. The writer is not of opinion that some quality suddenly appeared actively in excess in a cell or group of cells in an individual and gave to

the animal a better chance in the struggle for existence if this quality happened to be of value to it. The point of view that he wishes to express is the reverse of this, viz. that the environment of the animal was changed, in greater or less degree, and consequently the qualities of the cells required for survival are rather different in their various degrees than was the case before the environment was changed.

Expressing the matter in another way, we might say that change of environment has caused injury to a tissue consisting of cells having similar qualities but varying in the degree in which they possess these qualities. As a result of the injury, repair takes place not as a purposive act, but in accordance with the laws of natural selection. Those cells which can best withstand the injuring agent, that is the new environment, will survive and produce offspring possessing qualities similar to themselves, while those less fitted to resist the damaging influence of the new environment are destroyed and have no offspring. Consequently the individual animal which possesses the largest number of cells best fitted to resist the injuring agent will repair the injury most satisfactorily and most rapidly and will therefore survive. And in the course of generations as selection goes on, the cells of the part will all come to possess the particular quality or qualities required.

Thus in the case of the evolution of the muscle cell from the epithelial cell in cœlenterates just referred to, the writer would attribute its evolution to the varying dragging effect of the currents of water in which the animal lives. The epithelial cells which could best resist this varying dragging effect would be the ones which would develop into the muscle cells by a gradual process of selection. Thus injury is the initial factor in developing the

muscle cell, and the latter is not a *spontaneous* variation from the epithelial cell in the primitive metazoa such as cœlenterates.

Yet another way of expressing the same idea, and one which will lead on naturally to the writer's conception of the process of evolution, is as follows :

A number of animals of a given species are living in a certain environment. All these animals have cells and tissues which possess respectively similar qualities, but no two possess them in identical degrees. Now let it be supposed that the environment becomes changed, as is constantly happening in nature, *e.g.* a marsh or shallow lake gradually tends to become dried up in whole or in part during a dry season, or the sea gradually tends to advance upon the land or conversely the sea retreats from the land and so on. The inevitable result is that in some way or other injury, using the term in its widest sense, will be inflicted upon some of the cells and tissues of all the animals concerned. The response which the tissues and cells make to the injury will be somewhat similar in all cases because the cells and tissues possess comparatively similar qualities. But in no two animals will the response be exactly identical because the tissues and cells in no two are exactly alike. Now the sum total of this response in the tissues will enable some of the animals to resist the injuring agent better than others and the former will survive and will produce offspring. These offspring will *on an average* possess the same qualities as the parent, that is to say, there will be, latent in them but not necessarily active, the power of repair from the particular injuring agent which decimated the previous generation. But variations will also be present in this second generation, some individuals possessing this requisite power of repair in greater and some in less degree. When these indivi-

duals are again subjected to the injuring agent for selection some will repair even more quickly and more satisfactorily than the parent, and survive. Others will repair less rapidly or satisfactorily and many will perish. In other words, the new type of tissue is produced more and more readily in each successive generation until the stimulus required to call it forth becomes so insignificant as to be negligible. Thus, the ovum, as succeeding generations ensue, comes to possess the potentiality for developing the type of tissue or tissues suitable for the environment in such pronounced degree that practically no stimulus is now required to produce the requisite tissue. Thus a process which at first was not purposive at all comes to possess the complete appearance of a purposive phenomenon.

Now it is to be noted that this explanation of the differentiation of tissues does not necessitate the acceptance of the view that acquired characters are transmitted. It is not the wound or mutilation, or injury or repair produced by the injuring agent which is transmitted. What is transmitted is the faculty possessed by the ovum from the beginning, of responding to the injury in a way particularly suited to resist the injury when next inflicted. This quality was potentially present in the ovum before the injury or inimical environment was present. All that has occurred is that by the process of natural selection ova have been produced which have this potentiality more and more strongly present and therefore requiring less and less stimulus or injury to call it into active existence, until in such ova the potentiality is so markedly present that practically no stimulus is required to bring into being the type of cells requisite to resist the injuring agent. Thus it comes about that the evolution of a given tissue in the individual has the *appearance* of a purposive act.

I hope to show in the later pages that upon this fact is based the occurrence of almost all pathological processes.

At present, however, it is desirable to illustrate further in a general way the process by which, according to the writer's view, the various normal tissue structures and organs might have been evolved, and to point out wherein and to what extent that view differs from the ordinarily accepted one of spontaneous variation.

For the sake of clearness let a concrete example be taken and discussed. Thus, assuming evolution by natural selection to be a true doctrine let the problem be—How have the fore-limbs of the amphibians, reptiles, birds and mammals come into existence? Let it be assumed further, which probably no biologist will call in question, that the amphibians have been evolved from the fishes. Thus the problem becomes—how from a limbless animal has the limbed amphibian arisen? According to the view of differentiation by *spontaneous* evolution, we must suppose that, without any exciting cause tissue changes and structural adaptation have appeared while the animal was still living in the water or was, for some reason, attempting to take to a more or less terrestrial life. Contrast with this the hypothesis put forward above and for which the name of Induced Variation may be suggested. According to this view the variation arises in a different way and its occurrence is not spontaneous, but is called into existence by change of environment. Thus as a result of this change the component tissues, such as the skin, cartilage and joint surfaces, will have to respond to the injurious effects resulting from the wear and tear and altered stresses and strains. Now in response to this injury the process of repair takes place, but it is to be noted that though this process of repair may be very similar in all the individuals concerned, it is not identical in any two because the cells

of the part not only vary among themselves, but vary still more between individual animals. Further, it must be emphasised that the way in which the process of repair takes place in each individual depends upon qualities which are innate and therefore inherited. This does not mean that these qualities were actively present before the injury took place, but that they were potentially present. That is to say, *had it not been for the injury*, i.e. *the change of environment, the variation in the nature of the repair would never have been called into actual existence.* In other words, the power of repairing the injury when it occurred was inherently, though only potentially, present in each fertilised ovum, but although only potentially present it was still different in each ovum. Each fertilised ovum then was destined to repair the injury when it occurred, in a different way, and, according to the way in which the process of repair took place in each animal, the animal was either more or less suited than its neighbours to resist the injury the next time it occurred. In this way those which repaired the injury most rapidly and most satisfactorily survived, and produced offspring like themselves. Thus the next generation would, on an average, repair more easily and more rapidly than the previous one. But in the second generation the power of repair in this way also varies in each individual and again, when the injury is wrought by the environment, natural selection plays its part, and those which respond most rapidly and most suitably survive. Put conversely, it may be expressed thus: in each succeeding generation the fertilised ova come to possess a stronger and stronger tendency to develop in the direction most suitable for the environment. Hence it requires less and less stimulation from the injuring agent, that is the environment, to call forth the potentialities of the fertilised ovum, until ultimately the stimulus required to do so may

be considered negligible, and the ovum develops the organ or tissue required *apparently* spontaneously and *apparently* with purpose. Originally the process was neither spontaneous nor with purpose. It was not spontaneous because injury was first required to bring the process into existence, and it was not with purpose because the cells of the part injured behaved in the way which would best protect themselves without regard to the individual as a whole. Only those individuals survived in which the autonomous response of the cells of the injured part happened to coincide best with the preservation of the life of the individual.

As with the early portion of the evolution of the limb of the amphibian so also with its further evolution. For example, in the formation of the bones, muscles and joints, the theory of spontaneous variation can account for these only by assuming that without any particular reason they appeared of themselves in some primitive way, and, being found to give the possessor of them an advantage, they became inherited. This is a very difficult position to maintain, and it is a significant fact that many biologists even among those, and they are the great majority, who will not accept the theory of the transmission of acquired characters, feel the inadequacy of the explanation. Indeed a few biologists show a tendency to return to the view that within a limited extent the transmission of acquired character may occur.

Furthermore, in the hands of those who are not primarily biologists, but philosophers or metaphysicians, this theory of evolution by spontaneous variation is a weapon by means of which the biologist is scourged. Thus Bergson cites an example which in its significance is almost destructive to the theory of evolution by spontaneous variation. Consider the evolution of the eye and the sense

of sight. According to the theory of spontaneous evolution we must assume that without reason a certain cell or group of cells appeared in some individual, low in the animal series, which was sensitive to light. Next we must assume that, again without stimulus or reason, nerve fibres appeared spontaneously connecting these visual cells with nerve ganglion cells. Again we must assume that without stimulus these fibres increased and that others were formed connecting various ganglion cells together, and so on until by the most extraordinary sequence of coincidences the extremely complex structure of the mammalian eye and its central connections was built up, natural selection being the agent which differentiated the species.

But, as though this were not sufficient difficulty in the way of accepting spontaneous variation to account for the origin of complicated structures and organs, we have the wholesale difficulty of accounting for the innumerable examples of the parallel evolution of structures which unquestionably were not derived from some common ancestor. Thus the chordo-tonal organ of insects is a structure found on the anterior limbs, and is undoubtedly an organ of hearing, and indeed even anatomically bears not a little similarity to the organ of Corti of the higher vertebrates. Both these organs are exceedingly complex, are as stated fairly similar in structure, and subserve exactly the same function, and from both nerve fibres run from the terminal sensory organ to the nerve ganglion cells. Yet in one case the organ is evolved probably from the integumentary covering of a limb, in the other it is undoubtedly derived from the deeply placed otocyst. They have no common origin at all. By the theory of spontaneous variation, therefore, we must account for this identity of function and similarity of structure by a most remarkable series of, so to speak, double lists of coincidences each similar

to that cited above in the case of the evolution of the eye. Is it not surprising that many biologists refuse to accept the explanation of evolution by means of spontaneous variation either in the sense of a gradual accumulation of minute spontaneous variations or in that of sudden mutations? It will naturally be understood that these theories are not necessarily excluded as factors in evolution. It is important to emphasise that they do not account for the evolution of tissues and structures of any great degree of complexity. Above all from the present point of view they fail entirely to account for the histological changes that occur in pathological conditions.

But there are many other arguments to be used against the view that tissues and structures are formed by spontaneous variation alone. Of these objections let one only be cited. In a number of amphibians the appearance of the limbs may be retarded or even completely prevented by keeping the animal permanently in water. Now if the limb arose originally as a spontaneous variation it should develop independently of its environment, especially as the tendency to develop the limb has been emphasised through numerous generations. So also with the development of the lungs and the loss of the gills, both these processes may be interfered with by placing the animal in a suitable environment. All goes to show that these structures have been evolved not by spontaneous variation, but they have been called into existence by a definite environment—in other words, they have been *induced*. To repeat what was said previously, the demand is made before the supply is produced, whereas according to the theory of spontaneous variation the supply is first offered and then the demand is found.

Now let us consider how the evolution of these structures would be explained by the theory of "Induced

Variation " as described in this paper. As regards the case of the evolution of the vertebrate fore-limb this has already been considered in general and it is only now necessary to examine the process more in detail. As a result of injury upon the cells of the integument and subcutaneous tissues some of these cells are destroyed and some are weakened and unable to perform their function, others may be less affected, and some perhaps not affected at all, because all living cells vary from each other. The ones which survive and remain active are now enabled to reproduce, because of the room left by the dead cells. But this is not all. The surviving cells, when they reproduce daughter-cells, reproduce them not in the adult form, but as comparatively undifferentiated cells. This fact may or may not be well known to biologists but it is very well recognised by the pathologist in the case of the repair of a wound. Thus when the integument or mucous surface along with the subcutaneous tissue is wounded the epithelial cells surrounding the wound, no matter what type they may belong to, squamous, columnar, cubical, ciliated, or other, give birth to daughter-cells quite unlike themselves in most respects. Thus the daughter-cells are rounded or spherical, they possess the power of motion, and they become phagocytic, differing in all these respects from the mother-cells. Further, the daughter-cells have not the power of producing keratin, or of secretion, and are not possessed of cilia as are the mother-cells according to the type of epithelium to which they belong. So also with the cells of the connective, vascular and other tissues which are injured ; those which have the power of reproduction at all give rise to daughter-cells which are not like the mother-cells, but manifest qualities such as phagocytosis and mobility, which are very different. This, however, is not all. These daughter-cells, although so unlike the mother-

cells, have yet the potentiality of ultimately developing into cells like the mother-cells, and if the environment is suitable they will do this. Under certain circumstances, however, when the environment is not suitable the successive daughter-cells in the course of a few generations may develop into cells quite unlike the ancestral cell from which they were evolved. This is seen in the case of polypi from the nose, ear or uterus in which a columnar epithelium gives rise to a squamous epithelium if the polypus be sufficiently large to become exposed to the air or in some other way be subject to injury.

Now without going further into the consideration of the process of repair at present, I suggest that a similar process of metaplasia takes place in the evolution of the tissues and therefore in the evolution of the different orders, species, etc., of the animal and vegetable kingdom. When a given tissue is injured it undergoes repair in the way above described. Should this injury be inflicted upon a large number of animals of the same species, the process of repair will be very similar in all, but at the same time it will never be identical in any two animals. If the injury be due to some factor which comes to be constantly present or constantly repeated, then a divergence in structure from the original species will occur because the inherent potentialities of the fertilised ovum to repair in the most suitable manner become more and more emphasised by natural selection, and this inherent potentiality of the fertilised ova becomes more and more pronounced in each successive generation. In the earlier generations when the injury is inflicted, all the cells or living elements of the part multiply and struggle for existence. Some of these act in such a way as to produce a result in the nature of repair which is satisfactory in protecting against the injury, other cells try to hinder this process, the whole

process not being purposive, but each cell individually acting for itself.

The individual animals, in which the cells tending to produce a satisfactory process of repair are most predominant, and those hindering this process most in abeyance, will survive. Consequently in the next generation, the fertilised ovum will possess more of the elements tending towards satisfactory repair and less of those hindering it, and so on by natural selection, until ultimately all the factors tending to hinder satisfactory development are removed and all those tending to promote it are present. As a result, in the course of generations, by the mere process of growth of the fertilised ovum the tissues and organs are produced which are most satisfactory for the purpose of resisting the injurious agents which act against the individual.

On the other hand this hypothesis of Induced Variation enables the biologist to dispense with the unsatisfactory one of Spontaneous Variation, except, of course, merely in so far as it postulates a variation among the individual cells, a postulate which makes perhaps no greater demand upon the logician than do Euclid's axioms upon the mathematician. This, however, is not the meaning which biologists attach to the word "variation" in the multicellular animals. The spontaneous variation, as understood by the biologist, is a structural difference between individuals, either in degree or in quality, of an organ or tissue and having a real existence, coming into existence spontaneously, and of value to the animal in its environment. What is meant by the term "an Induced Variation", as suggested in this hypothesis, on the other hand, has no real existence at all until certain factors either within or outside the body act upon certain tissues and cause injury in greater or less degree. In other words the induced

variation is the structural alteration in a tissue or organ which results from the sum total of the activities of all the living elements of a part injured or stimulated in some special way. Before the injury such structural alterations were only *potentially* inherent in each fertilised ovum and were potentially different in each ovum. The injury has made the potential structural alteration an actual one, and the potential difference a real difference in structure.

Now by employing this hypothesis of Induced Variation as distinguished from that of Spontaneous Variation, let us examine some of the cases of evolution of an organ or structure and judge how it explains the origin of their existence, and further how it explains some of the biological problems which are difficult or impossible of solution by means of the spontaneous variation theory.

A very good example of what, in the writer's opinion, illustrates the evolution of a tissue is bone. For in dealing with this tissue it is possible to consider not only speculatively the evolution of bone in general from cartilage or connective tissue, but direct examples under pathological conditions of its evolution in the individual animal can be cited.

Taking the evolution of bone as a normal constituent of the body of vertebrates, it is clear that the most instructive stage is that which must have occurred when the amphibians were being evolved from the fishes. The skeleton of the fish is admitted by all morphologists to have been primitively cartilaginous, while in the amphibian grade the skeleton is bony.

The theory of spontaneous variation is obviously of little or no value in explaining the transition of the skeleton from cartilage to bone. The innumerable spontaneous variations and mutations which would be necessary to explain the process of this evolution of a bony framework

for the body are beyond the wildest possibilities of coincidence, and there is no necessity to waste time in pointing out the insufficiency of such an explanation.

Such difficulties do not present themselves when the theory of induced variation is employed to explain the evolution of the bony from the cartilaginous skeleton. Indeed, it is so obvious as hardly to require description. When certain fishes were compelled to leave the water, even were it only for a part of the year, the stresses which would fall upon the various structures would be very great relative to those which were present when the animal lived in an element of a specific gravity almost identical with that of its own body. The various skeletal elements, which in the fish are for the most part cartilaginous, would, when the animal came to live on the earth, be subjected to stress which could not fail to injure the structures which hitherto had only been adapted for a watery existence. Such injury must mean repair, and those animals in which the repair resulted in a more rigid condition of the injured structures would be better adapted for the new mode of existence than those in which the repair had merely left the structures in the pliable condition in which they originally existed. This was achieved by some cells having the faculty of depositing mineral salts round about them in a particular way in order to protect themselves, and replacing the cartilage cells which could not do this so efficiently. On the other hand, it would clearly not be a very satisfactory result if the skeletal structures throughout the body were united into one rigid mass; hence those animals in which pliable portions of cartilage or connective tissue remain during the process of repair will have an advantage over those in which the process of repair did not end so satisfactorily. And in a similar way it is not difficult to see how by the means of

induced variation, a bony skeleton with joints, etc., came to be built up.

Entering a little more into detail in regard to this process, it is probable that it is not so much the actual cells of the injured part that begin to repair in the way described. At any rate such is not the method of repair which we know takes place under pathological conditions in the human body when injury occurs. What takes place in the latter instance is that the cells of the injured part begin to multiply and it is these daughter-cells and the subsequent progenies which determine, at least for the most part, the process of repair. And this fact explains further why a variation should arise so comparatively easily during repair, because the daughter-cells are much less specialised than the adult parent-cells and are therefore capable of deviating into types of cells rather different from the parents if the environment is different from that in which the parent developed. In the particular case under consideration, for example, the daughter-cells which will be most fitted to survive will not be those most like the mother-cells in that they deposit cartilage round about themselves, but rather those, if any such should be present, which have the faculty of depositing rigid calcium or other salts round themselves as a protection. Further, as before, the individual animal, other things being equal, which during the process of repair possesses most of these latter type of daughter-cells will survive and the following generation of individuals will therefore have the innate potentiality for producing the same kind of daughter-cells still more pronounced. Thus the potentiality becomes so strong in the course of many generations that the deposit of bone becomes the natural sequence to the deposit of cartilage in those situations in which it is more suitable for the preservation of the individual animal. On

the other hand cartilaginous portions may remain in situations where such tissue is sufficient to withstand the strain, and at the same time it allows of a certain degree of mobility which is an obvious advantage to the animal.

Bone, however, does not only replace cartilage, for in some cases it is deposited directly in, and replaces, ordinary connective tissue. An example of this is to be found in the case of man in the bones of the vault of the skull, a portion of the manubrium sterni, the patella and other parts. In these two processes, formation of bone in place of cartilage, and formation of bone in place of connective tissue, we have an example of what may be termed parallel evolution of a tissue, and it is a strong argument against the theory of spontaneous variation as a factor in evolution. For it is difficult to believe that, by mere chance and without stimulus, in two different tissues, should be evolved a tissue (bone) which is indistinguishable and almost identical in each case. The theory of induced variation on the other hand explains the evolution of bone in both cartilage and connective tissue, because the injury is produced in the two tissues by the same agent, namely pressure or tension, and during the process of repair it is only to be expected that in both cases the cells which survive of the two tissues will come into being (wherever they are derived from respectively) and will possess somewhat similar characters. Among such characters the power of laying down lime-salts round themselves as a protection may well be one.

The case of the evolution of bone in both cartilage and ordinary connective tissue also illustrates a point already indicated, namely that during the process of repair the newly formed tissue is not produced directly by daughter-cells exactly like the mother-cells, but by daughter-cells which are (whatever their origin) more primitive in type

than the parents from which they sprang. Therefore they are less highly differentiated in their characters and more capable of diverging as they become adult, and of developing into cells different from the parent ones. Hence, owing to this plasticity, the daughter-cells both in the injured cartilage and in the injured connective tissue, being subject to the same environment, may very naturally come to resemble each other more closely than they do their own ancestral parents.

Now in regard to the evolution in the phylogenetic stem of bone from cartilage and connective tissue as described above, the subject must obviously be merely speculative, although the facts are very strong in support of the view of their evolution as given above. But in the case of the production of bone in cartilage and connective tissue under pathological conditions, the matter is fortunately capable of direct inspection and proof and therefore gives further support to the hypothesis of the origin of the tissues as enunciated above.

An example of bone replacing cartilage under pathological conditions is the very common case in which the costal cartilages become ossified in cases of emphysema. The writer had frequent opportunities of seeing this condition during his twelve years' experience as pathologist to the Glasgow Cancer Hospital. In these cases increased pressure is brought to bear upon the walls of the thorax on account of the continuous severe coughing, prolonged over many years, which causes the emphysema. Thus we have an example in which increased tension causes the substitution of bone for cartilage. There appears to the writer to be little doubt that the same factor of stress is responsible for the evolution of the bony skeleton from the cartilaginous one.

This view of the evolution of the tissues in the phylo-

genetic stem appears to render clear the significance of several phenomena well known to the anatomist and pathologist. For example, many structures will not reach full development unless they be used. A muscle will remain small and feebly developed unless it be put to use, and may even undergo degeneration under certain circumstances. A bone will not reach its full normal anatomical proportions unless the muscles to which it is attached are used, and so on. In other words, although the potentiality in the ovum will evolve the structures up to a certain point, there is still required the final condition of injury, for of course use necessitates injury to the cells.

Similarly the curious fact that the development of the limbs and gills of many of the amphibians may be arrested by enforcing a prolonged stay of the tadpole in water acquires a deep biological significance. The potentiality in the ovum for the development of the limb is very great, but it has not yet reached that stage at which the external environment of injury can be altogether dispensed with, as is the case in reptiles, birds and mammals.

But there is the still further remarkable fact concerning neoteny, that it frequently occurs in individuals which have been reared in exactly the same environment as others which have gone on to full development. Now in this case, according to the view expressed in this paper, the explanation is simple. Those individuals which do not develop the gills as soon as their companions are derived from ova in which the potentiality for so doing was originally rather weaker than in their companions who went to full development. And it is interesting to note in support of this theory that in total neoteny the animal still retains its gills, but at the same time it develops to sexual maturity. The explanation of this remarkable fact is not difficult in the light of the hypothesis of induced varia-

tion. For the substitution of lungs for gills is a recent acquirement as compared with the development of sexual maturity. In other words, the potentiality in the ovum for the development of gills is less pronounced than that for the development of sexual maturity.

Yet another fact in respect to neoteny now becomes clear. It is in regard to the development of the eye and the middle ear respectively. In those individuals in which the animal retains the gills, but nevertheless develops into sexual maturity, the eye also develops normally. *On the other hand the tympanic cavity and columellar chain do not develop.* Here again the explanation appears to the writer to be that the organ of vision has a long ancestry behind it, being present in the fish and very possibly in the invertebrate animal from which the fish was evolved. The organ of hearing, on the other hand, is not present in the fish, for the otocyst is not an organ of hearing in these animals. The sense of hearing is first definitely developed in the amphibia, and is no doubt called into existence as a result of a terrestrial or aerial existence. Hence, the external stimulus or injuring agent is required in greater force to complete the development of the ear than that required to complete the development of the eye, the innate potentiality for the development of the latter being greater than that for the ear and therefore requiring less of the injuring agent.

The comparatively recent appearance of the organ of hearing in the vertebrate animals is, as will be shown later, a fundamental fact in its further evolution in the higher vertebrate and also in its pathology.

In the foregoing pages it has been suggested that in place of " Spontaneous Variation " as being the fundamental factor in evolution by natural selection, the really important factor is not "spontaneous" but "Induced Vari-

ation". That is to say, the variation is only a potentiality and has not a definite existence until injury acting on the various cells causes such actions and reactions among the latter that during the process of repair differences or variations among the animals result which were only potentially present.

While, therefore, these variations are somatogenic, and therefore not directly inherited, the potentiality towards them is present in the ovum, and by natural selection this potentiality becomes more and more pronounced in successive generations; the injury required to transform it into an actuality becomes less and less until practically no injury is necessary. The potentiality, in other words, becomes so marked that the actual variation appears and ultimately becomes a normal structure of the species and is no longer called a variation.

REPAIR

In the preceding pages, I have formulated the hypothesis that variations upon which the process of evolution depends arise not so much spontaneously as by the effect of environment.

The change in environment (and there always must be some change of environment) causes injury, and the process of repair which follows this injury, being different to a greater or less degree in every individual, gives the opportunity for natural selection.

Those individuals will survive in which the result of the process of repair most satisfactorily enables the animal to exist in its new environment. In the course of generations, by natural selection, the potentiality for responding to the stimulus of the environment becomes more and more pronounced until practically no such preliminary stimulus is required. The effects of the environment may almost be said thus to be forestalled, and a process which at first was not purposive at all, comes to have an apparently purposive significance.

The basis of this hypothesis of the origin of tissues and organs is, therefore, the process of repair, and it is important to give some consideration to the facts known concerning that process. After that the relationship of the process of repair to pathological conditions will be considered, and the writer hopes to correlate the processes which occur under pathological conditions with those which exist under normal physiological circumstances

and to show how, and in what way, pathogenesis is merely an expression of biological laws.

The process of repair has been studied by many investigators, but it must be remembered that all such investigations are from their nature made upon comparatively gross lesions. Such for example are the repair of bone after fracture, the healing of a wound in the skin or soft parts of the body after injury more or less gross. By the mere reason of their slowness and minuteness the processes of repair which must be constantly occurring in the tissues can hardly be studied in the laboratory. From large accumulations of pathological facts, inferences, no doubt moderately correct, may be drawn. When correlated with the facts known from clinical history, a rough idea may be formed of the nature of the process of repair, or attempted repair, in acute and chronic disease.

Of these the process of repair after gross injury will be considered first, because in such circumstances the facts are most directly and definitely demonstrated. And a few lines will be devoted to consider the extent to which the various structures and tissues are able to repair at all. After that the general process of repair of a wound when several tissues are involved will be considered. Finally, the process of repair in pathological circumstances will be discussed, and the writer hopes in that portion to show that disease processes of many kinds are simply deviations of the process of repair from its normal course in accordance with well-known ordinary biological laws.

REPAIR OF TISSUES AFTER GROSS INJURY

The rule is general, but possibly there may be exceptions, that after injury new tissues are formed from the corresponding tissues in the neighbourhood of the wound.

Thus the cells, from which are ultimately formed the new connective tissues, are derived from the connective tissue in the neighbourhood. The new epithelial cells are derived from the pre-existing epithelial cells in the neighbourhood and so on with other types of cells.

Passing from this general principle the mode of origin of the new tissue from the old has now to be considered in detail.

EPITHELIAL TISSUES

Excluding the epithelial elements of certain glands, it may be said that epithelial tissues have very great powers of repair. Indeed in these and the connective tissues the process of regeneration and repair is almost unlimited. And if the preceding pages concerning the evolution of the tissues have been understood properly it is not difficult to see why this should be. The epithelial cells lining surfaces must throughout the whole animal kingdom be constantly subject to injury of various kinds, physical and chemical. If in any animal, therefore, they do not repair themselves satisfactorily, such an animal would quickly be destroyed and leave little or no progeny to inherit its weakness in this direction.

In all cases with a few doubtful exceptions the epithelial tissues taking part in the process of repair are derived from the pre-existing epithelial cells in the neighbourhood. The epithelial cells in the deeper portions of the skin or mucous membrane at the edge of the wound begin to multiply and give birth to new cells. But the remarkable fact is that the new cells are quite different from the mother-cells in almost all their qualities. They are spherical or pear-shaped, they are mobile and glide over one another and on to the surface of the wound, and they are phagocytic. Ultimately, of course, if they live suffi-

ciently long and the environment in the wound becomes suitable, these daughter-cells may become like the original mother-cells—that is, they may become fixed and squamous or columnar in shape, and lose their phagocytic qualities. But the important fact to be emphasised is that in the process of repair the epithelial cells become undifferentiated both as regards structure and function. In other words, in the process of repair they pass through the stages of evolution by which, if the writer's hypothesis is correct, the epithelial structures were originally differentiated in the evolution of the multicellular from the unicellular animals.

The epithelia of the mucous membranes in the course of repair pass through stages similar to those just described in the case of the epidermis. Thus, columnar cells, ciliated cells or squamous cells all become rounded, cilia are lost, and the cells become mobile. As repair proceeds the cells regain the characters of the mother-cells from which they originally developed, and it is interesting to note that they regain their characteristics in the direct order in which they probably were evolved. Thus in the case of columnar ciliated epithelium, the cells which go to form the new layer, from being spherical and mobile, become first fixed, then gradually columnar, and finally ciliated.

GLANDULAR EPITHELIA

The epithelium of many of the simple tubular glands undergoes regeneration readily, but the epithelial elements of the larger glands show less readiness. In the liver, for example, the epithelium lining the bile-ducts undoubtedly does repair by means of cell multiplication, but it is very doubtful if there is any true and complete regeneration of the liver cells, with the curious exception of the regenera-

tion which takes place in acute yellow atrophy of the liver. In the kidney also the extent to which true regeneration of the epithelial structures takes place is insignificant if it occurs at all. No doubt, however, cellular multiplication and repair can occur in the epithelium lining the collecting tubules, especially in the medullary portion of the organ.

CONNECTIVE TISSUES

The connective tissues vary in their power of repair according to the particular variety. The ordinary white fibrous tissue repairs without difficulty and to an almost unlimited extent. The process is parallel with that which, as above stated, is found in all or practically all the processes of repair. The fibrous cells in the neighbourhood of the wound give rise to daughter-cells quite unlike themselves ; they are spherical, mobile and phagocytic. They are indeed, of course, the fibroblasts known to the pathologist, though it is possible that other tissues, such as the capillary and lymphatic endothelia, may give rise to fibroblasts. As the young fibroblasts mature they become fixed and then elongated and spindle-shaped and sometimes star-shaped. The cytoplasm is reduced to a mere trace and the nucleus becomes elongated, and the whole tissue appears as a mass of white fibres with the elongated nuclei embedded among the latter. As is the case in other tissues the cells lose their phagocytic qualities as they become mature.

ELASTIC TISSUE, FAT, CARTILAGE

There is no need to enter into a lengthy discourse on the process of repair of other forms of connective tissue. It need only be said that the process is fundamentally similar in all, but varies in the extent and speed at which the re-

generation is carried out. Thus in yellow elastic tissue the process of regeneration is very slow. Fat is merely a local modification of connective tissue, the fat globules being incidental, if the term may so be used. Cartilage is extremely slow in repair, but this does no doubt occur and its occurrence takes place in two ways. First by multiplication of cells from the perichondrium, in which case the daughter-cells are very similar to fibroblasts, but ultimately develop into cartilage cells. The second way is by multiplication of the cartilage cells proper ; and in this case there does not seem to be any preliminary stage similar to fibroblasts. In any case this second method of repair in cartilage is very imperfect. Indeed in general the process of repair in cartilage is altogether very incomplete.

BONE

In the case of the repair of bone, the process may be undertaken either by the cells of the periosteum, or those of the endosteum or by the bone-cells themselves in the bony tissue.

MUSCULAR TISSUE

Striped muscle does undergo repair according to the researches of modern pathologists to a very limited extent. It is, however, very incomplete, and as a matter of fact when extensive injury to a muscle occurs, repair is for the most part carried out by the formation of new connective tissue bridging over the gap in the muscular substance.

Unstriped muscle tissue undergoes repair more completely than the striped variety, as indeed might perhaps be expected, as it is probably a less highly differentiated tissue than the latter.

NERVE TISSUE

Nerve tissue in the human subject never undergoes repair by cell multiplication of the proper nerve cells. In fact it has been definitely established that after birth there is no multiplication at all of the nerve cells of the central nervous system of any of the mammalia. Whether the nerve cells of the sympathetic system ever multiply after birth or not, has not, so far as the writer is aware, been definitely investigated. If they do so at all, it is probable that the extent is very limited. Nerve fibres, outside the central nervous system, of course, easily repair, but this is quite unassociated with multiplication of the cell to which the fibre belongs. If the nucleus of a nerve cell is destroyed the cell dies and is never replaced.

From the foregoing brief remarks on repair of the tissues it will be seen that the latter obey a general well-known rule, namely, that the more highly differentiated a particular type of tissue cell is, the less is its power of repair by cell division.

Now when an injury involves, as it almost always must do, a tissue or structure composed of cells of different type, a very interesting state of affairs occurs. The cells of each tissue which have the power of repair by means of cell multiplication proliferate in the way described above. That is to say, they each produce daughter-cells which are not like the mother-cells, but possess, nevertheless, the innate tendency ultimately to become like the latter. The wound, therefore, becomes a general hunting-ground of round, mobile, phagocytic cells all comparatively similar to each other although derived from mother-cells of very different types. This stage, therefore, corresponds to the primitive stage of the evolution of the multicellular

organism. But there is this difference, that in the latter case even, the daughter-cells come from mother-cells which were all comparatively speaking similar to one another, whereas in the case of the repair of a wound in the human subject the daughter-cells although apparently so similar to each other have pronounced innate tendencies to develop into cells similar to their mother-cells.

Hence those daughter-cells which come of an epithelial ancestry have latent qualities which enable them to survive on the surface when the environment becomes suitable, but are not able to survive below the surface. Those cells which have a fibrous tissue ancestry on the other hand have the latent qualities to survive in the deeper parts and not on the surface and so on. So that as time goes on the wound is repaired, not by any mysterious purposive force, but by the ordinary process of natural selection amongst the individual cells.

From the brief description above given it will be seen, therefore, that the process of the repair of a wound is an epitome of the process of the differentiation of the tissues in the evolution of the race as suggested in the hypothesis put forward. It indeed parallels, in a small way, the development of the embryo which is an epitome of the history of the race to which the individual belongs. And the reason for this parallelism is that the two processes according to this hypothesis are ultimately the same, viz. the response of the living cells to injury.

Upon this theory that the process of differentiation of the tissues in the repair of a wound represents in epitome the differentiation of the tissues in the course of evolution, the following pages upon the origin of diseased conditions are based. It is hoped by the writer that he will be able to show how pathological processes are not to be looked upon as something apart and outside the ordinary biological

processes, but merely one expression of the latter, and further how the pathological changes come into existence and pursue the course of development which they do in certain diseased conditions.

The case of repair in ordinary physical injury has already been described, and by means of the hypothesis here suggested we are able to see why repair occurs at all after an injury, and further why it takes the course which it does. It is not teleological in the true sense of the term at all. The infection of the whole body by micro-organisms is not prevented by any purposive action on the part of the leucocytes and fibroblasts, etc., to protect the individual. The individual is a matter of indifference to the phagocytes, but their own lives are a matter of supreme importance. Hence they tend to protect themselves against their enemies and even to use them for food, and in so doing incidentally they save the life of the individual. The first step in the repair of a wound, therefore, the protection from enemies from without, is carried out by the leucocytes and later by the daughter-cells of the fibrous and probably also epithelial cells. As time goes on, however, and the fibroblasts, etc., have time to increase in numbers, and the opportunities for their development into adult cells occur, they do the latter, and fibrous tissue, very loose at first, begins to appear in the walls of the wounded area. Similarly the daughter-cells from the epithelial tissues develop in adult epithelial cells, where the environment is suitable for them, that is to say at the edges and on the surface of the wound, because coming of the cell ancestry which they do, they have potentialities for living in such situations which the daughter-cells of the fibrous tissues have not.

In this way the wound becomes repaired in a fairly satisfactory way, connective or fibrous tissue occurring

where it can best survive, that is below the surface, and epithelial cells on the surface for the same reason. On this hypothesis it is now possible to answer the problem enunciated at the beginning of this paper:—why does a wound undergo the process of the repair at all? This appears to the writer to be one of the most important problems, if not the most important, in pathology. Indeed, it is perhaps not too much to say that most pathological processes are in reality the process of repair modified in various ways.

The contraction of the scar which follows on the healing of an injury now begins to have a biological as well as a medical and surgical significance. It is, of course, brought about by the fibroblasts and the surgeon accepts this as though it were the complete answer. As a matter of fact this is only the beginning of the answer, because the questions at once occur—Why should the scar be occupied by fibroblasts or fibrous tissue cells to the exclusion, more or less complete, of other cells, and further why should they cause contraction in the affected area? As regards the first of these questions, a little consideration will give the answer. The fibroblast gradually occupies the injured area during the process of healing to the exclusion of other cells, because the latter are unadapted for continued existence in that position. The epithelial cells can only live on the surface. The leucocytes only exist as mobile cells and, moreover, their tenure of life is short, therefore they are excluded. The cells of other tissues such as muscle, etc., have poor capacity for multiplication, and so on. The connective tissue cells on the other hand have almost unlimited capacity for rapid multiplication, they can live below the surface, they are phagocytic and mobile when young, but can develop into adult fixed cells and give up their phagocytic qualities when the environ-

ment is suitable. Hence as time passes the young connective tissue cells at the edge of the injured area become fixed, and, becoming adult, manifest the quality of contracting which has been inherited from the parent ancestry.

Going still further back it may be asked why should the fibroblast tend to contract at all? The answer to this question lies in the evolution and differentiation of the tissues. When the metazoa were gradually evolved from the unicellular animals, and the differentiation of the tissues began, it is clear that no individual could long exist unless there was present some method of holding the various cells and tissues together. This necessity resulted in the evolution of the fibrous or connective tissue. Thus the mass of comparatively undifferentiated cells of the early metazoa must have been subjected frequently to distortion by physical agencies such as moving water, etc. Among this mass of cells some would possess in rather higher degree than others a certain quality of elasticity or resiliency even when they themselves were distorted out of their normal and presumably more or less spherical shape. Here again, therefore, injury would be the factor which induced the variation which previously was only a potentiality, not an actuality.

Now after this differentiation, the ordinary fibrous tissue cell need undergo no further evolution throughout the animal kingdom. Further, even this degree of differentiation appears, if carefully considered, to be comparatively slight, though, of course, we are entering an obscure region when dealing with the mysterious changes which must take place within a cell as it undergoes evolution from one type into another. We can say, however, that the differentiation into a fibrous tissue cell from the original undifferentiated cells of the colony preceding the metazoa does not appear to require such a fundamental intra-

cellular change as, for example, the differentiation of a rhythmically contracting muscle cell and its still further mysterious evolution bringing it into association with nerve fibre and nerve cells. And the same may be said, though to perhaps a less extent, of the evolution of the various secreting epithelial cells from the ordinary epithelial cells of the epiblast and hypoblast. I venture to think that this is one of the reasons why the connective tissue cells and the simpler types of epithelial cells have retained their power of active multiplication ; for it is a general biological law that the more highly specialised the type of cell is, the less power it has of multiplication.

The difference in the faculty of repair at different ages of life in the human subject is strikingly and interestingly manifested when the prenatal period is considered. Thus, a limb may be amputated *in utero*, so that the whole forearm is lost, and yet from the seat of injury at the end of the stump rudimentary fingers and even nails may be reproduced.

It is, of course, well known that in some of the fishes and amphibians and many other of the lower animals the power of regeneration is very remarkable in the early stages of development of the individual. The well-known experiment of amputating the growing limb of the tadpole is an illustration of this. Regeneration and repair are, therefore, according to this view, not different processes, but merely different degrees of the same process. If the animal be injured at a sufficiently early stage of its career, the cells of *all* the various tissues are still sufficiently undifferentiated that they can reproduce themselves, and consequently the structure, whatever it may be, is regenerated. In the later stages of the life of the animal, on the other hand, in most of the tissues the cells have so far lost their power of multiplication that regeneration is incomplete. Only the simpler forms of connective tissue cells and epithelial

cells and blood cells are able to multiply to any great extent, and the result is, therefore, only a partial regeneration or what the pathologist terms repair.

Now, on the hypothesis of the origin of the tissues suggested, it is not difficult to see why the processes of regeneration and repair are of the same nature and differ only in degree. Accordingly the tissues all originally arose in the course of evolution as a process of repair the result of injury. Hence, if in the embryo of the higher animals injury should occur at any part, then all the cells of that part being as yet comparatively undifferentiated, and therefore possessing all the more the qualities of multiplication, the repair from the injury will be so complete that it is termed regeneration.

If the problem be considered in the light of the hypothesis of the evolution of the tissues as described in the foregoing pages it appears to be less difficult of solution.

In the cases in which, for example, a limb is amputated *in utero,* and from the stump there have arisen fingers and even finger-nails, it is evident that in the tissues of the upper arm at that period of development there are potentialities present which do not under ordinary circumstances manifest themselves. Now it is but a short step to suppose that if, instead of the limb being amputated, it were subjected to some injury short of amputation at an early period of prenatal life, among the cells thus injured there would be obviously the potentiality for the regeneration of a lost limb. When the process of repair takes place it is not difficult to suppose that such a process may end in the formation of another rudimentary limb such as occurs when the injury has resulted in complete amputation. I venture to think that this explanation best accounts for certain of the abnormalities such as are met with in animals with supernumerary limbs, supernumerary breasts,

supernumerary auricles, etc., in the cases in which there is no evidence of inheritance.

But there is more than hypothesis to support this view. In his very valuable work on the *Teratology of Fishes*, J. F. Gemmill quotes Stockard[1] as having shown how the abnormality of cyclopia in fishes, brought about by injury or other similar means, is not distinguishable anatomically from similar abnormalities arising spontaneously. The only difference in the two cases is that in those in which the abnormality arises spontaneously the feature is heritable, while in those produced artificially it is not. The analogy between the congenital abnormalities met with by the surgeon and pathologist and those described by Gemmill is complete. The abnormalities whether produced by injury or arising spontaneously differ in no way, structurally. The only difference is that those arising spontaneously are frequently inherited and heritable, while those arising as a result of injury are not noticeably so. Hence it must not be supposed that because an abnormality consists of various and highly specialised tissues it cannot have been produced by prenatal injury as is so frequently assumed. The complexity in tissue structure of the abnormality depends on the period at which the injury is inflicted. The earlier in fœtal life this occurs the more complete can be the process of repair.

This statement, of course, is not in any way inconsistent with the main hypothesis enunciated in this paper, viz. that all tissues ultimately arise as the result of repair caused by injury. Stockard was only able to produce an abnormal eye by injury in a region in which there is in the fish a comparatively strong innate potentiality for the evolution of an eye. I should be surprised if the same

[1] In Stockard's experiments cyclopia was produced by adding Magnesium Chloride to the water of developing embryos.

abnormality could be produced on any region of the fish except that in the neighbourhood of the ordinary or of the pineal eye.

These and similar experiments are instructive in many ways and throw a bright light, as shown above, on the effects of injury during that period of embryonic life when the tissues are comparatively undifferentiated and therefore possess, when injured or stimulated, a potentiality for the production of abnormal and highly complex structures far beyond that which they possess in adult life. Their evidence is also in favour of the view that acquired structures are not transmitted, using the term in the sense as accepted by biologists. Such experiments were not concerned with the question as to how far a potentiality for the production of variations of structures may be increased by selection. I do not possess the technical knowledge nor the technical skill necessary for such experiments, but I feel that it would be most interesting to make a series of experiments as follows, if it were possible to carry it out.

First of all carry out the experiments as performed by Stockard, in a large number of individual fishes, male and female. Of these a certain proportion will in response to the injury produce an eye as described by Stockard. From these so affected raise a brood, and again injure the brood, but let the injury be less in degree than in the first instance, so slight in fact that out of the whole brood only a small proportion produce the abnormal eye. From these raise another brood and so on, diminishing the degree of the injury and selecting for breeding those individuals which responded in the desired way to the minimum degree of stimulation. The question would then be either definitely settled, by a positive answer one way, or probably settled by a negative answer the other way, as to whether injury and selection acting together can produce the abnormality

under consideration. Thus, if after a large number of generations treated in the manner described, a generation occurred in which *without injury* a relatively large number of individuals occurred in which the abnormal eye made its appearance, then the question would be approximately settled in the affirmative that even where no structural variation is originally present, it can be produced by increasing the potentiality for such variation by the combined processes of injury AND selection. Further, if the generation so produced furnished offspring in which also a relatively large number of individuals again possessed the abnormal eye without preliminary injury, then the question would be definitely settled and the further fact would be established that the increased potentiality for the particular variation is transmitted, and that so markedly, that the variation actually comes into existence without previous injury. In other words, to put the matter in the terms expressed in the principal hypothesis in this paper, what was originally a process of repair has become by selection an inherent part of the normal structural development of the individual and of the species.

It is not unreasonable to suppose that mutations that are heritable arise in a similar way to that suggested above, except that the environment, the injuring agent, is omitted. That is to say, mutations according to the view expressed in this paper are really the expression of potentialities towards the same variation which have, by chance mating over a few generations, grown stronger and stronger without actually expressing themselves as structural changes and then again, by a chance mating of male and female having the potentiality strongly marked, the potentiality towards the particular variation is so strong that the actual structural variation appears.

If the evolution of tissues and structures be considered

from the point of view expressed, the meaning and applicability of Mendel's laws and the significance of the Mutation Theory become clearer. As regards "mutation", for example, as just pointed out, we can now see a good reason for the fact of its occurrence as well as for the fact that the characters it deals with are heritable and stable. Chance mutation, therefore, may quite well account in some instances for the origin of some species, but to insist upon its being the sole factor in the process is making far too wide a claim.

Similarly we are now in a position to understand why Mendel's laws of inheritance are applicable to many conditions which are inherited but not to others. If for example two contrasting characters are so definitely present in two different individuals that they inevitably appear or inevitably do not appear in successive generations derived from these two individuals, then the Mendelian laws will be applicable and are a correct statement of the truth. Such for example are almost all normal structures and not a few abnormal, which are congenital, such as albinism, Daltonism, probably hæmophilia, and several other pathological conditions which appear to be independent of environment.

But when the characters are not of the nature just referred to, then it is not to be expected that Mendel's law will be applicable. Probably the majority of cases in which there is an inherited tendency to pathological changes come under this category. A good example of such a case is the tendency to arterio-sclerosis. In probably all human beings there is a tendency greater or less to the development of arterio-sclerosis in old age. So much indeed is this the case that some physicians look upon the condition as almost to be expected in the later registers of life. In the very young on the other hand it is

hardly known. It increases in frequency from youth to age, and undoubtedly various poisons such as lead, the syphilitic virus, the internal secretion of suprarenal bodies, tend to produce arterio-sclerosis in excess. At the same time there is no doubt that in some families the tendency towards the condition is very strong, so much so that occasionally few of the members of the family survive early middle life.

In such conditions it is obvious that Mendel's law must not be applied in too strict a sense. The subject will be considered more in detail subsequently, but in the meantime it may be noted that among other pathological conditions similar to that of arterio-sclerosis in this respect, are mental affections of an inherited type, to which subject Mott[1] and others have made such valuable contributions in recent times showing that Mendelian principles are not applicable. Even Bateson, the most staunch adherent of Mendelism, admits that these laws are inapplicable to such cases. Otosclerosis also belongs to this category, and I shall discuss in a future portion of this paper how the disease does not admit of the application of Mendel's laws.

It must not be supposed that the facts stated in any way impair the greatness of Mendel's discovery. As Karl Pearson says, the importance of Mendel's work and of his followers lies in the observation of the fact of segregation.

Further, if the hypothesis of the evolution of the tissues suggested be considered, it will, I think, be seen to explain why Mendel's laws are applicable to certain inherited characters and not to others. Where the determinants, as Weismann terms them, are so definitely present or definitely absent that the character is from the first destined to appear or not to appear, then Mendel's law may still be applicable. But in cases in which the determinants are still,

[1] Archiv : of Neurology, vol. v.

if one may use a contradiction of terms, so indeterminate, then this law does not become manifest.

Thus there are certain characters which are not inherited in the strict sense of the term, but in which there is potentiality towards inheritance. Such are the majority of most inherited characters of a pathological nature, for example, arterio-sclerosis, malignant disease, otosclerosis, rheumatoid arthritis, many psychoses, and many affections of the skin. It is not a good use of the term to speak of these as being the result of " determinants " in the ovum or sperm cells. That word carries with it the meaning of something destined to occur, and we know that in many cases although the tendency is inherited the character is not necessarily destined to appear. Such manifestation depends in part on environment. Such factors are much better referred to as tendencies or, better still, potentialities. By the gradual strengthening of potentialities by natural selection, the tendency towards a given character becomes so strong, that it manifests itself ultimately independent of environment. Then we are justified in speaking of the determinant of that character. How this may come about, I have already shown.

The hypothesis I have offered to account for the differentiation of the tissues is that this occurs by the process of natural selection among the cells of the tissues already in existence. The selecting agent or environment is usually injury, using the term in its widest sense, and the differentiation occurs during the process of repair. The reason why this should occur is that, in the process of repair, the mother-cells of the injured structure do not themselves directly take part in the process, but give rise to daughter-cells undifferentiated in structure and function. It is this condition of undifferentiation among the daughter-cells that enables them to carry out the process of repair.

Being undifferentiated they possess, in a sense, the chief qualities of the original undifferentiated colony of simple cells from which the metazoa must have arisen. These qualities are mobility, phagocytosis and reproductive activity. But besides this their undifferentiated condition enabled some of them to develop (according to the special nature of the injuring agent) certain qualities which were only potentially present in the parents from which they sprung. Such qualities being useful in enabling the cells to survive, and incidentally useful, therefore, in preserving the life of the colony or individual animal as a whole, gradually by natural selection call a new form of tissue into existence. Certain qualities such as protect against the poison (in particular the bacterial ones) must obviously be retained by all animals. Hence active phagocytic cells are found, and even masses of comparatively undifferentiated cells, such as lymph glands, the spleen, etc., in the most highly specialised animals.

Further, since injury of some kind must constantly be taking place, both on the surface of the body and in the deeper parts, the cells of these parts retained the potentiality of protecting themselves, by giving birth to daughter-cells which possess the qualities of phagocytosis, mobility, and in some cases at least by the production of anti-bodies to annul or prevent the effects of numerous poisonous substances which may attack them. Hence occur the qualities possessed by the fibroblasts and the young epithelial cells.

It must again be emphasised that these qualities were not originally teleological in the sense that they were designed to protect the individual animal. The individual cells were and are only fighting for their own hand. The individual animal survived and survives because the cells do or did this in a particular way. But the cells did not

originally and do not yet do this in order to make the animal survive. Of course, as shown previously, the process ultimately comes to have the appearance of a purposive act.

It is on this last fact that the whole existence of disease processes depends, and the physician, the surgeon and the pathologist will never understand the significance of these processes until they have grasped this fundamental principle.

CHRONIC INFLAMMATION

Professor Muir [1] has very shrewdly pointed out the dangerous uses to which the term "chronic inflammation" is put. The tissue changes which are grouped under the term are widely different in character and arise from many different causes. On the other hand it is remarkable how in the same region or tissue these changes may be, and frequently are, very similar in character, in fact indistinguishable from one another even when we know that the exciting cause is different. Thus, for example, in the case of the skin, eczema may be produced by irritating substances applied externally or by different irritating substances reaching the skin by the circulation, as in gout. Similarly the changes in the arteries classed under the name of arterio-sclerosis may be produced by gout, by the presence of lead in the system, by syphilis. It is true that some pathologists maintain that the anatomical changes in the arteries vary slightly with each of these causes, but many are sceptical in this matter, and I venture to doubt if any pathologist would stake his reputation on being in all cases able to distinguish between the different forms from macroscopic and microscopic appearances

[1] Now Sir Robert Muir.

alone. It is not difficult to understand, therefore, why such a condition is referred to by some pathologists as "inflammatory" while other pathologists do not apply that term to it.

Yet in spite of these differences of opinion among pathologists in regard to the application of the term "chronic inflammation", probably all would agree in admitting that in almost all tissues there are changes, slow in progress and characterised by a general similarity in design. Instead, therefore, of discussing the meaning of the term "chronic inflammation", it would be advisable to consider what these anatomical changes signify from the biological point of view, and try to bring them into harmony with known biological laws. When that is accomplished names and phrases can be applied more satisfactorily.

According to the hypothesis of the evolution of the tissues described, it has been pointed out that the differentiation of the tissues has probably occurred by a process of natural selection among the cells of a given region or structure. The original factor which was most active in promoting the struggle among the cells was constantly repeated injury. There was originally nothing teleological about the process, each cell was fighting in its own interest. It has also been shown how, in the course of evolution, this process of differentiation of the tissues came to have the appearance, and in one sense also, the reality, of a purposive act.

It has also been shown why the process of repair, after injury, takes place; and further why that process of repair presents the characters that it does; it is characterised by activity among the cells of certain tissues only, and even among these by great activity only among few of the epithelial tissues, the leucocytes and a few of the connective

tissue cells. Among the latter the fibrous tissue stands out conspicuously as having very great power of repair. And the reason for this noticeable capacity is that the fibrous tissue cells are, comparatively speaking, not very highly differentiated, and have further great reproductive capacity, and also the power to become differentiated to a certain extent in special directions that may be required to resist various injuring agents whether the latter be mechanical, chemical or biochemical in nature.

In a given organ or structure, therefore, after being injured, there will be a tendency on the whole for the fibrous tissue elements to predominate provided, of course, the injury is sufficient to cause death indiscriminately of the various types of cell found in the organ or structure. The reason for this is, as just stated, that the fibrous tissue cells are less differentiated than the cells which are associated with the special functions of the organ or structure. Besides this, of course, they have great reproductive capacity. Hence, to take a concrete example, if a muscle is ruptured the union of the parts is accomplished by fibrous tissue, not by muscular tissue. Again, if the skin is lacerated the wound is repaired by those elements which have the greatest capacity for survival in the particular regions, that is to say by the fibrous tissues below the surface and by the *simpler* epithelial elements on the surface, but not by the more highly specialised cells, such as the cells of the sebaceous or sudoriferous glands or of the hair follicles. These are examples of repair after injury of short duration.

But suppose the injuring agent is slighter in degree, but active over a longer period of time, e.g. the slow absorption of lead or the poison which is the exciting cause of gout, and so on.

In this case the poison is carried by the blood stream in

equal doses to all structures of the body. All the cells of the body are probably more or less injured by the poison, for the reasons just given, but the result will be very different according to the various types of cell. In the case of the walls of the arteries, for example, though all the different types of cell may be affected, those which are more highly specialised, such as the unstriped muscle cells, and those which have less power of reproduction, will be restored in relatively much fewer numbers than those of the fibrous tissue cells. Consequently after a period of time the wall of the artery changes its character, the fibrous tissue elements begin to predominate, and though in their earlier stages they are rounded and possess in most respects the characters of embryonic cells, in their adult form they develop the character of their ancestry and hence cause not only thickening of the arterial wall, but also, by their contraction, bring about a narrowing of the calibre of the blood vessel.

This explanation of the genesis of arterio-sclerosis accounts among other things for the clinical fact emphasised by Sir Clifford Allbutt, that although arterio-sclerosis is very frequently preceded by, and associated with, increased arterial tension, yet it is not very uncommon to find the sclerotic change in the artery without any sign of increased blood pressure. There is no doubt that prolonged and excessive increase in arterial tension will tend to induce arterio-sclerosis, because of the wearing out of the more highly specialised muscular cells of the arterial coat, and their consequent replacement by fibrous tissue cells, because the latter have the greater reproductive capacity and survival value. But it is quite conceivable that other factors besides increased arterial tension may act upon the more highly specialised cells of the arterial wall, injuring and destroying the muscular fibres without causing in-

creased arterial tension. In such circumstances, arterio-sclerosis may arise, therefore, in the absence of previous or present hyperpiesis.

In arterio-sclerosis there is comparatively little evidence of round-celled infiltration in the walls of the arteries. And according to the view of pathogenesis enunciated in this paper the explanation of this fact is not difficult. The process of destruction of the more highly specialised cells and their replacement by fibrous tissue cells is so very slow, that at any given time the latter type of cell is only reproducing young round cells in comparatively small numbers. Further, these young round cells soon develop into the adult elongated fibrous tissue cells similar to the parent from which they sprang. In any given microscopic section, therefore, the number of round cells will be extremely small, and there may even be none visible at all.

In many cases of chronic disease there are occasional "acute exacerbations" as they are termed clinically. Such conditions are not difficult of explanation if we view pathological processes from the biological point of view. Thus, from some cause, the injuring agent becomes more active, and the cells upon which it acts are injured or killed to a greater extent than during the more quiescent periods of the disease. Hence there is a more numerous and more rapid multiplication of the cells of the injured part and in almost all circumstances the fibrous tissue cells outstrip the others in their multiplication. Furthermore, the increased activity of the injuring agent tends rather to prevent the young fibrous tissue cells from reaching the adult stage, because in that state they have less capacity for resisting the injuring agent. Hence, if a microscopic section of a tissue in a state of chronic inflammation during an acute exacerbation be examined, a

comparatively large number of round cells will be seen. If the injuring agent again becomes less active there will be less destruction of the adult cells and therefore less reproduction of young round cells. At the same time the young round cells, already present, are given the opportunity of developing into the adult condition, that is to say, they form fibrous tissue.

Biologically, therefore, we may consider that chronic inflammation is the result of slight but constantly active injury upon a given structure, and that this result will depend upon the survival value of the different types of cells in the structures injured. Consequently in the majority of cases chronic inflammation is synonymous with fibrosis, because in most structures the fibrous tissue elements have, on account of their great reproductive capacity and their comparatively inferior differentiation, the greater survival value to the majority of injuring agents. Such is the case, for example, in muscle, nerve tissue, the great majority of glandular tissue such as kidney, liver, pancreas, etc. But there are notable exceptions, such as the skin, in which the epithelial cells of the cutis have quite as great a survival value as the fibrous tissue in regard at least to many injuring agents. Consequently in chronic eczema there is great proliferation of these cells.

EVOLUTION OF TISSUES AND STRUCTURES

In the following pages an attempt will be made to give a comparatively satisfactory explanation of the differentiation of the structures and tissues of the body in the course of evolution. Upon this differentiation of the tissues and structures the differentiation of species does, of course, ultimately depend, but into this aspect of the subject of evolution it is not the intention of the writer to enter deeply. The objective aimed at is rather to bring the pathological changes which occur in disease processes into relationship with the normal process of evolution in the animal kingdom.

Few biologists would deny that the differentiation of species has been brought about by evolution. But all would admit that the process by which that differentiation has occurred is extremely difficult to ascertain.

At present two possible explanations are given. First, that differentiation occurs by the accumulation of minute spontaneous variations and second that it occurs rather through sudden heritable mutation. The difficulties of accepting either of these appear almost insuperable when the question is considered carefully. The probable chances that any spontaneous chance variation or mutation would be of survival value to the animal are extremely remote. But even if such an improbable occurrence took place, the possibility of its becoming a permanent acquisition in the successors of the individual who possess it is very questionable. As Romanes has pointed out, such a

variation would be swamped in successive generations unless isolation of the individuals possessing it was brought about.

Besides this difficulty there arises another just as great. A change in one structure of the body almost invariably necessitates changes in some other parts to a greater or less extent. And this requires the presence of another chance variation or still more probably of several chance variations. Take, as an example, the case of the long neck of the giraffe. Suppose by some chance variation or mutation occurring in some deer-like or antelope-like animal, the neck became elongated. This would give to those possessing it an advantage over their fellows either by enabling them to see their enemies at a greater distance or by giving them the faculty of reaching foliage at a greater height. But the increase in length of the neck necessitates an increase in weight and this increase of weight must be borne by the forelimbs. Another chance variation must, therefore, now occur in the forelimbs, and it is probable that other changes would be necessary in other organs and structures such as the heart and blood vessels. If these variations are chance or spontaneous ones the likelihood of their occurring together must surely be extremely remote, and in recent times several biologists have pointed out how heavily this factor weighs against the possibility of accepting the theory of evolution by the occurrence of chance variations. For this latter reason the writer feels that there is no need to spend time on the matter except in regard to one aspect of this subject which appears to be of great importance although, so far as he knows, attention has not yet been drawn to it. Moreover, as this subject will be frequently alluded to throughout this work, it may suitably be introduced here.

All tissues and structures of the body require a supply

of blood, and, furthermore, that supply must vary from time to time in accordance with the functional activity of the structure. When it is functionally active the supply of blood must be increased, and when at rest it is diminished. This regulation of the blood supply is carried out by the vasomotor responses. It is outside the scope of this work to go into details of the vasomotor responses, and the reader is referred to the work of Lewis and Dale in regard to this subject. Here it need only be said that the supply of blood to the tissues is governed for the most part by the vasomotor portion of the autonomous nervous system. There is, however, in addition a faculty of constriction present in the capillaries independent apparently of the nerve fibres, but the general statement remains true that the blood supply to a structure is regulated by the vasomotor nervous system in accordance with the functional activity of that structure. Now the nucleated cells of the neurones concerned in this vasomotor control of the blood supply may be, and frequently are, in a region of the body far distant from the structure whose blood supply they govern. Furthermore, the neurones are always of epiblastic origin, while the structures whose blood supply they govern may be epiblastic, mesoblastic or hypoblastic, or a combination of these. If, therefore, we accept the theory of evolution by chance spontaneous variation in the structure of a part, we are driven to the necessity of assuming that simultaneously another chance variation must occur in the neurones which govern the blood supply of that structure. It appears to the writer that such a coincidence of simultaneous occurrence is in the highest degree improbable, and when this improbability is added to the other improbabilities previously referred to, one must arrive at the conclusion that the chances against all these variations occurring together

would reach to figures that are astronomical or even ultra-astronomical.

The association of the structure with the blood supply of the structure, which has just been cited as one of the difficulties of accepting the theory of evolution by chance spontaneous variation, has been introduced here with another object in view. It forms in considerable part the theme which will be found to run throughout the whole of this work, as the reader will observe when the story is unfolded, and it is desirable, therefore, that he should be in touch with it from the beginning. For the sake of clearness, however, it is necessary first to consider the way in which new tissues and structures arise, and then discuss the method by which their nutrition is established.

The following explanation of the origin of new tissues and structures is offered by the writer. Briefly stated it may be expressed as follows. Change of environment causes injury, injury is followed by repair, and the process of repair gives the opportunity for variations to occur which are better equipped to withstand the changed environment.

A good though perhaps rather crude example of the process of repair calling a variation into existence sometimes occurs in the practice of surgeons. When a surgeon makes an incision in the middle line of the abdomen in order to relieve some abdominal condition, the wound repairs in the usual way, the thin scar being at first red and then ultimately turning white, the union being composed of fibrous tissue. In a very large percentage of cases this condition remains permanent. But there is a very small percentage of cases in which bone develops in the scar and remains there. Now bone in this situation is distinctly a mutation or a variation, but the ultimate

fact remains that it would not have appeared there unless injury followed by repair had occurred.

Of course, as stated above, the writer only cites this as an extremely crude example of what he holds to occur in the production of new tissues and structures in the course of evolution, in which the injuries to the tissues would be comparatively slight and the repair microscopic in magnitude. It is cited in order to illustrate the fact that without the process of repair the variation would never have come into existence, and the other fact that the innate potentiality for producing this variation when repair occurred is present only in a very small percentage of individuals. Of course in this case the variation has no survival value.

When an animal is compelled to change its environment, as for example when some species of fish such as the dipnoid or crossopterygian or other species were forced to adapt themselves to an existence on land owing to the drying up of lakes or swamps during part of the year, it is clear that *injury* must have been sustained by many of their organs and tissues. Consequently repair of the injured parts took place, and according to the writer's view it is this process of repair which gives the opportunity for variations to arise. That form of repair which is best suited to resist the injury when it is again sustained will give to the animal or animals which possess it an advantage in survival over their fellows. These animals, male and female, when they mate will produce offspring which on the average will have the potentiality for producing such a form of repair in considerably stronger degree than either of their parents, and such repair will be reproduced more easily (that is to say by a slighter degree of the same injury). Furthermore it will also be able to make its appearance more quickly. Natural selection again acts upon the survivors of that generation and eliminates

those which are least able to produce this form of repair satisfactorily and quickly. And so on with each succeeding generation the potentiality inherent in the fertilised ovum to produce the best form of repair becomes stronger and stronger until no injury is necessary to bring about its occurrence. With the development of the ovum the form of repair (which we may now call a variation) will make its appearance without stimulus or injury because all the potentialities which tend to produce the variation are present in very high degree. All those potentialities which tend to interfere with development in that particular direction have been reduced to a minimum. This is the writer's view of the manner in which a new tissue or structure is evolved. It is necessary to consider a little more in detail the reasons which appear to give it support.

It is first essential to emphasise that by the word "injury" the writer does not mean merely gross mechanical injury, but includes the damage inflicted by chemical agents, poisons and physical conditions such as dryness, moisture, heat, cold, etc. A moment's consideration will show that it is not easy to draw a hard and fast line between injury and stimulus. Strictly speaking every stimulus which a living cell receives produces changes in the internal metabolism of the cell which are associated with the production of chemical substances which damage or even kill the cell unless rapidly excreted. The most satisfactory definition of which the writer can think might be expressed as follows: If the products of disintegration induced by the agent are excreted with sufficient rapidity that the cell can still carry on its function in full activity then the agent might be termed a stimulus, but if the normal functional activity be interfered with then the agent might be termed an injury. This definition is obviously not altogether satisfactory, because a living cell may

be able to adapt itself in such a way that though at first its functional activity was affected by the agent, it becomes able, after a little time, to resume full functional activity, and thus the injuring agent may become the stimulating one. Indeed, upon this fact depends one of the themes in this volume, as the reader will see later.

When a structure or tissue is injured, repair takes place by the reproduction of the remaining living cells of the part and these cells may be of various types, such as epithelial, connective tissue, etc., according to the locality at which the injury was sustained. When this process of reproduction occurs the young daughter-cells are at first not like the mother-cells from which they sprang, but are undifferentiated, and possess qualities such as mobility and phagocytosis. As the process of repair proceeds, if the conditions be normal, these daughter-cells ultimately develop the qualities of the mother-cells, becoming fixed and producing connective tissue or keratin or some secretion according to the tissue ancestry from which they sprang. In this way the normal process of repair is carried out.

But the fact that the cells are undifferentiated gives an opportunity to the newly formed daughter-cells of manifesting other qualities, which, though *potentially* present in the mother-cells, had not the opportunity of becoming *actually* manifest so long as the latter were carrying on their normal functions before the injury occurred. If the injury was brought about by a change of environment which remained permanent or was to be repeated constantly at intervals, then certain of the newly manifested characters might be better suited to resist the injurious effects of the new environment and thus enable the individuals which possessed them to survive while those which did not possess them would be eliminated.

The view just expressed as to the evolution of a new

tissue or structure might at first sight be considered as supporting the theory of the transmission of acquired or impressed characters. But a moment's consideration will show that such is not the case. The new character acquired by the adult parent is not transmitted to the offspring, but the potentiality for acquiring the character is transmitted. This potentiality was also present in the ancestors. It did not become manifest because change of environment causing the injury; and repair, necessary to develop the potentiality into an actuality, did not occur. Ultimately by the process of natural selection this potentiality becomes more and more reinforced in each succeeding generation until it becomes so strong that it produces the tissue or structure without the necessity of any injury or stimulus at all. It makes its appearance with the growth of the fertilised ovum, and what was originally a process of repair becomes a feature of normal development.

It might also be objected that the theory described above of the origin of new tissues and structures is teleological. But here again it only appears to be teleological at first sight, but in reality is not so. When the injury has been sustained and repair begins, the cells of the injured part multiply and each individual cell protects itself as best it can without any purposive consideration of protecting the life of the individual animal of which it is a unit. These cells with their varying potentialities are struggling for existence against one another and also against the injuring agent. When the process of repair is finished it represents the sum total of activity of all those cells which have been successful in the struggle. Those individual animals, in which this process of repair has occurred in the way most suitable to withstand the injuring agent when it recurs, are the ones which will survive, and transmit to

their offspring the potentiality for repeating the same process of repair with increased intensity in each succeeding generation when the injuring agent again applies its selective action. Ultimately, as stated above, this potentiality becomes so strong that it develops with the growth of the ovum into an actual existence without the necessity of the injuring agent. Thus a process, which at its beginning was not purposive at all, ultimately becomes purposive, and the developing embryo is prepared beforehand to meet the injuring agent, and the latter we now call the natural stimulus of the tissue or organ under consideration.

The writer has expressed very briefly his view as to the origin of the tissues and structures and therefore ultimately the differentiation of species in the animal kingdom. This is not the place to enter into more detailed discussion of the subject, and it is introduced into the present paper because he felt that it is necessary to do so in view of the pathological subjects which are discussed in the second part. *It is important, however, to state that while he holds that the tissues and structures have for the most part come into existence in the manner described above, he must not be understood to exclude the possibility of chance variations or mutations having also played their part in the evolutionary process.* Such characters as mimicry and protective colouring, for example, can be more easily explained on the theory of chance variations or mutations, but the view that the variations occur as the result of repair appears to be more acceptable as an explanation of the origin of most of the tissues and structures, and the well-known epigram, " The body is a bundle of variations," might be more correctly expressed in the form, " The body is a bundle of repairs."

According to the view of the evolution of new tissues

and structures described, these are the result of repair occurring after injury resulting from a change of environment which continues in existence or is frequently repeated over a vast period of time.

Injury to a living tissue is associated with an increased supply of blood to that tissue. This at first is what is termed an active congestion, in which not only is the supply of blood increased by the dilatation of the blood-vessels of the part, but the blood passes actively through the blood-vessels. In many cases this active congestion is followed by passive congestion in which the blood stagnates in the local blood-vessels. When, however, the process of repair begins to occur after the injury, then the increased blood supply continues, but it now again occurs in the form of an active congestion, the extra supply of oxygenated blood being necessary for the increased metabolism which the process of repair requires.

This is not the place to enter into a description of the bio-chemical factors which account for the dilatation of the smaller blood-vessels when injury is inflicted upon living animal tissue. On this point the reader is again referred to the work of Dale, Lewis, Laidlaw and others by whom it has been demonstrated that, whenever slight injuries are sustained, histamine appears in the damaged tissue, or a substance closely allied to histamine. This substance produces a reaction, consisting of contraction or dilatation according to circumstances of time and of position in the blood-vessels of the injured part. Furthermore, it is to be emphasised that, at any rate so far as the dilatation is concerned, it lasts long after the stimulus of the injury is withdrawn and continues until the process of repair is complete, as is shown in the scar after healing of a wound in the skin, which remains red for a considerable time before it finally becomes white. This later

aspect of the reaction, indeed, may be looked upon as the necessary condition both for the removal of the injurious products resulting from the injury and also for the increased supply of nourishment required by the cells for the process of repair. Now if we apply these facts to the hypothesis of the evolution of the tissues and structures, it will not be difficult to see that we are within reasonable distance of being able to explain the origin of the vascular or vasomotor reaction which occurs when any tissue, structure or organ is subjected to its normal stimulus. Just as the variation which occurs in the injured tissues appears during the process of repair, and in each succeeding generation becomes so adapted to the injury that we no longer call it an injury, but the normal stimulus ; so does the vasomotor response to what was originally an injury, followed by repair, become vasomotor response to the normal stimulus.

The views expressed may be illustrated by taking one organ of the body and examining its vicissitudes in the process of evolution. And it must be remembered that an organ or structure may and often does undergo involution while the species as a whole is undergoing evolution.

The organ which will be considered in this way is the labyrinth. The writer has chosen that structure because it is the one with which he is most acquainted. For the detailed facts of the comparative anatomy of the labyrinth the reader is referred to the works of Retzius [1] and the present writer.[2]

[1]Retzius, *Das Gehörorgan des Wirbelthiers.*
[2]Gray, *The Labyrinth of Animals.*

In its fully developed form the labyrinth consists of three portions, the cochlea, the vestibule and the semicircular canals. The cochlea is concerned with the sense of hearing and with that alone. The vestibule and canals are associated with the senses of equilibration and direction. The cochlea is stimulated by sound-waves, the vestibule and canals by variation in pressure of the fluids and solid particles contained in their cavities. As the cochlea will not play an important part in the following discourse, except for purposes of comparison with the semicircular canals, it may be disposed of first.

In spite of its supreme survival value in the higher vertebrates the story of the cochlea in evolution is comparatively simple and straightforward. It is not present in fishes, but makes its first appearance in some of the amphibia as a circular neuro-epithelium in the neighbourhood of the lagena. From there it undergoes a continuous process of evolution through reptiles to the birds and the mammals. The writer knows of no evidence of retrograde changes occurring in the developmental history. And this may readily be understood when it is remembered that sound waves can reach the animal whether it live in the air, the water, on the earth or under it. In this respect it differs from the eye. It is, however, of course possible that retrograde changes in the cochlea may yet be found in some animal hitherto not examined. Accompanying this evolution of the cochlea there is the inevitable concomitant evolution of the blood-vessels upon which the nutrition of the organ depends. Furthermore this evolution of the blood-vessels must be accompanied with an associated evolution of the vasomotor reflexes which cause dilatation or constriction of the blood-vessels in response to the condition of the organ whether actually functioning or at rest.

The evolutionary history of the semicircular canals is in striking contrast with that of the cochlea. They are present in all fishes, and in the more recent, such as the teleosteans, they reach a degree of development which is never surpassed in the other vertebrate animals. These fishes are remarkable for the rapid turning movements of the body, so that although the head may not be particularly freely movable on the trunk, the sudden changes of pressure in the semicircular canals will be very great because of this faculty of making rapid and delicate turning movements of the body. In tailless amphibia, frogs and toads, the semicircular canals show a poor degree of development, both as regards size and nerve supply, and correspondingly the movements of the head are anything but rapid and delicate as regards turning in different directions. A greater degree of development is found in the reptiles than in the tailless amphibians and this corresponds with more freedom of movement of the head. In the labyrinth of the bird the canals show a remarkably high state of development and approach the fishes in that respect. Not only is this true in respect to size, but also in regard to the nerve supply and complexity of the cristae acousticae. Here again the high degree of development is found to correspond with the great flexibility of the neck, which permits of the beautiful, rapid and delicately adjusted movements of the head. In mammals the semicircular canals reach a fairly high standard of development, though far short of that found in fishes and birds.

In regard to the blood supply of the semicircular canals and the vasomotor control of the blood, it need hardly be pointed out that these must develop *pari passu* with the structure and functional activity of the organ just as they do in the case of the cochlea and all structures, and where

the canals undergo retrograde changes, so also must similar changes occur in the blood-vessels and the neurones of the vasomotor system which regulate the calibre of the blood-vessels.

Now we come to consider the light which these facts throw upon the process of evolution of the organs concerned. If we accept the theory of evolution by the accumulation of minute spontaneous or chance variations or by mutations, we must assume a remarkable series of coincidences. In the case of fishes the accumulation of these spontaneous variations has been greatest of all, and presumably chance has thus given to these animals the faculty of making rapid and sudden changes in the direction of their movements of body and head, which are certainly of great survival value. Few such accumulations of variations apparently occurred in the amphibians, but in the reptiles they were greater. Suddenly in birds this phenomenon of accumulation of minute chance variations occurred in a striking fashion, but in mammals it has apparently been rather less than in birds, though more than in reptiles. And another series of similar chance variations must have occurred in the blood-vessels and their controlling vasomotor neurones in order to provide the extra supply of blood which the developing structures must require. The chance of all these series of spontaneous variations occurring simultaneously in such a way as to be of survival value to the animal must be extraordinarily remote.

Now let the subject be looked at from the point of view suggested by the writer, that the variation does not arise by chance, but appears as the result of repair following injury or stimulus. In the most primitive fishes or in the particular species of invertebrate from which they sprang, the environment became such that in the pursuit of prey or to escape from their enemies, they were compelled

constantly to make efforts in the way of rapid turning movements. Such movements would produce excessive stimulation or injury upon the walls of the simple spherical or elliptical otocyst from which the vertebrate's labyrinth evolved. In the repair which followed (or rather kept on constantly following) in the neuro-epithelium on the wall of the otocyst, some of the animals would repair in a way more satisfactory in regard to withstanding the injury when it was again inflicted. Probably this process would be simply that when repair occurred the neuro-epithelium was larger in extent than before, some parts of the outer fringe of the neuro-epithelium extended farther out and thus produced new accessory portions of the neuro-epithelium. Similarly the variations in pressure on different parts of the wall of the otocyst, caused by movements of the animal in different directions, would, during the process of repair, permit of variations making their appearance in the form of bulgings, which, by continuation of the process, ultimately develop into the semicircular canals. Accompanying this process of repair following injury or stimulation, is the elaboration of a means for increase of the blood supply which repair always requires. When injury of a tissue takes place, chemical products, resulting from the disintegration of intra-cellular protoplasm, bring about change in the flow of blood to the part. Dale and Lewis have shown with scientific accuracy how histamine does this, by its action on the local capillaries and minute arterioles. Their experiments, it is true, were carried out on the higher vertebrates, and the writer is not aware whether in the case of the lower vertebrates histamine is the substance which, resulting from the destruction of cells by injury, produces the effect described. However that may be, the repair which follows injury must require an extra

supply of blood no matter how slight the necessary amount of repair may be.

Thus, if we accept the view that evolution of a structure or organ is the result of variation occurring during the course of repair, we are not in any difficulty in regard to accounting for the development of the change in the vascular and vasomotor system which must accompany the progressive evolution of the structure. The whole phenomenon may be looked upon as an entity in which the cells of the part, the blood-vessels of the part and the vasomotor neurones which govern the supply of blood which goes to the part, all contribute their share. Injury affects all these structures, and, in the process of repair, minute variations have the opportunity of making their appearance, which would not have done so had the injury and repair not taken place. Now these variations which have occurred as the result of repair in the otocyst are impressed characters and, though they enable those which acquire them to survive, are not transmitted to the offspring. But the potentiality to produce these variations is not acquired but was present in the fertilised ovum from which the individual developed, and this potentiality is, therefore, transmitted. Such potentiality is increased in every successive generation.

It has often occurred to the writer that some light might be thrown upon the evolution of structures and organs by a consideration of their involution. For it would logically be assumed that the one process is a reverse of the other. Indeed, while evolution of some structures is going on in any given species of animal, involution of other structures is simultaneously taking place. The mammalian labyrinth offers a remarkable example of these processes of involution and evolution occurring simultaneously, as will be understood from the following description.

Examples of the mammalian labyrinth are shown in figs. I to VII. The illustrations are taken from the writer's work on the subject.[1] Fig. VII shows the labyrinth of the monotreme mammal, *Ornithorhyncus anatinus*, the duck-billed platypus, which was prepared and photographed by the writer. It shows the mammalian labyrinth in its primitive form. The cochlea has not yet become the spiral structure which it assumes in all mammals except the monotremes, but ends in a hook-like process. The semicircular canals are well developed and differ in hardly any respect from that which is found in the typical mammalian structures as seen in man (figs. I and II), and the black ape (fig. III). In the cetacea and sirenia the cochlea shows a great advance upon that found in the monotreme labyrinth and has acquired the spiral arrangement characteristic of all mammals except the monotremes. In dimensions relative to the size of the animal it does not differ perceptibly, but it has fewer whorls. The semicircular canals, on the other hand, show unmistakable retrograde changes, as is obvious on inspection. These are more striking in the case of the cetacea, as for example in the porpoise (fig. V), in which these structures are no larger than in a mouse. The retrograde changes in the sirenia as exemplified in the dugong (fig. VI), are obvious, but not so marked as in the cetacea. The reason for these differences will be given in the following pages.

It appears to the writer that some light may be thrown upon this difficult subject of the origin and evolution of tissues and structures by a consideration of the facts which we know concerning their involution.

Every structure is kept up to the normal standard of the species by the action of its ordinary stimulus. If this stimulus is removed over many generations the tissue or

[1]Gray, *The Labyrinth of Animals*.

structure gradually undergoes retrograde changes and ultimately disappears. If we accept the theory of evolution either by the accumulation of minute spontaneous chance variations or by mutation, then we would naturally expect that the process of involution was brought about by similar causes acting in a reverse direction. That is to say, if the structure came into existence by a chance spontaneous variation or a mutation without some other factor to call it into existence, then we would expect that a similar chance variation or mutation in the reverse direction would bring about retrograde changes and thus lead to gradual increasing loss of function. But we do not find that this is the case. On the contrary, the structure does not undergo retrograde changes unless its normal stimulus is removed.

A very good example illustrating the gradual involution of an organ is to be found in the semicircular canals of mammals. In the large majority of the orders of mammals the semicircular canals are well developed and have a rich nerve supply. In the sirenia (sea-cows), however, as was pointed out by the writer, the size of the canals relative to that of the cochlea and of the animal itself, is comparatively small and the nerve supply distinctly diminished. In the cetacea this retrograde change is much more striking ; the canals are, in the porpoise, no larger than those of a mouse, and the nerve supply consists of comparatively few fibres.[1] Now the sirenia and cetacea have not, according to zoologists, arisen from a common stock, although both have adopted a marine life. If, therefore, we are to regard involution either as the result of an accumulation of minute chance variations or of a sudden mutation, then we are faced by the fact that these must have occurred coincidentally in two orders

[1]Gray, *The Labyrinth of Animals.*

FIG. I

THE RIGHT MEMBRANOUS LABYRINTH OF MAN

Homo sapiens

× 4

The posterior canal is above and to the left. A vein, which leaves the labyrinth on the posterior surface of the vestibule, may be seen running parallel with the aqueduct of the vestibule. Pathological deposits of calcareous salts are present in various parts of the vestibule and canals. The black specks in the vestibule are minute hæmorrhages.

FIG. II

THE LEFT MEMBRANOUS LABYRINTH OF MAN

Homo sapiens

× 4

The organ is suspended by the superior canal, and is viewed from behind. It was stained with eosin before preparation in order to show the veins. The white fragments on the canals are due to insufficient decalcification.

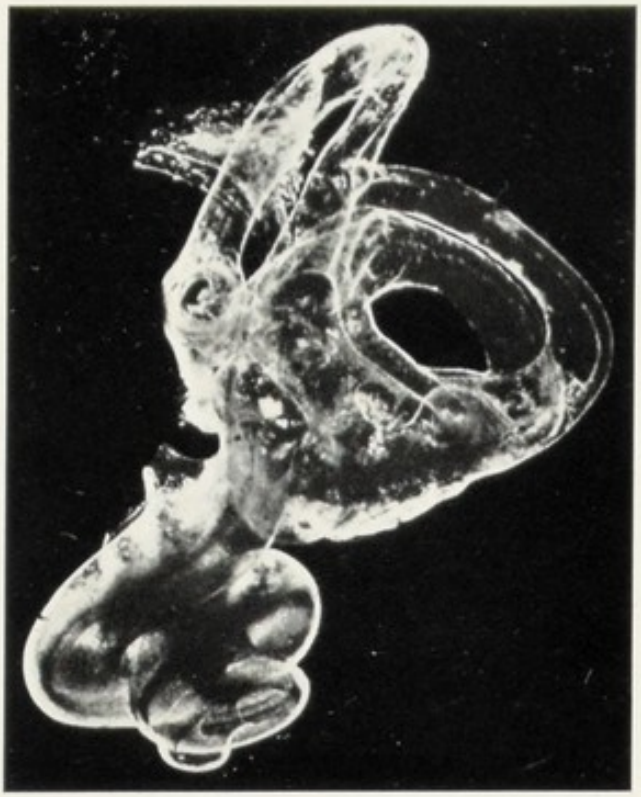


FIG. III

THE LEFT MEMBRANOUS LABYRINTH OF THE BLACK APE

Cynopithecus niger

× $5\frac{1}{2}$

The organ is suspended by the superior canal and is viewed from in front and below. The aqueduct of the vestibule is seen at the back. There is no pigmentation in the ampullæ of the canals such as is found in many of the monkeys. The ampulla of the horizontal canal has been injured in the process of preparation.

FIG. IV

THE RIGHT MEMBRANOUS LABYRINTH OF THE AARD WOLF

Proteles cristatus

× 5

The organ is suspended by the superior canal and is viewed from below and without. The canals are rather small in comparison with the rest of the organ, and the horizontal canal is elliptical in shape. The round window is large, as is also the aqueduct of the cochlea.

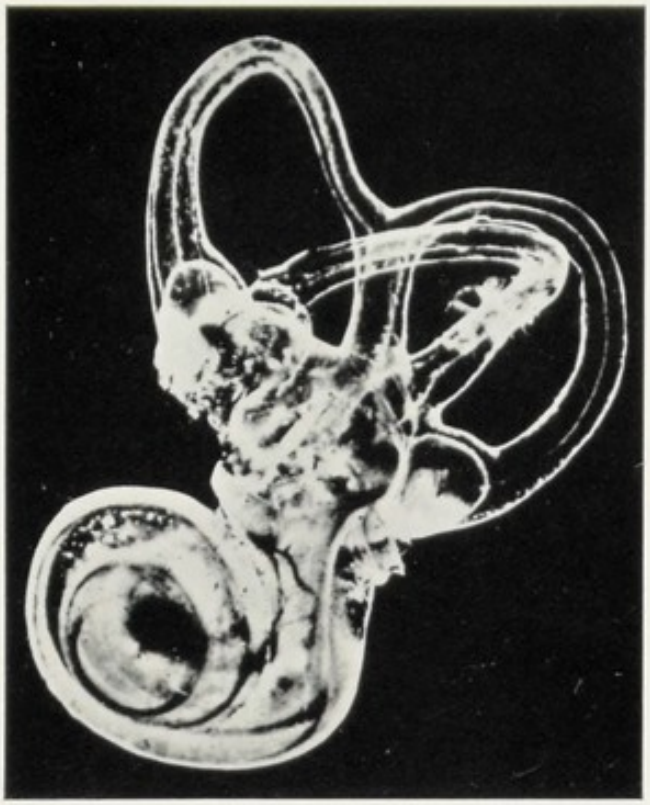


FIG. V

THE LEFT MEMBRANOUS LABYRINTH OF THE COMMON PORPOISE

Phocæna communis

× $5\frac{1}{2}$

The organ is suspended by the superior canal and is rotated a little clockwise ; it is viewed from in front. The canals and vestibule are very small. There is a deep cleft between the scala tympani and the scala vestibuli. The veins are seen very clearly passing inwards over the upper surface of the whorls towards the modiolus. The intracranial end of the aqueduct of the cochlea is just seen at the back at the left lower part of the photograph.

FIG. VI

THE RIGHT MEMBRANOUS LABYRINTH OF THE DUGONG

Halicore australis

× $3\frac{1}{2}$

The organ is viewed from the inner aspect and in front, and is rotated clock-wise to a considerable extent, so that the horizontal canal is in the vertical plane. The otolith is seen immediately below the ampullæ of the superior and horizontal canals, and the aqueduct of the vestibule is also shown. The lateral view of the cochlea shows very clearly the division between the scala tympani and the scala vestibuli.

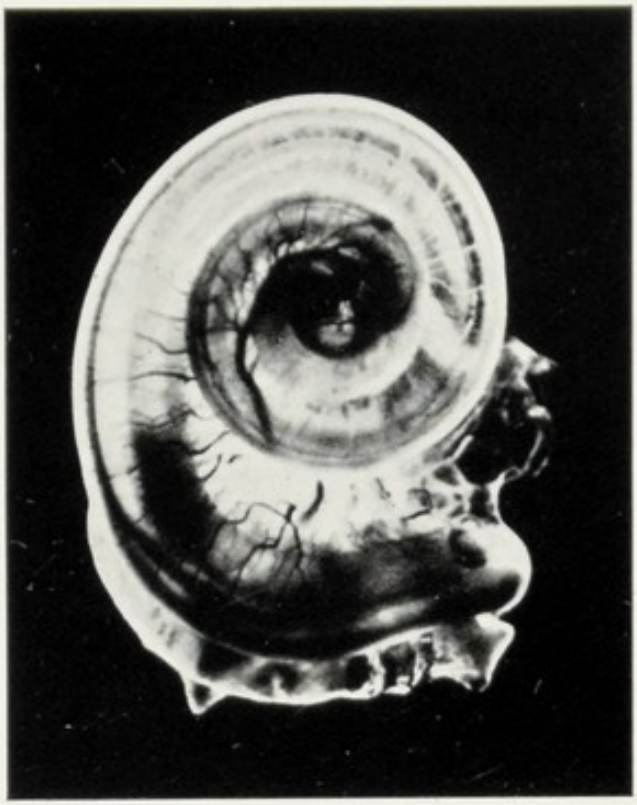


FIG. VII

THE LEFT MEMBRANOUS LABYRINTH OF THE DUCK-BILLED PLATYPUS

Ornithorhyncus anatinus

× $5\frac{1}{2}$

The organ is suspended by the posterior canal and is viewed from in front, below and outside. It is also rotated a little counter-clockwise. The specimen is a poor one owing to the hæmorrhages which have occurred throughout the whole organ. The cochlea only possesses half a turn, and is not unlike those found in birds and some reptiles. The superior canal, which is to the left, is angular, and suggestive of the reptilian type ; but the vestibule is not so large as in the latter. The aqueduct of the cochlea is seen to the right side of the organ as it leaves the vestibule.

FIG. VIII

THE RIGHT MEMBRANOUS LABYRINTH OF THE CROWNED PIGEON

Goura coronata

× 5

The organ is suspended by the superior canal and is viewed from the inner aspect and behind ; it is rotated counter-clockwise to a slight extent. The superior canal is of the upright type. There is a communication between the horizontal and superior, in addition to the usual one between the horizontal and posterior canals. The recessus utriculi is seen between the superior and horizontal ampullæ with a flat otolith lying on its floor. The cristæ in the ampullæ are complex. The cochlea is not very large, and in the lagena is a saddle-shaped otolith. The perilymph recess is large, and the aqueduct of the cochlea is seen rising from its inner wall and curving upwards for a short distance in contact with it. The horizontal canal dips slightly downwards about the middle.

FIG. IX

THE LEFT MEMBRANOUS LABYRINTH OF THE STUMP-TAILED LIZARD

Trachysaurus rugosus

× 6 ca.

The organ is viewed from the outer aspect and is rotated clockwise to the extent of 90°, so that the ampulla of the superior canal is at the top and that of the horizontal canal immediately below it. The large vestibule contains three collections of otoliths indicated by the black patches. Pigment is scattered generally over the blunt cone-shaped cochlea and adjacent portion of the vestibule, and also over the superior canal near its junction with the posterior, at the left side of the photograph. The oval window is seen at the junction of the cochlea with the vestibule.

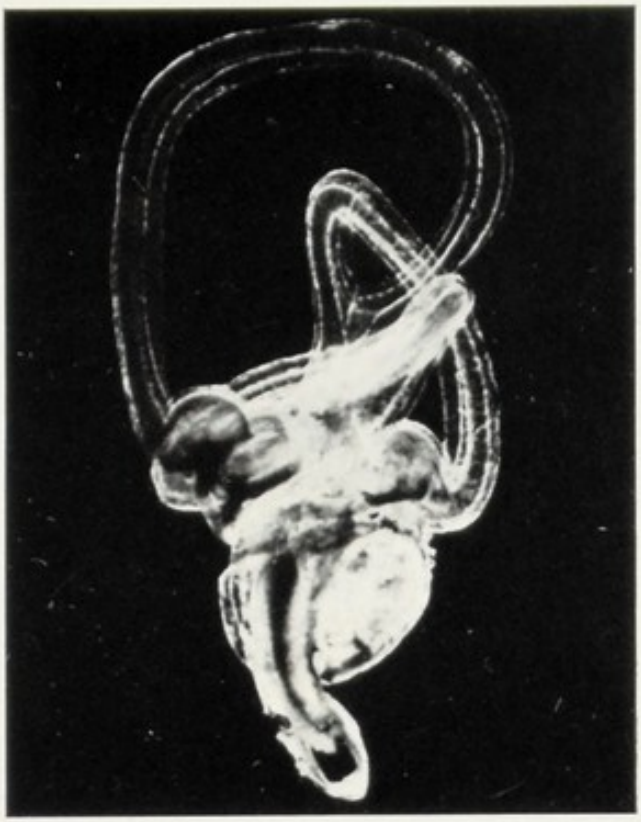


FIG. X

THE RIGHT MEMBRANOUS LABYRINTH OF THE WEST AFRICAN PYTHON

Pytho sebæ

× $5\frac{3}{4}$

The organ is viewed from the inner aspect and in front, and is rotated counter-clockwise to the extent of about 30°. At the right corner of the photograph is the ampulla of the superior canal, and that of the horizontal canal is immediately behind it. There is a communication between the upper surface of the vestibule and the middle of the superior canal similar to that found in the teguixin. The vestibule is very large, and projects downwards and outwards, this portion being termed the recessus labyrinthi. The otolith mass is large and disc-shaped. The small conical cochlea is seen in the lower right-hand corner of the photograph, and on its surface a very few scattered granules of pigment may be seen.

FIG. XI

THE LEFT MEMBRANOUS LABYRINTH OF THE GIANT TOAD

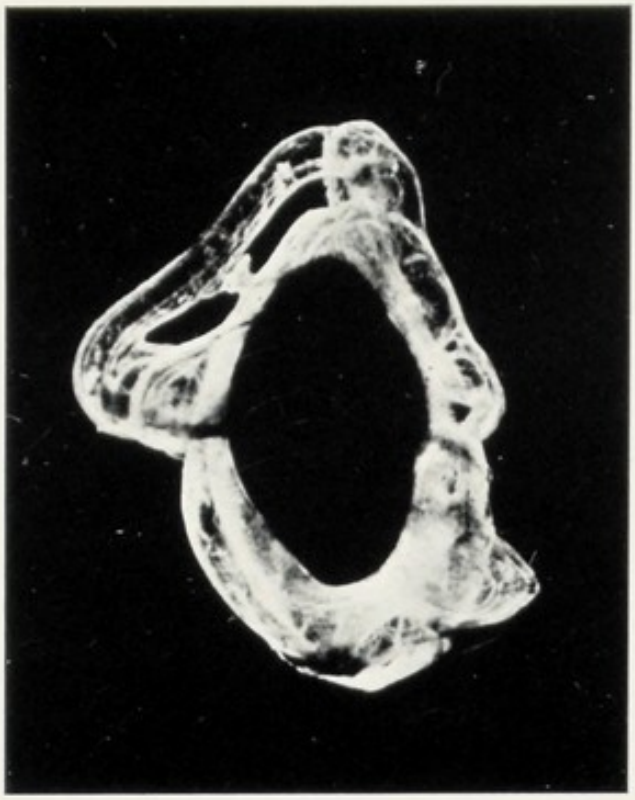
Bufo marinus

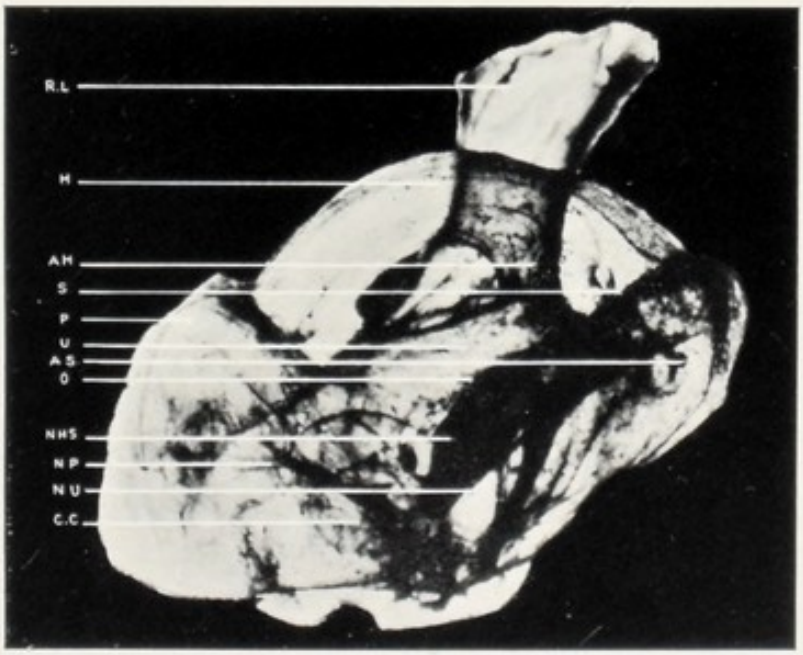
× 12

The organ is viewed from above so that of the three canals the superior is seen to the right, the posterior to the left and the horizontal above. The letters indicate the different structures.

R.L. Recessus labyrinthi (recessus utriculi).
H. Horizontal canal.
A.H. Ampulla of horizontal canal.
S. Superior canal.
P. Posterior canal.
U. Utricle.
A.S. Ampulla of superior canal.
O. Otolith apparatus.
N.H.S. Nerve to ampullæ of superior and horizontal canals.[1]
N.P. Nerve to ampulla of posterior canal.
N.U. Nerve to utricle.
C.C. Common crus of superior and posterior canals.

[1] The line opposite N.H.S. should be continued eight millimetres to the right.




R.L
H
AH
S
P
U
AS
0
NHS
NP
NU
C.C

unrelated to one another in their ancestry. Such a coincidence appears to be most improbable. It might be thought that the marine life which these animals have adopted might in some vague way account for these retrograde changes in the semi-circular canals, but this explanation is unacceptable because the seals, which live in the water almost as much as do the sea-cows and cetacea, have remarkably well-developed semicircular canals, and in fishes these organs reach their highest development.

This retrograde development of the semicircular canals offers a very good example for illustrating the difference between the theory of evolution by the accumulation of minute chance spontaneous variations or by mutations, and the writer's view that evolution has occurred by the process of variations resulting in the course of injury and repair of the tissues or structures.

The normal stimulus of the semicircular canals is the pressure exerted upon the cristae acousticae by the intralabyrinthine fluids caused by the movements of the head. And the rapidity and delicacy of these movements depend upon the flexibility of the cervical vertebrae and the muscles and tissues surrounding them. Now in the sirenia, sea-cows, the neck is short and the cervical vertebrae, although consisting of the invariable seven, characteristic of mammals, are correspondingly small, and the tissues of the neck prevent any free or rapid movements of the head upon the trunk.[1] In the cetacea (whales, porpoises, etc.) this fixation of the neck is carried to an even greater extent than in the sirenia, and in some there is actual bony fusion of the cervical vertebrae.

Pari passu with the process of evolution of the tissues the vasomotor response is evolved. When the new environ-

[1]The Manatee has in fact only six cervical vertebrae—which strengthens the argument.

ment caused injury to a tissue, structure or organ, the ordinary vasomotor response to injury and subsequent repair occurred as it always does. But in the course of many generations as the process of the evolution of the new tissue proceeds, the latter becomes more capable of withstanding the injury and more responsive to it. As the injury becomes the normal stimulus, so the vasomotor response to the injury beomes more and more easily elicited until it becomes the normal vasomotor response to the normal stimulation of the tissue, the structure or the organ.

There now falls to be considered the bearing which this hypothesis of the differentiation of the normal structures of the body and their accompanying vasomotor responses have upon pathological processes. But before proceeding to discuss this portion of the subject it is necessary to point out that the views expressed in the following pages are not dependent upon the correctness or incorrectness of the hypothesis suggested in the preceding pages. They do follow more naturally upon it than upon either the theory of evolution by accumulation of minute chance variations or by the theory of evolution by mutation. Whatever view we may hold, therefore, of the evolution of the tissues and structures of the body with their accompanying vasomotor responses, these are inherited by the individual from his ancestors.

In the present paper the writer intends for the most part to deal with only one aspect of the bearing which the views expressed above have on pathological conditions. The aspect referred to is that of pathological conditions which are hereditary in many cases though certainly not in all.

One of the facts concerning hereditary pathological conditions which has long puzzled the writer is the occur-

rence in families of hereditary disease arising in various organs and structures comparatively well on in life, after those organs or structures have functioned in a perfectly normal manner for many years. Arterio-sclerosis, for example, is frequently found to run in families, although, of course, there are many cases where there is no evidence of a family tendency to the disease. Otosclerosis is another such condition in which deafness is known to run in the family and shows itself in generation after generation. Diabetes and rheumatoid arthritis are further examples of the same nature, and no doubt many other diseases belong to this category.

But heredity may express itself in pathological conditions in a way quite different from those to which reference has just been made. Thus an organ or tissue may be structurally, and therefore also functionally, defective from its first beginning in the growing embryo. Among such hereditary conditions are inherited deaf-mutism, polydactylism and syndactylism, colour-blindness, hare-lip and cleft-palate and others. Of course it is understood that in neither of the two types of inherited pathological conditions mentioned is there evidence of hereditary transmission in every case. Many cases of rheumatoid arthritis and otosclerosis, for example, occur in individuals in whose families and relations no other cases appear. Nor is this statement of the evidence of hereditary influence in some cases and its absence in others an erratic one due to mistakes in clinical diagnosis. The fact can be demonstrated by pathological examination in the case of otosclerosis at any rate. For when examined post-mortem the changes found are the same in individuals in whom definite evidence of heredity is abundantly present, as in those in whom there is no evidence of hereditary tendency whatever.

It has surprised the writer that in investigating the nature of hereditary disease no attention, so far as he knows, has been paid to the remarkable fact that an organ or tissue may reach full structural development and function in a perfectly normal manner for many years, and then show a gradual loss of function, and that such cases should show clear evidence of hereditary transmission. If, as is generally and probably correctly assumed, the normal structure of an organ depends upon the normal arrangement of the formative genes in the fertilised ovum, then it would be only logical to assume the converse to be correct, that, if an organ is anatomically and physiologically normal after many years of life, then the formative genes in the fertilised ovum must have been normal. But if the formative genes of the organ have been normal how can the diseased condition be hereditary ?

The writer offers the following solution of the problem, although it is important to point out that it is only a partial solution, as will be noticed more in detail later.

In the preceding pages to explain the origin of the tissues the hypothesis was suggested that change of environment causes injury and subsequent repair to a given structure or tissue and the new type of tissue results from the process of repair. If the change of environment continues permanently the potentiality to produce the type of repair best suited for that environment becomes stronger and stronger in each succeeding generation because the individuals, male and female, which have most noticeably that innate potentiality in the fertilised ovum, survive. In the course of generations this potentiality becomes so pronounced that no injury is needed in order to produce the particular form of repair referred to ; by the mere growth of the embryo the potentiality becomes an actuality and the structure or tissue that has thus become gradually evolved

we term the normal tissue or structure, and the formative elements of the fertilised ovum that contain this potentiality are termed genes. Now, if in the fertilised ovum the genes which are destined to form a given structure are defective in number or arrangement or quality, then it is obvious that that structure cannot, as the embryo grows, develop in a normal way, and when birth occurs the structure cannot function in a normal way. Furthermore, since the potentialities of the genes in the fertilised ovum are derived in varying degrees from both parents, and from the ancestors of these parents, then the defective adult structures, which result when the defective genes develop in the embryo, will show evidence of hereditary transmission. This appears to the writer to account for those hereditary pathological conditions which are present at birth and, indeed, during foetal life. Such for example are hereditary deaf-mutism, polydactylism, etc. This is, of course, the ordinary accepted view of hereditary transmission, and in many cases the Mendelian principles of heredity can be applied to them. They appear independently of environmental influence.

There remains to be explained, however, the much more difficult problem of how hereditary influence may make itself felt in tissues, structures and organs which are structurally and physiologically perfectly normal at birth and function in a normal way for many years. So far as the writer is aware, pathologists and clinicians who have interested themselves in the hereditary aspects of pathological conditions have never made any special differentiation between the two types of inherited pathological conditions referred to in these pages :—the type just described in which a structure or organ is defective anatomically and physiologically from its first appearance, and that type which makes its appearance in an organ or a struc-

ture after the latter has functioned in a perfectly normal way for many years. Yet it appears to the writer that, both from the point of view of scientific accuracy and from that of medical treatment, the distinction between the two types is of the utmost importance.

As regards the second type of these inherited pathological conditions, which only make their appearance after many years of normal physiological activity, the writer offers the suggestion that they are the result of a defect in the vascular supply of the tissue or organ concerned and his reasons for this are as follows :

In the process of evolution many structures are evolved which come to serve a very different function from that of the structure from which they were produced. A very good example of such is the organ of hearing. The cochlea which serves the function of hearing was evolved from one of the neuro-epithelial maculae of the otocyst in fish which did not possess the sense of hearing. Whether any species of fish hear is doubtful ; but even if a few species do possess that faculty, they have been evolved from a more primitive type which did not. The original function of this neuro-epithelial macula was concerned with the function of equilibration or perhaps with muscle tones. At that stage the stimulus which brought about the vasomotor response of that neuro-epithelium was movements of the head and body. But as the neuro-epithelium became gradually evolved into a structure which responded to harmonic vibrations of certain frequences the stimulus which, acting through the neuro-epithelium, called forth the vasomotor response, was those harmonic vibrations which constitute sound.

Thus in the long course of evolution a complete change has occurred in the character of the stimulus required to elicit the vasomotor response. Hence the qualitative

change in a structure which has been evolved to fulfil a different function from that which it originally subserved is accompanied by a qualitative change in the stimulus which, acting through that structure, calls forth the associated vasomotor response.

Now obviously both these characters in an animal, viz. the structure which serves a given function and the vasomotor mechanism which governs the nourishment of that structure, are inherited qualities and indeed are a common inheritance of the race. But do the genes, the formative elements in the fertilised ovum from which are ultimately evolved these two mechanisms, belong to one single group? That is to say, does a single group of genes form both the anatomical structure which performs a given function and also the neurone which governs the blood-vessels concerned in the nourishment of that structure, and of which the nucleus may, and usually does, lie in a far-distant part of the body, *e.g.* in the spinal cord or in the sympathetic ganglia? It is, of course, true, as was demonstrated by Sir Thomas Lewis,[1] that there exists an important local vasomotor response in the walls of the capillaries which is independent of nerve control, but even in them there is an additional local response which is under the control of the vasomotor nerves. The healthy functioning of any tissue or organ is, therefore, under the control of nerve cells whose nuclei and a large portion of the fibres themselves lie in regions far remote from the structure whose nourishment they regulate. It remains open to doubt, therefore, whether the same genes are concerned in the formation of the tissue or organ and the nerve cells which govern its nutrition, or whether a different set of genes are concerned in the structural and the nutritional elements. For reasons which will be given later, it appears

[1] Lewis, *Clinical Science.*

to the writer that the latter is on the whole the more probable.

It is, of course, obvious that both these characters of any tissue, the structural and the nutritional, are inherited. It would naturally follow that if there should be a defect in the genes out of which these characters develop, then these defects are also heritable, and as a result inherited pathological conditions appear and are transmitted in certain families from one generation to another.

But, if the writer has made his meaning clear, it would naturally be inferred that these inherited pathological conditions may be separated into two different types :— those in which the defect lies primarily in the actual structure of the organ or tissue concerned and those in which the defect lies primarily in the nutritional mechanism. And when we come to examine these conditions clinically and pathologically, we find that the inference above made is fully justified in some organs at any rate. The organ of hearing for instance offers an excellent example of each of these types of pathological defects. There are two pathological conditions in the organ of hearing which are definitely inherited, using that term, of course, in its strictest biological sense. These two conditions, inherited deaf-mutism and inherited otosclerosis, represent in the writer's opinion the primary structural defect and the primarily vasomotor defect, respectively.

When the organ of hearing from a case of inherited deaf-mutism is examined, striking changes are found in the cochlea. Minor differences in the pathological conditions are found in different cases, but all show defects which would prevent the organ functioning in anything like a normal way. The hair cells of the organ of Corti show either a lack of differentiation or more often are absent altogether, and even the rods of Corti are fre-

quently absent and the tectorial membrane is absent or malformed. The stria vascularis shows great departures from the normal, and it is interesting to note that it very frequently presents an appearance remarkably similar to the tegmentum vasculosum which is its homologue in birds and reptiles. The nerve cells of the ganglion spirale are usually defective in number, and the nerve fibres running from the organ of Corti to the ganglion spirale may be absent altogether or their fibres have not got a medullary sheath in the region where in normal conditions they possess it. The bony capsule of the labyrinth is unaffected.

The pathological changes found in otosclerosis, on the other hand, are entirely different from those just described as occurring in inherited deaf-mutism. In otosclerosis, except in the very late stage of the disease, the structures in the cochlea show no departure from the normal. The hair cells of the organ of Corti are normal as also are the rods of Corti, the tectorial membrane, the membrane of Reissner and the stria vascularis. The nerve cells of the ganglion spirale are quite normal in appearance. On the other hand the bony capsule of the labyrinth undergoes definite pathological change in the region in front of the oval window. The bone at this point undergoes a process of rarefaction and becomes more susceptible to staining with haematoxylin and other dyes. Another pathological change which was demonstrated by the writer is a degenerative process in the neurokeratin filament of the fibres of the cochlear nerve, while the axis cylinder appears normal. It is interesting to note that this degenerative process was not found in the nerves contiguous to the semicircular canals and vestibule.

Another change in otosclerosis which was described by the writer is sometimes, though not always, found in the

muco-periosteum of the tympanic cavity in the immediate neighbourhood of the stapes and oval window. This consists of an increase in the fibrous elements of the muco-periosteum which tends to absorb the recently formed porous otosclerotic bone and even in some cases the normal bone of the crura of the stapes. As stated above, this change in all the cases so far observed is confined to the immediate neighbourhood of the oval window and stapes.

We find, therefore, in the organ of hearing two entirely different types of pathological changes, both of which cause deafness and both of which are heritable and both are found in animals other than man. But there is this noticeable difference between the two types, that in the first type the defect is always present at birth, in the second type the defect is not present at birth. It has been shown how in the case of inherited deaf-mutism the defect in the structure may readily be explained by a defective arrangement of the genes from which the organ of hearing is derived, but it is obvious that a similar explanation cannot account for a defect which does not make its appearance until after many years during which the organ is structurally and functionally normal. The problem therefore is to account for the occurrence of otosclerosis.

Before attempting this solution, however, it is important to point out a fact in order to prevent confusion. It is this, that these two types of inherited deafness do not show any signs of inter-relationship with one another. Thus a family tree which shows clear evidence of inherited deaf-mutism does not show any evidence of producing individuals who become the subjects of otosclerosis. And conversely, it is found that in family trees in which the tendency to otosclerosis is abundantly present there is no evidence of any association with deaf-mutism. In the

writer's investigations with respect to the inheritance of otosclerosis he found in eleven family trees showing evidence of inherited otosclerosis only two cases of deaf-mutism. Each of these two cases occurred in family trees that were in no way related to one another and in each the deaf-mute was an isolated case without any other cases in preceding or succeeding generations. In both of these deaf-mutes, the condition was no doubt the result of congenital syphilis, or cerebro-spinal meningitis or some such well-recognised environmental condition and was not the result of any inherited tendency in the true biological sense.

In his paper on " The Otosclerosis Problem " the writer, employing a number of facts derived from the pathological and clinical examinations of patients suffering from otosclerosis, gave reasons for his belief that the essential factor in the production of otosclerosis was a gradual loss in the vasomotor responses of the organ of hearing. There is, therefore, no need to go into the details of his argument here, since they may be obtained from the article to which reference is given below.[1] But some of these facts may be enumerated here. In a large percentage of cases of otosclerosis the hearing may be temporarily improved by the inhalation of nitrite of amyl which, by the sudden redistribution of blood which it produces in the body, allows of a temporary increase in the supply of healthy oxygenated blood to the organ of Corti and its associated nerve structures which constitute the essential elements of the organ of hearing. A similar condition occurs in those cases which the writer observed and described under the term otosclerosis paradoxica. Another clinical observation which lends support to this view of otosclerosis is the fact that in a large percentage of cases the vasomotor response of the tympanic membrane is either absent or

[1] *Journal of Laryngology and Otology*, October 1934.

sluggish. But perhaps the most convincing evidence in favour of this view is that obtained by treating the patients who suffer from the disease in such a way as to produce dilatation of the blood-vessels of the organ of hearing. In these circumstances improvement in the hearing results in consequence of the greater supply of healthy oxygenated blood to the organ of hearing.

Assuming therefore, tentatively, that the active factor in the causation of otosclerosis is an innate defect in the local vasomotor response of the organ of hearing it follows that defects in this vasomotor response may be heritable. And if this be true of otosclerosis the natural inference would be that other pathological conditions may perhaps owe their existence to this same factor, a defect in the local vasomotor response.

Since these defects in the vasomotor response show clear evidence in a large percentage of cases of true biological inheritance it follows that the factor, whatever it may be, that is responsible for their occurrence must be present in the fertilised ovum. Consequently the question arises—Why are the actual defects not present from the beginning, to be revealed at birth in the way that the structural defects such as those present in deaf-mutism are? To this question the writer frankly admits that he has at present no solution to offer. It might be suggested that the vasomotor defect is really present from the beginning but that the structural changes that are found in otosclerosis and rheumatoid arthritis and arterio-sclerosis for example, only come into existence after the causative vasomotor defect has been in operation for a long time, many years in some cases. But a moment's consideration will show that such an answer to the question is unsatisfactory. It is conceivable that the structural changes found in these conditions might be delayed in making

their appearance, but the difficulty still remains to explain the perfectly normal *functioning* of the tissue or organ during all these years. It is hardly possible to believe that a structure such as the organ of hearing or a joint could continue to function in a normal fashion if the vasomotor responses which control the nourishment of those tissues and organs are defective. Conjectures can, of course, be made in explanation of this delay in the appearance of the vasomotor defect which occurs in cases of hereditary pathological conditions. But at present the writer has no facts to offer on which such conjectures can be satisfactorily based and it would be a waste of time to discuss them until such facts can be produced.

In regard to these defects in the vasomotor response there are one or two other characteristic features which are interesting. One of these is the fact that they are sometimes influenced to a considerable extent by environmental conditions. An excellent example of such is the case recorded by the writer in his work on otosclerosis.[1] The patient referred to came of a family in which the hereditary tendency to otosclerosis was very strongly marked. Her hearing was perfectly normal until the age of 25. At that age, when out hunting, she was exposed for a long time to a very cold wind blowing on the left side of her head. A few hours later she developed an acute middle-ear inflammation with acute pain, deafness and some degree of fever. Suppuration did not occur and there was consequently no perforation. The condition subsided in the course of a few days, so far as the pain and fever were concerned, and the exudate in the middle ear was absorbed. Now in any ordinary case of acute middle-ear inflammation, as all aurists know, the hearing would have returned to normal in the course of a few days or a

[1]Gray, *Otosclerosis*, p. 34. H. K. Lewis, 1917.

week or two. But in this patient's case the deafness remained, and as time passed it became obvious that otosclerosis had developed in the left ear. The right ear continued to hear normally for about sixteen years and then otosclerosis gradually developed in it also. In this case, therefore, it is hardly possible to doubt that the acute middle-ear inflammation precipitated the occurrence of otosclerosis which would not have developed for many years, because as is well known when otosclerosis appears under ordinary circumstances both ears usually become affected simultaneously or at least within a short time.

But there are other pathological conditions besides otosclerosis in which a similar divergence of opinion in regard to etiology exists among physicians. It is, however, with some trepidation that the writer enters upon this territory, since his clinical and pathological experience of these diseases is so very limited. He would suggest, however, that rheumatoid arthritis is one of these. It might be suggested that the divergence of opinion in regard to the etiology of rheumatoid arthritis arises from the same source as that found among otologists in respect to otosclerosis. In both diseases the physicians and otologists respectively are ascribing the occurrence of the disease to environmental conditions, whereas, according to the present writer's view, the essential factor is innate in the individual and consists of a gradual failure of the vasomotor response, whose healthy functioning is necessary for the proper nourishment of the tissues concerned. The environmental conditions are only precipitating factors.

Speaking in general terms, when a pathological condition shows evidence in many cases of a heritable tendency and at the same time makes its appearance after the tissue or organ concerned has functioned in a normal way for

many years, the probable explanation of its occurrence is to be looked for in a failure of the vasomotor response in the smaller blood-vessels which supply that tissue or structure. Arterio-sclerosis, for example, would fall into this category, and in this case the defect would lie in a loss of the vasomotor response in the minute arterioles and capillaries of the vasa vasorum. In this and some other analogous pathological conditions, however, he is not able to bring the convincing evidence of the results of treatment in support of his view such as is the case in otosclerosis. Those conditions, therefore, will be left over for consideration at a later date.

The views expressed may be summed up briefly as follows. The evolution of a tissue, a structure or an organ, is the result of variation occurring during the repair which follows minute injury on the tissue already in existence at a given locality. The injury is caused by a change greater or less in the environment, constantly present or constantly repeated over a very long period of time. Accompanying this process of the evolution of a new tissue or structure which is adapted to resist the injury inflicted by the new environment, there is a corresponding evolution of the vasomotor response in the minute arterioles and capillaries of the part injured. As generation succeeds generation the process of natural selection preserves those individuals in which the fertilised ovum has the greatest potentialities for rapidly developing that tissue or structure best fitted to respond to the changed environment, until those potentialities are so strong that they appear as the fertilised ovum develops and are ready to function at birth, in responding to the injury which may now be called the normal stimulus. *Pari*

passu with this development is the development of the vasomotor response in the minute arterioles and capillaries, and what was originally the local vasomotor response to the injury and the subsequent process of repair evolves into the normal local vasomotor response to the normal stimulus. In this way a new tissue or structure and its accompanying means of nutrition become the common inheritance of the species. Defects may occur in the genes which determine either of these two characters, the actual structure, and the associated vasomotor response of the blood-vessels which nourish it. In the first, the defects in the genes prevent the normal structure coming into existence or functioning normally, and are therefore congenital. In the second type, the structure develops normally, but the vasomotor response upon which the structure depends for sufficient nourishment for its normal functioning is defective. This defect is apparently not usually congenital, but may only make itself manifest after many years of normal functioning. The writer does not pretend to give any satisfactory explanation of this delay. It is important to observe, however, that this defect in the vasomotor response is affected to a considerable extent by environmental conditions. Since in the process of evolution both the structure and its accompanying vasomotor response have become part of the inheritance of the race, then it follows that defects in both these characters are liable to be inherited. In the case of the organ of hearing an example of inheritance of defect of structure is found in inherited deaf-mutism, and an example of inheritance of defect in the vasomotor response is found in inherited otosclerosis. . . .