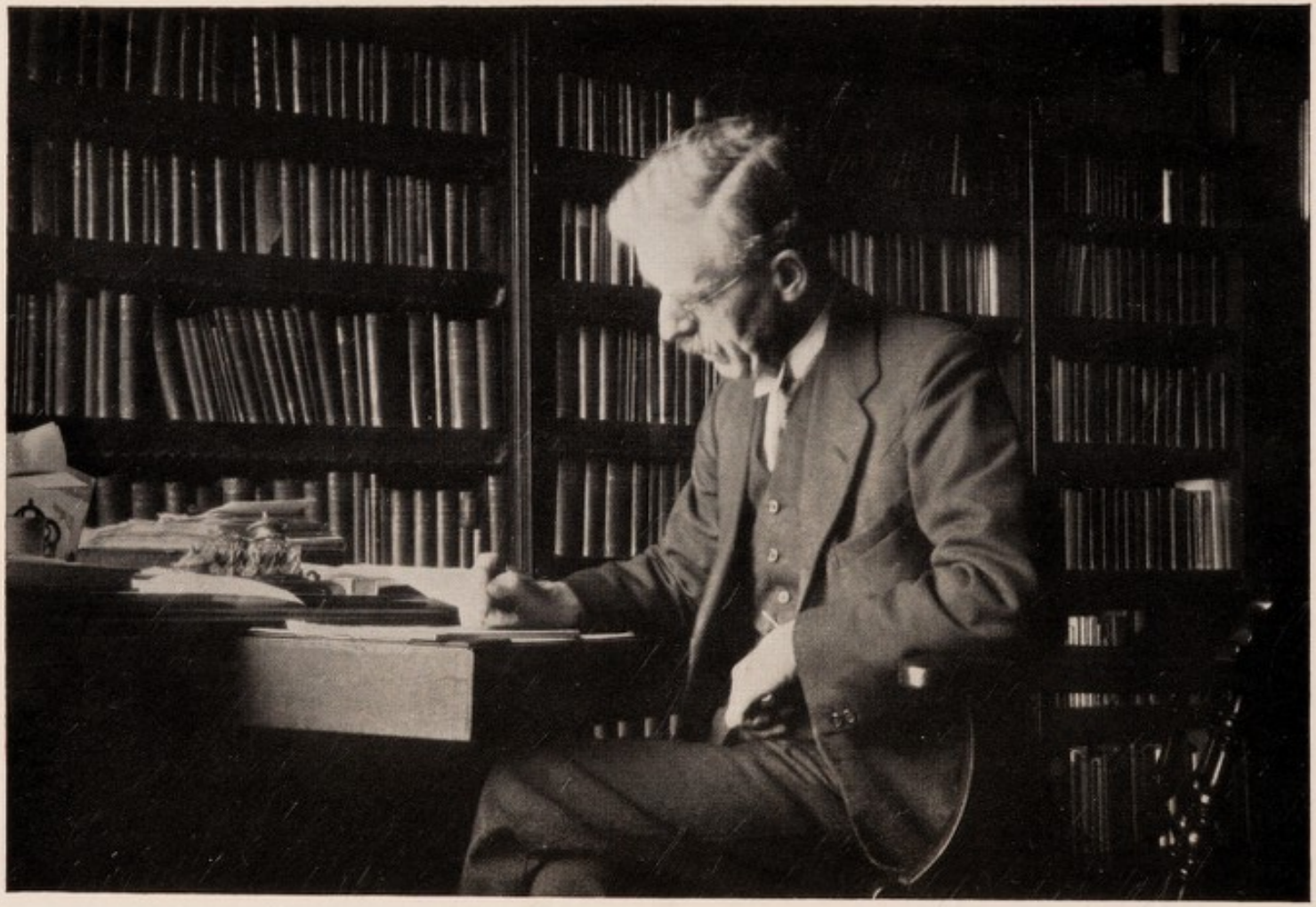
Growth / by the late James Lorrain Smith ; edited by J.S. Haldane.

GROWTH



J. Lewis Smith

GROWTH

BY THE LATE

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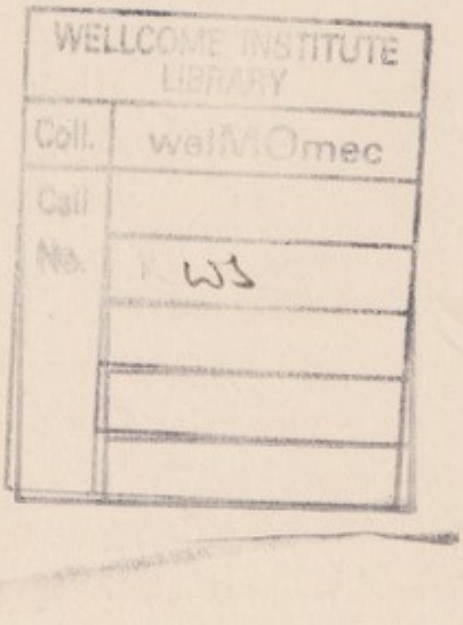

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EDITOR'S PREFACE

During the last years of his life Professor Lorrain Smith was engaged, during such time as he could spare from his many duties, in the preparation of a book on Growth. This was interrupted by his illness, and though he hoped to have strength to work at it again, he was never able to do so, and died with the book unfinished.

Seeing clearly that the key to the problem of normal growth is the understanding of life itself, he had meant the book to embody the general conclusions which he had formed as to the nature of life, and the bearing of these conclusions on the abnormal forms of growth with which Pathology deals. His early training as a distinguished student of philosophy at Edinburgh University helped him greatly in planning the book.

Although it was unfinished, his friends considered that, in view of the great interest of the subject, the large part which was practically complete ought to be published. The manuscript had been brought together by his daughter, Dr Jean Pilcher, and as he and I had often discussed the subject of the book, I was asked by his family to edit what now appears. The Introduction and fourteen chapters were, though

unrevised, in a completed form so far as they went. He had clearly, however, intended to add considerably to some of them. But for the remaining chapters only imperfect sketches existed, and it would obviously have been unfair to publish them. Hence only the Introduction and fourteen chapters are published, and I have had to make hardly any emendations in the manuscript of them.

Unfortunately, he had not yet written a chapter summarising his general conclusions. In the light of many conversations with him, I have endeavoured in a supplementary chapter to fill this gap, and so make the book more of a whole such as he was aiming at.

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INTRODUCTION

THE PROCESSION OF GROWTH

SINCE growth is an attribute or property of all living organisms, inquiries into the nature of the process are among the most fundamental inquiries of biology. The universality of the property, however, makes the problem it presents the more difficult, and the inquirer is compelled to recognise that he is working on a problem the key to which is to be found in an understanding of the nature of life.

Biology is an experimental science, and by experimental methods the facts must be discovered. To work at the facts in this way is the aim of all inquirers; but they recognise that the final interpretation of their results involves the study of far-reaching questions raised by philosophers.

The ordinary observer, even before he betakes himself to the strict methods of scientific observation, comes to certain conclusions regarding growth as he reflects on the gradual passage of the young animal to the adult stage of maturity. In early life growth is active: the body as a whole increases in bulk. Later the intense activity of growth subsides and there comes a time, definite in date, though varying in different species, when growth of the body as a whole ceases. The normal stature has been reached and thereafter there is no addition. In this observation there is de-

fined a contrast between growth and the other activities of the body. Growth is most active before the master activities of gland, muscle, and nerve have been established. These activities, once they have come into play, continue throughout the remainder of life, while the impulse to grow has ceased. Growth has proceeded to its limit, and made the activities of gland, muscle, and nerve possible. The structures required have been formed, and thereafter the only purpose to be served by growth is that of maintaining the structures it has produced. In this restricted form growth continues when the body as a whole has ceased to grow. Growth may therefore be described as the creative principle of the body. It is the originating activity, and the results of its action make all the other activities possible.

The mere statement of these observations raises many questions, and of these the most urgent is concerned with what actually happens in a body or tissue that is growing. To answer this we have at once recourse to the microscope; for growth, like all other bodily processes, must be described in terms of cell-activity. The microscope shows that cells grow by dividing; one cell becomes two. By a single step in growth the unit cell is replaced by two units. Cell-division is well described by the term self-multiplication. The cell has a complex structure of nucleus and cytoplasm, each of which contains certain formed elements which are essential to the life of the cell. When division occurs these formed elements divide also, and having divided they separate into two groups; each group becomes the essential structure of a new cell. This stage of division having been accomplished, the new cells separate from each other and become inde-

pendent units. The impulse to grow is an impulse to create new units. Division, therefore, is a constructive movement, creating new cells and preserving in them the structure of the parent cell from which they are derived. The impulse to grow is not an impulse in each cell to increase its size, though cells do vary in size from tissue to tissue.

The living substance of the body consists of cells, each single cell of a mass so small that they become visible objects only when magnified many times. The same rule holds for all animals. The cells of the tissue of the mouse are about the same size as those of the elephant. That there are many organisms still smaller than animal cells we need not stop here to consider. The point which demands attention is that to interpret the process of growth we must investigate the conditions under which cells move to the construction of new units by the process of division. The next question to consider is how growth by division takes place.

The process of growth may be described as a procession of cell-units in which each member in its turn disappears in producing its successors. The growth procession differs from all other processions. There is no gathering of units to join it from outside sources. The units increase in number as the procession moves onward; but their coming means that former members of the procession have disappeared in producing them. Generation succeeds generation until the tissue is formed. Only in the earliest phases of life are the whole of the cells in active growth. Growth is gradual, yet cell-division as a process cannot be regarded as gradual, for it is clear that if all the cells of an organ, say a liver, were at the same time to move in division, the liver would, in the short time which is required

in order to complete a single division, double its size. Growth then would not be gradual, but would be enormously rapid. Yet growth is gradual because cell-division does not take place at the same time in more than a limited number of units in a given tissue. Hence the progress of growth is gradual. Again, from a new point of view the question arises what the conditions are under which a cell-unit here and there in a tissue moves into activity while its neighbours in apparently identical conditions fail to move. Thuringer has shown that in the skin the epithelial cells divide in groups or areas.

The cells which are not moving in division are resting, and in this condition they perform the function of the tissue in which they are placed. For though the cells are the progeny of one original mother-cell, the ovum, division has not proceeded far before there begin to appear in cells structural changes in the cytoplasm which we learn to associate with special function. Special function is the activity of a resting cell. A cell moving to divide shows no sign of special function of the gland-muscle-nerve type. It is probably true to say that division and function, other than the common function of metabolic change, is impossible at the same time; but whether or not that statement be capable of proof, there is no doubt that with the development of special function the capacity for growth is lost.

The setting apart of cells for special function generally results in definite modifications of the cytoplasmic structure of the cell. Of these the striped muscle-fibre is one of the best examples, and it shows the cytoplasm evolving the regular complex structure of contractile tissue. The nucleus remains without obvious struc-

tural modification, and round the nucleus is a zone of cytoplasm which still resembles that of all undifferentiated cells.

The red corpuscle of the blood is also a living cell set aside for a highly specialised function, and the cytoplasm and nucleus in this case are both modified. The cytoplasm is loaded with haemoglobin, and it is not possible to give a satisfactory description of the change in the cytoplasm which has taken place with the coming of the haemoglobin. Before the red cell passes from the marrow to the circulation it has lost all trace of nuclear structure. Yet the cell continues to serve the special function of respiration. While it has no power of growth, it is at the same time numbered in the regulation of the blood as strictly as any other group of cells forming the so-called solid structures. And where by haemorrhage blood-cells are lost, it is as if a wound had been made and the wound heals by the growth of cells, and the red cells are restored to their normal number. The red cells of the blood are cells deprived of their nucleus and reduced to a minimal quantity of granular cytoplasm so small that it cannot be demonstrated except perhaps in the recent reticulocyte. They are loaded with haemoglobin, and in this condition they survive in the circulation for a short period. From this point of view the study of blood-cells would indicate that differentiation means not only the loss of the capacity to grow, but ultimately means the death of the cell. It would indicate that the nucleus is killed off first and may perhaps be going because the granular cytoplasm has been so far reduced. Finally, we observe the vitality of a cell reduced to cytoplasm only, or, if there be nuclear matter left, at least there is no visible structure left. It has been proved experi-

mentally that cytoplasm without nucleus will survive for a short time, but not indefinitely.

Another example of differentiation destroying the power of growth is afforded by the epithelial cells of the skin and other squamous-celled layers covering surfaces. The accumulation of keratin in the cytoplasm and finally in the whole cell takes place so that both cytoplasm and nucleus are replaced by a scale composed of homogeneous material with granules in it. These scales are the final form of surface-protecting cells forming a layer of horny material over the surface exposed to wear and the external atmosphere. The scales are worn off, and the wastage of them closely resembles the wastage of cells which have been reduced to the condition of discs of haemoglobin. The keratin scales are thrown off the surface : the red corpuscles are thrown into the plasma of the blood, where they are still controlled and where in their differentiated condition they take an active share in the metabolism of the body. Here again the function of keratin formation is a form of differentiation which rapidly leads to death of the cell.

Another cell which differentiates but does not suffer in this definite way is the fat-cell. The cell which is an adipose cell loaded with fat has lost the power of growth, and should there be a demand for more fat-cells these spring from areolar tissue cells, but not from fat-cells. To become a fat-cell, however, does not, as in the case of the squamous scale, involve the death of the cell, but it is a cell that no longer grows. All these examples, muscle, blood-cell, skin-cell, and fat-cell, give abundant evidence of their differentiation ; and with differentiation set up the power to divide disappears. It is possible that an epithelial cell becoming

differentiated might still have left enough of the original capacity for growth to undo the differentiation and begin to grow. This seems to be certainly true of connective tissue. From this fibroblasts are derived. The call for reorganisation having arisen, connective tissue cells become primitive growing cells. How much this power remains in other tissues has not been determined. The question will come up again in regard to the healing of wounds and the growth in regeneration.

The question of growth must also be taken up in regard to the cells of secreting glands, including liver, kidney, pancreas, salivary gland, thyroid, suprarenal, etc. The point now before us is that differentiation is in some ways incompatible with growth. A growing cell has little if any differentiated function and a differentiated cell has little power of growth. Growth is dominated by the nucleus : differentiated activity is the property of the cytoplasm. It is no purpose of this argument to push to any extreme limit the distinctions laid down here between nucleus and cytoplasm. They are mutually dependent on each other ; neither can exist separately, and the relation of growth and differentiation is one of gradual emphasis of one side.

Growth demands a cell with unchanged cytoplasm: a protoplasm stuffed with keratin, or fat, or haemoglobin, cannot grow. At the same time it is interesting to see that the most highly organised structure in the cell itself is the dominating element in the process of division. From the nucleus springs the impulse to group the elements in two.

The nucleus is the bearer of heredity, and of heredity which initiates the constructive movement of the cell. Here is the basis of continuity, and so distinct is this that the factors of heredity carried by the chromosomes

are described as independent units or even as self-multiplying units. The living substance of which these units are composed divides into two parts in the parent cell, each part not only preserving its own identity but a nature which enables it to amass substance, and with substance, power. Hence in the daughter cell it takes the place which was originally taken in the parent cell, and in time it shows again the capacity for dividing into two equipotent centres, and in so doing initiates the movement towards the construction of two new cells.

CHAPTER I

CELL-DIVISION AND CELL-GROWTH: THEIR MERISTIC CHARACTER

THE simplest form of growth is that of the single cell, that by which it adds to the mass of its living substance. Cells are formed by the division of a parent cell. At the beginning of their independent existence they are smaller than the normal full-grown cells from which they are derived. Accordingly, they grow until they reach normal size. A growing period is an early phase in the life of every cell.

In the formation of tissues growth becomes more complex. A tissue grows by orderly multiplication of its constituent cells. Multiplication is increase in number followed in due course by increase in the substance of the dividing cells.

By co-ordination of tissues organs are developed, and by the arrangement of these in morphological order the form and symmetry of the body are attained. Growth factors control the process at every stage and determine its progress to the extent and in the direction required by the structural plan of the body.

The present chapter is an account of growth as it occurs in a single somatic cell.

The growth of an individual cell is essentially an increase in size due to the formation by the cell of additional new living substance. The living cell is con-

tinuously using up energy-carrying substances. There is constant waste of material to be met by the assimilation of substances gathered from the environment. The elements of nutrition are incorporated in quantity sufficient to maintain the integrity of the cell in structure and function. Simple nutrition is maintenance without increase. When growth occurs there is increase in the living substance. To define the process by which a cell passes beyond mere maintenance and adds to its size is a primary problem in the investigation of growth.

The cell-units have a limit of size beyond which they do not enlarge. In other words, the cell in normal conditions does not add to its substance more than a certain amount. Variations in cell size occur in both physiological and pathological conditions. Cells of one kind may be normally smaller or larger than those of another kind. Again, a cell may be reduced below its natural size by pathological atrophy, or it may, in other conditions, be enlarged by hypertrophy. The uniformity in the size of somatic cells, however, is dependent on the limit of growth which is a fundamental condition of cell-activity. The size of animals varies widely, but that of the component cells varies little. Even from species to species uniformity in the size of the cells is the rule. As has been noted above, the cells of the elephant are approximately of the same size as those of the mouse.

While individual cells have limited power of growth, tissues grow by multiplication of their cells. At a point in its activity the cell divides into two equal portions, and the division is of such a nature that two independent cell-units are formed. The portioning is such that in each half resulting from the division there are

the elements of complete cell-structure. The dividing cell hands on its substance in two equal portions, each capable of forming a complete new unit. These new units, to begin with, have at most only half the normal amount of substance, but after they have become independent and separate they proceed to amass new substance, and the building up of it continues until they have reached the normal dimension of the full-grown cell.

The cell before division, having reached the limit of its growth, had no power of adding further to its substance. How the power of assimilation for the production of new protoplasm is controlled and checked or inhibited by the time a certain normal size is reached is a subject of far-reaching and fundamental inquiry. It is clear, however, that with division there is a restoration of the power of growth in each cell. Division, therefore, is a direct step in the process of growth. It is at the same time obvious that without growth mere continued division would soon reduce the units of living substance to dimensions minute beyond measure. When the statement is made that a tissue grows by division of cells, it really means that division is the process which continually restores power of growth. Otherwise growth comes to a definite limit, since it ceases when the cell reaches its normal size.

Growth, which is addition, is complementary to division. Division, which is separation, is essential to growth. They are alternating phases in cell-activity. Before division took place the two halves of the cell were controlling each other, balancing each other, each for the time being complementing in some way the inherent power of construction of the other. The halves having separated, each proceeds to reacquire the

amount of living substance which it had lost by division. In spite of their diminution of substance the new cells, from the point of their formation, possess the structure and function of the parent cell. Every element in the organisation of the parent cell has its place in the new cells from their beginning. Though they are new units they have with the parent unit a continuity which is as nearly as possible an identity. When they are formed there is no longer any surviving parent. Cell-growth is the building up of new substance equivalent to that which has been thrown apart in spontaneous division. The cell may therefore be described as a dividing structure. Division creates the condition in which normal growth takes place.

The changes which the cell exhibits in the process of growth have been the subject of a vast amount of cytological investigation. The division of a cell is accomplished by the division of each of its component parts. It is a spontaneous movement occurring in one part of the cell after another in definite order. The central body initiates the movement. It divides into two, and the two new central bodies produced by the division separate from each other, one proceeding to each pole of the nucleus. In these positions each body becomes the centre from which a group of fine fibres pass towards the equatorial line of the nucleus. At this line the fibres meet and join. The two groups of fibres radiating from each central body and uniting with each other at the equatorial line form the achromatic spindle. The next movement of division occurs in the chromosomes.

At the time of division the chromatin substance of the nucleus assumes an arrangement of threads. The number of threads is constant in each species, but from

species to species the number varies. In *Ascaris megalocephala* the number is four, while in man the nucleus contains forty-eight.

The individual thread is the chromosome. In certain states it appears as a homogeneous structure, but in other phases it shows a particulate structure as if the thread were composed of a series of small round masses adhering to each other. These particulate structures are the chromomeres. The chromosome is composed of chromomeres arranged in longitudinal series. The chromomeres are component parts of the chromosome, each an essential element of the structure, each in its own place in the series, and each a centre of specific activity in the cell. Before the chromosomes separate they gather at the equatorial line of the nucleus. While they occupy this position each chromosome divides longitudinally, and each chromomere takes part in the division. Following this the two halves separate, and, moving along paths defined by the lines of the spindle, they pass to the opposite poles of the nucleus, one half of each chromosome passing to each pole. The groups of new chromosomes collect at the poles of the achromatic spindle. Following this the cytoplasm divides in the equatorial line of the cell from which the movement of the chromosomes started. This is the last step in the complete division of the cell.

The process is described by the term meristic division. It is not a mechanical division to be expressed in terms of a mere weight or mass of substance, but a spontaneous separation of each individual component part of the cell. Separation occurs in the nucleus before it occurs in the cytoplasm. The participation of the individual parts of the nucleus is easily demonstrated : the order of the corresponding process in the

cytoplasm has not been so clearly defined. Yet that meristic movement in the cytoplasm takes place to some degree also can hardly be doubted, since each of the two new nuclei in its separation takes with it a corresponding portion of the parent cytoplasm, and the life of the new cells as independent units is secured.

The definition of division as a meristic process leads to a further question. How is this process related to the cell-growth which follows division? The cell having separated into two independent cells, there follows a period of assimilation during which the new cells increase their substance until they reach the limits of normal size. The increase in substance is an increase in each component part of nucleus and cytoplasm. The component parts of a cell are essential to each other. Without any one of them the cell is defective, and if there be much defect continuation of life in the cell is impossible. In meristic division there is evidence of a common capacity for balanced separation into two parts. Following the independent division there is a corresponding independent growth. Nucleus and cytoplasm will, in the period of assimilation after regular division, increase their substance to the normal amount, but a mass of cytoplasm cannot grow its nucleus. A nucleus deprived of cytoplasm does not build it up anew. The principle of meristic growth applies similarly to individual chromosomes.

A well-known example is that of the chromosomes which determine sex. They are handed on in division, determining the sex of the fertilised ovum which includes them. There is no evidence that these chromosomes are ever formed anew in a cell either from the cytoplasm or even from the chromatin

substance which forms other chromosomes of the nucleus.

Further illustrations may be found in the results of recent experimental work such as that of H. J. Müller [1] on injury of the germ plasm of flies by X-rays or radium rays. That injury may be of various degrees. It is often fatal, but when less severe the eggs may survive in spite of the injury and develop an organism defective, yet capable of reproduction. The progeny of these injured cells show a similar defect. The rays have caused a destructive lesion which is in these cases a partial destruction only, but having suffered the destruction the individual produced cannot in its development recover from the defect. As there are various degrees of injury, we may suppose that the action of the rays reached only a chromomere or part of a chromomere.

Living tissues are not all equally susceptible to the action of X-rays. One kind of tissue is more easily destroyed than another. A similar difference has been observed among chromosomes. A cell surviving after damage due to X-rays is defective in some element essential to perfect development, and the progeny of this cell shows the defect in succeeding generations. Were the cell able, it might recover by growing again the part that has been damaged by the rays, but to repair the loss is not within its power.

Similar evidence may be adduced from the results of Mendelian experiments, or from the investigation of hereditary disease such as haemophilia. From these grounds the conclusion follows that growth, like division, is a meristic process. Each component part of a cell grows the kind of substance of which that part is composed, and no part can produce the substance of

another part. A cell does not regenerate component parts that have been lost.

To trace the connection and similarity of growth and division leads to the question how far they are the same process. Growth is construction and division is separation. The construction is the formation of a system of equivalents. This in the ordinary form of somatic division is a simple system of two equivalents. When the system is formed (grown) there comes division, which is a separation in every element of the cell-structure. The question may therefore be expressed as follows. Is division merely an incidental phase of construction, or is the construction throughout dominated and regulated by a principle of equivalence which results in the separation of division ?

The presentation of this question turns attention to a remarkable demonstration of cell-division given recently by Dr Canti.[2] He has applied to the study of mitosis the method of continuous photography, and has prepared a cinema film which presents a marvellously complete picture of the movement of division. The cells studied were those of embryonic connective tissue, grown in Locke's medium, to which extract of embryonic tissue has been added. In these conditions mitosis is active, and he found it possible to obtain a continuous photographic record of the migration of the chromosomes and division of the cytoplasm. I may quote his own description of the phenomena he observed.

" The chromosomes are seen forming an equatorial belt, and as they migrate rapidly to the poles of the cell it seems as if they were pulling away from each other as in a tug-of-war. During this time bubbles of proto-

plasm are repeatedly shot out from the surface and withdrawn and the constriction appears in the middle of the cell. The constriction deepens slowly at first, then moves rapidly until finally there is only a narrow isthmus remaining. This persists for some time and then is finally broken away, sometimes with a snap as the two newly formed daughter cells wander away from each other."

In Dr Canti's photographic record the process of division is presented in sequence as it appears to direct observation. The separation of the chromosomes from each other at the equatorial line and their movement to gather in a group at each nuclear pole ; the energy shown in pulling apart compared to a tug-of-war ; the turmoil in the cytoplasm ; the constriction of the cytoplasm in the equatorial line, a line of separation for both chromosomes and cytoplasm ; the final snap and the movement away from each other in opposite directions of the two daughter cells, indicating the amount of energy expended in the separation, sufficient to fling the two halves away from each other in opposite directions for a considerable distance, in the free fluid of the medium.

This direct demonstration of the process, though it is taking place in experimental conditions and in a fluid medium, yet reveals in a striking way the steps in the process of separation. The dramatic flight in opposite directions of the two daughter cells, following the migration of the chromosomes and the bubbling of the cytoplasm, leaves a vivid impression of the outlay of energy involved in division.

The final outlay of energy brings about separation of the whole mass of the cell. Meristic division of each

component part prepares for, and initiates, the movement of separation. The cell as a whole, as its last act, develops energy sufficient to move apart the two masses which have gradually formed by meristic separation.

CHAPTER II

GROWTH OF THE BODY AS A WHOLE

WHILE the growth of the body as a whole is continuous, it is possible to distinguish three periods. During the first or embryonic stage growth is dominant, and as yet the activities of gland, muscle, nerve, are elementary. Gradually differentiation comes in cells and tissues, and the body passes into a second period in which growth and differentiated functional activity are combined. This combination continues to the point where youth passes into adult life. During adult life the discharge of function is the dominant activity. Growth in stature has ceased.

To explain the growth of the body, therefore, is to discover by what means and to what extent growth is brought to a natural termination.

Growth of tissues involves multiplication of cells. Mere multiplication, however, does not result in construction of tissues and organs. This is illustrated by a familiar experiment in tissue culture. A portion of connective tissue removed from the body of an embryo chick will grow *in vitro* if planted in a suitable medium. If left where it is planted it will survive for a short time only. On the other hand, if it be transplanted at short intervals to fresh medium, growth will continue. This experiment can be repeated indefinitely, and the growth of the cells is correspondingly

prolonged. In the well-known experiment in the Rockefeller Institute a strain of fibroblasts from the heart of a chick embryo was cultivated for a period of more than ten years. A fragment of this tissue doubled itself in about forty-eight hours. It was then divided, washed, and a fresh culture was made with each piece. The growth (multiplication) was as rapid after ten years as it was at first. The general character of the culture and of the cells did not alter during the period; the cells remained typical embryonic fibroblasts. In 1922 Ebeling[1] published an account of the experiment in the *Journal of Experimental Medicine*. At that time 1860 generations of subcultures, with 30,000 cultures, had been reached. The cells of this tissue, in showing capacity for indefinite growth, prove that, so long as they are kept in the conditions of experimental culture, they have the form of immortality which biologists ascribe to primitive unicellular organisms such as the amoeba. The growth that takes place is a continued division of cells, and a continued growth of protoplasm in each cell, without development in the direction of differentiation. The tissue originally planted was embryonic, and after ten years the cells have still their primitive form. It is to be noted that for even this primitive growth it was necessary to add to the medium an extract of embryonic chicken tissue. Extract of adult tissue was not sufficient. The extract of primitive tissue set division and growth going, but only primitive cells were formed. Had the fragment of tissue been left in its native site it would have gradually differentiated into fibrous tissue and in due time ceased to grow. In these experimental conditions, however, where the influences of the differentiating organism are not sup-

plied, primitive growth goes on and on indefinitely. The tissue survives in this form longer than it would have survived in the body of the chick maturing to adult life, and indeed it shows no limit to its growth so long as the conditions of the experiment are maintained. In contrast to this, the natural conditions of growth in the body bring about differentiation. The primitive cell becomes a fibroblast and finally a connective tissue corpuscle ; and further multiplication is duly regulated and controlled, and there is no indefinite formation of new cells.

Connective tissue, therefore, in its development passes through a phase in which it is capable of inexhaustible growth. The artificial conditions of the experiment permit this type of growth to continue, since they do not introduce those factors which in the body lead to differentiation and keep the growth within the lines of tissue development.

The law of tissue-growth which this experiment brings out applies more or less to all tissues. The factors influencing growth are many, and to explain their influence on the inexhaustible capacity for growth is to trace the natural sequence of the development of the body. Factors which act as stimuli are present along with factors which cause growth to cease. In the normal body they bring about regular physiological development. When the body becomes pathological, irregularities arise. At one time there may be excess, or at another deficiency, each with its effect on the integrity of the tissue, each in its action laying the foundation of disease.

The most general principle of control is differentiation. Differentiation inhibits growth. It restricts growth in various degrees ; in some instances it brings

about entire cessation. An example of the complete arrest of growth is seen in the red blood-corpuscles. These cells originate from a protoplasmic stem cell in the bone marrow. As they become differentiated they become loaded with haemoglobin. The nucleus, the prime mover in growth, disappears and granular cytoplasm is reduced to a minimum. The red corpuscle, though it is still alive, has become little more than a vehicle of haemoglobin. It is no longer capable of growth.

The development of the body seen in childhood and youth involves a gradual increase in differentiation and a gradual subsidence in the activity of growth. When the stature of the body is spoken of, the primary consideration in the mind of the speaker is the height. But height is only one element among many in the conception of stature. While height depends on the length of the bones, development which brings about the growth of bones to a certain length also involves the growth to a corresponding amount of all the tissues and organs of which the body is composed. Stature means the form and symmetry of the normal adult body. The size of the normal body, its height and weight, approximate so closely to the average that stature is one of the most definite elements of human heredity. Among the chief branches of the human family there is close similarity in stature. Tall men and short men are distinguished from each other in the vast majority of cases by a difference in height of a few inches. Among the uncivilised peoples pigmy races occur, the members of which are all of small stature. In them also there is a standard height and weight, a stature regular and uniform with only slight variations.

Among animals the law of uniform stature prevails also. In certain kinds of animals, however, there are wide variations in stature from variety to variety. Horses, for example, are of the great breed of Clydesdales or they may be small Shetland ponies. But within the variety the law of uniform stature is observed with a regularity like that seen in the human species.

The same principle holds among birds. The stature of the species is determined, and though unfavourable conditions such as cold and starvation may stunt development to some extent, granted a sufficiency of food, growth proceeds to full regular stature and excess of food does not cause increase of stature.

The law of stature is, on the other hand, less strictly observed in the growth of fish. Fish respond to variations in the conditions of their life much more than birds or mammals. The size of fish varies with the feeding value of the waters in which they are living. Good waters have large fish, and poor waters have small fish. In certain lochs in Scotland the mature trout, though plentiful, are all about a quarter of a pound in weight. In other lochs they grow much larger, some to weigh twenty to thirty pounds.

In the case of fish, therefore, there is no stature associated with maturity which can be regarded as the normal stature. When the angler recounts his sporting adventures he is still faithful to the biological principles that apply to the stature of fish. While the fact is recognised, the cause of the difference between one feeding water and another has never been fully explained. And for lack of this knowledge it has not been possible to provide in the hatcheries the diet or other conditions which breed the great fish. Nature alone has as yet the secret of the breeding. In view of the importance

of fish in the food supply of the human family, the study of their diet in relation to growth has practical as well as theoretical interest. The large fish have the same skeleton, the same number of vertebrae and other bones, as the small fish. Where increase in size occurs, it involves increase in the size of the bones as well as the other tissues. In mammals increase in the size of bones reaches a definite point, after which the bones do not grow in length. In the fish there are no long bones, and there is no corresponding period. Another question of great interest is the growth of muscle. The great bulk of fish tissues apart from bone is muscle. The growth of muscle, as distinct from hypertrophy, in man and other mammals has been one of the unsolved problems of physiology and pathology. Is there here an example of muscle-growth under the stimulus of "better feeding waters"?

The rearing of sheep and cattle and pigs is one of the oldest occupations of the human race. The effect of rich diet on these animals is to increase their adipose tissue, but in no other sense is there any well-defined addition to the stature. The animals' height does not increase however rich the diet. No change of pasture will give the sheep bones distinctly larger than normal. Nor could it do so without overriding the law of mammalian stature. There is known only one agent which can override the law, and that is excess of the hormone of the pituitary gland. Reference will be made to this point later. The observations on the subject are chiefly derived from pathological investigations.

Fish do not grow by increasing adipose tissue only. The whole of the tissues grow. It is more profitable, therefore, to feed a fish than to feed a sheep or a pig or any other mammal. Had man the same degree of

knowledge and experience in the breeding of fish as he has applied to mammals, he would be in a position to supply his hungry generations with liberality. Even as regards the production of fat, fish are not wanting. The friendly cod stores in his liver a supply of fat of rare nutritious quality and great value to the children of men. Further, the mud fishes of Paraguay prepare for their annual hibernation period by loading up the intramuscular stroma with abundance of fat.

The normal limit of growth in stature is difficult to define. It is limit set for all the tissues of the body, but set in a variety of ways ; for the original capacity for growth is still present in many, even though it may be latent. In certain tissues growth continues active throughout life, as, for example, in the epithelium of the skin or in the haemogenetic tissue of the marrow. In others growth is active for a period and then subsides by a process of involution, as in the mammary gland or the thymus gland. In connective tissue it is quiescent, but is readily reactivated by various stimuli such as those which cause inflammation. In muscle and nerve it is commonly said to have finally subsided when adult stature is reached, though even in regard to these it is doubtful if this dogmatic statement is justified.

In one case there is no doubt : the long bones close the chapter of growth in their length when adult life is reached. For this there is a constant date, and any departure from the date is an abnormality, an interference with the law of stature—too soon or too late to be normal. With the growth of the bones in length the other tissues grow in proportion.

While the cessation of growth in the length of bones appears to be a dominant change in the organisation

of the body, it is to be regarded as a particular instance of a general change in the whole body. Because of its definite structural basis the growth of the bone becomes an index of the growth of the whole stature. While this is admitted, it must not be overlooked that it is in animal forms which have long bones as important parts of their structure that the limit of stature appears in the definite form it has in mammals and birds. The evolution of long bones is associated with that control of growth in the whole body which is expressed in definite stature. Animals with arm, leg, or wing bones have a definite stature.

What factors are at work in the determination of stature? Two types of growth have been considered, the first the inexhaustible growth of the embryonic connective tissue in the experimental conditions of a tissue culture. In that experiment the process of cell multiplication and growth did not take place indefinitely unless the tissue were put into new medium at frequent (forty-eight hour) intervals, and supplied with extract of embryonic tissue. Extract of adult tissue failed to maintain growth. This result makes two points clear. Even the simple elementary form of growth in a very plastic tissue failed to continue without the specific stimulus of tissue extract. The ingredients of the extract are formed by embryonic tissues only. The same stimulating ingredient is not to be extracted from adult tissue. It has been shown by Baker and Carrel [2] that extract of adult tissue inhibits primitive growth. Inhibition increases with the development of differentiation and finally takes the form of a definite limit of stature.

Another instance of control is found in the action of thyroxin on the process of growth. Without a

sufficiency of thyroxin, growth of the body as a whole does not continue in regular course. An excess of thyroxin produces profound metabolic disturbance. An experiment by Marine and Rogoff [3] on the effect of excess of thyroxin on the organism at an early stage of growth was carried out by feeding tadpoles with thyroid tissue. The result was to hasten the metamorphosis of the tadpole form into the frog, and maturity in form was developed before the normal size was attained. A group of miniature frogs was the result. In this experiment excess of thyroxin created an artificial limit of growth. It caused the tissues to assume the adult stature before the normal bulk of tissue had been formed. The bones did not grow to their normal dimensions.

Thyroxin, which has a fundamental influence in the growth of the body to maturity, has no effect comparable to acromegaly when the limit of stature has been reached. Gigantism is the overstepping of stature due to the effects of excess of pituitary hormone in the body in early life while it is growing in stature.

The limit of growth is difficult to define. So far and no farther is the law. To reach the limit is the end and aim of the process of growth. The growth of the body is a procession of cells. The procession begins from the fertilised ovum. The body in its earliest stage consists of one cell, a cell created by the union of two cells which have passed through reduction. The reduced cell in this case does not proceed to build up its full form by growth, but by union with another reduced cell. The somatic cell is simply divided so that each half is a reduced cell. It is well worth while to compare somatic and germ-cell division.

I. Somatic Cell-division

The somatic cell divides into two equal halves. Each half proceeds to grow by increasing its substance. Each element was halved in division; each cell resulting from division has to grow till it creates substance equal to the half that was separated in division. Then it ceases to grow. Again, it may divide or it may become quiescent for a long time. We have seen that division lasts an hour, but only rarely takes place, and in the intervals the cell rests or passes from a simple dividing condition to a state of differentiation in which division no longer occurs.

II. Germ Cell-division

Here the chromosomes do not each divide. They separate into two groups of equal number. How does the cell count them? They must be counted by their relation to others, by the force which drives one chromosome to the north pole of the nucleus, and at the same time, and by the same force, drives another to the south pole. The north-going and the south-going are in relation to each other. This may be compared with the splitting into two halves longitudinally. Here the connection is demonstrated. Here we argue from the equality of the division that the same rule applies. Now the germ-cells separate with half the number of chromosomes. New cells so formed, like the dividing somatic cells, have half the chromosomes and half the cytoplasm—twenty-four, etc. They have no power of growing the other half. They remain for a while alive, but only for a period. They do not survive indefinitely. They seem incapable of the second act of division, the growth of

substance. What is the reason why a meristic division leads to additional growth, and a reduction division does not lead to growth, but leads to arrest of growth and finally to death? On the other hand, this cell, halved by reduction division, may have its lost half restored by fertilisation. This means that a germ-cell from the genital tissue of the one sex, having also passed through reduction division, having also lost entirely its power of growth because of this, may unite with the reduced cell of the opposite sex. By this union, with the addition to the half-cell of its complement from the other sex, a beginning is effected of the procession of cells of which the subsequent history of the body consists. The cell has had restored its power of division which had gone, and its power of growth, by each daughter cell, so that somatic division returns. Somatic division leads to differentiation. With differentiation there comes also the limit of growth, and the two are connected, but how no man knows. Somatic division is not germ-cell reduction. It differs in its effects.

From the fertilised germ-cell the growth-procession begins. The time required for cell-division gives, however, no hint of the rate of growth of the body. Brailsford Robertson [4] has given a table of weights of Australian children as follows:

SOUTH AUSTRALIAN MALES

Age of Infant in Months.	Weights in Ounces.	Age of Infant in Months.	Weights in Ounces.
0	127	5	254
1	155	6	270
2	187	7	287
3	206	8	300
4	224	9	311

It will be seen from this table that the child's weight at birth of 127 ozs. rose in five months to 254 ozs., or exactly double. The first five months are a period of very active growth. But if every cell in the child's body had divided once in the five months, and increased the amount of the tissues by the addition which a single division would cause, the whole of the increase in weight would be accounted for. There are in five months 3600 hours, and if we may reckon an hour for each division it means that $\frac{1}{3600}$ part of the tissue is in active division at the same time. Or in a given tissue, one cell is active and 3599 of its neighbours are quiescent as regards growth. The increase of a tissue is gradual, because division takes place in a limited number of units. There arises from this the question: What are the conditions under which here and there in a tissue a cell-unit moves into activity while its neighbours in approximately identical conditions fail to move?

Thuringer has shown that in the skin the epithelial cells divide in groups or areas, while those in neighbouring areas are quiescent. The stimulus to divide has a certain hint of distribution, and when this has been defined the regulation of growth may be made clear.

The end of growth is the production of a certain number of cell-units. When the number reaches a certain point growth is complete, and till that number is reached growth will continue. The secret of the number sufficient for the body is not contained in the inherent power of growth. We have already seen in the tissue-culture experiment that mere growth may continue indefinitely. In the conditions of the experi-

ment where mere growth is maintained there is no limit.

The difference in size between the ox and the frog implies that the number of cells in the ox is greater than that in the frog. What determines the number of cells in the frog or the ox? Some indications of an answer to this question have been obtained, though they are scanty indeed. If a tadpole is fed with thyroid tissue so that it gets excess of thyroxin it undergoes rapid metamorphosis into a frog and rapidly becomes a mature frog, but it is a miniature frog. In other words, excess of thyroxin has had a direct influence in determining the number of cells which the frog's body is to contain. It sets a limit other than the normal. The normal limit is the limit which is reached when the body is supplied with a smaller amount of thyroxin. Another influence is revealed in the Mendelian experiment on the growth of peas. The length, in other words the number of cells, in the stalk of the peas was found to be determined by the hereditary factor.

Lastly, there is the fact that the characteristic structure of the frog is determined by the continuity of the cells. The invariable froggishness of all that grows in a frog is due to factors of continuity, invariable, essential characteristics, and including the capacity to respond in growth to all the stimuli regulating and controlling in such a way as to produce a frog.

While every cell of the body is set to a certain scale of activity, we may note in passing the particular case of plethora of blood-cells in subjects who live at high altitudes. From this it may be gathered that the demand is for more active respiration in the thinner air of the heights. The blood is a tissue which can be grown beyond normal by the functional demand of rare

air. It is this scale of activity which is the limit of stature. Stature is a limit of growth for all the tissues of the body. The limit is determined by the control of the body as a whole. The fundamental fact of the experimental control of growth is that which has been discovered by the method of tissue culture. The embryonic tissue will grow and continue to grow indefinitely only when it is supplied with extract of embryonic tissue. Embryonic extract will not carry the tissue beyond the embryonic phase of cell-division.

On the other hand, adult tissue fluid will not keep the embryonic tissue growing. Embryonic tissue keeps division active. Adult tissue extract does not stimulate growth. Tissue will not grow of itself. For the differentiated adult tissue thyroxin is a factor, as shown in cretins. Cretins have passed through the embryonic stage, but have come to a stop. If to a cretin, which is a case of arrested growth, thyroxin be administered, growth is stimulated and the arrest stops. Adult tissue in itself has changed, because it will not grow if transplanted to a medium and given embryonic extract. Will it not grow in any condition in tissue culture? It can be transplanted. The limit must be in some way the final stage of development. How is it determined by the tissues?

We must come back to the conception of stature. One essential element is the height, and if we were asked to single out one element as dominant, this is the one we would select. The connective tissue may be said to be laid down for the purpose of giving size to the body. It is a cellular tissue, but each cell is surrounded by a framework of the most definite construction. This definite construction determines the form and symmetry of the whole body. Any growth of soft tissue

which is out of proportion is abnormal. Such excessive growths are observed in mal-developments. Gigantism is an affair of the bones ; but when gigantism occurs the other tissues correspond. They are in proportion.

The whole function of the connective tissues in construction is not yet understood, but it has been made out by Drew [5] that with connective tissue in a *planted* tissue the epithelial cells fall into the morphological form of glandular structure as tubes and columns of cells. Without connective tissue there results merely a mass of cells.* The connective tissue generally has a morphological function : i.e. it determines the cells to the development of differentiated form and function.

The limit of stature lies in the bones. As the bones lengthen, so do the ligaments, the blood-vessels, the muscles, the nerves. Secure the bones and the rest follows. The bones of the skeleton are the substitution of one tissue for another. The first tissue is differentiated cartilage. The cartilage is replaced by bone. The gradual replacement will not proceed without the stimulation of the endocrines. The cartilage remains until the whole body unites to bring its growth to a close. The cartilage line disappears and the bone is then fixed in its length. It may grow in thickness from the periosteum. The cartilage transformation is the key process. Cartilage of a eunuch does not change, yet growth stops. This may explain the tissue-changes which occur in the definition of stature, but the question remains as to how the regularity of the termination of bone-growth is determined.

* According to Fischer (*Tissue Culture*, 1925, p. 193) the differentiation described by Drew may also occur without the presence of connective tissue, though its presence brings about very rapid differentiation.—[EDITOR.]

Here the current argument would fall back on the theory of genes. The postulation of genes to control the size of the bones and thereby of all the other tissues directly or indirectly, means that in the chromosomes, forming part of their material substance, arranged in all the substance, is the capacity for division into two. This capacity is found surviving in all its power through the process of division ; growing again as all the elements grow ; self-amassing to divide with the rest of the elements, and to go on dividing indefinitely, like the other elements.

What has the gene to do ? The gene is the structure of heredity ; a " hypothetical elementary entity that is essential to and determines the development of a particular character."

It may be questioned how far stature should be regarded as a particular character. On the other hand, it was on the size of peas that Mendel made fundamental experiments in heredity. But the gene does not sit aloft and enumerate the number of cells which are to be produced and determine stature by the accuracy of its arithmetic.

Growth is controlled by differentiation, by the products of differentiated tissue. Differentiation controls in the first place the cells differentiating, and also may produce a substance which acts on the growth of the whole body.

A cell which differentiates into a muscle-cell or -fibre thereby loses power to grow by division. The growth of the bone, as has been pointed out, depends on (1) normal supplies, (2) function, (3) endocrines, (4) vitamins. All these are essential, and in regard to the question of determining the bones from the point of

view of stature the thyroid seems important. It is found that absence of thyroid leads to failure in the development of bone. The tissue remains stationary : ready, however, to proceed when thyroid is forthcoming.

Again, if excess of thyroid be administered to tadpoles there is not excessive growth, rather the opposite, but there is excessively rapid metamorphosis and the tadpole is transformed into a minute frog.

Here is an artificial determination of stature by excessive thyroxin. But that it is not thyroxin alone is suggested by the observations of Sydney Smith [6] on the skeleton of a eunuch. Here at the age of seventy the diaphyseal line still persisted, though there was no excessive growth in stature. The presence of the line (diaphyseal) was not in this instance accompanied by continued growth. In any case, however, the cessation of growth in bone-length is accompanied by cessation in the growth of cartilage all over the body, including trachea, larynx, etc. The eunuch's cartilage was behaving like a costal cartilage in the ordinary individual.

The influence of the sex glands, of the thyroid, of the vitamins, is complex, so complex that it seems hardly to be followed. The important point, however, is to realise that some at least of the essential elements are produced by differentiated tissues of the body, and that the progress of development of the individual is progress towards development in differentiation ; and it is in this progress of differentiation that these very bodies that control growth are evolved.

Much investigation requires to be carried out to follow the process step by step, but the general con-

clusion is that throughout all the tissues there is a halt in stature-growth. More particularly is this seen in length of bones in the mechanism of the epiphyseal line. An organ which was first cartilage, but in the progress of development became fibrous tissue, became ossified. The cartilage phase having passed, the ossified fibrous tissue takes its place. A hyaline chondrified matrix saturated with lime salts is replaced by a white, fibrous, ossified matrix. The perichondrium producing cartilage and ossification becomes a periosteum producing bone.

H. B. Fell and Robert Robison[7] (*Biochemical Journal*, 1929) have shown that the limb-buds of the chick can be cultivated *in vitro* on coagulated plasma to which extract of embryonic tissue has been added. The early bud, three days, consists of undifferentiated mesenchyme cells. This will grow into cartilage of the small-celled variety but will not go further in development. A bud of five and a half or six days, which by that time has differentiated and formed small-celled cartilage but has no trace of bone and no definite perichondrium, if planted in the medium shows remarkable power of self-construction. The cartilage cells become larger, and with them phosphatase is produced. There now appears on the surface a layer of bone as bone-cells in a fibrous matrix, and calcification of this takes place over the central segment of the femur. There are no blood-vessels, and consequently the changes in the cartilage which accompany the invasion of the bone by periosteal capillaries do not take place. Sufficient evidence has been shown, however, to justify the conception of the bone as an organ which has a remarkable power of self-determination.

On the other hand, the power of self-determination fails to bring on the three-days bud beyond the stage of small-celled cartilage. How can this be explained? Is it that the later tissue had power of development greater than the earlier tissue?

There is one agent which will cause the bones to grow beyond the limit of stature. If the adult human is supplied with excess of pituitrin, certain bones will overgrow and the subject will suffer from the deformities of acromegaly.

The sharp definite point at which the limit in length of a long bone is reached does not apply to the thickness of bone. Length is a feature or property of the cartilage phase. A time comes when all cartilage growth ceases—bones, larynx, ribs, and everywhere else. The cartilage remains unchanged except that in the bones, and that is completely converted from cartilage to bone. Other tissues have doubtless the same kind of change. There comes a date or point when they cease to grow any more. The liver, lungs, cease to grow, cease to exercise a capacity they still possess. The liver-cells have still the capacity to grow though the growth has ceased.

It is of no purpose to push further the consideration of this question except to point out the intense interest to pathology of the limitation of growth. In the definition of this process we could not fail to throw light on the unlimited growth of cancer and of other forms of new growth. New growth is distinguished from other forms in that there is no limit. To determine the significance of this limitless growth on the part of one tissue is the aim of cancer investigation.

In these observations there are hints of the means the body possesses of inhibiting its own growth. But

our knowledge of the factors that may contribute to this is too scanty for more than a suggestion of the means of determining the stature of the body. In the chapters that follow, the discussion of normal and abnormal growth in the several tissues will bring out the play of other regulating factors which contribute to the general control of growth.

To speak generally, growth is the creative principle, the origin of all developments. Developments proceed by the differentiation of tissues, and as developments proceed, growth comes to an end.

The evolution of the body from the single ovum is the result of growth; but to make an individual, growth must come to an end. The creative activity brings about its own cessation. When the life of the individual is considered in relation to growth, it is evident that, as the years pass, the activity of growth changes in form and extent.

CHAPTER III

GROWTH OF TISSUES AND ORGANS

THE examination of the various tissues and organs shows that there are marked differences in regard to growth. Certain tissues continue to grow throughout life. The skin and the blood are both characterised by continuous wastage of cells and for this there is physiological and normal repair. The tissues of the lymphatic system have a similar if less obvious activity. The connective tissues, though quiescent in normal conditions, are responsive to special stimuli such as the call for repair. This group includes the stroma in all the various tissues of the body. And in the same category the blood-vessels and lymphatics are to be included. Bone and adipose tissue have special developments in relation to growth.

The connective tissues further form a group in which replacement occurs in physiological sequence. So that an area or stratum having been occupied with one form of connective tissue, comes to be occupied with another in the course of development. So far growth has been considered (1) from the point of view of the cell and (2) from that of the body as a whole.

Two conclusions are clear. Growth does not take place otherwise than by division, because, when the process of division is considered, it is found that the

essence of it consists in a balance of the system, and in virtue of the balance there are three phases of the cell.

(1) *A resting phase* in which the two sides of the balance hold each other, and the cell proceeds with the activity of metabolism, with the activity of function, and with the activity of the formation and storage of cytoplasmic bodies and substances. In this phase of activity we see the evidence of differentiation in structure, and sometimes, as in muscle-fibre, a large development of substance of special structure in the fibres, or, as in connective tissues of various kinds, development of special structure outside the cell, though in relation to it. The formation of these differentiation structures is the origin of the various forms of tissue. Cytology has traced them to the heredity inheritance of genes, on the one hand, and in themselves, in the individual cell and organism, to the special cytoplasmic inheritance which is the basis of differentiation, the axis of division, which is less meristic in cytoplasm than in chromosome.

(2) *A phase in which the two sides of the balance are thrown asunder and separate.* This is an active meristic movement originating in the very build of the cell and of every element in nucleus and cytoplasm. The energy accumulates to a point of separation. The central bodies separate first, then the chromosomes, then the cytoplasm, then the cell.

(3) The last of the three phases is *the phase of growth proper.* When a cell has broken in two, each part is half the parent cell. The two together were the parent cell, but each has the power of growing again to the original size. This is the most characteristic phase of the whole process. Here is a process of

creating living matter out of dead matter. The whole substance of the material world might be converted into living substance, this being accomplished by the substance already living. The question needs careful consideration. What is the change which takes place? It seems to be mostly the making of energy more available. It is energy measured in calories and other units. There is no energy that cannot be explained as the equivalent of the recognised sources, but the living substance may increase until the whole earth is covered and populated. The principle of growth takes the whole world—solids, liquids, and gases—and creates a system of combination. The living substance universally, in whatever state it may be, is the seat of ceaseless change. This is true of all matter whatsoever, but it is true of living matter in a direct and obvious sense, and it arises from the fact that while all matter is in ceaseless activity, this same matter is endowed with special qualities of movement in virtue of which we speak of it as living. Living matter consumes energy, evolves heat, effects movement, produces electric changes, sound, light, and does mechanical work. In all this it acts like a physical system, deriving its energy from the ordinary physical sources of chemical change. These changes occur in the physical world with a regularity which makes them laws of action. They are experimental laws, no doubt. We know that the element oxygen unites with carbon and in that union a great deal of energy is evolved, and from the same quantity, the same energy. The source of our knowledge is experimental observation. We see that they unite and we measure the energy they produce in uniting. We believe that the cause of their uniting is something in their constitution. It

is something inherent in the structure of the two that brings them together. Other elements we know that do not seem to unite, e.g. sodium and potassium both unite with oxygen, but they do not unite with each other. Why union will take place in the one case and not in the other will some day be demonstrated. In the meantime, we know experimentally that it does, or does not, regularly, and this we call experimental law, and to law we attach the word experimental to signify that it is the result of controlled observation and that it is the result of the thing observed and not a contribution of our minds. The same kind of knowledge we have regarding the changes, chemical and physical, that we observe in living organisms. We observe their regularities and we find that the elements which unite in the dead world, carbon and oxygen, unite also in the living substance and produce heat in so doing, and in the same quantity per unit of substance. The remarkable feature of living substance is not that it does not contradict the regularities we can make out in observing the phenomena of the physical and chemical world, but rather the complexity of the physical and chemical combinations which in their regularity go to make up the subtle regularity of the living unit. Perhaps this is saying no more than that living organisms are a part of the real world, and to know them we must know the whole real world. Our knowledge, or science, has far to go to become a mirror of reality. The living organism has gone this distance because it is of the real world—a part of the real world. Without accumulating what we call science, it has contact and continuity with the whole world of reality. The organism can appreciate rays of light ; they stimulate its nerves, they stimulate its

chlorophyll, they stimulate its metabolism, they are fatal to it, and kill it, i.e. they destroy the physical system without which matter is dead. All dead matter is potentially living, and we see the transformation of dead into living matter going on ceaselessly.

The chief point which comes from a study of the process of growth is the continuity of capacity. It is often spoken of as the continuity of material or of substance. It should be expressed as the continuity of capacity. Even in the earliest stages of development there is evidence that determinate capacity is already defined in one part of the primal cell, so that division, when it comes, produces cells which have different capacities, and from this comes the whole development of differentiation. Differentiation introduces a limiting factor or a condition in which the opposition is not assumed, or becomes less and less so, and differentiation means that the living substance is moving out of the range of division. We have to recognise in living matter a power of amassing living substance. Living substance is created by the adding to the living cell of material which, till it is added, has not this quality of life. When it is added, it acquires the power of further adding more and more from the outside environment. The primitive cell finds its elements in the sea-water in solution. The sea-water is not living, but the sea-water may be endowed by the amoeba with the properties of life. The whole ocean might be converted into a vast swarm of living amoebae in virtue of this power. It is a far-reaching speculation to consider the change in molecules of sea-water to living molecules. It has been suggested that the molecules of the dead world are waiting to be delivered from the bonds of death. If this be so, they are not

different from the molecules of the mechanical world, but their capacity of life comes only when they are acted on by living matter, and so placed that they can display the activities which give them the creative power of growth. Is the power of growth inherent in all molecules, a power which they are ready to display when they are carried into the system? Does a complete account of a molecule include an explanation of its latent power of life? The dying away of life in differentiation is a demonstration of the process of construction reversed. From the point of view of the growing cytoplasm, the formation of structure is a destructive process, for it is a loss of the elemental power of growth.

The fertilised ovum is a gamete: a union of two cells each of which has passed through reduction and neither has the power to grow further. Somatic cells have a form of division which leaves them possessed of the power of indefinite growth. The oöcyte and spermatocyte have no such power. They have come to a limit, but when they unite, they produce an ovum —they fertilise each other. They begin to grow and are now potent to produce cells which develop into an individual, and cells which are germ-cells. The cells which pass to form the individual are somatic cells, and these cells have a diminishing potency which in the end is restricted to produce more and more highly differentiated cells. Finally, the body is formed, and bone-cells produce bone, and epithelium produces epithelium.

To maintain this capacity for growth is to maintain in restricted form the original potency. To maintain in sufficient form is to maintain health, to maintain recovery and regeneration. Disease is an interference

with function directly. The body is poisoned by toxic substances, as in microbic diseases such as diphtheria. Remove the cause, and the tissues recover their normal function of differential activity. Disease also proceeds to profounder changes. It may destroy tissue by killing the cells, and recovery depends on the power of the tissue to grow the part that disease has destroyed.

Disease also takes another direction, for, in some tissues particularly, it leads to excessive growth. This form of growth appears in its simplest type in the irregular form in which recovery takes place in inflammation. It appears as excessive tissue in progressive growth in various tissues. It appears in new growth in innocent tumours and in malignant tumours.

It is the task of pathology to discover the cause of disease in all its forms, its direct effects on active function, and no less its disturbance of the fundamental reaction of the tissues in growth and differentiation, which are the basis of normal function. It is the task of pathology to define the basis of recovery. Recovery is a restoration of inherent power. Recovery is but another illustration of self-construction. To heal is to provide the conditions in which the tissues will reassert their inherent powers of repair.

The tissues and organs of the body vary widely in their power of growth. Certain tissues, such as the skin and the bone marrow, continue to grow throughout the whole period of life. In each of these there is a continual loss from the wastage of normal activity and there is corresponding repair. A very similar activity of wastage and maintenance is seen in the lymphatic tissues.

The group of connective tissues has a common characteristic in a responsiveness to the call for growth.

Normally in adult life these tissues are quiescent, but they are readily responsive to a call for repair. In the same responsive category may be placed the blood-vessels. The terminal capillaries show great power of growth in conditions of inflammation, and the healing of wounds is a process in which outgrowths of capillaries take a dominant share. The response of bone to inflammation is worthy of thorough study. Adipose tissue is a form of connective tissue in which responsiveness to the effect of diet is seen as in no other tissue. There are various points of interest in the connective tissues. For example, there is the morphological sequence of form, the principle of replacement of one form by another in development.

The history of bone development is the most striking illustration of this principle. A cylinder of cartilage is the first specialised form of the long bone. This is replaced by ordinary fibrous bone on the one hand, and on the other by marrow-cells and fat-cells; and again there is an alternation of fat-cells and marrow-cells in the medullary cavity throughout life. This law of replacement is an important principle in genesis, and throws much light on pathological forms of growth.

Another point of interest in regard to fibrous tissue is that at any point in the body the cells appear to retain the power of dedifferentiation. They separate from their surrounding fibres, and the formed material in which they usually lie is dissolved. They assume the form of primitive fibroblasts and grow by active multiplication. When the stimulus has subsided, they pass back again to the differentiated form.

Another point of interest in their growth is their power of survival in conditions which are fatal to other

tissues. This survival enables them to replace more delicate cells which have been lost in disease, and the result is imperfect repair and an ill-balanced, irregular structure in consequence. Not a few of the effects of chronic disease are due to this comparative power of growth. Connective tissue cells are also subject to keloid growth, the frequent site of tumours, innocent and malignant.

The glandular tissues have varying powers of growth. Growth in these organs, such as the liver, is naturally related to functional call. And when disease has destroyed a part of the liver there is a reaction of regeneration, as in the group of liver atrophies.

In glands, growth in relation to function has a curious aspect in so far as, e.g., the quantity of liver is more than sufficient for the needs of the body. Yet it is rigidly restored to the full amount when disease has destroyed a part. Of special interest in relation to growth are the ductless glands and all tissues which have an internal secretion.

Finally, there are tissues in which differentiation has brought about a condition in which the power of multiplication is lost, of which nerve-cells are an example. The same is true, but less so, of muscle. Muscles have the power of growth by increase in size; but it is differential growth, not implying cell-division.

The consideration of growth is a problem of the individual organism. The organism having been formed in the ovum, fertilised into a potential individual, growth of the individual takes place forthwith. This falls into two stages: (1) the period of intra-uterine life during which the various tissues and

organs are formed ; (2) the extra-uterine life in which the body passes by growth to the stage of maturity. We may indeed consider cell-division as a prior stage of growth. Here there is consideration of the mechanism of cell-multiplication : there is a study of the minute structure and function of the components of the cell. We have then cytology, embryology, and histology—three phases of the same problem, not distinguished from each other by any sharp line of separation. Growth characterises each period, but the conditions of tissue-growth differ from the conditions of cell-growth, because of the sphere of activity which cells have when they become elements of definite tissue structure; and their activities become and are part of the influence which controls growth. The same factors are at work in each stage, but cell-division, which may be carried through by unicellular organisms, comes to be dominated in various ways by the activity of other cells in the complex organisms, so that certain forms of activity of the complex become the conditions under which growth proceeds.

The study of this aspect of the problem is of fundamental interest to pathology. Many processes of disease are disturbances of the process of growth directly. The activity of cell-division becomes abnormal, and abnormal tissues are produced. Other processes of disease are more or less destructive of the existing tissues in the organs. The destroyed tissue has to be built up again by growth. To maintain the power of growth is to maintain the power of recovery from disease. This is not a mere commonplace, but a fundamental principle broadly recognised in pathology. Failure in recovery means often inability to grow again, sometimes inability to differentiate, e.g. bone. The

disease which has destroyed a tissue partially has also made it impossible for the tissue to grow again. To complete the cure, all that is done often is to remove the cause, and leave the tissues to struggle back to restoration. This is passive medicine, but a beginning has been made in devising measures which directly aid the body in regrowing what has been lost, or what, from lack of the normal stimuli, remains quiescent. Similarly, we cannot as yet control overgrowth ; and when a tissue breaks into excessive proliferation as in tumour, we have little resource to control it, apart from removing it from the body altogether. It is for the future to discover the law of growth in each tissue so that the activity may be controlled, stimulated, and maintained, or repressed. The cells of the body are capable of indefinite growth. Tissue culture has shown that tissues kept in conditions favouring growth may survive indefinitely. The survival is a condition of continuous growth. It differs from the conditions in the body where the tissues survive, but they survive in a differentiated form, or survive by continuous growth maintaining the differentiated form, and maintaining it in the amount which is required,—so much and no more. The maintenance in control is the law of growth. The control arises with the progress of growth : as the various tissues grow, control is reached. The variety of organism depends on the point at which the limit is set up, but the determination is throughout, not merely at a stage. The limits are determined in the original cell. This has been the great discovery of cytology—that the ovum contains in it the elements which control division, the elements which set a limit to the process. When, as in tissue culture, these limits are not set up, the process of growth continues indefinitely.

CHAPTER IV

GROWTH OF THE SKIN

THE skin is formed by a combination of two structural elements—a stratum of vascular connective tissue, and on this, as a foundation, a layer of squamous epithelium. These two elements, though united in one structure, differ in form, function, and manner of growth.

The connective tissue layer is fibrocellular in structure, well supplied with blood-vessels and nerves. As the body grows the skin keeps pace with the general increase until full stature is reached. During the adult period growth in this tissue is quiescent. The capacity to grow, though it remains latent, is readily responsive should a stimulus be applied, such as that of a demand for repair of a wound.

The growth of the epithelial layer, on the other hand, has two phases. It grows in extent to keep pace with the general growth of the body. By this means it continues to form a protective covering over a larger and larger area. It produces more and more skin. When adult stature is reached extension-growth ceases. Again the capacity for this type of growth remains latent. So far growth in the two layers is parallel, each responding to the demands and control of the whole body.

There is, however, a form of growth in the epi-

thelial layer associated with its function as a protective covering. To carry out the protective function the cells differentiate. Keratin is gradually formed in their cytoplasm ; by the time they reach the outer surface they are horny scales. They have lost all capacity for growth. By surface friction, to which they are exposed, they are removed and lost. To keep the skin intact the loss must be made up. There is accordingly a restorative growth which continues throughout life.

In the epithelial layer, therefore, what may be called the architectural constructive growth ceases with maturity. Thereafter it may be called into activity for massive repair after wounds. When the wound is healed it again becomes quiescent. Functional growth, which keeps up the supply of scales to form the protective horny layer, proceeds continuously. Strictly speaking, the contrast is between two forms of regulation, between regulation for function and regulation for tissue architecture. The functional regulation of growth maintains the normal quantum. The architectural control determines the quantum. The distinction applies not to the skin only, but more or less definitely, as will be seen, to all tissues, and is of importance not only in the study of histogenesis, but also in the interpretation of disease. Pathological changes in tissues may show that one or both forms of regulation have been abrogated.

In the histological account of the skin the epithelial cells are described as forming four layers or strata: the stratum germinativum, the stratum granulosum, the stratum lucidum, and the stratum corneum. In the stratum germinativum there are two forms of cells—the basal cells and the polyhedral or prickle cells. The basal cells are of a low columnar form ; they are simple

protoplasmic cells with granules of melanin pigment in the cytoplasm. Light rays have a destructive action on naked protoplasm. The function of the melanin pigment is interpreted as a barrier to the action of the rays. The basal columnar cells form a single layer, and though they show characteristic mitotic division, they remain a single layer. They do not increase in quantity except in pathological conditions, such, for example, as those which give rise to tumour. In basal-celled carcinoma there is a massive accumulation of basal cells. The normal single layer of basal cells is then replaced by an abundant growth of cancer cells, basal in form. Normal cell-division in the basal layer is a differential division. A basal cell divides into two. One of the new cells remains a basal cell, the other becomes a polyhedral or prickle cell. The polyhedral cell has an angular shape different from that of the columnar basal cell. It also forms connecting bands with its neighbours, the intercellular bridges, and each cell is separated from its neighbour by a narrow channel. The narrow channel surrounding each cell, crossed at intervals by bridges, is a very distinctive histological structure. The polyhedral cells still continue to divide though they are differentiated. The polyhedral cells so formed occupy the outer part of the stratum germinativum. They are gradually moving outward, and on the outer border they assume a form flattened parallel to the surface of the skin. They accumulate granules of differentiated substance, keratin and eleidin, and become the stratum granulosum. The granulosum cells at their outer surface are in turn transformed into clear structures. The nucleus has disappeared : the granules are fused : the layer of the stratum lucidum is formed as a homogeneous layer, the cells hardly to be

distinguished from each other. The final transformation occurs when the elements of the stratum lucidum dry up and become keratin scales still firmly glued to the surface. The skin, therefore, is a procession of cells. The procession is maintained by the preservation of the germinative layer, and especially by the basal cells which divide to preserve the basal layer, and to supply differentiating cells to pass in the procession to the outer surface. The basal cell may be called a mother cell. When it divides it forms a mother cell, and a differentiating cell. As in the case of the red corpuscle, differentiation brings cessation of growth. There is loss of nucleus, loss of cytoplasm, and the cell is finally a horny scale. The basal cell divides but does not increase. It produces one basal cell and one polyhedral cell. It divides again and produces again one basal cell and one polyhedral cell. The result of the two divisions, therefore, is one basal cell and two polyhedral cells. The polyhedral cells also divide, and at each division two polyhedral cells are produced. These are the forms of division in the regular procession of epithelial cells. After the stage of polyhedral cell formation there is no more division. Differentiation then converts the cell into a unit incapable of growth. It is the special function of the skin to supply the waste of the non-growing units. The demand for non-growing units is the stimulus to growth. The loss of cells at the surface keeps the procession moving.

The horny layer is described in general terms as a protective surface—a layer which prevents injury because it is tough, and smooth, and elastic; a layer that keeps out the bacteria and the viruses which abound and make the journey of life perilous. But there is much more to be considered. The skin is the layer

exposed to the light, and there is reason to believe that the action of light is of fundamental importance in the physiology of the whole body. The cells exposed to light are by that very fact made a factory of substances to be absorbed into the circulation for distribution to the active tissues of the body. The horny scales have to do with this in some degree. The skin is not a mere mechanical protection but a physiological structure essential to the well-being of the whole body. The growth of the skin is responsive to a complex of physiological activities.

Earlier in this chapter a comparison of the vascular layer with the epithelial layer of the skin led to a contrast between them as regards the regulation of growth. While the two are essential to each other, their structural connection is comparatively simple. The vascular layer or corium contains blood-vessels, nerves, and connective tissue. Neither blood-vessels nor connective tissue penetrate the epithelium. The nerves, on the other hand, ramify freely, forming either definite end organs for reception of various sensory impressions, or breaking up among the epithelial cells into minute terminal twigs with a small globular expansion at their free end. These globular expansions lie among the epithelial cells, in contact with them in an external fashion. The epithelial cells are continually moving, and the ramifying twigs exert their control on a succession of cells as they pass. Along with general physiological influence, the nerves have a very definite influence on the activity of growth. Atrophy of skin areas, even to the point of ulcer formation, is an effect of certain diseases of the nervous system, for example the trophic ulcers of tabes or syringomyelia. Again, with nerve-supply damaged as in myelitis, the skin suffers

severely from trivial injuries, from friction, or pressure. With damage to nerve-supply the skin fails to maintain its normal power of recovery from injury. In what sense the nerve-supply controls cell-division directly it is not possible to state. That there is some direct control by the nerves is suggested by the results of Thuringer's [1] observations on the distribution of mitoses in the epithelium of the normal skin. He found mitoses occurring in one area but absent from surrounding areas, as if division occurred in foci or segments, or as if the activity of mitosis was carried out by the cells in relay groups.

The procession above described, which characterises the growth of the skin, is confined to one kind of cell in the sense that only epiblastic epithelial cells are concerned. There is no interpenetration by the mesoblast, no stroma, no blood-capillaries, no lymphatics. The only element in addition to the epithelial cells is a connective tissue base, beneath the first layer, but not entering it, and terminals of the cutaneous nerves.

If there are nerves to a flowing current of cells like this, what are they connected to? Are they applied to the cell? Or do they enter the cell? If they enter, are they torn off when the cell passes out to the outer layer? If they are torn, what do they do when a new cell comes along? Is there a new fibril for each cell? Do the nerves grow new fibrils and new connections? Throughout life? Strange that nerves should do this, when they have lost the power of growth. Yet perhaps this is the very reason why they do not grow. Should a nerve-cell divide there would be two centres similar in their regional origin and relations, and therefore tending to obtain similar cellular connections at the periphery, for when a nerve is sutured the fibrils grow

out and find their way perfectly to the distribution, so that there is no confusion in the innervation.

Apart from the nerve connection the skin consists of epithelial cells passing through stages of differentiation, losing the power of growth, and finally being for one reason or another cast off. This indeed is like the history of the body as a whole: the beginning in growing cells, the passage through the layers with differentiation and differential function, and finally the casting off.

It is worth while to examine the matter further. How does the tissue secure the permanence of the procession of cells of which the skin, like the body, consists? The cells of the rete mucosum remain. They do not contribute to the thickness of the layer, yet division is continuous in the sense that, great or small in measure, it is present throughout life. The cell in the rete mucosum divides into two. One of the cells remains in the rete mucosum and the other passes to the second layer of polyhedral prickle cells, and finally moves on with or without further division to become a squamous scale. The division could not take place in any other way. Should neither cell become a prickle cell, the skin would not be formed. Should both become prickle cells, there would be no rete mucosum left. The only explanation that can be offered is that in the division a certain difference in the two cells is made manifest. Division is not into two equivalent cells but into two kinds of cells, one that remains a columnar cell of the rete mucosum and the other that passes by stages to become a keratin-holding scale. The rete mucosum, therefore, does not increase in thickness, though growth is continuous, because one cell derived from the division, and one

only, keeps the place of the dividing cell. There appears to be in the division of the rete mucosum cell not only the formation of two units, but the formation of a rete mucosum cell on the one side of the division and of a polyhedral cell on the other. In basal-celled cancer there is no such distinction in the cell progeny. All the cells produced are of the basal cell type, not eventually to remain basal. The normal tissue preserves a layer of cells from which growth can begin continuously, and growth having begun, then differentiation sets in and the cell is ultimately cast off.

With a gap in the skin the part that is lost is restored by growth from the edges. This is more than normal repair, for there is here an increase in tissue or growth which adds. The normal procession must in the circumstances be interrupted to the extent that new basal cells are formed which do not pass to differentiation but both continue basal cells, and when the gap is filled this process of adding ceases. The defect in the tissue appears to be the stimulus, though when an attempt is made to explain how a defect exercises this power it is difficult to reach a satisfactory interpretation. It is the same difficulty as appears in explaining the regulation of growth generally. Growth is a multiplication of cells, and when a certain number has been reached, growth ceases. We might also say basal cells are able to maintain their activity only when they are surrounded by basal cells. This is the condition of tissue-growth generally. When it is not provided, the naked cells will first of all try to provide this fundamental condition. To obtain this is the first effort, or prius of differentiation. When physiological growth is compared with this, it is seen that it is for another purpose than that of constructive repair of

basal cells. It is now repair of squamous scales which have been lost, and the call for growth which such a physiological gap makes leads to growth not of squamous cells which cannot grow, but of basal or polyhedral cells. This arrangement of a reserve of cells with undiminished capacity for growth occurs in other tissues, and conspicuously in the blood-tissues.

When a deficiency arises the cells which should supply the deficiency are stimulated to produce the required substance, but when they are insufficient, the insufficiency may have two effects :

(1) more cells may be needed and growth occurs ;
(2) more cells may be needed to produce the secretion, and hyperplasia takes place.

From this it is clear that the body as a whole controls the growth. The thyroid itself needs thyroxin as the body needs it, and if the thyroid tissue be satisfied, the body will be satisfied. Therefore hyperplasia of the thyroid is for the whole body, because it is primarily for the thyroid itself. The cause of the growth of the skin is conditioned by the local influences. The cells of the skin are all connected with each other by protoplasmic bridges, and a cell which is deprived of this by the wound will be stimulated by the deficiency to repair, and this will proceed till the whole surrounding cells have been replaced.

The cell of the animal body grows under the stimulus of growth factors. Till these are provided growth does not proceed. A cell system does not pass into the process of division apart from these stimuli. What is the relation of these stimuli to deficiency as a cause of growth ?

This may be the explanation of addition. The

conditions are these of tissue culture experiment. In these conditions there is growth which continues until the conditions of differentiation are established.

The condition of the blood-vessels, and consequently that of the circulation in them, also has a direct influence on the growth of the skin. When the venous circulation is embarrassed the epithelium atrophies and the connective tissue frequently becomes oedematous. Oedema is followed by hyperplasia of the connective tissue. The epithelial layer becomes inflamed, ulcerates, and more or less refuses to heal. To refuse to heal is to fail to assume the phase of active growth characteristic of normal skin.

Factors affecting growth of the skin may also be of a general kind which cannot be associated with the direct function of local structures such as nerves and blood-vessels. For example, the metabolic upset associated with deficiency of endocrine secretion, particularly thyroxin, is accompanied by a definite failure of growth in the young subject. In the adult there is atrophy and the other changes of the skin characteristic of myxoedema. The series of local and general conditions which lead to pathological irregularities in its growth reveals the complex function of the skin.

In discussing the effect of the nerves and of the circulation on the growth of the skin the destructive lesion of ulceration has been mentioned several times. A lesion that involves a massive loss of tissue on a free surface such as the skin, or mucous membrane of the stomach, is called an ulcer. The destruction is such as to remove over a defined area the whole structure of the skin or mucous membrane. This lesion is of great interest for two reasons: (1) the nature of the growth which heals an ulcer; (2) the failure to heal and the

conditions in which it occurs. To fail to heal is to fail to grow, essentially.

The growth which heals an ulcer may be described as architectural or extension growth. There is a gap in the skin, and to fill that gap there is growth, which is not merely the repair of units lost because of differentiation, but the creation of new skin because a mass of skin already grown has been destroyed.

The characteristics of this type of growth are manifested in the healing. A certain amount of cell-division occurs until the quantum needed to fill the gap has been produced, then growth ceases. It has, in bringing about healing, reached again the normal limit. So far and no farther is the rule or law of growth ; to heal is to grow up to the limit. The law of limit which applies to the stature of the body applies in a single structure also. Again there arises the question, what definition can be given to the limit, what determines the quantum of skin tissue which is the normal. In the growth of the healing ulcer there are a number of points of interest. The simplest example is the mechanical wound which has removed a portion of skin. From the underlying connective tissue there springs up a crop of granulations—a form of primitive blood-capillaries with wide lumen, with their simple endothelial walls, with a perivascular accompaniment of fibroblasts in various stages of development, and of wandering cells of the blood. According to Hamilton [2] the capillary buds have at first a wide lumen. Later the lumen narrows and the whole structure contracts. When this occurs, proliferation in the epithelial cells of the germinative layer follows, and extends in ring form as a thin pellicle over the surface of the granulations, spreading from

the periphery of the wound to the centre. The cells of the pellicle increase and form a stratum germinativum with a single-celled basal layer and over it a polyhedral layer several cells deep, and finally an outer covering of fully differentiated cells. In this sequence the connective tissue takes the lead. Should there be no growth of granulations, or should their growth be excessive, the epithelial growth fails. When the wound is small, and in healthy tissue, repair is approximately complete, though special structures, nerve-endings, hair-follicles, sweat and sebaceous glands, are not restored. When the wound is larger the restoration is apt to be irregular, and is sometimes attained only by the process of skin-grafting.

The process of repair is an approach to the original architectural growth. The basal cell forms new basal cells to cover the denuded surface. Later it passes back to its normal differential division. What is the stimulus which causes the epithelial cell to resume this more primitive form of growing? All over the body the skin is growing in the regular adult functional way. Here, because a defect in structure has occurred, the type of growth is immediately changed and continues until the defect is made good. Destruction of tissue is one of the commonest effects of disease, and recovery means the reawakening of the constructive type of growth. To stimulate this growth has been the aim of the surgical treatment of ulcers. When, for example, the skin is injured by burning, the destructive effect of the heat produces an ulcer. The ulcer due to burns is always a "weak ulcer" and the healing process is slow. The delay in healing is interpreted as an effect of the heat on the surrounding tissue, an injury short of destruction, impairing the power of repair.

The injury to the skin due to heat takes a special form in cases where the effects include new growth. The best examples of this effect are kangri cancers. Normal repair is controlled growth. In kangri cancer the skin devitalised by heat injury shows the uncontrolled growth of cancer. A lesion similar to the heat lesion occurs in tissues injured by X-rays. The effects of an X-ray burn appear after a latent period of about two weeks. Swelling, redness, blisters, necrosis, and ulceration are the signs of the inflammation. Healing of such ulcers is slow and imperfect. The cellular reaction is irregular. Some areas show cells with excessive keratin formation, while in other areas the formation of keratin is absent. Nor does the epithelium keep to its normal site but forms processes growing downwards into the underlying corium. In certain cases this irregular growth passes into active cancer-cell formation, finally spreading through the body.

The interpretation of the major growth lesion of neoplasia will be fully discussed in the chapter on New Growth.

CHAPTER V

GROWTH OF THE BLOOD (*A*)

A COMPARISON of the process of growth in the blood system with that of the skin reveals certain interesting points of resemblance. Chief among these is the fact that growth is continuous through life in both. From the early embryonic period, through childhood, adolescence, and adult age, growth in each system never ceases.

The reason for this maintenance of active growth is that in each system there is in the cells produced a form of differentiation which leads to their destruction. The supply of these differentiated cells must be kept up; for in the last stage of their differentiation they perform a function of vital importance to the body, a function which they cannot perform until they are at the stage of differentiation which involves their ultimate destruction.

The production of a progeny of cells which within their functional period are passing to destruction is an extreme example of the general effect of differentiation on growth.

In Chapter II reference was made to the general law that differentiation inhibits growth. In both these tissues inhibition of growth is complete in the cells by the time they become capable of performing their essential function.

The cells of the skin arise from growth in the germinative layer: they accumulate keratin in their cytoplasm, lose their nucleus and the power to grow, dry up and form the squamous scales of the outer surface layer. At this stage they adhere closely to the surface and give the body a protective horny covering, but in this state they are worn away by friction and lost. When they are little more than horny scales, and only then, they serve the important function of protecting the body. To supply the continuous loss there is continuous growth in the germinative layer.

The growth of the blood is in many ways similar. The cells grow in the red marrow of the bones; differentiation follows growth, and the cells are normally changed into a form in which growth does not take place. They are then dropped into the current of circulating plasma. In the short period of their survival after they reach the circulation they perform their respiratory function. The leucocytes still retain their nucleus but they do not multiply in the circulation. The red cells have no nucleus. For the red cells to appear in the circulation before they have lost their nucleus indicates an abnormal condition created by some severe incidental strain on the normal marrow, or a blood disease.

The control of growth in the case of the blood is part of a regulation which includes the plasma as well as the cells. The quantity of plasma, though it varies slightly, is nearly constant. The number of corpuscles per unit volume of plasma is nearly constant also. There is a double regulation, of the quantity of fluid, and of the number of cells. To test whether the blood is normal, the blood-corpuscles per cubic millimetre are enumerated; for in normal blood the regular

number is maintained. These are easily enumerated by the haemocytometer, and they are found to show in their numbers the characters of a physiological constant. Per cubic millimetre of blood there are normally 5,000,000 corpuscles. The number may vary in individuals, and between one individual and another, without coming to be pathological. The variations in the vast majority of cases, however, are not more than 10 per cent. above or below the 5,000,000 figure. The regulation of the plasma is relative to the activity of fluid exchange in skin, alimentary tract, kidneys, and lungs. By each of these channels fluid leaves the body. At the same time the number of corpuscles is constant, as if some agent who could enumerate were watching them pass in the current, and letting so many go through each minute. The regulation may fail in regard to plasma, as in chlorosis, where there is a plethora of fluid. Abnormalities in the cells in chlorosis disappear when the plasma is regulated to normal volume.

In pernicious anaemia the outstanding lesion is in the regulation of cell-production. There is a deficiency in the hormone which regulates differentiation. When the extract of liver or stomach wall is supplied, the cells are produced in normal non-nucleated form.

The cells in the circulation are detached from each other. As free, wandering, independent cells they can therefore influence each other through the plasma only. They function according to their number. The average amount of oxygen in normal blood is dependent on the average amount of haemoglobin, the average number of cells in each unit of plasma. The cells of the blood are formed in the haemogenetic tissue of the bone marrow. To determine the exact origin of

the various forms of cells red and white a vast amount of investigation, histological and experimental, has been carried out.

Early in the history of the embryo, the formation of blood-corpuscles takes place in the mesenchyme. At that period of development the capacity for blood-production is a general property of this tissue. In foci in the mesenchyme multiplication of cells takes place, and forms the groups of cells, red and white corpuscles, fluid in which they float, and endothelial cells which make a wall to the space occupied by the fluid and the cells which float in it. The fluid is the first form of blood plasma; the free cells are the earliest blood-corpuscles, and the endothelial wall defines a space which, by uniting with neighbouring spaces, becomes a blood-vessel. Later, the formation of blood-cells, to keep pace with the growing embryo, becomes restricted, and before the end of foetal life takes place it is chiefly in the marrow of the bones, in the spleen, and in the liver. The spleen and the liver cease to form blood-cells at the close of foetal life. Thereafter the activity is continued in bone marrow generally. About the time of puberty there is the final restriction. The haemogenetic marrow in the medullary cavity of the long bones is then largely, though not completely, replaced by fat-cells, and the activity of blood-cell production is thenceforward confined mainly to the marrow of the short bones, and to the cancellous tissue of the ends of the long bones.

The process of blood-cell growth in the adult marrow differs in various ways from that observed in the early embryo. Foci of cell-multiplication are still formed, but now a focus produces white cells or red cells. It is generally believed by haematologists,

however, that there are in the marrow primitive stem-cells from which the foci are formed. At what stage the determination of the stem-cell to form red or white takes place has not yet been clearly determined. Dr Sabin [1] and her workers would connect the red-cell formation with the stem-cell which is associated with endothelium. The primitive blood-cell, according to Dr Sabin, is derived from the endothelium lining the intersinusoidal capillaries of the marrow. From these come primate red cells, still protoplasmic and still nucleated, called megaloblasts. This stage is followed by the production of normoblasts, nucleated reds, and the cytoplasm is gradually loaded with haemoglobin.

According to Krumbhaar [2] :

" The endothelial cells of Doan's intersinusoidal capillaries are first seen to be in a stage of active proliferation, swelling the capillary with cells which gradually acquire haemoglobin in their cytoplasm. In the first few generations with marked power of proliferation and growth these are called megaloblasts, in the more mature stage erythroblasts, and in the semi-final stage with pyknotic nuclei, normoblasts. Eventually the growth becomes so great that the distended capillary pours its more mature and less sticky elements into the sinuses and then into the circulation."

The growth of marrow-cells as a whole is an alternating process, at one time leucoplastic, and at another erythroplastic ; and again it may be a recession of marrow and replacement by fat-cells, or a removal of fat-cells and a hyperplasia of haemogenetic marrow. The process of alternation, growth and division, normally takes place in the marrow only.

Growth is of two kinds. The stem-cell may divide

to form stem-cells. The division in that case is equatorial division and there is true hyperplasia of the marrow. There is also differential division in which the stem-cell produces one cell that remains a stem-cell, and one cell that becomes a myeloblast. It is doubtful if the myeloblast divides. That question has still to be decided. It may be that there is a division of the myeloblast, which division produces two myeloblasts, and later a division which produces a myeloblast and a myelocyte. It is more probable that myeloblasts produced from stem-cells do not divide, but change by differentiation into myelocytes, and the myelocyte further differentiates into a non-dividing leucocyte. This is a subject of great interest in the general doctrine of growth. Differentiation is the development of a factor, the effects of which are not seen in the stem-cell, but which at the time of division become a factor of differentiation in one of the two cells produced. The division produces another stem-cell, and along with that a differentiated cell, a myeloblast. The factor was present in the parent stem-cell but it did not express itself then. Not till division takes place, and then only in one of the new cells, does the factor possess power to develop differentiation.

The leucocyte, which is the final stage of differentiation, is a wandering cell in the circulation. There is a relatively large nucleus, characteristically lobed ; there is power of amoeboid movement ; the cytoplasm is studded with granules, eosinophil, neutrophil, or basophil ; there is phagocytic activity and digestive action on particles absorbed into the cytoplasm. The myeloblast has changed into the leucocyte with or without the process of division. It is differentiated to the point where division does not occur.

Leucocytes empowered for these activities fill the blood to a regular number per cubic millimetre. In a variety of conditions—*e.g.* when the products of certain microbes are poured into the blood, as from a boil or other septic focus—the leucocytes increase, and the activity of cell-production increases. There is hyperplasia of stem-cells and myeloblasts to become leucocytes.

The question which remains is at what stage of the development of the leucocyte from the myeloblast growth ceases and the subsequent changes in the cells are a continued differentiation.

The changes in the red corpuscle are even more striking.

The stem-cell produces erythroblasts. At the first stage of division the stem-cell produces a stem-cell and an erythroblast. The erythroblast produces by division, or by differentiation, megaloblasts. The megaloblast changes into a normoblast, and the normoblast concludes the process by changing into a normocyte. This cell is ripe and is discharged into the circulation. In the normoblasts, before they are discharged into the circulation, the nucleus is in the form of a degenerate mass of chromatin often described as a decadent nucleus. This nucleus finally disappears and the normocyte is then discharged into the circulation. The disappearance of the nucleus is a change of great interest. The nucleus is essential to growth, the initiator of division. Further, the destruction of the nucleus is an example of physiological karyolysis. There is a long-standing controversy on the question whether the nucleus is removed by simple lysis, melting away of the chromatin substance, or by extrusion of

the nucleus. That is a question still to be settled. That a cell cannot live for any time without its nucleus is a fundamental principle of cytology. Here the nucleus is normally destroyed and the cell survives, but the survival is of a duration so short that it cannot be described as other than a very slow destruction.

Let us consider again the scheme of growth for the blood-cell, which holds also throughout the tissues of the body more or less. The stem-cell divides and produces two cells. One of these passes to differentiation and becomes a red cell either immediately or through further stages of division. The other remains a stem-cell, and continues the division original in blood-formation. It remains a permanent source of division. It remains to represent the permanent power of originating new tissue. Here then is a scheme of growth which holds in the tissues more or less generally. Differentiation modifies cells to the purpose of this organ and that, and in so modifying them causes them to lose their capacity for division. While this is the case, there is in division a cell produced which is determined for differentiation, and a cell which remains in the state of non-differentiation. The differentiated cell may divide, but it does not divide into anything but differentiated cells: the red cell may divide, but if it does in, say, the stage of normoblast, when it has a nucleus and a protoplasm bearing haemoglobin, it does not produce any cell less differentiated than itself. So the polyhedral cell of the skin divides, but it does not produce a basal cell and a polyhedral cell. That would be dedifferentiation, and dedifferentiation occurs, but it means a loss of differentiation and then a division on the old lines. We have therefore in the blood two ways of dividing:

the ordinary division, the result of which is that a primitive stem-cell divides and forms a stem-cell and a differentiated cell ; the other way is for the nucleated red cell to divide. Nucleated red cells showing mitosis are found in the circulating blood. There may be some other explanation of this. It may be that the cell persistently held on to its nucleus when it should have been discarded. While it did this haemoglobin accumulated, and the appearance of mitosis is not a sign of vital progress in the cell, but of incoherence.

The discovery of a hormone of blood-development by Whipple,[3] etc., and the investigation of its applications by Minot and Murphy,[4] have brought the inestimable benefit of a therapy for pernicious anaemia. When the extract of liver, the stomach, etc., is administered the nucleated red cells cease to appear in the circulation. The pernicious anaemia blood is characterised by the presence of red cells which are undeveloped, which contain nuclei after they reach the circulation. The hormone contained in the liver extract restores development, and the imperfect nucleated cells disappear. Part of the perfection of a red cell is to be free from its nucleus, and without the hormone this element of perfection is not reached. The hormone is essential directly or indirectly for the completion of the destruction of the nucleus. In pernicious anaemia there is great hyperplasia of the red marrow. The marrow is crammed with primitive blood-cells red and white. The fat is largely removed. In the circulating blood there is diminution of the red cells per cubic millimetre of plasma. There is leucopenia, with no lack of myeloblasts and myelocytes in the marrow. There is abundant marrow and deficient blood-cells in the circulation. The administration of

hormone restores both white and red cells. It reduces the marrow to normal. Fat-cells return to occupy as before the large part of the medullary cavity of the long bones. It restores the disturbed balance of production of cells and destruction of nuclei (red) or restraint of nuclear growth, without destruction of nuclei (white). The administration of excessive quantities of liver extract may lead to a plethora of cells per cubic millimetre (Gulland).[5]

The administration of hormone does not cure the disease. It supplies the hormone that is lacking, but it does not bring back the power to produce the hormone. It has not as yet been proved that loss of the capacity to produce the hormone is inevitably progressive until the anaemia is fatal. The hormone is a necessity. The disease appears in middle life. The coming on of the deficiency therefore indicates that there is a loss of a capacity which was formerly present, present up till middle life. Pernicious anaemia does not come on suddenly, though in some cases its oncoming is more rapid, in others more slow. Should the extract be supplied at the beginning there is still the possibility that the power to produce it might return. That can be answered only by further experimental investigation. Yet it is true that the disease, if not arrested, is progressive until the administration of extract has no curative effect. It will be made out in the chapter on the thyroid gland and the effect of thyroxin on growth that, if administered at the proper stage, the gland under its influence begins to grow and is regenerated.

Again, it is the case that the administration of insulin, if it be early enough in the deficiency, may cure the diabetic. It is still to be discovered whether

or not the hormone has, in the early stages of pernicious anaemia, an effect similar to that of thyroxin or insulin.

Later, the disease passes to an incurable stage. The fact that it is finally incurable indicates that the lesion to which the disease is due is a loss which cannot be restored—a destruction of some essential factor, a removal of some capacity or break-up of some structure : that it is a deficiency in the hereditary growth-factors of the stomach-wall or the liver. And it follows that we have an example of the gradual decay of the power to maintain the development of the blood : the decay of a hereditary factor—the power to produce the liver hormone.

Such lesions are found in the cytoplasm. This will be dealt with in the chapter on the nature of cell-injury.

In the marrow there is: (1) Growth-activity, continuous, responsive to special demands, a continuous generation of stem-cells. (2) A production with that of stem-cells, of differentiated cells, red and white, a difference leading to arrest of the growth of the leucocytes while the nucleus is retained. (3) An arrest of the growth of red cells associated with lysis of the nucleus before or after extrusion. (4) There is also, in the blood, lysis of all foreign cells. (5) There is in Ehrlich's haemolytic experiments a demonstration of an increase of the haemolytic power by the development of antibodies in the plasma.

Haemorrhage or massive loss of blood is like a wound in the solid tissues. The lost fluid and the lost cells are restored, and the volume of the blood is brought back to the normal quantity, as when a mass of skin is removed the tissue surrounding and bordering on the

area of removal grows and fills the gap which has been made. The local tissue in this case restores what is necessary to complete the whole. On the other hand, the marrow all over the body responds to the demand for restoration of the blood. In each bone there is hyperplasia of haemogenetic tissue. The stimulus to growth of the marrow is the loss of blood. That a deficiency becomes a stimulus to activity depends on the nature of growth ; so much, and neither more nor less, of what the body as a whole requires for normal life is maintained, as in other plastic tissues. Perfection is the normal. To maintain the normal is the regulation principle of all growth.

The blood-cells in the circulation are free and independent units. The marrow-cells, while they are localised in the bone spaces, cancellous and medullary, are in groups often described as islands. They are not directly controlled by nerves. Their activity is controlled by the ingredients of the plasma stimulating to growth at one time, inhibiting growth when the quantity is normal. After haemorrhage the stimulating ingredient works until the deficiency is abolished. Centres in the fatty marrow spring into activity. Throughout the fatty marrow there are islands ready to be activated by the stimulus to growth. The awakening of these quiescent strands of tissue is the hyperplasia of the marrow. When restoration is completed these islands pass again into quiescence.

Conditions of the blood arise, abnormal in regard to plasma and cells : plethora and anaemia ; irregular blood-production ; irregular maintenance ; imperfection in quantity and quality. These conditions are the manifold diseases of the blood.

CHAPTER VI

GROWTH OF THE BLOOD (*B*)

As has been noted in the previous chapter, one of the most exact processes of regulation in the body is that of the number of cells per cubic millimetre of the blood. The regulation of the blood apart from the regulation in quantity is twofold. These regulations interest us now in so far as each form of regulation becomes directly or indirectly a stimulus to a cause of growth. The cells of the blood are free from any direct structural connection with each other or with the nervous system or with stroma. They are set completely free, and in this condition they float in the plasma. They may affect each other or other cells by bringing about changes in the plasma and thereby give rise to stimuli. Gases, oxygen and CO_2, salts, proteins, fats, and lipoids are all concerned in this, and one or other of these in simple or combined form may give rise to such changes in the composition of the plasma as to stimulate growth of blood-cells. The simplest change to consider is that of a haemorrhage. A mass of the blood is lost more or less suddenly. This loss, like the gap in the skin, is repaired as I have already pointed out. The lost red cells are reproduced by an increased rate of growth in the marrow. It is not, as in the skin, a response to a direct loss. There is no loss of marrow-cells. There is a loss of red cells, etc., originally

derived from the marrow, and these cells are replaced as if they were marrow-cells. The procession of cells includes red cells, and they have the call like other cells in the procession. When the actual growth in the marrow is considered, it is to be observed that a process very similar in its development to that of the skin takes place. The marrow-cell, again, like the epithelial cell of the rete mucosum, is a mother cell which by division gives rise to two cells, one again to be a future mother cell and the other to pass through a combination of division and differentiation to become a red corpuscle. In this process it is to be noted that the division of the marrow-cell does not increase the bulk of the marrow, nor does the development of the red corpuscle diminish or drain the marrow. There is a continuous wastage of red corpuscles so that the whole of the red cells of the blood are destroyed and replaced in a few weeks.

Here, beyond any other tissue of the body, do we realise in what a real sense the procession of cells has developed. The growth is active to a point which no other tissue reaches. Here, more than in any other tissue, the continuance of growth is essential to life.

With this before our minds it is interesting to consider the history of the haemogenetic tissue of the body. In the original embryological movement the formation of blood-vessels, blood-cells, and plasma of the blood seems to have practically one movement. At that time the formation of blood and blood-vessels in the mesenchyme was general, and the whole mesenchyme was in this semi-haemogenetic.

This general function was gradually lost and the haemogenetic power became restricted to certain organs or areas. The spleen and the liver retained the haemo-

genetic power until after birth. The marrow cavities of the bones are completely filled from end to end with haemogenetic marrow. After the spleen and the liver have ceased to function as centres of haemogenesis the marrow still continues until the age of puberty has been reached. After that it recedes from the main cavity, and thereafter occupies the cancellous spaces at the ends of the long bones, and the marrow cavity of the short bones. The main medullary cavity of the long bones is then occupied by adipose tissue and blood-vessels, and this remains throughout life unless special circumstances arise in which there comes a special demand for blood-production. This may be a demand following a haemorrhage or it may be the effect of disease or some haemogenetic poison. The result is that in one form or another the marrow comes back and occupies the main cavity of the long bones and the fat-cells disappear. Here the marrow shows a unique character. The excessive demand for blood-cells leads to the production of marrow-cells in order that the requisite number of blood-cells may be forthcoming, or the endothelium of the marrow-cavity capillaries which is among the fat-cells, and which is only endothelium, becomes transformed into marrow-cells capable of producing red corpuscles. To complete the story, mention must be made of certain toxic conditions in which the marrow loses its fat and the tissue becomes oedematous; the so-called gelatinous degeneration which occurs in septic cachexias, etc.

When the phenomena of disease are considered, it is found that it is growth and differentiation that is the field of change. Anaemia means a failure to produce a sufficiency of red corpuscles; in other words, the marrow fails to grow the number of red corpuscles

required; the number per cubic millimetre of the plasma is reduced; the patient is anaemic.

The outstanding and common change in all anaemias is that corpuscles are too few. There are conditions also in which the corpuscles are too many: diseases in which there is an excessive number of corpuscles per cubic millimetre, and this is due to an excessive production of cells, possibly.

In leucaemia there is an overwhelming growth of white corpuscles. Hence leucaemia specially has been thought by some to be of the nature of a tumour.

The whole question of blood-production in pernicious anaemia is of interest in relation to the problem of growth. There circulate in the blood too few corpuscles. These pass down to excessively low numbers like 500,000 per cubic millimetre. Corpuscles large in size are frequent, and are sufficient in proportion to give a characteristic high colour-index. This means that the blood-cell has not matured properly and that the corpuscles have reached an early stage of growth and become arrested at that stage, and are thus sent into the circulation sometimes with a nucleus but in most cases without. This is the type of growth which occurs in embryonic blood. It is the type of growth which is never completely given up; but the predominant growth in the normal adult is normoblastic, and none of the larger red cells reach the non-nucleated stage; whereas in the pernicious anaemia type of blood-growth the large megalocyte type of corpuscle not only appears in the circulating blood, but a certain percentage of the large cells are still nucleated.

It seems not quite settled what the sequence is. Probably the megaloblastic blood-formation is gradu-

ally replaced more and more by the normoblastic, and the question is a sequence of stages. The other way of regarding it is that the sequence is endothelial cell; haemoblast; megaloblast; normoblast; normocyte. Whether megaloblast and normoblast make a sequence or run parallel from the haemoblast is a question yet to be settled.

Another point of interest in pernicious anaemia is that there is marked growth in the marrow. The marrow extends along the shaft of the long bones until the fat is completely replaced by red marrow.

This is true hyperplasia of marrow, a replacement of fatty tissue by the growth of marrow-cells. In this tissue, therefore, there are two stages of growth. In the ordinary type the marrow-cell divides into two. One cell remains a mother marrow-cell and the other cell passes to develop a red corpuscle. From this type of growth the blood is repaired. But in addition there is also a growth which leads to an increase in the number of marrow-cells, a growth which affects an earlier stage of the general process, and the two can go on together.

From this point of view there is to be drawn a distinction between primary and secondary anaemia. Primary anaemia is failure to grow, involving the earlier stage of megaloblastic anaemia. Secondary anaemia is failure to grow at the stage of adult normoblastic anaemia.

In considering the developmental history of the red cell it is difficult to understand why there should be at one time a stage of megaloblast, at another of normoblast. The outstanding fact which is observed in the resuscitation of the earlier type of blood-cell is its excessive haemolysis. For some reason the blood-

cells of the earlier phase of blood-production are lysed to excess. The conditions of normal lysis have not been fully explained. There is plasma lysis and phagocyte lysis. The cause, whatever it may be, leads to an excessive amount of haemosiderin as a deposit in the cells and the tissues.

It is not clear as yet how this phenomenon should be interpreted. There is excessive haemolysis. Is this due to an excessive haemolytic activity? Is it due to the presence of a type of cell which is more susceptible of lysis? Is the condition of the extra-uterine circulation in general more actively lytic than the intra-uterine? Is the effect due to lytic substances absorbed from the alimentary tract as in Hunter's [1] hypothesis. The existence of this degree of lysis requires, in general, more resistant corpuscles. The normocyte is more resistant than the primitive cell. The introduction of the intestinal bacteria into the circuit demands the development of the normoblast and normocyte. The failure of the pernicious anaemia blood is failure to maintain the type of blood which the intestinal bacteria necessitate. The presence of toxic substances, which prevents the development of the blood, suppresses the normal development. Bothriocephalus shows this. Other agencies may cause this, e.g. sepsis.

When bothriocephalus is removed the toxin is removed and the blood recovers. The introduction of the new type, a phase of blood-production, can be interpreted as a toxic inhibition of development. The disease is a perversion of development, the change from the adult to the embryonic type of blood-production. In what way is it essential that the embryonic should be the first phase? Why does this phase need to occur before the adult phase? Embryonic blood in

embryonic plasma does not haemolyse. Embryonic blood-cells in adult plasma haemolyse. The adult requires a corpuscle which will not lyse in adult plasma.

What is the effect of bothriocephalus? It is to an extent determined by the individual. Not all individuals infected show pernicious anaemia. Those who have had pernicious anaemia from bothriocephalus, even if cured, tend to take the disease later from ordinary causes. They are in a sense susceptible. Is the haemolysis an effect on an imperfect blood or is it a primary effect on all blood?

The interpretation of pernicious anaemia as defective growth of the blood is confirmed by an examination of the white cells. The facts observed are that in pernicious anaemia there is leucopenia as a rule. There is deficiency of white cells in the blood. On the other hand, there is in the hyperplastic marrow an ample production of myelocytes. This hyperplasia, however, does not lead to the appearance of an increase of white cells in the circulation. There is an interruption in the development of the leucocyte from the myelocyte. The last change in growth, the passage from the embryonic form of white cell, the myelocyte, to the adult form, does not take place in normal order. There is a difference between white and red. The embryonic red cells appear in the circulation and give it a distinctive character. The white cells form in the marrow and then development ceases. From this we may conclude that the meaning of pernicious anaemia is an interference with development rather than an effect of haemolysis of reds. Again, it happens that, as a terminal change in the blood in pernicious anaemia, myelocytes appear in numbers and the blood begins to show numbers of white cells as in myelogenic

leucaemia. For these white cells to appear would seem to be an indication of a step farther away from the normal control. The myelocyte is no longer restricted to the marrow.

Another series of facts observed in relation to pernicious anaemia is made out in cases of aplastic anaemia. In these cases there is deficient hyperplasia of the marrow. In the blood in this case there are the typical blood-changes. Blood-production has shifted to the embryonic phase, but there has been failure to bring about the hyperplasia of the marrow. Such cases are the most rapidly fatal. The hyperplasia is a beneficial effect; its absence means a graver form of the disease, which includes a common failure of white and red. The hormone failure affects white and red equally at this stage. From this the conclusion is that the primary change is an interference with growth. Recent observations have led to the discovery of the function of liver hormones in the regulation of haemogenesis. That this is not a specific hormone of liver has been demonstrated by Robscheit-Robins and Whipple,[2] since kidney tissue has the same effect. The passage of blood from embryonic to adult phase is conditioned by the metabolism of liver and kidney.

Here is an important physiological example of the control of growth. The growth of haemogenetic tissue and of blood is dependent on the action of other tissues.

The action of the hormones may be compared with the action of thyroxin and the control of growth generally. Here it is a control of a specific tissue. The liver is loosely associated with blood-production, and originally the mesenchyme generally.

The development of the body leads to a recession of the haemogenetic functions, a restriction to certain localities. In one sense pernicious anaemia is an excessive restriction and finally a deficiency in hormone.

The growth of the blood is for the organism as a whole. Cell-division is an act of the cell itself, but in so far as its growth is for the organism as a whole it is controlled. The liver action is on the growth limits.

CHAPTER VII

GROWTH OF BONE

In the bones is an example of growth and differentiation combined. The bones contain marrow, but marrow is a modification of vascular tissue; a tissue which makes blood-vessels also makes the blood to fill them.

A bone like the femur grows in cartilage. The cartilage is replaced by bone, but at the same time, in the epiphyseal line, cartilage-cells are maintained which continue the replacement till adult life is reached. Then the cartilage is completely replaced and the bone no longer increases in length of shaft. In the growth of length is a cartilage phase, and when the length has been secured the cartilage is entirely replaced by bone. A period is reached and the bones in the two limbs cease growing at the same time. The cartilage is calcified, then to a large extent replaced by growth of the periosteum, which at first is vascular and fibrous; but the cartilage becomes enclosed in bone, because with the process of fibrous growth there is an accompaniment of osteoblasts from which the bone is deposited.

The final growth of bone is from the periosteum. Little of the original cartilaginous framework remains. The power of growth is retained, however, in the osteoblasts which are left surviving in the periosteum,

and under certain stimuli new bone is formed, and that quite readily. Injury to the bone from disease or trauma leads frequently to new bone formation. In this tissue, therefore, the capacity to grow is latent, hidden as if sufficient stimulus were not available to awaken the activity, yet not in any way lost. The cell can still grow and form bone, and here again is the differentiating division, for the osteoblast forms two kinds of cell. One is destined to be an osteoblast mother cell and the other to be a bone-cell. The bone-cell becomes encased and surrounded with calcified matrix in the Haversian system and no longer able to partake in further growth. This is the law of division. Should osteoblasts form only osteoblasts, there were no bone ; and should osteoblasts form only bone-cells there would be an end of growth. But with division as it is, growth is maintained as a power and bone is formed at the same time.[1]

The causes of active growth in bone are :

(1) Injury to the bone itself. Trade effects.
(2) Injury to muscular attachment, exostosis.
(3) Excess of pituitary, acromegaly.
(4) Osteitis deformans.
(5) Common inflammations.
(6) Vitamins.
(7) Osteogenesis imperfecta ; etc.

CHAPTER VIII

GROWTH OF CONNECTIVE TISSUE

THE connective tissues consist of cells, or corpuscles, and fibres, white or yellow. The cells are applied to the fibres, or rather, the nucleus, with a certain amount of cytoplasm round it, is applied to the fibres, and the fibres are developed by the cytoplasm. The tissue composed of these cells, areolar tissue, is quiescent, inactive, not growing in normal conditions. In the embryo it consists of small round cells with nucleus and cytoplasm. These begin to assume their connective tissue character by becoming elongated, and in this condition they form fibroblasts. The elongated fibroblast becomes in tissue an areolar cell with more or less fibrous matrix in relation to it. The fibrous tissue is like bone, but differs from it at several points. The power of growth, as in bone, is latent, but can be waked up by various stimuli. There is no division as in bone into a primitive mother cell and a differentiated cell. Rather, it appears, the fibroblasts continue to multiply as fibroblasts only, and then each and all sink back into the quiescent life of connective tissue-cells.

But, on the other hand, no connective tissue-cell is differentiated to a point when growth is impossible. The cell reverts to the primitive physiological condition of the fibroblasts. In this condition it grows, and

having grown, it settles down and all the cells pass out of the growing phase.

Another character of connective tissue is its readiness to grow to excess. This varies from tissue to tissue and from individual to individual. When disease, inflammatory or other, destroys tissues the period of recovery is a period of growth. Growth fills up the gap. In this process of reconstruction not only the special elements of the tissue involved but the common elements of the stroma are concerned, and it is a fortunate result when recovery occurs with the equal balance of the original structure. Often, however, there is excess of connective tissue, and it would appear that connective tissue can continue to grow in conditions where growth of epithelium is impossible, and grow even to excess. The growth of connective tissue is often an accompaniment of sprouting of blood-vessels, and with the capillary loops there is a stream of fibroblasts. The fibroblasts in their abundance overwhelm the other elements, and as a result of the irregular activity the area of recovery becomes an area of fibrosis. The excess of fibrous tissue becomes an evil, and the tissue contracts unduly as scar tissue. Recovery is therefore imperfect, and the imperfections bring in their train new difficulties in the way of function. The variations in the power of growth are striking in this tissue. Cases of progressive fibrosis seem to be an example of excessive responsiveness to growth stimuli in localised areas.

CHAPTER IX

GROWTH OF FAT-TISSUE

FAT-TISSUE is an example of a connective tissue the cells of which have the function of storing fat. The wide distribution of fatty tissue in the body would indicate that the capacity for storing fat is as wide as connective tissue. On the other hand, the fat appears first in certain sites and accumulates in the cells of these areas, and this indicates that the connective tissue cells in these areas are specially ready to store fat. In the omentum there are bands of cellular tissue in which this activity is concentrated.

It is a question difficult to decide how far growth is involved in this system. The bands of cellular tissue show that, in development, the tissue for the storing of fat is laid down in anticipation of the function. The young animal has these bands, but as yet they are only very partially occupied by fat. When the animal grows older they are filled and the fat-cells spread beyond the margin of the band. And the interesting question arises: Is this the spreading of fat-cells, or growth of connective tissue-cells, or is it merely an occupation of cells already present? It is obvious that growth of fat-cells does not take place. A cell loaded with fat does not divide. This form of differentiation, like others, is incompatible with division. The mechanical theory of the accumulation of fat is difficult to reconcile with the

observation on definite limit of size. The fat-cell, like the organism as a whole, has a definite size beyond which it does not pass. There is no limit to the size of a mechanical collection of fat, but individual fat-cells have definite limits beyond which they do not enlarge. Is the limit physiological like other limits of growth or is it determined by the cell? There is always in the fat-cell a mass of cytoplasm round the nucleus; a mass which maintains the original structure of the cell before it has become a fat-cell. A fat-cell, therefore, has two areas—an area of original cytoplasm, free from fat, and an area in which fat is abundant. For when we examine the globules of fat carefully it shows through the fat a network of cytoplasmic processes. This network indicates that the fat is contained by the cytoplasm and that it does not coalesce into one mechanical globule. When the tissue is allowed to autolyse, *post mortem*, this network disappears and the globule form is then single, coalescent.

Let us determine the facts with regard to the bulk of fat that is stored in a cell. The fat is taken into the cell in excess and is then deposited as a definite mechanical mass. Later, at another time, the fat which has been so deposited will leave the cell and pass away in the blood or lymph to be used in the metabolism of the tissues. The fat enters the cell in the form of particles, or as a colloid solution, or in some way of combination. It is laid down in the form of glyceride and becomes a large mass, much larger in bulk than the mass of the cell substance.

How does the cell determine the bulk of fat it may contain? Measurement of these cells shows that fat does not accumulate indefinitely. There is a standard amount which each cell reaches, and then it takes no

more. How is this defined? Is the bulk of the mass regulated by the cell itself, and how is the regulation carried out? Is it based on mere bulk? Is it regulated by the content of fat in the pericellular fluid? This does not seem to be the case, for the addition of further fat to the tissue is attained by adding new cells. It would seem probable that the quantity is regulated by the cell metabolism; that a certain quantity having been reached, the capacity for absorption of fat is saturated; and that the quantity present in the cell so completely saturates the absorptive power that no more can be taken in. The protoplasm of the fat-cell can obtain fat from the surrounding fluids or from its own store. The more it holds in its store the less it can take in, and gradually taking in ceases. The bulk of fat stored is not merely mechanically present; it is available for the cell. When fat is wanted by the pericellular fluid it leaves the bulk and passes out of the cell. The cell holds a balance between the two, and the cell's capacity for storing fat is to be understood by defining this balance. This balance is knocked out in toxic conditions, e.g. tuberculosis.

When a tumour of fatty tissue comes to be considered we have a tissue which grows indefinitely, and sometimes to a tumour of very large size. In this condition the division is of the ancient type; the tumour grows not by a division of fat-cells but by a division of a mother cell—one of the daughter cells remains as a parent, the other becomes a fat-cell. Another point of interest in the growth of the tumour is that the tumour continues to grow though the subject is emaciating. Here comes a difference in metabolism in tumour tissue and ordinary tissue. For when emaciation comes, all the fat of the body is diminished more

or less uniformly through the various depôts. Here is a depôt which actually amasses fat, stores it, and takes it from the blood, though the blood is so poorly supplied that it is drawing on the stores of other fat-tissues to supply that of the tumour.

Adiposity is an increase in fatty tissue in the body generally. This in moderate degree is physiological. In greater degree it is passing to pathological conditions, because it tends to crush other tissues.

The excessive development of fat is called lipomatosis, and it occurs in muscle and gland. It does not occur in skin or skin-glands ; in nerve-tissue, in kidney, in spleen, in liver, in suprarenal ; in lung, brain, cord, or meninges, uterus (?), tonsils. In all these tissues stroma occurs, but for some reason the stroma is devoid of the power of infiltrating fat. It does not invade epithelial membranes, though it invades the stroma of them. It does not invade the media of blood-vessels, but it invades the wall of the heart.

The epithelial gland-cells, e.g. liver and kidney, may infiltrate fat, but the stroma of the portal tract does not. Ordinary muscle stroma may show lipomatosis in pseudohypertrophic paralysis. Here there is a form of replacement (growth ?) which has very definite limits.

CHAPTER X

GROWTH OF BLOOD-VESSELS

THE responsiveness of blood-vessels in the reconstruc tion of tissues is similar to that of connective tissue. They can hardly be separated in consideration.

Connective tissue does not grow without blood-vessels, as in the avascular tissue of the walls of blood-vessels. On the other hand, in certain forms of repair there is a superabundance of capillaries. In both cases there is excess of one element more or less independent of the other. Yet, as a rule, the two are so intimately related in the process of tissue recovery that they form a combination, a real partnership in the process. This partnership is apparent in other tissues also. In liver and kidney there is a growth of fibrous tissue with the growth of epithelium. But it is also vascular, and though it is predominantly stroma it is to be regarded as combination. The ordinary wound begins to heal by the budding of capillaries from those already present, which pass out into it. The process of budding is a growth of the endothelial cells of the capillary wall in that area. What is the impulse? In the direction of the wound the growth takes place. But as they grow they hollow out and form channels in which the blood circulates, and so the process continues until the raw surface of the wound is covered with buds forming a meshwork of channels freely

communicating with each other. Alongside these new capillaries there comes a procession of fibroblasts, the product of the connective-tissue corpuscles in the wounded tissue. These accompany the blood-vessels and range themselves around the new channels. So the process advances until the defect due to the wound has been filled up by the new tissue. The subsequent history of this tissue is that the plastic fibroblasts pass into a stage of fibre production and the structure becomes tough and firm. The early capillary buds gradually close their channels and disappear, and finally there remains a strand of tissue with much fibre, few cells, and none of them active, and few blood-vessels, the typical scar tissue. Scar tissue is not the perfect tissue of the original growth. When it is abundant in amount it may contract and distort the area. It may produce adhesions, strictures, and contractures. Again, as we have seen in other instances, the basis of growth is narrow, incomplete, and the original form of the tissue is not restored.

It is a rule that prolonged recovery leads to abnormality. If the recovery fills up the defect rapidly there is less excessive growth of fibrous scar. This reveals the abnormal element in prolonged recovery. The first form of growth is the endothelial cell, and the connective-tissue corpuscle is awakened by the stimulus ; but it is an abnormal stimulus and not the original balanced movement of tissue formation seen in normal development. Hence there is irregular development. This is ascribed to the action of irritants, for when a wound is clean it heals rapidly and the return to normal balance is as complete as possible. The delayed wound is an example of continuance of the process of growth in abnormal conditions. It is

clear that in some way, directly or indirectly, the regular process of growth is made irregular by these abnormal stimuli. Growth can be stimulated by extraneous stimuli. In what way these act is not easy to explain. The irregularity is excess of the normal. The connective-tissue corpuscle remains a connective-tissue corpuscle, but in these conditions its inherent impulse to grow leads to irregular structure.

Another point of interest in this connection is found in those cases in which a trivial injury leads to an abnormally plentiful growth in response. Keloids are examples of growth in which a small mechanical injury leads to overgrowth of stroma. These are almost tumours. In these cases the stroma tissues are hypersensitive to injury.

Blood-vessels and connective tissue penetrate other tissues—muscle, bone, fat, gland, brain, lymph gland, etc. They do not penetrate skin. The skin layer is simple epithelium; not penetrated by any blood-vessels. Is this connected with the ceaseless growth of the epithelium? In nerve tissue there is only blood-vessel and its coats, but no stroma of connective tissue. There is a stroma of neuroglia. The nerve-cell, however, stretches out by the axon to the furthest limits and controls activity; controls growth indirectly if not directly.

Endothelium lines the blood-vessels and in these has ceased to produce blood-cells, ceased to be actively phagocytic, has become a mechanism of exchange, a permeable cell passing through fat and sugar, and other constituents of the plasma as may be required. The tissue fluid becomes lymph, but lymph varies in composition, and it is not yet known how far the composition is determined by the endothelium and how

far by the tissue-cells, for the lymph is tissue fluid, and tissue fluid is the mother fluid of lymph, and plasma of blood is the mother fluid of tissue fluid. But when an area is inflamed, the composition of the tissue fluid becomes more and more like plasma. The control of the endothelium is paralysed by the inflammation; the endothelium becomes more permeable because it is inflamed.

Endothelium in the sinuses of the spleen is actively phagocytic and on stimulation proliferates and is set free, and the sinuses show on occasion a large number of free endothelial cells—active still, though set free from their connection with other cells. Endothelium may apparently revert—metaplasia—into fibrous tissue and form fibres and become connective-tissue corpuscle, etc.

Endothelium of Kupffer is active in the liver, in the production of bilirubin from haemoglobin, in relation to haemosiderin, in relation to fat, etc. etc. It also seems to get set free, but disappears, in the capillaries of the lungs.

In ulcer of stomach there is no granulation tissue. Further back, in the adjoining tissue, there is endarteritis and stroma-growth. Why not in the immediate zone? And why not in tubercular lesions? The concentration of the inflammatory agent may explain in tubercle, and possibly in peptic ulcer.

CHAPTER XI

GROWTH OF SECRETING GLANDS : LIVER

THE process of growth in secreting glands has been the subject of investigation in relation to development, in repair of wounds, in disease, and as a seat of tumour.

Liver

The liver is composed of lobules, and each lobule consists of columns of epithelial cells closely applied to sinusoid blood-channels. Alongside the channels are prominent endothelial cells, Kupffer cells, which are active in relation to the formation of bile pigment, etc. These columns of epithelial cells terminate in bile capillaries and pass to the portal tract, where they unite to form bile-ducts. In the portal tracts there are also lymphatic channels. These, however, do not extend into the acini ; their terminals are found in the stroma of the portal tract surrounding the acini.

The liver is a solid organ, therefore, consisting chiefly of epithelial cells, but with stroma to carry the vessels and ducts.

The liver secretes bile. It has a function in the regulation of protein, fat, and sugar metabolism. In view of its basal function it is found in evolution from earliest forms. It is, until embryonic life has ceased, a locus of blood-production. The endothelial cells of the sinu-

soids are a source of blood-cells. With the passage to post-embryonic life, this function of the liver ceases. But the liver continues to have relation to the circulating blood-cells in its biliary function. It is the function of the liver in regard to this to regulate the amount of bile pigment in the plasma. When there is disease of the liver this function may be so disturbed that bile pigment accumulates in the plasma, and there is jaundice.

With this complex function the liver growth is of corresponding interest. It appears as a development of the epithelium of the primitive gut. It grows in size until adult life is reached. The growth in this instance has still to be analysed. Is it a growth of new acini, or do the old acini enlarge ?

When the body is full grown the liver ceases to grow. In the adult it measures one-fiftieth of the weight of the body. In the newly born infant it weighs one-twentieth. So that the relative growth of the body is much faster than that of the liver. Yet the liver grows.

The liver has great power of regeneration. Experiments on this point were carried out by Ponfick,[1] who found that a large portion of the liver could be excised without causing the death of the animal. From this it was clear that for the immediate necessity, function could be carried out by a small fragment of liver. Ponfick found that a dog would survive if he took away 70 per cent of the liver. Further, that the dog with 30 per cent of the normal liver would in forty-eight hours bring the liver up to 75 per cent of the normal. The 30 per cent makes itself into 75 per cent by adding 45 per cent. To add 45 per cent would mean that each cell of the liver left would divide once

in forty-eight hours, and the half of them would divide twice. This is naturally a rough calculation, but even this apparently enormous volume of growth is a mere nothing compared with the rate of growth of bacteria, which complete the process in half an hour and require no rest at the end of it, but go on to increase at this magnificent rate so that in forty-eight hours vast numbers have arisen from a single original.

From this experiment of Ponfick's come various considerations. The first is that the animal should survive with less than a third part of its liver. That the observation is true is confirmed by a study of liver atrophy. Atrophic cirrhosis is a disease the essence of which is a destruction of the functional liver-cells. What causes the destruction has never been exactly defined. It can be produced experimentally, as shown by Davidson,[2] by an injection of coal tar or by the alkaloid of senecifolia. It has also been produced by manganese salts and other agents. In clinical experience it has been associated with concentrated alcohol, but the effect is indirect and is associated with other factors. When the destruction occurs the liver responds by regeneration as it does in Ponfick's experiment. But the condition is not allayed or abolished by regeneration. The regenerated cells also atrophy; they are not immune to the atrophy; the disease, in spite of regeneration, is progressive, and in the end the liver becomes reduced to the limit compatible with life—a functional limit. At this point the liver may be reduced to one-third of the normal bulk, and of that one-half is stroma. There is, therefore, one-sixth of the normal liver left, and though obviously this is not an exact calculation, it is sufficient to show that the body will survive for a long period with a much-diminished

quantity of liver tissue, and without evidence of gross insufficiency of liver function. No doubt such a reduced liver is not sufficient for conditions of strain. It has not, for example, the capacity of storing carbohydrate. The reserve has been diminished, but life is not dependent immediately on reserves, and the fact that life continues without normal reserve raises another question in relation to growth. The provision of reserve is the controlling influence in the growth, for the animal with 30 per cent of its liver proceeds with due rapidity to replace the reserve. Should this growth to what is called reserve be regarded as a response to a demand for hyperplasia for the sake of function while some subtle metabolic purpose, which we are yet unable to define, is at work stimulating growth till the reserve has been supplied ?

This would mean that for that function, say, the anti-pernicious-anaemia hormone, if we understood it fully, there is no reserve. All is required for the normal function, and we must add for the immediate function, e.g. production of the hormone for blood development. That this is the case might be regarded as the natural conclusion from the observation of the regular result of normal growth that provides so much liver in proportion to the rest of the body. Or should we approach the subject from another point of view and say the cells of the liver have an inherent power of growth which is uncontrolled or unlimited till a certain point is reached, and that the growth having reached a certain point, further growth is inhibited ? The regeneration of the liver in cirrhosis is a growth not only of liver-cells, but of bile-ducts and of stroma.

The question may be asked, if the liver can regenerate in the free way indicated in Ponfick's experi-

ment, how does it come to permanent and progressive atrophy? The answer to this question is not yet. In general, the regeneration of the liver is imperfect. The simple morphological plan of the liver is not followed and the lobules are irregular and distorted, and the circulation among other things is imperfect, so that abdominal venous congestion arises, and ascites, and the consequences of this are often the immediate cause of death in patients with cirrhosis. That the regrowth should be irregular may be naturally expected, for the disease-atrophy falls with extraordinary selectiveness on liver-cells. Indeed, it seems to be strictly a cell-condition, for some cells in a lobule are disappearing in atrophy while others in the same lobule remain surviving and apparently functional and growing to replace. The other elements of this tissue are apparently only slightly, if at all, damaged. The blood-vessels, the bile-ducts, the lymphatics, the stroma, and the nerves of the portal tract remain, and are to all appearances active, while the liver-cells suffer. It is a disease in which the virus fastens on a certain functional cell, the liver-cell, and on individual cells, for one suffers and its neighbours survive. The nature and incidence of the disease therefore provide the basis for irregular restoration. The mechanism of growth is a mechanism for the growth of liver-lobules for the whole unit. The whole unit is not destroyed and the restoration is therefore inco-ordinated.

Reference to the mechanism of growth brings up another question, and that is the nature of liver-growth. The liver of the infant is composed of fully formed lobules. Columns of liver-cells form the walls of secreting channels which are continued as ducts in the portal tract, when their walls are still formed of epi-

thelial cells, but of a structure differing from that of the liver-cells. Embryologically the liver-cells are expansions of the bile-ducts, terminal expansions in which the epithelium, which is common to the whole tract, differentiates for hepatic function. When this has been completed the liver lobule is formed. Yet somewhere there must remain a capacity for growth, for the liver of the infant grows through the years till the adult limit is reached. It has been taught that the power of forming new columns of liver-cells remains in the differentiated columns, or it remains in the epithelium of the bile-duct.

In the same line of argument the controversy remains as to how the regeneration of the liver atrophy takes place. Neither the natural growth of the normal liver from that of the infant to the adult nor the recovery of the adult liver are understood. It is clear that here a fundamental inquiry into the growth and regeneration of the liver is needed so that we may understand what is happening both in health and disease.

A problem of great interest lies in the effect of regeneration in liver atrophy. The disease is progressive, and this means that the new tissue formed, while it supplies the functional power of the liver, does not provide immunity to the virus of the disease. To destroy the virus or to neutralise the poison would make the recovery by regeneration more perfect. It is a recovery by simple growth, but somehow fails to develop immunity. In general, we might agree that immunity to coal tar ingredients is not within the range of the immunity reaction.

When cells are injected into an animal the reaction they cause is the development of cytotoxic antibodies.

Does this give us any hint of the control of growth? It is true to say that while tar produces cancer, the epithelioma continues to grow after the tar has ceased to be administered.

Let us consider the mechanism of growth in repair. It differs from the mechanism of development, e.g. when a wound in the skin heals it is a growth of the skin layer without hair follicles, without glands. It is not the complete architecture of the skin. It is not the original developmental mechanism in its complete form. The same is true in some way in the liver, but we do not know the mechanism of the liver, and hence the lack of a comparison. The blood, on the other hand, shows the most complete repair, for the repair is but an exaggeration of the normal growth. The repair of blood in physiological conditions is the normal development complete, hence repair of blood is simple repair. The original mechanism has never been changed in the development. In skin, on the other hand, the growth has been located in a definite layer, definite in the sense that it is restricted to the growth of squames. But the whole growth of the skin is a growth not only of squames, but of glands and hairs and other appendages. Growth, however, must therefore be defined in relation to restriction. It is retained in a limited sense. It is the original mechanism which is controlled—limited—defined. The retention of growth is to maintain this as required in the body. Repair is irregular, except in the blood, which is a constantly repairing tissue. The same restriction is seen in mucous membranes.

In arranging the series of growth capacities there should be a definition of the place in the series where tumour comes in. It seems to come in at any stage

as long as growth survives. It is dependent on this; it does not convert non-growing units into growing units, but may enter at any stage and overwhelm the regulation factors. It is the more active the earlier the stage; but tumour tissue forms at a stage when the cells are passing into final differentiation and with the tumour-growth differentiation continues as in squamous epithelioma. It follows the track of repair. Hence we have liver-celled carcinoma—a new liver.

Tumour therefore appears as an interference with tissue at all stages of growth. Growth should subside, should not take place, at the point where tumour arises.

The cause of tumour is in the tumour cell itself. It is a cell whose cytoplasm is thrown into the condition of balance which leads to division. Many agents may do this. Many agents may stimulate the dividing arrangement of the cell substance.

The growing edge of tumour is always the protoplasmic fluid system. The tumour-cell has this power, for it grows *in vitro*, and when it is grown and reinoculated it again grows tumour. It creates its own growth then in spite of the regulation. Normal cells atrophy in these conditions and disappear when implanted. Kupffer cells are cast off and destroyed in the lung (Mann [3] on Special Cytology) and they are regenerated. This is like the blood.

CHAPTER XII

GROWTH OF MUSCLE

MUSCULAR tissue is striped and non-striped. Striped muscle in the heart forms a syncytium. The cells are connected with each other in one system. In ordinary muscle each fibre is separate. In heart-muscle the nucleus, surrounded by undifferentiated cytoplasm, is situated in the centre of its area and surrounding it is a cylinder of striped substance. It is striped from a development of the finer structure of the cytoplasm, the mitochrondria. The mass of this substance is relatively large, and its relatively large size is a sign of the maturity of the tissue. In the beginning the cells do not have the large surrounding mass of cytoplasm, and even the mass of differentiated cytoplasm is not great relative to the nucleus. The result is that the tissue at first glance has the appearance of a very closely packed series of cells with prominent spindle-shaped nuclei. It is generally accepted that the main growth of the heart is an increase in the size of the individual fibres. When the multiplication of cells ceases has not been made out. But whatever the exact story may be, muscular tissue early in life loses the power of growing new cells. The cells have become fibres with striped muscle substance, and the division of nucleus and undifferentiated cytoplasm no longer takes place. The investigation of the healing of wounds in muscle shows

at most an attempt at growth in the form of a multiplication of nuclei ; but there is no free production of new cells. A system which divides is a meristically arranged system ; a balanced system, balanced in opposition. The opposition creates turmoil, and the issue of the turmoil is a grouping of the units of nucleus and cytoplasm in opposition and a movement of repulsion. Opposition becomes repulsion, and repulsion, when it reaches a certain degree, becomes the movement of division, and the movement of division becomes a separation of two independent cells.

The consideration of muscle, therefore, is that of a tissue fixed in early life with no power of growth by cell-multiplication. The increase of bulk is a function of activity. When a muscle has less work it atrophies. When it has more it hypertrophies. The size of the muscle is a register of the work it has to do.

There are other influences. The action of certain poisons on muscle is striking, e.g. tubercle. The muscle wastes away to a degree that is striking. This is a metabolic effect ; for there is so little tendency for tubercle infection to settle in muscle that this is an effect of a circulating soluble toxin. Some muscles do not hypertrophy with action. The finger muscles of pianists are not hypertrophied to any extent, but the muscles of the arm of the blacksmith are conspicuous for hypertrophy.

Hypertrophied muscle is a muscle liable to degeneration. The substance has become less resistant than normal to the degenerating influences. In cachectic diseases muscles atrophy.

CHAPTER XIII

GROWTH OF THE NERVOUS SYSTEM

THE growth of the nervous system is of interest because nerve-cells lose the power of growth by division, but maintain the power of growth in their fibres. Also, neuroglia cells are of the same origin, and they retain the power of growth. The development of the nerve-cells is a series of stages of growth from the primitive epiblastic cell, from which come neuroblasts, and from neuroblasts come neuronoblasts, spongioblasts, astrocytes. Associated with each stage in the process is a tumour, and the classification of brain tumours of Bailey and Cushing [1] is based on the structure of the stages. The neurone, once it has formed, can no longer grow and the number of nerve-cells is fixed. They are numerous enough (9,000,000,000 ?). Only certain groups of these take part directly in the central activity. The body provides many nerve-cells that are unemployed. When a nerve-cell is injured it is not replaced by another. When a nerve is injured the axis cylinder grows out from the end, and not only so, but finds its way to the tissue supplied by the severed nerve, and the function is restored.

Here is a great marvel of growth. How is the direction of the fibre brought about ? The fibre is attracted to the area so that its distribution is determined. This raises the question of how growth is influ-

enced by the relation of one cell to another. There is a response of glia with the blood-vessels. The glia—like a connective tissue corpuscle, though differentiated into a non-growing astrocyte—loses its differentiation to the point of becoming a cell with nucleus and granular protoplasm, and then multiplies. Having grown, it ceases to multiply and again becomes an astrocyte.

Another interesting point is disclosed in the disease syringomyelia, in which growth of the glia occurs in the cervical segment of the cord. As far as is known, this is a developmental condition with excessive activity or loss of the usual inhibition of "so far and no farther." And many diseases — locomotor ataxia, G.P.I., disseminated sclerosis, etc.—show disappearance of the cells and fibres of the neurones and a replacement of increased glia. Is this a repair? Is it on a parallel with progressive fibrosis?

We have, then, from the epiblastic cell, a cell which has lost the power of growth, a cell which remains quiescent at the limit of growth set by the tissues, but which can take on a growing phase in response to injury, in replacement, when the neurone or its fibres are destroyed.

Why should a nerve-cell lose its power of growth? How far is the nerve-cell differentiated? It is remarkable for the development of the axon. It is also remarkable for the evidence it shows of the control of cell-activity other than its own. This controlling influence is conveyed from the neurone to the controlled cell by the fibre, a structure which is carefully isolated by a sheath. We cannot push this question further until we can interpret the conditions of cell metabolism more completely, so that we can distinguish differentiation from growth, etc.

Two tissues have on examination proved to be devoid of the power of growth : first, the master tissue of the body in regard to regulation and control of function ; and second, the muscular tissue. These two which cannot grow are the tissues which are most directly connected with human conscious experience : the nervous system in the first place in sensation, on which our knowledge is based. Through the nerve mechanism we become acquainted with the world in which we live. Through the nervous system and muscular action we also become acquainted with the motor side of our experience. By volition we can cause our muscular tissue to contract.

Growth is a process of the living matter which never has any such direct relation to conscious experience. It is beyond the direct range of conscious voluntary action. Mental volition controls in full consciousness the action of the muscles, and in the mind there arises a conscious sensation in association with stimuli of the sense organs, e.g. of the eye by light. But the stimulus of growth never is associated with an impression on the mind.

The relation of nerve-fibrils to epithelial cells raises a point of interest in relation to growth. The epithelium of the skin is supplied by nerve-cells which are described as applied to the cells. These cells are continually growing. What happens when a cell divides ? Does it happen that the two cells each retain connection with the fibril ? Does the fibril divide ? When a cutaneous nerve is cut, the skin atrophies.

CHAPTER XIV

TUMOUR: HISTORICAL SURVEY AND STUDY OF CHARACTERISTICS

THE history of the tumour question is a record of stages in the investigation of growth. Modern investigation began with Virchow's cellular pathology. Previous to Virchow tumours were regarded and interpreted as parasites. With Virchow's generalisation came the conception of tumour as a variation in the process of cell-growth and a definition of the abnormalities which tumour reveals. The history of the tissues was searched to discover the stage of growth at which the tumour began to manifest the break-away from normal development. The embryology of tissues supplied a basis of tumour classification. The working out of this in histology has been carried as far as available methods will go. The reason for the variation expressed the ideas as to the causation of tumour.

The general result of these investigations was to draw a distinction between the external factors and the internal. Of the external factors, irritation in various forms—chemical, mechanical, heat, light, bacterial, protozoal—were found so associated with tumour that they could be described as the exciting cause of tumour-growth. The exciting cause, it was recognised, was not the whole cause. It did not explain the nature of the process which was excited into existence, which,

once started, continued increasing in its momentum, showing no tendency to become exhausted. That was the hidden moment still to be explained. Irritation might merely irritate and produce changes in a tissue without arousing the tumour process; but in certain cases the process was aroused, and so frequently that no doubt remained that irritation did contribute to the causation.

With the advent of bacteriology there was a great effort made to apply the experimental methods and conceptions which had been so triumphantly applied in the interpretation of bacterial diseases. The most diligent and strenuous search, however, failed to isolate and cultivate any microbe which could be regarded as the abnormal agent. Microbes or protozoa, etc., could be demonstrated to be the primary cause of granulomata, and in tubercle, syphilis, yaws, bilharziosis, coccidiosis, etc., there was, directly associated with the presence of the irritant, a proliferation of tissue: sometimes even of a specific tissue so that by the examination of the tissue the specific organism could be diagnosed to be present. The granulomata, however, differed from tumours fundamentally in that there was in them no growth of the persistent and continued kind to which the term spontaneous growth could be applied. Two points, therefore, were clearly brought out: the negative result inasmuch as the micro-organism had not been isolated; and the positive, which consisted in an untransferable difference in the nature of the growth-reaction. About the same period, and partly before the bacterial effort, was Cohnheim's attempt to explain tumours embryologically. Cohnheim regarded it as a possibility that tissues which are embryonic are full of the impulse to growth.

Next in order of succession came the work of Jensen, and transplantation. It was clear that the adeno-carcinoma of the mouse could be transferred to other mice, and so on in an indefinite succession. From this came many results—immunity, etc. It seemed more than ever important to define the cause, and a great step forward was taken when Peyton Rous, in 1911, working with a spontaneous sarcoma of chickens, showed that a filterable virus could produce the tumour.

The cells which grow into cancer are independent cells. They have been in the soma for a long period. Whether or not they have been growing for a long period is impossible to answer. Probably they have, but in any case they are cells which have the heredity of endless generations. They are continuous with the ovum like the other cells of the body. The other cells of the body are normal because they follow the law. The cancer-cells act contrary to Nature. They have a nucleus; they have cytoplasm. Their metabolism is much the same as that of ordinary cells. Be it different in some respects or not, it is fundamentally and essentially the same as that of the normal cell. Even when they differ from normal cells it is not a fundamental difference. They have nuclei; their nuclei divide in the same way as ordinary mitotic cells. They have variations, but so have cells which are normal. They do not fall into the procession. They fall out. They do not keep step; the procession is moving slowly and they move fast. They grow rapidly, as if they were young embryonic cells newly stimulated into growth by fertilising. This growth continues indefinitely and to the utmost capacity. It is, however, not a growth which duly provides for organised

tissue. Were it possible for the cells to pass to unicellular existence, cancer would spread indefinitely; but such existence depends on blood-supply, and only a series of cells, a zone, within reach of the blood can survive. But in this way dependence on blood-vessels is an affinity with ordinary tissues. The tissue depends on blood-vessels and cannot produce them; no doubt certain vascular production does occur, but it is an inadequate organisation.

The connection with blood-vessels and blood is a feature of animal tissues as compared with vegetable tissues. Vegetable tissues have little tendency to tumour and never have malignant growth, but animal tissues have intense activity. They have the catalysts of vegetable tissues and they have added their own active principles, hormones. Muscular activity depends on a great contracting tissue absent in the vegetable tissue. This activity turned into the circulation makes animal activity and functional life possible. How does it affect growth? The vegetable cell divides and differentiates as the animal cell. It has the same inherent capacity for continuous life. The point in cancer is that it departs from the ordinary line of activity with increase of energy. A cell which has been quiescent assumes a phase of activity.

Two essential changes occur. A cell, or group of cells, which has been quiescent or only moderately active, becomes active in growth, mere growth, not development. Hitherto, all activity has been in the direction of development: growth to produce a tissue that has a certain place in the organism, growth which when it reaches a certain point ceases to progress, growth which in this sense is controlled by the functional demands of the body. Tumour-growth is not called

for by any functional demand. It occurs in cells which should grow only for differentiation and so cease growing. Here there is a failure to differentiate, and the cells in growing retain the power of further growth, and this they do universally.

It is by differentiation in the soma that development takes place. It is probably as true to say that differentiation in the soma secures heredity as to say that heredity genes secure differentiation in the soma. The growth of cancer fails here. It does not fail as growth; in fact it is superabundant, but it fails to differentiate and with this to cease.

The control of growth is connected with differentiation. How far? The less differentiation the more malignant? There is no instance in which with increase of differentiation comes increase of growth. The balance is differentiation and non-differentiation. To preserve capacity for growth is essential for continuity, continuity from individual to individual. To preserve capacity for growth is no less essential than to reach differentiation. The body requires both purposes, and both are secured by differentiating division.

Differentiating division means that certain factors are unequally divided in the division. Meristic division is equivalent division. Meristic division is characteristic of the nucleus' central bodies. There is also the cytoplasm, and apparently the determination of differentiation is somehow associated with the cytoplasmic division. The growth of cancer frequently shows that it may occur while there is still differentiation. The cells that compose the cancer have something of the function of the cells from which they originate. The tendency to differentiation is not lost but is overwhelmed by the rush of growth, i.e. outstripped—the

growth which is differentiating but not under control. There is insufficient differentiation and insufficient relation to growth. The factors are there, but are insufficient to determine the development. If the factors are present and act, they act according to the Mendelian formula. They have relation to each other, e.g. one is dominant, the other recessive ; they are linked ; they cross over ; other relations may still be discovered. But growth can take place in new lines. The Mendelian factors have activity controlled by the conditions of growth, which may overwhelm these factors so that abnormal growth arises, abnormal to the point of new growth. The tumour is a competition between Mendelian factors and other conditions. What are the factors which are not Mendelian ? Growth cannot proceed with Mendelian factors alone. The body without thyroid does not develop. Supply thyroxin and it develops. Thyroxin is not a Mendelian factor. Thyroxin stimulates growth, makes growth possible—normal growth only ; the virus of growth (new) makes growth possible but beyond normal—out of control. What is the difference between thyroxin stimulus and virus stimulus ? What about Murphy's embryonic tissue stimulus—a stimulus derived from normal tissue which produces abnormal growth ? That is a remarkable result. What, then, prevents this stimulus, generated in normal tissues, from producing new growth invariably ?

As was noted in the Mendelian experiment, one of the factors was limit of growth. The dwarf pea had a limit of growth differing from the limit of the tall pea. The progeny were either tall or dwarf and in regular proportion. The limit of growth is in animals a characteristic fixed point. The average limit is subject to

comparatively slight variations. When the limit is reached no further growth occurs. That is true of each part of the body. The determination of the limit is one of the growth factors. If the tissues be injured by disease or excised in part, the surviving tissue grows to restore that which is lost, and growth then ceases.

Pathological variations occur in which there is imperfect growth, deficient in quantity or excessive in quantity, but with still an approximation to the limit. The factor is still at work, but conditions are abnormal and the result is beyond normal variations. In connection with experimental destruction there occurs reaction of the tissue. A normal reaction is simple regeneration, and there is recovery. In some conditions there is failure to heal. This may be due to various causes and the interference may be of various degrees. Sometimes there is cancer. Cancer is essentially unlimited growth. In this case the limiting factor in the cells has been destroyed by the injury. Should this happen in a single cell, that cell would grow indefinitely. There would be no means of controlling it apart from destroying it. The inherent mechanism for controlling growth has been lost. This can take place without injuring the life of the cell. The action of the factor was in one sense a restraint on the life of the cell, an inhibition. It set a limit. The factor of pigment production is a favourite experimental subject in Mendelian investigations. In some cases it is congenitally absent, and the man is an albino. There is no pigment production in his retina. That factor has failed at some point in development from the ovum and it is absent through life. If an albino father and mother have offspring, they are albinos and the race might continue. They are normal physiological bodies otherwise. The absence of the

factor does not injure the action of the other factors of growth. The individual body is complete apart from its normal pigmentation.

The absence of the factor limiting growth would explain cancer. It is a factor which has influence not on the individual cell but on the tissue. The individual cell in cancer may be of the normal size. It resembles the normal cell. It may even have the normal function of the cell as in keratin formation or in the thyroid, but it does not stop growing. It means that the controlling factor in setting the normal limit is a factor which has regard to other tissues. It limits the growth to given conditions. The skin-cell grows only in the skin, the liver-cell in the liver. When the limiting factor is lost or absent, the cell grows as it does in culture—indefinitely—anywhere in the tissues where it is nourished. The cause of cancer, then, is an agent which destroys the controlling factor.

There are many agents which can set up cancer. They are destructive or set up chronic irritation. Prolonged irritation seems to indicate the wearing out or exhaustion of the factor in some way. This is quite likely. Cohnheim pointed out the tendency of cancer to be associated with anomalous development, when the factor of growth had never been fully active, in complicated areas—in belated rudiments, etc. Cancer also prevails in the period of life when the physiological powers are wearing out, as in the breast in involution. Again, there is a gradual wearing down of the factor. Finally, the factor is wasted and destroyed and the tissue has now uncontrolled cells. Tissue culture has shown that cells set free from normal conditions will grow indefinitely. If there is enough in this to explain new growth, it is described in the following terms:

(*a*) It begins locally in a few cells or in one cell. That is exactly what we would expect. The handing on of a growth factor is an affair of cell-division, an affair of a unit; the injury need not therefore affect more than one unit. The destruction of a factor may occur early in life, sufficiently early, e.g., to be before all the pigmented tissues had developed. (*b*) The surrounding tissues are not malignant. The growth of the tumour does not convey any change to cells already formed. Their growth factors are normal. (*c*) Malignant cells may develop to some extent, e.g. glandular carcinoma forms alveoli, lined by columnar cells—sometimes forms secretion; but the lesion is probably in the basal cell and the imperfect development follows, with indefinite limitless growth. (*d*) Could it be inherited? That seems inconceivable in the simplest form. The control of growth is a cell factor and if inherited it would mean that from the ovum onwards there would be no control of growth. On the other hand, short of that there may be some individuals more susceptible than others.

The tendency to tumour in certain mice used experimentally is a tendency to the formation of local patches of tumour-growth—the rest of the corresponding tissue of the body is well regulated and normally developed. There may be a general weakness in the limiting factor. (*e*) The tumour serves no useful purpose. It is organised on a cellular basis and the tissue is not co-ordinated with other tissue. In all normal growth the control factor is not a control of one group of cells or one cell, but of the other tissues —stroma, blood-vessels, nerves. All this is deficient or absent in tumour. (*f*) What is a sarcoma? It is a mesodermic cell which has lost its gene control. It

fails to differentiate or does so only incompletely. The case to be kept in mind is the cellular tumour where there is no differentiation. (*g*) Might a tumour begin in more than one place? It depends on the lesion. Focal necrosis. Malignant tissue can be cultivated *in vitro*—cellular—and when transplanted is malignant. (*h*) Why is it not a commoner result of injury? Injury destroys the cell. It is a very fine point of injury to leave the cell intact and yet suppress or destroy the gene. The nature of the suppression also is not clearly understood. (*i*) The filtered extract of the chicken sarcoma is sufficient to set up the tumour. That looks as if the mode of action or the agent which destroys the gene were somehow generated in the tissue.

It is of great significance that the origin of tumour is so localised that it may well be regarded as springing from one cell. That this is the case always could not be proved, for in many an example there is reason to think that it is polycentric. The ordinary example is seen in its early phase to be at least very limited in origin, e.g. a small point on the lip—possibly one cell. Here it is a tumour of a growing tissue and the neighbouring cells continue to grow in normal fashion side by side. The normal tissue, further, is part of a properly organised tissue with blood-vessels and nerves, tissue-spaces, and cell-groups in proper relation to tissue fluid and to lymphatics. There is parallel with this a more or less disorganised tissue without the physiological architecture of normal tissue, the one growing according to the rule of growth—limited by the morphology of the skin—ceaseless growth, but controlled to normal purposes; the other limitless, uncontrolled, and invading.

If a piece of tissue from each of the two areas were

taken and planted *in vitro* for culture they would each grow and would be indistinguishable while they grew *in vitro*. They would grow indefinitely. So it would continue, but should they be planted again in the tissues they would reveal their differences. The one would grow in a limited, controlled way, if irregular. The other would grow as an invading tumour. Something inherent in the one cell is present which is absent from the other. The change is in the response to control. The one cell is controllable—the other is not. The mechanism of control, however, is in the cell itself. In pathological tissues it is a common experience to see isolated cells embedded in stroma, e.g. in the bands of increased stroma in cirrhotic atrophy of the liver. But these cells do not grow into cancer simply because they are isolated. Truth to tell, there are cases where there is a tendency to liver-celled cancer, but this is usually associated with the call for regeneration.

The factor which controls growth may be looked at in this way. Like the rest of the cell, it evolves or modifies so that one step makes another possible. Is there any evidence of this? A basal cell creates two kinds of cells. The factor in the basal cell continues a basal-celled factor, but the factor in the cell of the stratum spinosum is a prickle-celled factor. The prickle-celled factor increases its layer also, and at a certain depth determined normally, but often influenced by abnormal conditions, it becomes keratinised and the keratinised cell becomes squamous. Now are we to believe that there are three or four factors here or is there only one factor? The factor limiting growth is a final factor, or a final stage, when all the others have had their work. The limit of growth may be fixed and

final as in bones, or it may be at a level determined by physiology as in blood or skin. Regulation may be once for all, or regulation continues as in skin. The limit is to stop growing. It is the concluding phase, an action of a factor which comes after all the other factors have acted. Is this related to the case of the cytoplasm? The size of the units is controlled, and the number of the units. Is the secret of the limit in the internal medium? Somehow the regulation of the growth has to do with the activity of cell factors. It is true of plants and animals and therefore does not depend on animal physiology.

This factor acts on cells of an organ so that they cease growing. But if part of the tissue is cut away, the remainder which had ceased growing begins to grow and growth proceeds until the quantum is reached. Can we compare this with the relation of balance in a cell which leads to division? In division we find the fundamental control. Each half of the cell controls the other half. They are balanced as separate entities. Can we transfer to a group of cells a similar though more indirect control?

[The theory of tumours in this chapter is on similar lines to that of Boveri (*The Origin of Tumours*, Eng. trans., 1929), further formulated by Ludford (*Ninth Report, Imperial Cancer Fund*, 1929) and strongly supported by Lockhart-Mummery (see in particular his recent publication, *The Origin of Tumours*, Bale, Sons & Danielsson, 1932). The chapter, however, seems to have been written without Lorrain Smith having seen any of these publications.—EDITOR.]

CHAPTER XV

SUPPLEMENTARY CHAPTER BY EDITOR: GENERAL CONCLUSIONS

THIS chapter will deal with general conclusions which appear to follow from a consideration of the phenomena of growth. It is greatly regretted by those who knew him that Lorrain Smith did not live to formulate these conclusions himself; but from various talks with him, including one a few days before the sudden attack which caused his death, I believe that the chapter represents the ideas which he had formed or was forming.

In the Introduction it was pointed out that the key to the problem of growth is an understanding of life itself. General conclusions as to growth must, therefore, harmonise with general ideas as to life. It was also pointed out that growth in a higher organism is essentially a multiplication of cells, and may be described as a multiple procession of cell-units in which each member disappears in producing successors in the procession. Any part of the procession moves or may stop, either temporarily or in some cases permanently; and where the cytoplasm becomes much differentiated, as in a red blood-corpuscle or a nerve-cell, the procession usually stops permanently so far as the differentiated unit is concerned. The final result, however, of the procession, if it is normal, is that the adult structure

of the organism is reproduced ; and with this reproduction growth comes to an end and the procession ceases except in so far as new cells may be formed to reproduce those which die. Existing cells may, however, as in the case of the central nervous system, modify themselves so as to replace the functions of cells which have died, or parts of themselves which have died. Since, moreover, as was pointed out in Chapter I, cell-division and cell-growth are meristic, the parts of each cell are represented in the impregnated ovum from which the procession starts. Any peculiarity or defect in this representation influences, therefore, the whole procession.

In Chapter II and elsewhere evidence was adduced that the normal progress of the procession depends on conditions in the environment of each cell-unit. If these conditions are sufficiently abnormal, the procession becomes abnormal, and pathological observation furnishes numerous instances of this, many of which were referred to in other chapters. The procession may be either abnormally prolonged or abnormally shortened, as well as abnormal with respect to its individual members. In the successful culture, outside the body, of a pure living tissue in a liquid containing constantly renewed extract of embryonic tissue the procession is, for instance, indefinitely prolonged, and with the whole of the units in it abnormal. This is clearly owing to the absence of conditions dependent on the presence of other kinds of cell-units. These conditions control the course of the procession and the character of its units. In tumour-growth, whatever be the conditions which determine it, we have another instance of abnormally prolonged extension of the procession, together with, in many cases, marked abnormality in the character of the

units. Growth in presence of a known infection such as that of tuberculosis or syphilis is a further instance.

Under normal conditions in the living body the procession takes its normal course, and this depends evidently on the environment of the units in the procession being also of a normal character. If, however, we endeavour to ascertain by experimental methods what the individual environmental causes are of any part of the procession being normal, we are at once confronted by the impossibility of distinguishing environmental causes from internal causes—influences of "nurture" from those of "nature" of the cells. The "nurture" seems to depend upon the activities of other cells in the organism as well as on the manner in which they, in turn, react to the external environment. But the activities of all the cells depend on their "nature" no less than on their relations to their own environments; and even the influence of the external environment depends on the "nature" of the cells directly exposed to it. Thus we cannot distinguish causes referable to "nurture" from those referable to "nature." Nor can we distinguish any influence which we can separate as a cause, rather than as an effect, of normal growth. What we *can* learn to distinguish, however, are the accompaniments of normal growth, or the relations involved in it, and the fact that they are not only necessary to normal growth, but tend to present themselves in a manner which is just as normal as normal growth itself.

In the course of his experimental work Claude Bernard was struck by the fact that, in spite of great variations in the supply of food and drink, the composition of the blood varies very little, just as the temperature of arterial blood varies very little in spite

of great variations in external temperature or internal heat-production. This led him to the conception of the blood as the internal environment of a higher organism, and to the conclusion that "all the vital mechanisms, varied as they are, have only one object, that of preserving constant the conditions of life in the internal environment."

This was a very pregnant conclusion, of which subsequent investigation has greatly widened the scope, and has also greatly extended our knowledge of how essential it is for the maintenance of normal activity and normal structure that the conditions in the blood should actually remain normal. But when we consider the matter in a wider manner, and in the light of present-day knowledge, it appears that we might say the same of any part of the living body as Bernard said of the blood. For the structure, or the growth procession, of each part is most accurately and delicately determined, and this determination depends on the influences of other parts of the body and of the environment, which are therefore so co-ordinated as to keep the structure of the part in question normal, just as Bernard regarded the various organs of the body as acting in such co-ordination on the blood as to keep it normal. Structure is thus something actively present—the expression of constant co-ordinated activity, like the composition and volume of the blood.

What we find, therefore, is that, whatever influence we may call either "nurture" or "nature," it tends to appear in such co-ordination during growth and adult life that the adult form is re-established and maintained for a time. The normal growth of any organism is thus the manifestation of a specific form of co-ordinated maintenance ever renewing itself;

and from whatever angle we may approach the study of growth we always discover the tendency towards co-ordinated maintenance. As Lorrain Smith puts it on page 74, "to maintain the normal is the regulation principle of all growth." This tendency towards co-ordinated maintenance of both structure and activity is just, however, what we denote more shortly by calling it life. The life of an organism is the manifestation of a tendency towards a specific form of active co-ordinated maintenance, with a background in which we otherwise see no such co-ordination. The ground-axiom of every branch of biological science, including pathology, is the *objective* existence of lives as such. Thus biology is biology, and not merely physical science, into which the conception of co-ordinated maintenance is not ordinarily introduced.

The fact of inherent co-ordination in the life of any organism implies that it can only be perceived and understood as a whole, and makes it impossible to analyse the phenomena of a life into separable elements out of which we can reconstruct the whole. In attempting to do this we necessarily fail to express the specific co-ordination which is inherent in each element. But we can discover by observation and experiment the essentially related details of structure and activity which are involved in a life and the manners of their relations. Progress in biology is just progress in the discovery of these related details and how they are related. The tendency to regard living structure as just something given independently of its relationships —given originally in the structure of the fertilised ovum—has hindered the scientific investigation of life. The fertilised ovum, with all that is within it, is no less alive than any other living structure. How-

ever much a living chromomere means, an isolated chromomere means nothing for biology. We seem constrained to regard a living cell as a highly co-ordinated colony of specifically different units of life, each with its own heredity, but also bearing to the life of the cell a similar relation to that which the life of a cell bears to the whole life of the organism.

If we regard living structure as merely what can be regarded physically and chemically as details of structure, and not as the active manifestation of co-ordinated maintenance or life, we fail to express the fact that the details are present actively and in co-ordination with other details. The structure is alive, and this implies that each observable detail in it is actively related to other details, including those of external environment, as the expression of co-ordinated maintenance, continuous from cell to cell and generation to generation. We can investigate successfully the co-ordinated relationships involved in living structure just as in ordinary physiology we investigate successfully the co-ordinated relationships involved in such physiological activities as respiration or circulation. We can observe the consequences of interference as regards one relationship after another, and the manner in which the living structure, just because it is the embodiment of actively co-ordinated maintenance, tends to respond to the variations by compensatory changes.

In physiological experiments on intact or virtually intact organisms, and in observations as to the consequences of ordinary environmental changes in adult or growing organisms, we can observe readily these compensatory changes. In the healing of injury and disease we can also observe them clearly. But in the

immediate influence of serious accidents or diseases, and of injuries such as destruction by disease or excision of some part, the relationships inherent in the existence of normal living structure are most clearly and definitely revealed through the abnormal phenomena which result from interference with these relationships. Pathological investigation in connection with disease or accident has often furnished a clue for experimental investigation, including search for relations with the environment which are essential to the maintenance of normal structure. We can see from this that both pathology and anatomy are bound to become in the future more and more of experimental sciences, seeking after the physiological relationships which are implied in the maintenance of living structure, including its reproduction—seeking, in short, to be able to see structure as more and more clearly alive. This they can never do by holding to the idea that organic structure is just given physical structure. The structure is an expression of activity, and the activity in each part is co-ordinated in a specific manner, tending to be maintained or reproduced, with the rest of the activities of the organism. Living structure is a meeting-point of the endless biological relationships in which its nature is expressed, and it is the task of biological science—whether we call it anatomy, physiology, or pathology—to elucidate these relationships by observation and experiment.

In the light of the preceding discussion we can now look again at the procession of growth. It is a procession of living units, and the key to the normal movement of the procession is the specific form of life which is realised in the adult stage. Each step in the normal procession, and each slowing or hastening of it, is a step

towards the realisation of this specific form of life ; and the stoppage of growth when adult life is reached means actual realisation.

The procession starts from the impregnated ovum. Just because this cell shares the lives of the parent cells, but has cast loose from their realised organic relationships with surrounding cells, it proceeds to reproduce these relationships step by step ; and the normal growth-procession expresses this reproduction, which we can thus compare with the process of healing. In every stage of the procession the active co-ordination involved in life is represented, so that the multiple procession moves as a whole in its progress towards the adult stage. If, however, anything disturbs the relationships in such a way that the disturbance is not compensated for, the procession becomes abnormal or pathological, and it is the task of pathology to discover and specify as exactly as possible the nature of the disturbance. It was from this standpoint that Lorrain Smith regarded pathology.

The behaviour of each part of the procession depends at all times on that of the other parts and on the relations of all parts with the external environment. Of this fact pathological observation is constantly reminding us, as when there is uncompensated interference with the activity of an organ, or with some particular sort of assimilation from or excretion to the external environment. But the characteristic feature is that the different parts of the procession tend normally to be so co-ordinated that they together realise, and afterwards maintain for a normal period, a normal structure embodying normal activity. What is normal for the offspring is, however, never quite the same as what is normal for either parent, and a biological

normal is something individual and no mere statistical average. We can trace back the differences in biological normals to differences in normals of the fertilised ovum; but we can equally trace these differences in the developing structure of every single cell in the adult organism. This is implied in the fact that somatic cell-division and cell-growth are always meristic. The co-ordination in the procession is just the co-ordination expressed in all life, and apart from the conception that lives as such are objective realities the normal orderliness of the procession of growth would be wholly unintelligible.

The marvellous co-ordination in the phenomena of life would be for us a complete mystery or miracle if we made the assumption of physico-chemical "realism" that knowledge or science consists only in the analysis of our visible and tangible world into separable physical and chemical phenomena. The actual existence of life, and the fact that its existence is quite intelligible to us when we are not confused by the metaphysics of physico-chemical "realism," shows us that co-ordinated maintenance is a fundamental feature in our experience. In nothing is this feature more impressively manifested than in the multiple procession of normal growth, and the abnormal procession when normal physiological relationships are effectively interfered with.

I can say confidently that it was Lorrain Smith's ideal to make the distinctive conception of life the basis of pathology, just as it has been my own ideal to make this conception the basis of physiology. His training in philosophy had set him free from the mistaken "realism" which has for long introduced confusion into the biological sciences, and has led on the one hand to

vitalism and on the other to vain attempts to interpret life in nothing but the light of traditional physical and chemical conceptions. He was always thinking himself, and endeavouring to make others think and not merely repeat outworn creeds. In this unfinished book he was aiming at presenting some of the main results of his thinking.

On one point he was definitely inclined to an opinion which is somewhat difficult to reconcile with the theoretical conception formulated in the present chapter. In Chapter XIV he favours the view, which we had, unfortunately, never discussed together, that the growth in a malignant tumour has lost its co-ordinated character owing to an injury to chromosomes, this injury being transmitted as a mutation from cell to succeeding cells. The idea that a chromosomal injury may alter the character of the descendants of the injured cell is certainly well founded. But the known alterations in character which can be referred to chromosomal changes are of a much less fundamental kind than that which would be required to explain malignancy in tumours. Co-ordinated growth is just as characteristic, in spite of the chromosomal differences which are presumably associated, for instance, with the different limitations of growth in dwarf and in large pea plants, or the absence of definite limitations of growth in various species of fish. Even when a chromosomal mutation is inconsistent with the ultimate survival of the developing organism its growth is still co-ordinated.

The view, therefore, seems to me more probable that malignancy is due to the presence of an ultramicroscopic virus which can only grow within the living body of a particular kind of cell, and can usually gain a footing only under specially favourable condi-

tions which can be compared, for instance, with the influence of inhaled silica particles in facilitating tubercular infection of the lungs.

Further investigation can, however, alone remove the mystery which is at present associated with the growth of tumours.

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