NEOPLASTIC DISEASE
AT VARIOUS SITES

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INTRODUCTORY VOLUME

A CLINICAL PROSPECT OF THE CANCER PROBLEM

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S. LIVINGSTONE LTD.
BURGH AND LONDON

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PRINTED IN GREAT BRITAIN

A myth is, of course, not a fairy story. It is the presentation of facts belonging to one category in the idioms appropriate to another. To explode a myth is accordingly not to deny the facts but to re-allocate them.

Gilbert Ryle, 'The Concept of Mind', 1949.

INTRODUCTION

THIS book presents a personal view of the cancer problem. It has been designed as a general introduction to the series of monographs on neoplasms at individual sites being produced under my general editorship. This introductory survey differs from the other volumes, however, in that while their contents are intended to be factual and particular without being too controversial, this is intended to be general, speculative and philosophic and to provoke discussion. It is purposely strategic while they are tactical. It deals more with principles governing behaviour than with summaries of partly explained facts and the practical applications deriving from them. It is deliberately filled with conjecture. It presents reasons why the detailed factual particularisation about tumours at various sites, attempted elsewhere in this series, provides a sound approach to the clinical problems of neoplastic diseases, and also why generalizations about *cancer*, as though it were a single definable disease entity, have been so unproductive of worthwhile help to individual patients.

No attempt has been made here to increase the vast amount of information already available about neoplastic disorders, but rather to place in clinical perspective some portions of the knowledge we already have and to tread the path of science where people are concerned with disproving their old hypotheses and inventing new ones to be tested. Karl Popper described this aim of the empirical method in 1934 as 'not to save the lives of untenable systems but, on the contrary, to select the one which is by comparison the fittest, by exposing them all to the fiercest struggle for survival'.

It may be that we do not need more information about neoplasia at this time quite so much as we need more insight into the general problem of growth control. This book suggests that a multitude of apparently disconnected facts may have more general regularity ruling them than is commonly supposed, and that when seen from a particular viewpoint much of the mystery of neoplastic disease is replaced by a new respect for ordered growth and repair. It denies the contention that the real entity at the heart of *the cancer problem* is a fundamentally abnormal cell which through some special kind of mysterious change has become invasive, autonomous and malignant, a hypothesis quite out of tune with what we know of biological behaviour. It tries to get away from the anthropomorphic view of *a cancer cell* which has followed from this, in which this ill-defined entity is seen as a malicious, malevolent, spiteful and devilishly purposeful intruder bent on our destruction—a view fostered by the lay press and encouraged both by medical uncertainty and by an undue modesty about our present knowledge and achievements. It would like to change the habits of thought of those who speak of cancer in metaphysical terms, so that they begin to ask themselves what their general statements mean and if they can be verified.

It is here maintained that *cancer* stands for no real well-defined entity, but for varying abstractions of the more lethal forms of tissue malformation, each selection depending on the view and purpose of the individual making it at that time, and that the words *a malignant cell*, without qualification, have little—if any—meaning. I suggest that to talk of 'the cause of cancer' under these circumstances is unscientific, and that to expect to produce 'a cure for cancer' in the sense of the present-day common usage of this phrase is more like trying to provide a means to grace than a method of eradicating a disease.

I have also attempted to see the problem in relation to an anxious public which has no proper conception of the type of disease process involved, and which has been wrongly led to expect a dramatic new discovery which will one day take the sting from cancer as antibiotics have done from so many infections. I hope to influence the modes of thought of those members of the medical profession who are subject to many of the same misconceptions and who appear too little aware of what is already being achieved and of what more could still be done, without any new advances in our knowledge or skill, both in prevention and in treatment.

This book presents the proposition that cancer is not a specific disease of single cells which have suddenly acquired autonomy, obey no laws, and which must be destroyed before they destroy us, but that it is a word covering some aspects of the partial escape of parts of organisms from those controls which make them a whole and to which all cells still capable of division are liable. It suggests that injury and isolation leading to repeated demands for function or repair are potent factors in the escape of groups of cells from this organismic control. Finally, this book tries to look to the future to see where progress may be expected, and to enquire whether what we already know suggests that the demand for a single, simple solution to an ill-defined problem of this kind could ever be met, or whether steady progress in the understanding and control of tissue malformation on foreseeable lines at each individual anatomical site is not a much more reasonable expectation with a good deal better chance of fulfilment.

When a long look from one angle has produced little enlightenment, it is not unreasonable to want to move one's ground to take a different prospect. It is often difficult to persuade others to follow your eye—in fact such invitations have been known to produce quite violent reactions in those who either naturally tend to find such processes painful or whose interests, whether emotional, scientific or financial, are bound up with some settled outlook. Prejudice may stand in the way of progress in cancer research, just as it obstructs objective investigations of metaphysical experience, and for much the same reasons. Chemistry and physics are accepted with a respect which has not yet been accorded, for example, to the social sciences, chiefly because these more general disciplines touch our emotions and behaviour much more closely than the basic sciences. Investigation of matters too near to our prejudices is apt to be felt as a threat to our inner security. We do not reduce our difficulties when we use the basic sciences in an attempt to understand an emotional, social problem rather than a growth disturbance.

This book is addressed by a clinician primarily to clinicians, but it may perhaps provide some others who have a general interest in the subject with a cause for argument. It often seems to doctors that many scientists concerned in cancer research have little contact with the problems towards the solution of which their efforts are officially directed. Forty years ago Sir William Osler (1919) said: 'The extraordinary development of modern science may be her undoing. Specialism, now a necessity, has fragmented the specialities themselves in a way that makes the outlook hazardous. The workers lose all sense of proportion in a maze of minutiae. Everywhere men are in small coteries intensely absorbed in subjects of deep interest, but of very limited scope'. I suspect that there may be a special tendency to lack common sense about the everyday world in those who are most expert in complex but restricted fields. I feel strongly with Karl Popper when he says: 'For myself, I am interested in science and in philosophy only because I want to learn something about the riddle of the world in which we live, and the riddle of man's knowledge of that world. And I believe that only a revival of interest in these riddles can save the sciences and philosophy from narrow specialisation and from an obscurantist faith in the expert's special skill and in his personal knowledge and authority; a faith that so well fits our "post-rationalist" and "post-critical" age, proudly dedicated to the destruction of the tradition of rational philosophy, and of rational thought itself.' Fundamental cancer research workers are with equal justification no less prone to suspicion about the competence of doctors to understand neoplasia, and are apt to say that wide medical experience and many years of intimate contact with patients and their problems does not mean that the clinician necessarily knows anything at all about the nature of cancer. It is clear that *cancer* means very different things to different people working on the problem; it is not, therefore, surprising that there should be some confusion and a number of misconceptions in the public mind. To me it seems that too much cancer research effort, fundamental and clinical, is still directed towards the verification of preconceived notions rather than to the falsification of current hypotheses and is therefore basically unscientific in approach, however well founded on the basic sciences.

Since my own acquaintance with the basic sciences is superficial, much of what is done in the name of cancer research is beyond my grasp, with the result that, like many other doctors, I have a natural tendency either to underrate its importance or misunderstand its implications. It is much easier to recognize this state of affairs than to allow for it. Further, I have written about growth, differentiation, reproduction and repair, and I am no biologist. I have discussed hormone influences on normal tissues and on tumours and I am not an endocrinologist. I have repeatedly stepped out of my personal field of detailed study to attempt a general comment or a summary with all the risks which this procedure involves. My thesis may also be suspect on the ground that I shall maintain that the problem is neither explainable nor soluble solely at those intracellular basic science levels of biophysics and microchemistry with which I am least familiar, but is only to be properly understood—as it can most certainly only be ameliorated—in terms of the wholes with which I am best acquainted. For all our need of detailed knowledge of cell growth and differentiation at the molecular level, it is at the level of the complete organism, in this case the individual human being, that I suspect that understanding—like effective action—must really lie. It also seems reasonable to expect that fundamental knowledge of tissue malformation will continue to be derived chiefly from clinical observation and research. The discovery of evolution was made by naturalists observing whole organisms. While it is true that fundamental knowledge in science often precedes application, understanding usually comes between the two. It is no part of my intention to belittle fundamental observation and experiment on which we rely for progress, but progress comes when implications are appreciated and this requires a prepared mind. We never quite know how much of what we need to know is known already until we cry *eureka*. Whether this approach is right or wrong, one thing is certain: the cancer problem I am here writing about started with the individual patient and for a solution must one day be brought back to his bedside, however far it may have strayed in the meantime. The clinician's viewpoint does at least give directly on the situation with which we profess to be concerned, which is more than can be said with equal certainty of any other outlook on the cancer scene.

There are, of course, many clinical viewpoints, perhaps almost as many as there are clinicians who think about the problem at all. I do not suggest that mine is typical, original or truly representative of any body of medical opinion, though there seems to be far more reason for it to be broadly acceptable today than there was when I first advocated it. It is put forward to be disproved in the hope of promoting understanding. I reject the extreme views, both of complete hopelessness and of perfect confidence in the future, as being unjustified by the facts. The extreme form of statement about knowing nothing and failing to make the slightest impression on the course of neoplastic disease is manifestly untrue, tends to do a grave disservice to an uneasy public, and fortunately is seldom voiced by doctors. I regret that the other extreme where people talk glibly of simple solutions which are 'just around the corner' is one to which the profession is much more apt to adhere and which has, at times, even recruited a few of those in the highest positions in medicine. This attitude seems to me to be quite false. Unfortunately it dissuades some young doctors of high quality from making a career in radiotherapy which is responsible for the treatment of the majority of patients with invasive neoplasms but, unlike surgery, has only minor applications outside it. The facile belief in any easy solution to a problem we do not even define, relies on the myth of the single evil within the cell and the sudden discovery of the means to its correction and, as so often expressed, seems to me to display either a superficiality of private thought or a looseness of public statement which are quite shocking.

The writings of three people, a physician, a biologist, and a pathologist have particularly influenced the development of my views on neoplasia. The physician was Sir Thomas Lewis. In my copy of his book, *Clinical Science*, there are several passages scored by me when I first read them in September 1934, such as 'When we investigate clinically some disease, or some manifestation of it, we may be seriously handicapped by circumstance; but we are possessed of the certain knowledge that what we study is precisely what we set out to study', and 'The cause of human disease never has been, and never can be, found purely within the walls of a laboratory; there must be at least some association, direct or indirect, with patients.' The biologist was Charles M. Child, Professor of Zoology in the University of Chicago, who wrote that remarkable book *Physiological Foundations of Behavior* in which the first sentence is: 'Each living thing represents an order and unity of some sort maintaining itself with more or less success in a changing environment', and in which almost every page about the development and behaviour of *Amoeba*, *Paramecium*, *Planaria* and *Tubularia* seems to contain something bearing directly on the cancer problem. The pathologist was G. W. de P. Nicholson, that clinical microscopist whose twenty papers published in the *Guy's Hospital Reports* during the eighteen years before the Second World War were brought together by Willis in 1950 in a memorial volume entitled *Studies on Tumour Formation*, and remain an outstanding work in this field. He wrote of tumours: 'That they grow without regard for the laws that govern the growth of normal tissues, I flatly and most emphatically deny.'

I have drawn freely on published work, not always I fear with proper acknowledgement, but this is intended as a flow of ideas and not as a book of reference. References to less well known or accepted work which throw doubt on the old theories or with which doctors are not so likely to be familiar have been more freely included. I have drawn especially on that remarkable trilogy *The Spread of Tumours in the Human Body*, *The Pathology of Tumours* and *The Borderland of Embryology and Pathology*, by R. A. Willis, surely the outstanding contribution to this subject in our time. I only regret that the last of these three great books was not available to me before this book had been completed in typescript. My indebtedness to Professor Willis, both from personal contact and from the stimulation of his writings, is far greater than I could possibly indicate in the text, though I am afraid that there may be much here with which he will disagree.

I wrote the first draft of this book in 1945 on a wave of dissatisfaction with the comparatively small amount of effort in clinical research directed to neoplastic disorders, and with the divorce from clinical practice of so much of the energy which goes into fundamental cancer research. I put it away, meaning to reconsider it in six months' time, but was always too busy for the next ten years. In 1955 there appeared to be less reason to worry about the lack of interest in clinical practice by fundamental research workers who—largely through chemotherapy—were in fact at last appearing in the wards, but renewed cause to be concerned by their revival of old, over-simplified ideas about neoplastic disorders and their cause and cure which had been fading from the clinical stage. Much new evidence has appeared which is consistent with my thesis during these ten years and there has been even more since I took up this work again. I felt that the time for belief in magic was past and that perhaps the time for wonder had arrived. It seemed to me that in our search for cures there was a growing tendency to neglect the doctor's first duty to his patients to be a helpful friend, confidant, guide and softener of the blows both mental and physical which are dealt by serious disease. In this interval I had also become aware of the meagre efforts being made to relieve public fear and disgust over this group of diseases. This I would like to see corrected, not by teaching people about the possible significance of every sign and symptom (which has sadly gained in favour), nor by persuading them of the extremely doubtful proposition that a simple solution is about to be revealed (in which too many have indulged), but by trying to encourage a sounder intellectual approach to this most fascinating problem of organized living and disorganized dying.

D. W. SMITHERS

LONDON, 1960

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. . . Nevertheless, growth by continuous compound interest is the norm for all living systems. It is *departure* from exponential growth that calls for comment and explanation, just as with departure from uniform motion in a straight line.

P. B. Medawar, 'The Pattern of Organic Growth and Transformation', 1954.

CHAPTER I

DEVELOPMENT AND SENESCENCE

Life and Death

DESPITE our pretensions to maturity we remain extraordinarily ignorant of the basic facts of life. A completely satisfying account of every cell mechanism underlying all malformation must wait on more fundamental understanding than we have at present of what constitutes life, of how growth and differentiation lead to normal development, of how wholeness is maintained, and of the mechanisms of senescence.

Wholeness, growth regulation, differentiation and ageing are not exclusive properties of living matter, although they are characteristic of it. The world is a whole with a particular behaviour pattern in the solar system; crystals exhibit regulated growth; the surface of scalded milk becomes differentiated as it cools; metal fatigue has become a problem in industrial societies. Biological organization is not limited to individuals: the communities of ants and men both have obvious qualities of organismic pattern.

All the fairly simple basic materials necessary for the construction of living creatures are present in the sea and they can have come together at anv point within the universe; wherever life may have appeared, or wherever it may still be appearing, all that is required is organization of available material. This 'all' may cover more than we can comprehend, even though we seem to be well on the way to understanding the structure and replication of genetic material, but this does not alter the fact that it is *pattern* which is of vital importance. Life is not a complex conglomeration of organic molecules, but organized behaviour.

The most characteristic behaviour pattern of life is reproduction. The living cell divides into two similar cells which continue to grow and to keep dividing so long as the environment permits. With unicellular organisms growth only becomes controlled when the environment restricts further division. Asexual fission is virtually a continuous process providing immortality for the cell lineage in the right environment, even though individual cells are subject to the mortality of natural hazard. More complicated organisms can only be formed by differentiation. Growth control and the maintenance of individuality are prerequisites for their existence. Differentiating cells, by an intercellular action inhibiting cell division in their neighbours, provide the basis for what is probably the most fundamental of the many growth control mechanisms of multicellular organisms. The inherent characteristic of life is continuous reduplication; the imposed restriction on growth to form differentiated structure is part of organized existence.

Given favourable conditions and given time, even the development of such a complicated organism as man may not unreasonably be regarded as a natural outcome of a biological success story sequence governed by reproduction and death, in which almost everything has been tried, most found wanting, and in which many imperfections still exist. We boldly try to look back over this seemingly interminable process to learn how life arose, how we have developed and how we maintain our structure. We end by accepting the remarkable results achieved by imposed organization on increasing complexity, knowing that we cannot altogether explain them by saying that the process works, but seeing that this is in itself a kind of explanation. Evolution depends on an increasing complexity allowing the expression of new favourable characteristics which are themselves dependent on a growing efficiency of organization. It has also depended on death; for natural selection through survival of the fittest is its means of realizing continuity of expression of favourable mutations and of excluding the unfavourable.

The growth and differentiation of a complex organism is a triumph of organization, and cannot be considered apart from it. Since each human being starts life as a single fertilized cell no bigger than a full stop on a page of print, the organization achieved through evolution is wonderful indeed. The fact that all our individual hereditary potentialities are carried in this one, minute, fertilized cell has to be accepted, whether we can grasp the significance or understand all the mechanisms of inheritance or not. It is perhaps only a few degrees more surprising than that all our acquired knowledge and skills—from such activities as recognizing our parents and being able to ride a bicycle, to remembering the whole of *Hamlet* or playing the Emperor Concerto—should be capable of being imprinted on the minds and muscles of men. The reactions between our inherited potentialities and the environment in which the fertilized ovum finds itself, produce a sequence of physiological activities which result in growth and development. This impact governs the whole process from conception to death; it forms the central problem of biological research; its understanding is fundamental to any final comprehension of tumour formation. Neoplasia is a biological phenomenon. The whole basis of fundamental cancer research lies in coming to an understanding of normal growth and development.

The life of an organism seen from its inception appears to be one of development, but the same life viewed from its end seems to have been one of continuous ageing. Development and senescence are spread in varying thickness over the whole span of individual existence. Both represent the expression of inherited potentialities in a certain environment; both are manifestations of organized systems based on cellular elements. In terms of the power of cells to multiply, senescence has started by birth at least and proceeds much faster in childhood than in old age. In terms of the likelihood of dying within each succeeding interval of age, or of the force of mortality, the prime of life occurs at about the age of 12; the chance of surviving another year gets steadily and increasingly less from then on. We become progressively more vulnerable to whatever the influences are which govern senescence; the process is not exclusively one of the elderly, it merely acquires more force with advancing years. The rate at which it advances varies greatly. The senile old man of 55 and the sprightly young man of 75 are common phenomena while the extreme of old age seen in children with progeria is a fascinating rarity. Not all the assaults on the body leave a harmful mark or are less well tolerated with time, however; the system of immunity works towards protecting us from a second insult of the same kind. Increasing vulnerability may either be inherent, or acquired through the battering of environment. Liability to inherited defects which only become manifest after the reproductive phase of life is past, can increase readily in a population. Natural selection is able to do little to remove these deleterious genes. Senescence, which leads to reproductive failure before death, creates a post-reproductive period of life, establishing new conditions which still further increase the vulnerability of those who live to see it.

Few wild animals, other than the kings of the jungle, live long enough to undergo obvious senile changes. Senility is a product of civilization. The problems of neoplastic disease have only become serious to man in some communities where he has overcome so many other hazards to life that he lives long enough to meet them. Tumours occur in wild animals and in primitive peoples, but *The Cancer Problem* is exclusively one of domestication. Until a people have a fair degree of longevity, they have no reason to worry about the threat which neoplastic disease makes to the very much longer life many of them so ardently desire.

Development

The fertilized cell divides, the first divisions producing cells which are so alike that, if circumstances permit, they may each develop into identical twins, or even proceed by further division and separation as far as the fascinating result seen in the production of quintuplets. The development as individuals of the totipotential cells produced by the first divisions depends on their early isolation from the influence of their fellows in a suitable environment. When similar cells fail to separate and continue by division to form one morula, they begin to differentiate. Growth and differentiation occur simultaneously and it is misleading to consider them separately. The differentiating cell exerts an intercellular control on the division of the other cells around it, so that increasing differentiation slows down growth-rate and determines direction of differentiation in adjacent cells. Cells in a closely associated group, increasing in number by division, soon find themselves expressing their similar inherent potentialities under different conditions, some in the centre of the mass, some at its periphery. Different conditions excite different responses which themselves perpetuate and increase the differences. The point of entrance of the sperm into the ovum and the consequent direction of movement of its nucleus may determine the first cleavage plane and produce asymmetry in the daughter cells leading to polarity. Whatever the mechanism, polarity appears early, arises through contact with external factors and produces the first sign of non-uniformity of pattern, to be followed by many complicated processes of development which lead from the association of a few cells to a complete adult human being. A highly polarized system normally ensures that each part of it receives information from one direction only.

The circumstances determining polarity result in excitation and concentration gradients of energy or material, covering whole groups of cells. Whether these gradients are electrical, chemical or based on the space lattice of protein molecules (where one end of a molecule differs from the other so that the properties in those directions also differ), whether they depend on feed-back inhibition in which differentiating cells block the same process in their neighbours, persuading them towards the next most efficient reaction of which they are capable, or whether they depend on some combination or interdependence of these or other mechanisms, is not yet clear. Polarity in developing organisms is probably the symmetry of a number of physico-chemical phenomena, but whatever its exact nature it ushers in the first sign of organization within the new individual cell mass. This is the beginning of the long complex process whereby the specific hereditary constitution of the individual organism is allowed to express itself by contact with its environment. The appearance, growth and maintenance of each organ results from an interaction between a dominant group of cells and their subordinate neighbours. Disturbances of polarity due to external factors altering the directions in which information is transmitted may be responsible for initiating disorders of growth and development.

Heredity lays down a basis for development and function which are completed only through use. We have the organs for speech and for hearing, but can speak a language only by being taught and by practice. Cells have potentialities which can be realized in certain environments but only through specialization do they become expert and differentiated. Different sorts of protoplasmic behaviour are integrated into organs or systems, which are themselves integrated into the individual—who may be more or less well integrated into the community. Organismic behaviour is that of the whole organism acting as a unit, and is something more than, and different from, the behaviour of its constituent parts. The organismic mechanisms develop on the basis of heredity, which determines that we shall be men not mice, and they involve the whole process of evolution. Centuries have determined the basis for our comparatively stable structural development handed down with the chromosomes; generations have learned to use the apparatus and to hand on the accumulating knowledge and skills, instilling them into each new individual by tradition, example, instruction and practice. Each unit is moulded by function to take its place in co-operation with others in a larger unity, its behaviour at each stage being restricted so as to become integrated into that of the organization as a whole. We *are* behaviour patterns. The characteristics of organismic pattern must be of fundamental importance to any understanding of normal or abnormal growth and differentiation.

Behaviour

Each individual results from the vast variety of possible combinations permitted by sexual reproduction, the infinite diversity of personal and material surroundings which work on this basic inheritance, and the application shown to the practice of certain behaviour patterns in thought or deed. We are each the result of the impact of environment and experience on and within our individual, specific, inherited protoplasmic constitution. We are as alike as we are because evolution has standardized the behaviour patterns possible to our protoplasm and limited the environmental conditions in which they can be expressed. Our organismic behaviour is thus determined in relation to the world around us and must be studied as a vital phenomenon. Life cannot be confined within a morphology which is not interpreted in terms of the dynamic patterns of its performance. Tumours—like men—cannot be fully comprehended if viewed only when frozen and cut in slices. Since each of our cells inherits the same potentialities, the way in which individuals develop their complexity is understandable only in terms both of heredity and of behaviour; the theories of heredity alone can never fully explain the way in which we differentiate. Both we ourselves and our tumours are behaviour patterns in protoplasm of specific inherited type expressed in relation to environment. Each one of us is unique by inheritance, with differences not of kind nor of degree but of combination of available genes. We express our own peculiar combination of endowments in response to particular environments which are never exactly alike for any two individuals throughout their lives. Our growth disorders are not likely, therefore, to be pinned down very easily to a single common cause.

The chief importance to living matter of its contact with its environment lies in the reactions which organized units of protoplasm make to it. This response is an essential part of the development of all organisms. Such is the effect of environment on living things that it seems probable that no protoplasm acted on by an external influence ever returns to quite the exact state pertaining before such action. Defensive reactions usually modify the organism so that it is better able to react in future. Demand for growth increases the potentiality for overgrowth.

The relationship to environment of an organism, or of its parts, is both material and energetic. The material exchanges are mostly those whereby the protoplasm acquires nutrition and discharges waste. This whole process of development and maintenance is carried out by deriving orderliness from the environment. Every event in the living organism increases its entropy and only by deriving negative entropy from its surroundings can it continue on its way. Matter in an extremely well ordered state is absorbed as food, used, and returned in a degraded form, while the body delays its decay into thermodynamical equilibrium. Our orderliness of behaviour is maintained against a constant tendency to disorganization.

Material transport may range from such comparatively simple mechanisms as osmosis, to the passage of a chemical group from one molecule to another in a chain, and on to the diffusion of special substances which may dominate local development around their site of production, or which may enter the circulation to affect specialized tissues over the whole organism. Cells have a certain inherited repertoire which becomes more and more restricted as they specialize; they may be changed in direction of development, but not altered in capability by these transported substances. Some of these organizers can exert their influence only during certain stages of development when the surrounding tissues are susceptible or competent. Many substances may produce such effects—some hormones and some carcinogens, for instance. These material relations are specific, involving different quantities of different substances exchanging in different forms at different rates in that turmoil of coming and going which is characteristic of what we please to call steady-state systems. Correlation by transport cannot work until differences between tissues have arisen which can be correlated. This process does not, therefore, originate the pattern; hormones may regulate relations between parts already different, but do not initiate the first appearance of those differences. This type of correlation is a consequence of the existence of the pattern it helps to develop, control and integrate; it is not its cause.

The energetic relations are concerned with the transport of forces. Excitability is a fundamental property of protoplasm. It is excitable in varying degrees by all forms of energy, which is a basic physiological factor in behaviour. These energetic relations between cells and their environment are non-specific, involving no material change but dealing in terms of quantities of energy transferred. Organismic behaviour is seen as a non-specific dynamic pattern imposed on protoplasm engaged in exchanging specific material.

Physiological inter-relations within an organism follow a pattern of dominance and subordination of one part to another based on these material and energy transfers, leading to chemical and excitation gradients. Non-specific environmental factors acting on protoplasm of specific composition, produce organisms true to type because worked out in special materials with a limited repertoire. As Walter de la Mare put it:

'It's a very odd thing—
As odd as can be—
That whatever Miss T. eats
Turns into Miss T.'

The environmental factors may be similar for different organisms; polarity and gradients will not determine whether the organism is fish, flesh, fowl, or good red herring, but without them no creature can arise at all. The potentialities have to be realized and maintained in each particular region. The dynamic mechanisms of such realization and maintenance are the core of the behaviour of tissues and it is here that we must look for explanations of both ordered and disordered growth. Abnormal behaviour may result from alterations in either energetic or material relationships between different parts within a single organism or between those parts and their external environment.

Decay

All living organisms are subject to sudden death at any time in their existence when dealt a blow by fate. This is why the chances of immortality for an individual, even a potentially immortal unicellular organism living in a boundless nutritional medium, are infinitesimal. In a population which suffered no senescent tendencies, the force of mortality would be the same at all ages. Medawar (1952) pointed out that the age distribution of the population, however, would still be one which decreased with advancing years, not because of increasing vulnerability, but because the longer the span of life, the greater the chance of being struck down by the ordinary risks to which all are exposed. Once the population was stable, the younger would outnumber the older at each successive age group. Even though all individuals were equally fertile at all ages, breeding would be predominantly from the younger members of the group because there would be more of them. The force of natural selection, in fact, lessens with advancing age, even in a potentially immortal population.

If we now introduce senescence into such a population, its result will depend entirely on the time of life at which it operates effectively. Introduced late in life, its effect on the group will be negligible; if the natural hazards are sufficient to cause a high death-rate it might be impossible to detect its introduction. There are populations of living things, some fish for example, where the question of whether or not they undergo senescence is still unsolved. Introduced early in the reproductive period on the other hand, a senescent tendency might be disastrous to a population. If the age of operation of senescent tendencies introduced were genetically determined, natural selection would tend to make them occur later and later in life, steadily moving them on, at least to the end of the period of active reproduction. Individuals in whom the age of onset of a senescent tendency is relatively late have more opportunity to have children than those in whom it is relatively early. The genes for delay in operation or postponement of senility, tend therefore, to become more widespread in the next generation. Unfavourable inherited tendencies which are only manifest in a post-reproductive period of life have no direct effect on natural selection and are not, therefore, easily eliminated from the stock. Similar tendencies which are genetically determined for age of operation will be postponed generation by generation to older ages, but only to an age just beyond the peak of reproductive life. Postponement of those senile changes which have a genetically determined age of operation can, however, proceed further in men than in women because of their longer reproductive lives. Some tumours which occur at an older age in men than in women may perhaps be derived from senescent tendencies so determined. Medawar (1952) propounded the following general theorem: 'If hereditary factors achieve their overt expression at some intermediate age of life; if the age of overt expression is variable; and if these variations are themselves inheritable; then natural selection will so act as to enforce the postponement of the age of the expression of those factors that are unfavourable, and, correspondingly, to expedite the effects of those that are favourable—a recession and a precession, respectively, of the variable age-effects of genes.' We age from birth, the force of mortality increases from puberty, but senile changes become of increasing importance only as we pass the peak of reproductive life, itself a senescent change.

Many factors introduce senescence; one of the least well understood is