THE GROWTH PROCESS IN ANIMALS

A. E. NEEDHAM,

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LONDON
SIR ISAAC PITMAN & SONS LTD

First published 1964

SIR ISAAC PITMAN & SONS LTD.
PITMAN HOUSE, PARKER STREET, KINGSWAY, LONDON, W.C.2
THE PITMAN PRESS, BATH
PITMAN HOUSE, BOUVERIE STREET, CARLTON, MELBOURNE
22–25 BECKETT'S BUILDINGS, PRESIDENT STREET, JOHANNESBURG

ASSOCIATED COMPANIES
PITMAN MEDICAL PUBLISHING COMPANY LTD.
46 CHARLOTTE STREET, LONDON, W.1
PITMAN PUBLISHING CORPORATION
20 EAST 46TH STREET, NEW YORK, N.Y. 10017
SIR ISAAC PITMAN & SONS (CANADA) LTD.
(INCORPORATING THE COMMERCIAL TEXT BOOK COMPANY)
PITMAN HOUSE, 381–383 CHURCH STREET, TORONTO

MADE IN GREAT BRITAIN AT THE PITMAN PRESS, BATH
F4—(T.1054)

Preface

LIKE all scientific studies, that of growth in living organisms has become progressively more analytical, and increasingly concerned with what happens at the lower levels of magnitude. In the case of growth this systematic analysis began somewhat tardily, however, probably because growth was so very amenable to mathemetical treatment from the outset, whereas in most subjects an exact quantitative treatment is the ultimate goal, achieved only as the culmination of the systematic analysis. Because growth studies began with relatively quantitative methods this tended to obscure the need for an orthodox analysis, starting from the qualitative and the descriptive. Very often growth was studied as a piece of pure mathematics, quite unrelated to flesh and blood. Consequently Morgan (1907) was very conscious of the great paucity of knowledge of any aspect of growth except its rate, and nearly 20 years later De Beer (1924) found the position still little changed.

In fact the tide of systematic analysis had begun to flow as long ago as 1899, as may be seen in the admirable treatment of the subject by Davenport, and by the year 1923 Brailsford Robertson was able to present a picture sufficiently clear in outline to fire a general desire to fill in further details. Robertson's book was outstanding also for its bold attempt to relate the results of the mathematical approach to date with those of anatomical, physiological and biochemical analysis; although this relation has not stood up to the test of subsequent thinking and research, the book succeeded in the wider aim of establishing a more balanced approach to the whole subject. It became clear that the mathematics of growth were not so very exact, that an orthodox analysis must be encouraged and that it must catch up with the mathematical approach before this could make much more headway; in consequence a number of new analytical disciplines developed very rapidly, particularly in the fields of cytology, bacteriology, endocrinology and nutrition. Later the availability of heavy and radioactive isotopes opened up *biosynthesis* as a vast new field of biochemical research. Other technical advances, including electron microscopy, facilitated research on the proliferation of viruses as a particularly instructive example of growth. Bacteriologists began to isolate and breed mutant strains, each lacking the ability to perform one particular step in biosynthesis; thus they were able to map biosynthetic pathways and at the same time they broached in earnest the great problem of the genetical control of growth.

With this sudden flood of information it has scarcely been possible, as yet, to take stock of the situation in the subject as a whole. Those actually borne on the flood of one of the new disciplines have scarcely the leisure to attempt a synopsis; in any case, the more successful their own field the less they feel the need to seek liason with others. It is the general biologist who feels this need

most acutely and attempts to see the new fronts as extensions of the classical work of morphologists, histologists and embryologists. The present book aims at a synopsis of this kind, for the general biologist, though it is to be hoped that the specialist will find interest and help from the attempt to fit the results from his field into the plan of the subject as a whole. The further aim, in fact, has been to make a balanced assessment of the present position in the subject, with general conclusions which may serve as a basis for further work in the individual fields. The treatment therefore is not purely elementary: it assumes a knowledge of the elements and history of the subject. At the same time it should be well within the ability of the honours student in biology.

An attempt has also been made to see growth in its wider setting, as just one aspect of vital activities. At times in the past there has been a tendency to regard growth as something in a class apart from other aspects of physiology, a more pristine and fundamental property (Needham, 1959), but this is scarcely justified. In this work, where possible, the relationships between growth and other aspects of metabolism have been pointed out.

It is equally important to emphasize distinctions, and a particularly important one is that between growth and the other main component of development, differentiation. Technically the distinction is necessary as a preliminary to the specific analysis of growth. This does not necessarily imply that the two are completely distinct physiologically; there is necessarily considerable interdependence between them and one of the objects of the present analysis is to help in defining this more clearly. The definition is difficult, partly because embryologists have often made the simplifying assumption that they were dealing with differentiation alone, while workers in some of the newer disciplines have assumed that they were studying growth alone.

The separation of the present from the mathematical approach is largely a matter of topical necessity, and an ultimate welding of the two is to be expected. An indication of some of the points where they already impinge is given in the text. As an introduction to further literature in the mathematical field the reader is referred to Huxley (1932), Thompson (1942), Le Gros Clark and Medawar (1945), Brody (1945), von Bertalanffy (1960), Kavanau (1960) and Bonner (1961).

The book has been divided into two parts, a narration of the processes of growth as manifested at successive levels of magnitude, and the means by which these processes are controlled. In the first part the logical, historical order of analysis has been followed, from the highest to the lowest level of magnitude. In the control of growth it has been found most convenient to follow the sequence in the reverse order: consequently Part I is in the nature of an analysis and Part II of a resynthesis. The framework is one which should accommodate further developments in the subject.

The text has been supplemented with chemical formulae, equations and reaction sequences where these seemed essential for a full understanding of the text, but some which are very familiar, for instance the glycolytic sequence and

Krebs cycle, have been taken for granted. The same principle has been adopted for the pictorial illustrations, and a number of very obviously relevant pictures have been omitted because they are so familiar. An attempt has been made to offer mainly new illustrations or alternatives to those already available, those with a personal interest, and summarizing diagrams. The illustrations therefore are not intended to be comprehensive. I am greatly indebted to the following authors for permission to use their published illustrations for the figures indicated: Drs. H. Barnes and H. T. Powell (Fig. 25.1), Professor M. Calvin (Fig. 15.4), Dr. E. H. Cushing (Fig. 23.6), Drs. T. F. and N. I. Goreau (Fig. 4.10), H. K. Pusey, Esq. (Fig. 6.4), and Professor H. Selye (Figs. 23.1, 23.3, 23.4, 23.5, 23.7) and to the following editors and publishers of the works in which the illustrations were originally published: *Acta Endocrinologica* (Figs. 23.1, 23.3, 23.4, 23.5 and 23.7); The Company of Biologists (Fig. 6.4); Dr. D. P. Costello, Managing Editor of *Biological Bulletin, Woods Hole* (Fig. 4.10); Messrs. J. and A. Churchill (Fig. 23.6); J. B. Cragg, Esq., Editor of the *Journal of Animal Ecology* (Fig. 25.1); Dr. Dwight J. Ingle, Editor of *Perspectives in Biology and Medicine* (Fig. 15.4); and Dr. G. F. Stickley, Managing Editor of *Endocrinology*, J. B. Lippincott Co. (Fig. 23.2).

My sincere thanks are due to the Company of Biologists also for permission to use as Figures 3.5 and 23.9 previously published illustrations of my own. I am particularly grateful to Professor Selye and Dr. Barnes for lending me copies of their illustrations. To Professor T. Russell Fraser and Dr. Peter Curzen also I am extremely grateful for their generous help.

In order to keep the bibliography within reasonable bounds, it is designed as a key rather than a complete literature list. Where feasible, reference is made to good recent reviews of a particular field, rather than to the individual original papers. In some cases, however, it is necessary to refer to the latter and this reflects no discrimination against any papers not specifically mentioned. Usually the most recent contribution in a particular field is cited since this gives the key to the earlier literature, for those interested, and since this book is not primarily concerned with the historical background. No misattribution of priorities is intended by this.

I owe a long-standing debt to Sir Gavin de Beer as an inspiring teacher of this subject and to Sir Julian Huxley for the stimulus of his work and writings. To colleagues working in the field, and in particular to Professor P. B. Medawar, I owe a great deal of help and encouragement. In this book it is my hope to pass on these benefits, in some measure. My thanks are also due to those, in particular my wife and Mrs. J. A. Spokes, who helped in the task of typing the manuscript, and to Mr. P. L. Small and Mr. J. S. Haywood who prepared the photographs for many of the figures.

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List of Abbreviations used in the Text

THIS does not include common chemical and physical formulae and symbols, or abbreviations used only once, and defined. Presuperscripts, e.g. ^{32}P, indicate particular isotopes, usually radioactive ones.

Å	Ångström unit (10^{-7} mm)
a.a.	amino acid
a.a.a.	amino acid activating
a.b.	antibody
ACh	acetylcholine
ACTH	adrenocorticotropic hormone of the pituitary gland
ADP	adenosine diphosphate
a.g.	antigen
AMP	adenosine monophosphate, or adenylic acid
APGH	anterior pituitary growth hormone, or somatotropin
-ase	indicates enzyme hydrolysing the substance in question
asp . NH_2	asparagine
ATP	adenosine triphosphate, or adenyl pyrophosphate
C_1, C_2,..	compounds with 1,2, . . . carbon atoms in the molecule
CDP	cytidine diphosphate
CMP	cytidine monophosphate or cytidylic acid
C.N.S.	central nervous system
CoA	co-enzyme A, co-transacetylase
CoF	co-enzyme F, co-transformylase
CTP	cytidine triphosphate or cytidyl pyrophosphate
D-	optically active compounds based on dextrorotatory glycerose
DAMP	deoxyadenosine monophosphate, or deoxyadenylic acid
DNA	deoxyribonucleic acid
DNP	dinitrophenol
DN proteins	deoxyribonucleoproteins
FAD	flavin adenine dinucleotide
FMN	flavin mononucleotide
GA	glutamic acid
GDH	growth and differentiation hormone of insects (ecdysone)
GDP	guanosine diphosphate
GN	glutamine
glu.NH_2	glutamine
GMP	guanosine monophosphate or guanylic acid
GSH	glutathione
GTP	guanosine triphosphate or guanyl pyrophosphate

kcal	kilocalorie or Calorie (1000 calories)
α-KG	α-ketoglutaric acid or α-oxoglutaric acid
L-	optically active compounds based on laevorotatory glycerose
m.g.t.	temperature for maximal growth
MAH	moult-accelerating hormone of Crustacea
MIH	moult-inhibiting hormone of Crustacea
mV	millivolts
mμ	μ/1000, or 10^{-6} mm
NA	nucleic acid
NAD	nicotinamide-adenine dinucleotide
NADP	nicotinamide-adenine dinucleotide phosphate
N/C	ratio of volume of nucleus to cytoplasm
NP	nucleoprotein
NTP	nucleotide triphosphate
~P	phosphate bond with energy transfer value of 8000 calories per mole, or more
PGA	pteroylglutamic acid
P_i	inorganic phosphate, usually orthophosphate
P-lipid	phospholipid
PP	pyrophosphate
PRPP	5′-phosphoribosyl-1′-pyrophosphate
Q_{10}	van't Hoff's temperature coefficient (ratio of rates of a particular process at temperatures 10°C apart)
RNA	ribonucleic acid
RNP	ribonucleoprotein
rH	1/log concentration of hydrogen atoms, in atmospheres
SH	sulphydryl radical
—S—S—	disulphur bond
T	temperature
t	time
TCA	tricarboxylic acid (Krebs) cycle
TDP	thymidine diphosphate
TMP	thymidine monophosphate or thymidylic acid
TMV	tobacco mosaic virus
TTP	thymidine triphosphate or thymidyl pyrophosphate
UDP	uridine diphosphate
UMP	uridine monophosphate or uridylic acid
UTP	uridine triphosphate or uridyl pyrophosphate
u.v.	ultra-violet radiation
γ or μg	microgram, 10^{-6} g
μ	1/1000 mm (μ is also used for the "thermal increment" or "temperature characteristic" of physiological responses)
μA	microampere (10^{-6} ampere)
~	any bond with a high energy-transfer value

Contents

CHAPTER 1

Introductory

THE non-specialist has little difficulty in defining growth in living organisms: it is the increase in size and mass of the body or its parts, essentially a quantitative change. The early students were equally explicit; sixty years ago Davenport (1899, p. 281) emphasized that ". . . organic growth is increase in volume, . . . it is not differentiation," and he quoted T. H. Huxley's still earlier and terser definition "increase in size." T. H. Morgan (1907, p. 240) wrote "Growth and differentiation are . . . the two processes by which the embryo is transformed into the adult. . . . The most general definition of organic growth is that of increase in volume." Subsequent writers have usually made the same distinction, for instance De Beer (1924, p. 1): "Growing implies getting bigger and this increase in size is what should strictly be termed growth. . . . Growth alone cannot be responsible for the processes of development." This might be put in the form of an equation: Growth + Differentiation = Development. Other recent writers, including J. Needham (1942, p. 506) and J. T. Bonner (1952, p. 7), have maintained this distinction, but unnecessary seeds of confusion were sown by such definitions as those of Vines (1886, p. 291) ". . . a permanent change in form accompanied by an increase in bulk" and Sachs (1887, p. 404) ". . . eine mit Gestaltveränderung innig verknüpfte Volumenzunahme." Earlier still, Pfeffer (1881, p. 46) defined growth as "die gestaltliche Änderung im Protoplasma-Körper," with the emphasis entirely on qualitative change, though there would seem to be no justification for this in the word *Wachstum*, a fairly direct relative of *auxesis*. Unfortunately this type of confusion occasionally has been sustained by more recent writers: Robbins (1928) says ". . . this phase of growth is commonly called differentiation or development. . . ." This implies the equation: Differentiation (= Development) + (Other phases) = Growth, with the further uncertainty whether or no "phase" has a purely temporal connotation. Some have added the unnecessary confusion of baroque ornament: ". . . Growth is the coordinated expression of incremental and developmental factors and functions."

The confusion is particularly unfortunate because, as in any subject, there is plenty of genuine complexity, which necessitates considerable qualification of any basic definition. In the first place growth often depends on a number of associated processes such as cell division and cell movements, which themselves contribute nothing to synthesis and size increase. Secondly a variable and often large proportion of size increase is scarcely due to the synthesis of essential

biological materials. In the extreme case of the mammalian lung much of the later increase is due solely to progressive stretching of the organ, through distension with air (Short, 1952). In other instances it may be due to an increase in the amount of water, salts, fat or other relatively simple materials: these are sometimes significant components of the living system but in any case mere measurements may give little idea of what actually has increased. The difficulty of deciding what is a significant component is recognized by Young (1950, p. 6) in his definition: "Growth is the addition of material to that which is already organized into a living pattern." Even simple inorganic molecules, if they are part of an organized living system are significant components and their increase, in organized pattern, is true growth. Proteins are the most important components of the organized fabric but there are many others.

This definition has the further virtue that it does not postulate an inevitable increase in size, but covers a wider manifestation of growth. Material may be removed as rapidly as it is produced, for instance in the pancreas and other glands, and the organ may show no size increase over a long period of vigorous productive life. It is therefore a comprehensive definition, which recognizes the peculiarities of growth in living organisms yet remains as near as possible to the original intuitive definition. It envisages the repair and maintenance manifestations of growth, and most others.

The first essential is to distinguish growth, the quantitative aspect of development, from differentiation, the qualitative aspect, and this is not difficult in principle. The two show a considerable degree of independence in their course and control (Chapter 27) so that there is good justification for distinguishing growth and for studying it in isolation. Unfortunately closer examination shows the distinction to be less clear cut. A good deal of what is usually regarded as differentiation is due to differential growth, in which there may be no change whatever in the quality of the units responsible, but only in their number and arrangement. A population of identical cells may proliferate more rapidly in one direction than another and this causes a change in their pattern, and a change in shape at a higher level of magnitude. Similarly a multiplication of identical molecules, differentially in the different directions within the cell, could change the shape of the latter. What are essentially quantitative growth phenomena therefore come to produce a qualitative change at the next higher level of magnitude. Within the molecule, however, differential growth, for instance of one side-chain relative to another, would produce a qualitatively different molecule, with new properties, and this would be true differentiation, at that level of magnitude.

Another type of differential growth which may account for a good deal of what is normally included in differentiation is the differential rate of proliferation between two or more types of unit which are already qualitatively distinct. If one type of cell becomes relatively more numerous than a neighbouring type then the quality of the organ as a whole changes. Similarly at a lower level of magnitude one type of protein molecule in a cell may multiply more rapidly

than another. There might be no other significant change, yet at the next higher level a qualitative change would be registered, since the proportions of the cell constituents would have changed. In this case a qualitative change would be recorded also at the next lower level, in the sense that the amino acid composition of the proteins of the cell, collectively, would have changed.

Two aspects of differentiation must be recognized, the spatial aspect just considered, where one region becomes different from another, and the temporal aspect, when qualitative changes occur within a particular unit in the course of time. Some components of this temporal differentiation likewise may be due entirely to growth processes. Knowledge is scarcely adequate to say much about this at the cellular and higher levels of organization, but at the molecular level it is manifested as the progressive change in character of such molecules as the proteins actomyosin of muscle, keratin of the epidermis and haemoglobin of the blood. If the actual molecules changed, through the replacement of certain radicals by others, this would be one of the clearest cases of pure differentiation, but in most cases examined it seems that the whole population of molecules is progressively replaced by one of the new type, produced by a modification of the pathway of synthesis—that is by a growth process. The rate of destruction of molecules by wear and tear (p. 5) is probably always high enough to render direct transformation a minor component at the most, in any of these instances of molecular differentiation.

Other cases usually regarded as temporal differentiation no doubt are due to the establishment of completely new pathways of synthesis, or to new extensions of earlier pathways, so that again the change is essentially one of growth. Pigments (p. 245), which are particularly easy to study because they carry a visible label, often appear relatively late in development and the later stages of their synthesis, at least, must begin only then. Again, enzymes concerned with the definitive work functions appear only at the time of visible morphological differentiation (Løvtrup, 1959). Both would usually be regarded as ideal examples of pure differentiation, but in fact they are changes in the pattern of syntheses.

These considerations leave little which can be considered as pure differentiation except the rearrangements of parts at the various levels, what Dalcq (1960) has aptly called *morphochoresis*. An instance of this is seen in the early development of the eggs of many animals. There are often gross movements of material before cleavage, and subsequently a clear and progressive segregation of materials into particular cells and regions. Simple segregation is not the only process involved but no doubt it makes a major contribution. From the study of enzymic activity (Hermann, 1959) it is clear that the segregation becomes progressively sharper with time. The microheterogeneity of the egg is replaced by a more macroheterogeneity of the embryo and it is perhaps worth emphasizing that this is, therefore, an anti-entropic change in the sense of making larger local differences in the distribution of matter and energy. Both growth and differentiation, therefore, effect a reversal of entropy (p. 252), with the aid of their supply of energy.

It is necessary also to define the relationship between growth and other processes in the body, that is the work functions or orthodox physiological processes. There is very clear evidence that differentiation, judged by chemical or by morphological criteria, must reach a certain stage in an organ before its work function begins and that the latter improves progressively with differentiation. There is a roughly inverse correlation between the state of both and the rate of growth, though growth often continues for a long time after organs are fully functional; Huxley (1932) has called this auxano-differentiation because it increases the amount of material in the current advanced state of differentiation. It shows that the normal work function does not preclude further growth in an organ, and indeed there are aspects of growth intimately related to the active work function. The most important is *functional hypertrophy*, a tendency for an organ to grow in proportion to the demands for work made upon it. The response is, of course, a very useful biological adaptation and no doubt there has been natural selection in favour of the association between work and hypertrophy. A related response occurs when part of an organ, or one of a pair, is destroyed: the remaining part then shows *compensatory hypertrophy* and largely restores the size and work of the original organ(s). As in the situation which induces functional hypertrophy, there is an increase in the ratio of demand to supply. Regeneration is a special case, of replacement after accidental loss of part of an organ, or even of a major part of the body; in this case replacement may still be regarded as a compensatory growth, by the surviving portion.

There is also a reciprocal phenomenon of *disuse atrophy*, proportional to the degree of subnormality in the demand made upon an organ. This again is probably an acquired biological adaptation, economizing on unnecessary material, and on its maintenance cost (p. 254). The complete hypertrophy-atrophy mechanism thus produces and maintains material just sufficient to meet the demand on each organ. The normal size of the latter is an average value within its possible range of functional response. The auxano-differentiation phase of ontogenesis is probably to be regarded as the early and most dramatic stage of this functional response: if organs are inactivated then, they show little or no further growth, and remain subnormal. In the adult the response still may be remarkably powerful, in either direction, but since it is a typical manifestation of growth its power does decline with age (p. 26). The average size of the organ and the range within which hypertrophy-atrophy can operate are genetically determined (p. 385); they record the cumulative results of natural selection upon past generations of the species, for an optimal level and range of performance by the organ.

The relationship between the growth and the work function of an organ may be even more intimate than already implied, that is to say hypertrophy seems to be part of the actual recovery process in the organ, following a bout of activity. This activity itself is typically exergonic or energy dissipating, while recovery, like growth, is essentially endergonic. It seems a reasonable specula-

tion that after an increased demand recovery overshoots the mark, providing the necessary extra margin for functional hypertrophy; it may be significant that the nuclei of neurons enlarge during a bout of vigorous physical exercise (Chance, 1956). Reciprocally, when the demand is below a critical level recovery may undershoot, leading to some degree of atrophy. Overshoot is well known in some typical growth processes (Comfort, 1956), including some instances of regeneration.

A further probability is that the functioning of an organ usually involves a reversal of the later stages of the synthesis of its fabric, and the recovery after work a reiteration of these stages of synthesis. Growth and the work functions could be regarded as complementary halves of an endergonic-exergonic cycle and their interrelationship would be a very fundamental one. This seems a reasonably true picture, at least for the contraction cycle of muscle (p. 170).

On this view of the work functions we could further regard the recovery phase as one component of the maintenance type of growth, which continuously makes good any losses by wear and tear and keeps the weight of normal adult human beings extremely constant over many years of the most energetic phase of life. This maintenance growth, because of its quantitative precision, is perhaps even more remarkable than the prior phase of juvenile growth, with its continuous increase in size. The energy and material necessarily used up in the work functions may be regarded as part of wear and tear in the broadest sense. Living organisms are systems in dynamic and not static equilibrium, in point of fact open systems in a steady state (Prigogine, 1955; von Bertalanffy, 1949, 1960; Oparin, 1957), with anabolism exactly balancing catabolism; in this light the two are inseparable properties of living systems.

It is evident that there are two main components of catabolism (Needham, 1959), one involved in the regular endergonic-exergonic cycle of the work functions, and the other in the accidental losses by wear—fortuitous entropic errors of operation which make all processes, physical and biological, much less than one hundred per cent efficient (p. 253). Living systems may have their own sources of wear, in addition to those of simpler physical systems. It is a condition of survival that they shall be able to counteract all these errors: probably all have come to evoke the recovery-hypertrophy type of response.

Wear and tear at the cellular and tissue levels has been recognized for a long time. The rate of scarfing of the superficial epidermis of mammals and the rate of destruction of blood cells are very great, and that of the gut mucosa and other tissues also is considerable. The replacement of these losses is known as *physiological regeneration*, a term which stresses the normality and inevitability of the whole phenomenon. After accidents such as wounding and haemorrhage the restoration process is speeded up.

At the molecular level wear and tear was at one time thought to be very slight, as measured by the excretion of those nitrogenous substances, such as creatinine, which vary so little in amount from day to day. Since the use of labelled metabolites it has become evident that the endogenous component