RES MEDICA
Journal of the Royal Medical Society

Growth Normal and Abnormal

Professor Michael Swann
Department of Zoology, University of Edinburgh

Abstract
Growth as we see it in an animal or a plant, is a smooth continuous process. But the more we delve into it, the more discontinuous we find it to be. Individual cells do not grow indefinitely. When they reach a certain size, they undergo a drastic reorganisation, and divide into two. Even growth between one division and the next is not, as one might have expected, a smooth process of increase by compound interest. Instead, as Dr. J. M. Mitchison of Edinburgh University has recently shown, it is growth by simple interest, until shortly before the cells are due to divide, when they suddenly double their rate of increase, in readiness for the appearance of two daughter cells, each of which will grow at the original rate. The machinery for making new living matter is evidently duplicated quite suddenly.

ISSN: 2051-7580 (Online) ISSN: 0482-3206 (Print)
Res Medica is published by the Royal Medical Society, 5/5 Bristo Square, Edinburgh, EH8 9AL

Res Medica, Summer 1959, 1(4): 7-9
doi:10.2218/resmedica.v1i4.298

GROWTH NORMAL AND ABNORMAL

Based on an Address read before the Royal Medical Society on Friday, 28th November 1958.

By PROFESSOR MICHAEL SWANN
Department of Zoology, University of Edinburgh

Growth as we see it in an animal or a plant, is a smooth continuous process. But the more we delve into it, the more discontinuous we find it to be. Individual cells do not grow indefinitely. When they reach a certain size, they undergo a drastic reorganisation, and divide into two. Even growth between one division and the next is not, as one might have expected, a smooth process of increase by compound interest. Instead, as Dr. J. M. Mitchison of Edinburgh University has recently shown, it is growth by simple interest, until shortly before the cells are due to divide, when they suddenly double their rate of increase, in readiness for the appearance of two daughter cells, each of which will grow at the original rate. The machinery for making new living matter is evidently duplicated quite suddenly.

Various other facets of cell growth and division behave in a somewhat similar, discontinuous way. The chromosomes double some time before division. The main constituent of chromosomes is desoxyribonucleic acid (believed to be the essential substance of the genes) and this, not surprisingly, doubles a little before the chromosomes do. There is evidence too that ribonucleic acid, which is thought to be involved in transferring information from the genes, and in synthesising the appropriate enzymes and proteins, also varies cyclically. Yet further biochemical systems show characteristic ups and downs, in particular the sulfhydryl compounds, which seem to be closely concerned in the actual mechanical process of splitting the cell in two. Several more systems, whose biochemistry is quite unknown, have also been discovered, and all of them show discontinuous behaviour. The most important, perhaps, is one that is peculiarly sensitive to radiations. Another curious system is very sensitive to small changes in temperature, and this has been put to good use by cell physiologists who can now study cell division in mass populations of cells that have been made to divide in unison by means of temperature shocks. A final system enables cells to build up in advance all the energy they need to divide. Once launched they are then unaffected by any accident, except the most drastic.

To say that all these key mechanisms in the growth and division of cells are discontinuous, or to be more accurate cyclical in their behaviour, merely reflects the fact that they must all dovetail in with one another, and reach completion before one cell can divide into two. Holding up one system does not necessarily hold up all the others, though it will prevent division. A dose of X-rays for instance, stops cells dividing, though it does not stop them growing. Indeed they become far too big, and this may have something to do with ultimately killing them.

The fundamentals of cell growth and division have been investigated mostly by experimenting with rapidly growing cells, either microörganisms, or cells in tissue culture. When we turn to growth in whole animals the situation is rather different. In a very young embryo, it is true, most if not all the cells are growing and dividing at full speed. But as time goes on

more and more of them slow down. Some stop completely: the cells of striated muscle, and nervous tissue. Many stop almost, but not quite completely: the cells of liver, kidney, connnective tissue and the glands. A few continue to grow and divide quite fast, even in the adult: the cells of the skin, the alimentary tract and the blood. But even these are not growing at full speed. They can put on a spurt to meet the demands of a wound or of a haemorrhage.

What lies behind this elaborate pattern of growth and division, rapid in one place, slow in another, and non-existent in yet a third? The simplest explanation would perhaps be that one or other of the mechanisms we have talked about earlier should be blocked. But all the evidence goes to show that this is not the case. Even in the more rapidly growing tissues of a whole animal, the bulk of cells are seemingly quiescent and not growing or dividing at all. Their various key mechanisms for division are not blocked; they are apparently just not there. They do not seem even to be making any of the large amount of special protein required for the mitotic spindle. Their energies, on the contrary, appear to be devoted to their particular specialised task in the body—secreting hormones, excreting waste products or whatever it may be.

For such cells to grow and divide, a drastic reorientation of metabolism is clearly needed, away from making enzymes or proteins for some specialised function, and over to making materials essential for proliferation. And the evidence all suggests that the amount of growth and division in an animal at any stage after that of the early embryo, is a question of the availability of various special substances whose job it is to bring about this drastic reorientation.

A certain amount is known about these stimulants, and there appear to be a great many of them, each operative for different types of cell and tissue. The most familiar ones are the various hormones that affect growth—pituitary growth hormone itself, ACTH, thyrotrophic hormones, the sex hormones and a few others. But there are certainly a great many more, and the only reason they are not called hormones is that they are not secreted by obvious recognised glands. Red cell production for instance, is controlled by an α-globulin, erythropoietin, that circulates in the blood. And erythropoietin seems, somewhat surprisingly, to be made in the kidneys, presumably when the oxygen tension falls below normal. Kidney growth is evidently controlled by another specific stimulant. Its nature is unknown, but it must be something that is normally excreted, for if one kidney is removed the other grows rapidly, or if one kidney is prevented from functioning, by ligature of the ureter, both it and the other kidney again start to grow. The control of liver growth follows a rather different pattern. It is effected not by a stimulator, but by the absence of an inhibitor. And the inhibitor seems to be plasma albumin, or some fraction of it. A normal liver produces quantities of plasma albumin, which limit liver growth severely. Partial hepatectomy reduces the plasma albumin production for a while, and this lets the liver grow back to its normal size.

What exactly are these specific control mechanisms doing? They are, so far as we can tell, not affecting the detailed mechanisms of growth and division in any intimate way. Rather they are simply switching the whole synthetic machinery of a quiescent differentiated cell into a new pathway, such that the activated cell makes the proteins and enzymes that are needed for division. They are therefore not so much stimulating agents, as *switching* agents. And no doubt this explains why some of the control mechanisms, e.g. that of liver, are negative ones. There is after all no reason why a switching substance should always switch *from* differentiated activity *to* division. It might equally be expected to do the reverse, and liver is a clear case in point.

Recent research makes it fairly certain that enzymes, and indeed all proteins are synthesized by ribonucleic acid containing particles, known as microsomes, which are scattered through the cytoplasm. Any switch from one general pattern of metabolism and synthesis to another presumably therefore, involves activating or inactivating these particles. One may guess then that the recognised growth hormones, and the various humoral substances that control the growth of organs are acting directly or indirectly on the microsomes. This has yet to be shown, though it may be significant that repeated attempts to link them up with enzyme reactions have failed. If they are really concerned at a much more fundamental level with controlling the *synthesis* of enzymes, this is not surprising.

Finally, what is the relevance of all these discoveries to the question of abnormal growth? It may sound too optimistic to suggest that we are at last getting to the heart of the problem. Certainly, to say this in no way implies that there are any practical steps we can now take to cure cancer. But a large amount of evidence seems to show that tumour cells grow and divide just as normal cells do. On the other hand a steadily increasing amount of evidence suggests that it is their *control* mechanisms that are at fault. Cells that should be dependent on hormones for proliferation become less dependent, or even totally independent. At first, hepatoma cells are partially inhibited by plasma albumin; later they are not inhibited. The normal growth controls are evidently lost, quite gradually, as tumours increase in malignancy.

What exactly this means is obscure. Are tumour cells making their own hormones or humoral factors? Or are they contriving to do without them. Or when the system is an inhibitory one, are they failing to respond to the inhibitor? An understanding of cancer undoubtedly lies in this general direction, but it is still a long way off.