THE CHANGING PHYSIOLOGY OF MIDDLE AGE

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It is not easy to talk sensibly about middle age because there is real doubt as to whether it exists. It is something which rapidly recedes from us as we approach it and at the other end it blends confusingly into old age. During this century improvements in medical care and a general increase in living standards have led people to expect to retain good health until quite late in life. It is now unusual for a physician to attribute any illness merely to old age and he would be most unwise to do so in a patient under the age of 70.

It is still easy to define clearly the periods of growth and development which constitute childhood and adolescence. These are usually complete by the early twenties. This leaves a rather long period between the ages of about 25 and 65 when development is complete and old age has not yet appeared. Since this middle period is the major portion of the human life-span and since most people expect to be completely healthy throughout its entire course, it seems unreasonable to dignify this time of life with a special name. It could be the elusive middle age, but I suspect that people under the age of 45 would object to that definition. Perhaps it would be better to define middle age as that period of life when the symptoms of old age first appear. We could then limit our discussion to the onset of senescence, which would be quite a difficult subject in itself.

In animal populations, and in mankind through the centuries, old age has never been a common cause of death. Accidents, starvation and disease usually terminate the life of an individual before senescence is evident. I wonder how much of the human tendency to glorify war has its origin in the deep-seated knowledge that a heroic death in battle is a sure way of avoiding old age?

There is one school of thought which attributes most of the symptoms of old age to the accumulation of minor pathological assaults over many years. Although most biologists now accept that there is a physiological state of senescence, it must be admitted that in any study of ageing the possibility of an undetected infection or nutritional disorder having occurred can never be excluded completely. It has always been an attractive notion that if one could remain free of disease one might live for ever.

It is something of a paradox that some of the least controversial findings in various studies into senescence suggest that some animals do not seem to age at all. Only recently has the death occurred of a tortoise which was well known to Captain Cook and the terrible traumas which that animal had suffered from time to time were enough to terminate the life of most things mortal. There are also many well-documented reports of individual fish with incredibly long life-spans. The factor common to most of these long-lived animals is that they are cold blooded and belong to species which continue to grow throughout life. Any animal which matures to a finite adult size will almost certainly have a limited life-span. Maturation seems to be the first stage of senescence. Even in animals where the life-span is to some extent indeterminable the onset of senescence may suddenly occur. In the salmon, for example, old age and death rapidly follow the onset of mating behaviour.

Although we have this evidence that some species appear to be immortal, and while we must always entertain the doubt that ageing in any species may be due to external disease-producing factors, we should attempt to define what we mean by a physiological state of old age. Such a state would lead naturally and inevitably to a situation where the individual could no longer respond to the stresses imposed upon it by the environment. I like this definition because it enables us to concede that even in man, an individual might survive

well into the senile state if he could be protected from environmental assaults such as infection, extremes of temperature or limitation of food intake.

If we accept this definition we must identify the level at which the failure to adapt occurs. It is not profitable to attempt to unravel the mystery of old age by considering the animal as a whole. We should look for evidence of senescence in its constituent parts. For the purpose of this discussion the body has only two components, cells and inter-cellular matrix.

Some of the cells of the body are capable of division, but many cells such as nerve cells have matured progressively throughout development until, in their adult form, they are no longer capable of division. Such cells remain in their definitive adult form until they suffer their individual cellular deaths. The nuclei of non-dividing cells are by no means inactive. Although popular thinking usually associates the gene with sex and reproduction, in truth the main business of the gene is to give expression to its potential. The DNA of the nucleus produces specific molecules of RNA which are taken up on the ribosomes of the cell where specific proteins are constructed. The number of protein molecules which may be produced from one RNA template is limited. Thus the continued production of protein depends upon the maintenance of a chain of events which has its origin in nuclear DNA. Protein is important, not merely because it provides much of the structural material of cells, but mainly because all the enzymes which control the body chemistry are proteins of very specific structure. A minor defect in any step in the synthesis of only one protein could lead to a metabolic disorder which could be severe enough to cause the cell to die. A more subtle defect might allow the cell to survive but under circumstances where its malfunction might endanger the integrity of cells elsewhere in the body. Defects in gene function are so likely to occur that most organisms have evolved mechanisms for the repair of damaged chains of nucleic acid.

Apart from damage which may occur to the gene, the membranes of the cell are also subject to ageing. These membranes which surround the cell itself, the nucleus and the intracellular organelles, are complex combinations of fats and proteins. As well as acting as barriers to prevent the uncontrolled diffusion of substances in and out of the cell, these membranes have binding sites for many enzymes. The proper regulation of many chemical reactions within cells depends upon the maintenance of a specific structural relationship between the enzyme and the membrane. Certain reactions do not occur if the membrane is disrupted. There is some persuasive evidence that the ageing process may be due to subtle changes in membrane structure with consequent profound effects upon cellular metabolism.

Any discussion of membranes must consider the lysosome which is an intracellular organelle containing powerful destructive enzymes. When the lysosome membrane is damaged the liberated enzymes rapidly digest the cell which of course dies. Although some disease processes are thought to be due to instability of the lysosome membrane these diseases are by no means confined to the elderly.

Cells which retain the capacity to divide are subject to all the hazards which endanger non-dividing cells. In addition there is a high degree of probability that a defect may develop in the process of cell division and this adds a new dimension to potential ways in which such a cell may die. Epithelial cells, blood cells and fibroblasts are all capable of rapid and repeated division. The passage of food along the alimentary canal constantly abrades the epithelial surface. Any defect in the regeneration of the epithelium would result in ulcer formation in the gut. Suppression of cell division would also lead to deficiencies in blood cells, and the failure of fibroblasts to divide would cause delay in wound healing. Radiation toxicity and a number of other states which mimic the ageing process are characterised by failure to divide of one or more of these cell populations which normally have a rapid turnover rate.

Cells maintained in tissue culture do appear to have an inbuilt limitation upon their capacity to divide. Mammalian fibroblasts seem to be able to divide some 40 times before division ceases. Epithelial cells may be able to divide more frequently, but it is sobering to calculate

the vast number of cells which would be generated by 40 sub-divisions of one parent cell. Some tissue culture strains of cells do appear to be immortal. Cells taken from mice have been reported to survive in culture for periods many times the length of a normal mouse life-span. However these immortal cells usually have grossly abnormal genetic structure.

While failure to divide may be the cause of some disease, it is also possible that disease may result from the removal of restraining influences which normally limit cell division. The replacement of abraded epithelium is usually so well controlled that the defect is repaired without the elaboration of excess cells. It has been postulated that intact epithelial cells produce a local hormone which suppresses the division of surrounding cells. When epithelial cells are removed the inhibitory substance is also lost and the surviving cells are now free to divide and make good the defect.

With each successive division most cells gradually pass through progressive stages of maturation. The completely undifferentiated cells of the early embryo each possess the genetic potential to produce every protein which any cell of the body will produce in subsequent life. Mature cells on the other hand are capable of producing a very limited range of proteins. In most cases the process of maturation does not lead to the loss of any DNA from the cell. The genetic information is still contained within the nucleus but it is not available for transcription onto RNA. Abnormal division of cells may lead to re-activation of some of these genes and it is not unusual for neoplastic cells to produce enzymes which enable these cells to undertake elaborate chemical manipulations which are quite beyond the capacity of the normal adult cells or the tissues from which they were derived. Typical of this is the production of hormones by tumour cells of the lung.

The possibility of the uncontrolled growth of neoplasia taking place increases with the frequency with which a population of cells normally divides. Thus tumours of the skin, gut and blood are common while cells from more stable tissues rarely form tumours. In an area such as Queensland where almost the entire population develops cutaneous neoplasms in time, it is reasonable to ask whether the onset of neoplastic growth is part of the ageing process. This is not generally true however, for in other populations many senile individuals are quite free of tumours.

Extracellular structures such as the proteins and muco-polysaccharides of collagen, cartilage and bone also show signs of senescence which probably are more convincing evidence of the existence of a physiological state of ageing than is anything which takes place within the cell. While doubt may remain that senescence within the cells might be due to an undetected virus, the changes which are seen in the ground substance of tissues are relatively simple physico-chemical changes which are also seen in man-made macro-molecules such as plastics. Just as some plastic materials lose flexibility when exposed to prolonged sunlight, the macro-molecules of connective tissue also become brittle and rigid with age. This is due in both the biological and synthetic material to the formation of abnormal cross-linkages between different parts of the macro-molecule chain.

The similarities between old connective tissue and ultra-violet irradiated plastic suggest that radiation may be a contributing factor in senescence. Indeed excessive X-radiation does cause a disease state which is very similar to the ageing process. Not only are the connective tissues damaged but there is also damage to membranes and genetic material. Radiation is believed to cause displacement of electrons from the molecules by which it is absorbed. These disrupted molecules become highly reactive and are likely to form abnormal combinations with adjacent chemical groupings. Thus if an essential molecule within the cell, such as DNA, is irradiated, the subsequent change in its structure may lead to profound changes in cell function. If a collagen fibre is irradiated it may merely suffer some alteration in its elastic properties. Another suggestion is that senescence could be due to quite trivial defects in the immune system. It has been postulated that antibodies to the subject's own cells may be produced. While auto-immunity appears to be a real phenomenon, it does not appear to be confined to the elderly.

When we come to consider ageing in the whole individual we see how a minor defect in one group of cells is magnified by the consequent derangement of inter-related cells. A good example, which is not confined to old age, is seen when pancreatic cells lose the ability to produce one specific protein molecule in just the right configuration. If the protein lost is insulin the carbohydrate and fat metabolism of the entire body is disrupted and the structure and function of almost every organ is disturbed.

We have considered old age extensively and we have defined middle age as that period of life at which the first signs of old age begin to appear. Perhaps we should concede that there are some changes which are tolerable in younger people. The female menopause appears to be inevitable, but we should define the menopause as being merely the cessation of ovulation and we should not use it as an excuse for ill health. Ophthalmologists would probably insist that degeneration in the suspensory ligament of the lens and in the lens itself are acceptable changes in any person over the age of 40. A vigorous youth spent on the sports field may lead to some degenerative changes in joints. Beyond these minor defects, however, we should not accept malfunction of any organ as being normal at any time of life.

I have been careful to demolish the concept of a state of middle age because I believe much is to be gained from looking upon this age group as the healthy norm. Of course these people are not always healthy. During the middle years of life the population in general is ravaged by trauma and disease, but the young person who suffers a coronary occlusion and his colleague who is involved in a motor accident are probably both quite healthy in every other way. If it were not for their own specific disorders they would both expect to live entirely normal lives. I put it to you that you should find an exciting challenge in the task of helping these people to compensate for the defects caused by their various diseases. This is an age group in which you can expect to see a restoration to sound health and a total enjoyment of life.