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# A Unifying Biochemical Theory of Cancer, Senescence and Maximal Life Span

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The theory of cancer which we recently proposed and which was then in a rather speculative state has now been much extended and has been related to a great number of well-defined facts, amongst which the most important is the discovery that malignant tumours are characterized by an abrupt drop in the level of organic free radicals.

On this fundamental observation, as well as on the similar behaviour of embryonic tissues, we base the hypothesis that the accumulation of antioxidants is determinant to cancer. This might perhaps be related to an unbalanced chromosome set which would then be the ultimate cause of malignancy.

All this is then integrated with senescence and maximal life-span in a single theory which is characterized by a link between oxidation and reduction, bringing together organic free radicals and antioxidants.

## 1. Introduction

In a recent note (Duchesne, 1975), we put forward the hypothesis that cancer is caused by antioxidant substances which are known to accumulate in tumours in particularly high quantities (Harington, 1967).

In this connection, we must first consider the role of sulfhydryl groups in the mechanism of cell division. The work of Rapkine (1931) and Hammett (1932) drew attention to the importance of these groups in the initiation of mitosis. Although our understanding of the mechanism of proliferation has changed since these dates, the sulfhydryl proteins themselves are still considered to be the dominating factor in the phenomenon (Mazia, 1961; Swann, 1957, 1958; Stern, 1956). More recently, Burlakova (1967) has confirmed this interpretation.

The chemical behaviour of these substances may be expressed as an antioxidative activity. It is perhaps not too audacious to suggest that above a critical level of concentration these regulators of mitosis may initiate an

uncontrolled outburst of mitosis. If this is so, it would be a genuine dialectical effect; an inordinate aggravation of the process would finally lead to cellular disorder, after a prolonged period of resistance to senescence. The fact that the probability of spontaneous development of cancer in all mammals, including man, increases in geometrical progression with age (Burnet, 1974), is in excellent agreement with this point of view.

In the present paper we will support these former conclusions with further evidence. In this way, we will show the existence of a close link between the biochemical characteristics of cancer and those of certain fundamental aspects of life, such as senescence and maximal life-span.

## 2. Concerning the Behaviour of Antioxidants and their Inhibitors

Let us start by recalling the results of recent experiments with carcinogens such as, for example, diaminoazobenzene (DAB) and 2-acetylamino-fluorene (AAF). These compounds produce malignant tumours when incorporated into the diet of rats.

Liver extracts were studied by the method of electron paramagnetic resonance (Duchesne, Lion & Van de Vorst, 1969; Duchesne, Goutier, Maréchal & Van de Vorst, 1975). A progressive and regular decrease with time of the level of organic free radicals present in the liver was observed (normally some $10^{14}$ centres per gram of tissue).

At the time of the emergence of the tumour, the extratumoral concentration of these free radicals was about 50% of normal, whereas inside the tumour itself, the concentration was observed to fall to no more than 20% of normal. This occurred in an unpredictable area and was probably due to a fluctuation in the distribution of the anti-radicalar substances.

Therefore, it is perfectly normal that spontaneous malignant tumours affecting the liver or kidney in the rat and mouse reduce the normal intensity of the paramagnetic signal or even cause it to suddenly disappear altogether. This phenomenon, which also occurs in many types of human tumours, such as liver, kidney, lung and ovarian cancers, seems in fact to be a quite general property of this state (Duchesne and Van de Vorst, 1970; Swartz, Mailer, Ambegaonkar, Antholine, McNellis & Schneller, 1973). Moreover, we have found that the behaviour of the cancer is strictly independent of its specific generating agent, whether chemical or viral. This contention is supported by our recent study of the C3H strain of mouse where it was observed that paramagnetic signals disappear in the mammary carcinoma induced by the virus of Bittner (Duchesne, Maréchal & Poussel, 1975).

All this clearly shows that in no case can free radicals be responsible for cancer, since their concentration falls practically to zero, during its develop-

ment. This of course conflicts entirely with the point of view of other workers (Harman, 1969; Georgieff, 1971; Slater, 1972).

The mechanism described is easily explained by the fact that antioxidants, being electron donors, and free radicals, being electron acceptors, destroy one another. The characteristic decrease in the level of free radicals observed in tumours is also observed in embryonic tissues (Duchesne & Van de Vorst, 1969) which also contain such powerful mitotic stimulators as the sulfhydryl proteins. It must be because of this abundance of antioxidants that embryonic and cancerous cells grown *in vitro* immediately start to multiply (Haddow, 1975). This factor joins the discovery of the close relationship between these two aspects of life (Wolff, 1970).

We have shown (Duchesne, Gilles & Mosora, 1975) that the normal organic free radical content of rabbit diaphragm can be completely neutralized by antioxidants, such as ascorbic acid, 2-mercaptoethanolamine and glutathione. This gives therefore more weight to the assertion that it is these types of compounds which are responsible for the disappearance of free radicals in cancerous and embryonic tissues.

It is now obvious that chemical carcinogens, though having at high concentration the property of behaving as inhibitors of mitosis and thus also acting as agents of senescence, have, on the other hand, at low concentration, the peculiar property of being able to produce an accumulation of mitotic agents (Crabtree, 1945; Harington, 1967), that is, antioxidants.

For example, the concentration of glutathione, which is a specific antioxidant, rises rapidly to 200% of normal in rat liver after the intraperitoneal injection of a powerful hepatic carcinogen, 3-methyl-4-dimethylaminoazobenzene (Neish & Rylett, 1963; Neish, Davies & Reeve, 1964). Similarly very high levels of antioxidants were found in malignant tumours: a significant increase was observed in ascites tumour cells as compared to normal cells (Shuster, 1955). When the tumour is treated with 5-fluorouracil, a growth inhibitor (Lindner, Kutkam, Sankaranarayanan, Rucker & Arradondo, 1963), the ratio of SH-groups to reduced compounds diminishes by about 30%.

In studies on a certain number of animal tumours which were or were not sensitive to the action of an alkylating agent, it was shown that the higher the concentration of SH-proteins, the greater was the effect of the agent (Calcutt & Doxey, 1962; Calcutt & Connors, 1963).

It is interesting that studies on the oxygen consumption of Trillium microspores in relation to the mitotic cycle suggest that the active division of these cells can be associated with their anaerobic behaviour (Stern & Kirk, 1948). It would thus appear that those substances that are antagonists of antioxidants depend, at least partly, on oxygen. The fact that 13% of patients with tumours who were irradiated under high oxygen pressures (3–4 atm.),

have no recurrence up to 8 years, while in those patients treated at a normal air pressure, recurrence always occurred within 3 years (Knock, 1967), confirms this idea.

One could also consider the possibility that polyunsaturated fatty acids [which are prostaglandin precursors (Bailey & Dunbar, 1973)], give rise to peroxides through aerobic action (Wolfson, Wilbur & Bernheim, 1956). It is well known that peroxides considerably increase the activity of those inhibitors of SH-groups which oppose the formation of human tumours, and that they may even interact with substances such as vitamin E (Barber & Wilbur, 1959; Lewis & Wills, 1962; Strehler, 1962; Knock, 1965, 1967; Marx, 1974).

Szent-Györgyi (1965, 1972) suspected that a close connection existed between SH-groups and cancer. He suggested that retine, which is a derivative of methyl-glyoxal and is also a normal cellular constituent and electron acceptor, would be likely to prevent cancer, since its administration in sufficient amount would stop cell division, even in the presence of glutathione. However, Szent-Györgyi did not go so far as to propose that this implies a relation of cause and effect. But he considered that the cancerous cell is not a "wild-type" cell, with an increased vitality, but rather a sick cell.

Our hypothesis that cancer is caused by an over-abundance of antioxidants, thus now seems to be emerging. Moreover, it supports Knock's (1967) insistence on the importance of SH compounds associated with tumours. It also explains the fact that the cells of adult tissues, which remain inactive for several days when they are grown *in vitro*, immediately start to proliferate when extracts of carcinoma or sarcoma cells are added (Haddow, 1975).

Furthermore, possible modifications in the fundamental properties of antioxidants at high concentrations are based upon the well-known fact that if injected in high quantities they cause convulsions and result eventually in death (Di Luzio, 1964, 1973; Cawthorne, Bunyan, Gennitt, Green & Grasso, 1970).

It is also particularly interesting that both the rate of mitosis and the level of antioxidant activity in aerobic condition is very low in mammalian brain, liver, kidney and spleen, whereas the level of lipid peroxides is very high. The opposite occurs in intestine and blood where the rate of mitosis is much higher (Barber & Wilbur, 1959). It is essential to note that the formation of peroxides of polyunsaturated fatty acids is greater when the concentration of antioxidants is low, which means that an equilibrium exists between these two fundamental components of life (Witting, 1970).

An important consequence is that a tumour grows much more rapidly in a young animal than in an old one because the former possesses much higher levels of antioxidants.

Lastly, we should not overlook the fact that ionizing radiations are effective in cancer therapy because of their fundamental property of oxidizing

SH derivatives to disulfides, using free radicals formed from water as intermediates (Jocelyn, 1972).

As regards the specific problem of carcinogenesis induced by radiation, the recent observation that total irradiation of the rat increased the production of the well-known antioxidant glutathione three-fold may be of importance (Wernze, Braun & Koch, 1965; Zicha, Dienstbier, Borova & Neuwist, 1965).

### 3. Antioxidants in Plants: Role of Auxins

According to Gordon *et al.* (1967, 1972), there is no doubt that auxin, which is typical of plants, also exists in animal tissues. The main characteristic of this antioxidant is that, like sulfydryl compounds, it is a hormone regulating growth, i.e. cell division.

Remarkably enough, Yamaki, Shimojō, Yoshizawa & Namekawa (1974) recently found auxin in very large amounts in cases of human gastric cancer and breast cancer. The increase in concentration, as compared to healthy tissue, was of the order of five-fold. Thus, auxins would seem to play the same role in the cellular multiplication of cancerous tissues of animals as the different types of antioxidants mentioned above. This observation only lends further support to our hypothesis.

This parallel may, however, be drawn further. We have seen that the senescence of tissues is caused by organic free radicals. These destroy antioxidants which are normally present in the concentration range where they stimulate mitosis (Duchesne, 1975).

In plants, the antagonizing action of auxin-oxidases, destroying the auxins themselves, contributes to the senescence of the tissues. This is comparable to the activity of free radicals, and especially of peroxides of polyunsaturated fatty acids, in animals.

In young tissues, a low activity of these oxidases is observed, but this activity increases continually with age (Pilet, 1961), reaching three-fold higher levels in old cells, and leads to hypoauxinia (where only 1% of the normal level of auxin is found).

Furthermore, gall in plants is the result of structural disorders as well as of intense cellular proliferation. It is associated with the presence of far higher quantities of auxin hormones than found in normal tissues (Pilet, 1961).

Lastly, a definite hyperauxinia is found not only in the case of benign tumours, but also in true plant cancer, such as crown-gall (Pilet, 1961; Steward, 1968; Bayer, 1973). X-rays, which destroy auxins, have been reported to slow down the growth of crown-gall.

On the other hand, growth-promoting substances, such as the auxins themselves, may also produce cancerous-like growth in plant tissues (Morel,

1972). In general, it may be concluded that where auxins are particularly abundant, auxin-oxidases are less active.

We are confronted here also with an equilibrium whose function is similar to that of antioxidants and free radicals in mammals.

## 4. Origin of Cancer

All this would indicate a common origin of cancers, linked to the displacement of this equilibrium towards the overabundance of antioxidants, whether vegetable or animal. This point of view is in striking agreement with the basic observation of Hayflick (1965, 1974) who claimed that when the division of cells grown *in vitro* becomes unlimited or escapes from senescence-like changes, it is because they have assumed properties analogous to cancer cells. More precisely, this means that these normal diploid cells have undergone a heteroploid transformation and are able to produce tumours when grafted into suitable animal hosts (Koller, 1975).

It is possible to conclude from the foregoing analysis that cancer, which, like senescence, is a normal terminal phase of life, has a much broader biological meaning than what is called a disease. Indeed, it represents a last effort of the organism itself, in response to the advancing senescence of certain of its tissues, with the aim of restoring the vanishing capacity of mitosis. Unfortunately, however, the reaction is so excessive that it unleashes a process leading to disorganization of the cells, resulting in the death of the whole organism. This process, of course, could perhaps result, at least in part, from an anomalous chromosome constitution which might lead to the overproduction of antioxidants; as an example an excess of E16 chromosomes may have been found in human cancers, but the biochemical significance of this discovery has not yet been established (Atkin, 1974; Minkler, Gofman & Tandy, 1970; Bender, Kastenbaum & Lever, 1972).

## 5. The Problem of the Peroxides of Polyunsaturated Fatty Acids

The peroxides of fatty acids are known to bring about the degradation of proteins (Desai & Tappel, 1963) during the disruption of cellular membrane components, particularly the endoplasmic reticulum and also mitochondria. It seems obvious that only antioxidants can combat this disruptive action. We saw earlier how, in the artistry of biological mechanisms, antioxidants have radically opposite properties according to their concentration.

In the same way, peroxides of polyunsaturated fatty acids, which play a part in ageing (Gordon, 1974), are also capable of counteracting the development of cancer. This follows from their remarkable property of neutralizing

antioxidants and therefore of inhibiting mitosis (Crabtree, 1945; Dubouloz & Fondarai, 1953; Dubouloz & Dumas, 1954; Wilbur, Wolfson, Kenaston, Ottolenghi, Gaulden & Bernheim, 1957; Stillwell, Maroney & Wilbur, 1959; Knock, 1966; Mead, 1975).

In this respect, let us recall the well-known effect of these peroxides on the Rous sarcoma virus (Moloney, 1957). Moloney showed that the tumoral activity was practically stopped by the products of oxidation of lecithin and methyllinolenate. This proves, once again, that antioxidants play a major role in the development of cancer, even that of viral origin. It seems evident, too, that no oxidation products of polyunsaturated fatty acids are found in ascites tumours, where they would retard cellular division (Shuster, 1955). Furthermore, very low levels of peroxides were found in regenerating liver, just after a partial hepatectomy when mitosis is maximal; the peroxide concentration was even lower than in a normal liver (Wolfson, Wilbur & Bernheim, 1956). However, it must be pointed out that the polyunsaturated fatty acids themselves have been observed to hasten the development of chemically-induced tumours (Pearce & Dayton, 1971; Spector, 1975).

Both linolenic acid and linoleic acid have been found in ascites cells. Their oxidation products have been shown to inhibit cellular activity. The inhibitory effect of the former (three double bonds) is much higher than that of the latter (two double bonds). These striking differences were noted in studies on the inhibition of bacterial growth (Stillwell, Maroney & Wilbur, 1959) and also, notably, on the effect of depolymerization of DNA (Shuster, 1955).

Fisher & Wilbur (1954) found that DNA is depolymerized by oxidized methyl linolenate. This property could induce senescence in the brain, where, as we saw, polyunsaturated fatty acids are present in higher quantities than antioxidants. Together with endogenous free radicals, they cause erosion of the DNA (Duchesne, 1975), probably expressed as a decrease in molecular weight, which is known to decrease with age in rat liver (Massie, Baird, Nicolosi & Samis, 1972; Chetsonga, Boyd, Peterson & Rushlow, 1975; Massie, Baird & McMahon, 1975; Barton & Wen-Kuang Yang, 1975). This would correspond to a decrease in the information potential, and consequently, to senescence (Duchesne, 1975).

## 6. Conclusion

The present synthesis displays a remarkable unity. It considers senescence not only in general, but also specifically by its speed of development, on which maximal life-span closely depends. It is quite clear that, in the latter case, the mechanisms which determine this act mainly through the concentration of organic free radicals in the brain, whose neuronal cells do not

divide, and are therefore more susceptible to the erosion effect. Time, as well as the low value of the energy of activation, offsets the weak activity due to the extremely low concentration of the free radicals involved.

Both senescence and cancer, which are closely related, depend, but in opposite ways, on the peroxides of fatty acids. In fact, the fundamental characteristics of these phenomena is that they are expressions of a link between oxidation and reduction.

Further tests in relation to this theory are being carried out in our laboratory.

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