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A Mitotic Theory

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Evidence is presented that cellular processes have a cyclic nature. The theory is advanced that this is controlled by a periodic charge exchange between actin and myosin, regulated by the oxidation and reduction of sulphydryl moieties. Cellular characteristics and control including mitosis are determined by the redox state of these two proteins; mitosis being determined by both the amplitude and period of the thiol cycle. It is proposed that all carcinogens, including radiation, induce an oxidation of specific myosin sulphydryl units with a concomitant reduction of specific actin sulphydryl units. They thereby initiate a thiol cycle of increased magnitude which leads to mitosis. This theory leads to predictions concerning the manner in which reducing agents should be used in the prevention and treatment of cancer.

1. Introduction

One of the earliest mitotic theories is that of Löeb (1913: Brachet, 1950). According to Löeb the first period of fertilization consist of the elevation of the membrane by cytolysis of the cortex; this phenomenon appearing simultaneously with an increased oxidation. In the second period the egg is rescued from cytolysis by the return to a normal respiration. At about the same time Lillie (1911) considered division to be initiated by the action of unbalanced salt-solution on the plasma membrane, causing an increase in permeability and depolarization. For division to take place this increase in permeability must be followed by a normal permeability with an increase taking place again just before division.

Later Heilbrun (1956), studying muscle contraction, blood clotting and cell division came to the conclusion that whatever makes muscle to contract and blood to clot makes cells to divide. The stimulus increases calcium entry into the cell interior which, in turn, activates a protease and a clotting enzyme which causes the protoplasma to clot. In muscle fibres this results in the shortening of the fibre, in cells to increased viscosity which leads to spindle formation. Studying the variation of viscosity during the cell cycle

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and Rapkine's (1931) thiol cycle, Heilbrun concluded that the clotting reaction involves a change of SH groups to S–S groups which, in turn, leads to an increased metabolism.

Similarly, in Berridge's (1975) theory, membrane fluidity and intracellular levels of cyclic AMP and calcium are closely interrelated, the signal for division being given by an increased intracellular Ca^{++} in G_1.

Of the more recent theories the most published is the membrane potential theories of Cone (1971). Cone correlates mitotic activity with a downward shift in resting membrane potential which arises from an increased intracellular Na^+ concentration.

According to Papadopulos & Stanford (1977), the increased intracellular Na^+ in G_1 results from an increased membrane permeability to Na^+ which, in turn, leads to an increased A-system amino acid and sugar uptake. This increased uptake in turn leads to an increased metabolism, decreased permeability and increased membrane potential in the S-phase and eventually to division.

Szent-Györgyi (1976) believes that there is a close relationship between SH and cancer. In his hypothesis the living systems can be found in two states—the α state and the β state. In the α state, life is dominated by electron donors, fermentation and unlimited proliferation, with the protein molecules as insulator. In the β state, life becomes dependent on D/A (the ratio of donors to acceptors) with the protein molecules conductive. The cancer cell, due to a lack of methyglyoxal (an electron acceptor), remains in the α state and thus has an unlimited proliferation and fermentation.

The purpose of this paper is to outline a new theory and refer to some of the existing corroboratory experimental evidence.

2. Actin and Myosin in Non-muscle

There is considerable evidence that actin and myosin are among the most important cellular proteins. In 1965, Sandborn, Szeberenyi, Messier and Bois proposed a cellular model with a filamentous network within the cell containing contractile proteins and contributing to the basic structure and function of the membranes of organelles and the plasma membrane. They suggest that the model provides all the requirements for cellular movement, adhesiveness and active fluid and electrolyte transport with "pores" being opened at "contraction". Mazia & Ruby (1968) have also proposed a similar model. Similarly, in the Danielli–Davson (Danielli, 1975) and Singer–Nicolson (1972) membrane mosiac models, although the proteins are not identified, it is postulated that active transport takes place

via protein lined membrane "pores". It is proposed that the "pores" are lined with proteins which contain SH groups with the masked SH being important for structural membrane integrity and the free SH in cation and substrate transport (Knauf & Rothstein, 1971; Rothstein, 1970; Epstein & Konoshita, 1970; Kaback & Hong, 1973).

It has been shown, experimentally, that the cellular free SH and the actin filaments are non-uniformly distributed and in a dynamic state. They appear when the cell is in a certain functional state (sperm acrosoneal reaction, phogocytosis) or at some stage of the cell cycle, only to disappear at another state or stage of the cell cycle. The period of assembly and disassembly of the filaments can be as short as a few seconds which indicates that actin filaments are formed from precursors, most probably actin monomers, polymerization being induced by heavy meromyosin (Sanger, 1975; Brachet, 1950).

These contractile proteins have been found to play an essential role in cell movement, chromosome movement, cellular morphology and cellular adhesiveness, assembly of microvilli, secretion, membrane stability and integrity, capping of surface membrane receptors, pinocytosis, phagocytosis, exocytosis and endocytosis, sperm acrosomal reaction and platelet function.

Given the importance of the actin–myosin (A–M system) in cellular structure and function, understanding of its regulation is necessary.

3. Regulation of the Actin–Myosin System

It is generally believed that the muscle A–M system is regulated via cellular Ca^{++} and the regulatory proteins. However, there is evidence to show that Ca^{++} plays a secondary and indirect role in contraction and that contraction can take place in the absence of Ca^{++}. Thus, it has been shown that Ca^{++} release is preceded by a depolarizing wave, i.e. by the activation of the Na^+ channels which, in turn, are preceded by charge transfer and conformational changes in the membrane proteins (Hui, 1977; Margineanu & Schoffeniels, 1977; Hasselback & Seraydaryan, 1966; Inoue, Ishida & Kobatake, 1973).

Contraction can take place in the absence of Ca^{++}, or in the presence of low Ca^{++} concentration, when the ATP and Mg^{++} concentration are low, or when oxidizing and SH reagents are present. Furthermore, relaxation involves some process other than removal of Ca^{++}. For Ca^{++} sensitivity of the A–M system, myosin SH moieties are essential, and the Ca^{++}-ATPase is Mg^{++}, ATP and SH dependent and is associated with heavy meromyosin (Ashley & Ridgway, 1970; Briggs & Fuchs, 1964; Weber & Herz, 1964;

Dancker, 1975; Dancker & Hasselback, 1971; Bremel & Weber, 1971; Daniel & Hartshorne, 1972; Hartshorne & Daniel, 1970; Garnett, Kemp & Gröschel-Stewart, 1979).

The fact that all relaxing agents, either directly or indirectly, protect the myosin SH groups, and that oxidizing agents, SH reagents and flavin antagonist inhibit relaxation (Azzone & Dobrilla, 1964) indicates the necessity of myosin SH groups for the regulation of the A–M system.

It has been known for some time that at contraction, the SH concentration of the globular head of myosin, where the functional SH groups SH_1 and SH_2 are found, decrease and at relaxation increase (Bailey & Perry, 1947; Finály, 1952; Bailin & Bárány, 1967; Bárány & Gaetjens, 1971; Bárány *et al.*, 1975). Lately it has been shown that at contraction, the reactivity of cys-10 of F-actin is increased and the reactivity of SH_1 of myosin is decreased. At relaxation the converse takes place (Duke, Takashi, Ve & Morales, 1976).

It has also been shown that the low rate of ATP cleavage in resting muscle results from the formation of a ring structure involving the SH_1 and SH_2 of myosin and Mg ATP. Chemical blocking of SH_1 prevents formation of the ring and contraction, although ATP cleavage is unimpaired. The association of myosin with actin is a process where the ring is opened through binding of actin at or near the nucleophilic site SH_1, and accelerates energy conversion (Burke, Reisler & Harrington, 1973).

Sakai & Dan (1959), studying a non-muscle system, viz. cleavage of the sea urchin egg and the cyclic phenomena exhibited by the free acid soluble SH groups during cell cycle, observed earlier by Rapkine and Mazia (Rapkine, 1931; Mazia, 1954), found that the SH's were protein SH's and not gluthathion as was believed earlier. A water soluble and an acid soluble protein were isolated which behaved like actin and myosin respectively. Sakai (1968) also found that the strands made from the acid soluble proteins contracted under the influence of oxidizing agents or the water soluble protein but elongated under the action of reducing agents. Furthermore, the interaction between the water soluble protein and the acid soluble protein is by means of SS–SH exchange. Contraction is accompanied by oxidation of the SH groups of the thread and reduction of the water soluble protein, contractility being directly proportional to the SH concentration of the acid soluble protein available for oxidation. Elongation is brought about by the reverse process. This charge exchange also takes place between the acid soluble, protein and the spindle and involves only the free SH groups (the SH in the native protein which readily react with mild oxidizing agents). Sakai found that the SH groups of the acid soluble protein decrease after fertilization, reaching a minimum about the middle of G_1, then increase

to a maximum value in late S and again decrease at mitosis, whereas the SH groups of the water soluble protein change reciprocally.

It can be concluded then that:

(a) the acid soluble protein contains myosin, i.e. the acid soluble SH are myosin SH;
(b) the A–M system is regulated by charge transfer between the two proteins;
(c) myosin can be found in two states—an "energized" state in which the sulphydryl-MgATP ring is intact, and a "de-energized" state where the ring is broken;
(d) the ring can be broken by interfering with any of its components, i.e. decreasing the Mg^{++} concentration, decreasing the ATP concentration or chemically blocking or oxidizing its SH groups;
(e) when the ring is broken and a charge transfer takes place between myosin and actin, ATP hydrolysis and contraction occurs;
(f) the magnitude of contraction is directly proportional to the quantity of myosin SH available for oxidation and the amount of oxidant present;
(g) for relaxation to take place myosin has to be charged again, i.e. myosin has to be reduced and ATP synthesized in the presence of Mg^{++},
(h) Ca^{++} could induce contraction by directly or indirectly interfering with the myosin SH groups by; competition for ATP; or both;
(i) there is a periodic charge transfer between actin and myosin (thiol cycle) during the cell cycle, i.e. the cell goes through a cycle of contraction–relaxation;
(j) the thiol cycle is indispensable for division.

If contraction occurs, as proposed above, the problem then is how the cell reverts to the relaxed state, i.e. how cellular substrate transport and metabolism are regulated for ATP synthesis and myosin reduction.

4. Substrate Transport and Metabolism

As far as transport and metabolism are concerned a brief outline only will be given, which will indicate that they could be regulated by the A–M system.

Although there are a number of hypotheses concerning mitochondrial and bacterial substrate transport, such as the redox, chemiosmotic, conformational and others (Kaback & Hong, 1973; Mitchell, 1973; Hamilton, 1975), it is generally agreed that at least the mammalian cell membrane has a sodium linked transport system, A-system amino acid and sugar

uptake being coupled to Na^+ uptake. It is also agreed that the SH groups are involved but their origin and exact role is unknown. Some workers find an increase in sodium and A-system amino acid uptake with oxidizing agents and SH reagents, others a decrease. However, the increase is found whenever the Na^+ permeability and substrate uptake are determined simultaneously with the application of the oxidizing agents or SH reagent. A decrease is always found when the determination is done some time after the application of the oxidizing agent or SH reagent when the membrane free SH are already oxidized (Nelson, Glover & Magill, 1975; Sutherland, Rothstein & Weed, 1967; Hare, 1975, Rega, Rothstein & Weed, 1967; Vanstevenick, Weed & Rothstein, 1965; Flory & Neuhaus, 1976; Kilberg & Neuhaus, 1975; Archer, 1968; Kwock & Wallach, 1974).

The possible relationship between cellular SH/SS ratios, A–M system and cellular metabolism has been recognized for some time. (Baron, 1951; Szent-Györgyi, 1960; Tonomura, 1972; Neifakh *et al.*, 1965). Experimentally it has been also shown that there is a competition between actin and one of the best known uncouplers, 2,4-dinitrophenol and that binding of 2,4-dinitrophenol requires ATP and Mg^{++} (Levy, Sharon & Koshland, 1959; Chappel & Perry, 1955; Boyer, 1965). Currently it is generally agreed that ATP synthesis is the result of the oxidation of electron donors but controversy exists as to the nature of the coupling device, although in all hypotheses an ATPase (F_1), whose molecular nature has not been identified, is supposed to be involved (Boyer, 1975; Boyer *et al.*, 1977, Nagle & Morowitz, 1978).

However, the A–M system, regulated as proposed above, could satisfy the requirements of the energy transducer and explain the F_1 conformational changes, Williams' (Williams, 1973) "conductor" and "capacitor" being myosin and Mitchell's (Mitchell, 1966) proton gradient being a secondary event, regulated by the A–M system.

It can be concluded that:

(a) intracellular Na^+ concentration and thus membrane potential are determined by the phosphate and redox state of the A–M system; maximum intracellular Na^+ and thus minimum potential is obtained when the A–M system is contracted and minimum intracellular Na^+ and maximum membrane potential when the A–M system is relaxed; the intracellular concentration of K^+ is reciprocal to that of Na^+;

(b) The A–M system regulated as proposed above determines the Na^+ permeability and thus A-system amino acid and sugar uptake, maximum entry take place in the process of contraction and minimum entry when the cell is either in a relaxed or contracted state;

(c) cellular metabolism is regulated by the redox and phosphate state of the A–M system; "de-energized" myosin leads to an increase in metabolism, "energized" myosin to a decrease;

(d) the uncouplers exert their effects by competition with actin;

(e) the substrate taken up in the process of contraction is used to induce relaxation and for the synthesis of different cellular constituents in the relaxed state;

(f) the reduced substrate uptake and metabolism in the relaxed state eventually leads to a decrease in ATP and thus to contraction which, in turn, leads to increased permeability and metabolism; this leads to myosin reduction and ATP synthesis and thus to relaxation, i.e. cellular processes have a cyclic nature controlled by a periodic charge exchange between actin and myosin.

5. DNA Regulation

Some view cancer as being due to alteration in the cell DNA by carcinogens. However, the experiments of Gurdon (Gurdon & Woodland, 1968; Gurdon, 1968) and others which followed have indicated that DNA is regulated by the cytoplasm. Although no regulatory mechanism is given, it is currently believed that DNA is regulated via histones, non-histones chromosome proteins (NHCP), or both. The involvement of histones in genetic regulation is considered to be non-specific because they are constant in their concentration, not only from tissue to tissue but from species to species (Chambon, 1978; Stein, Spelsberg & Kleinsmith, 1974).

However, histone regulation of gene expression and chromatin structure is phosphate and redox dependent (Camerini-Otero, Sollner-Webb & Felsenfeld, 1976; Wilhelm *et al.*, 1978; Wong & Candido, 1978; Boseley *et al.*, 1976; Chao, Gralla & Martinson, 1979; Camerini-Otero & Felsenfeld, 1977*a*; Bina-Stein, 1977; Padros, Palau & Lawrence, 1977; Camerini-Otero & Felsenfeld, 1977*b*; Albert *et al.*, 1977; Hilton & Stocken, 1966; Bitny-Szlachto & Ochalska-Czephylis, 1978; Mac Gillibray, Paul & Threlfall, 1972; Patil, Narashimhan & Sreenivasan, 1977). Significant is the fact that although histones, which are acid extractable nuclear proteins, do not vary in concentration during the cell cycle, their thiol and phosphate status does, having maximum SH and phosphate in S and minimum in G_1 (Ord & Stocken, 1969; Sadgopal & Bonner, 1970). In fact, Ord & Stocken (1968) do not exclude the possibility that histones are related to the acid extractable contractile protein described by Sakai. That histones are myosin subunits is also suggested by the fact that histones combine with actin and induce actin polymerization (Magri, Azccarini & Grazi, 1978) and that

their molecular weights are similar to the molecular weights of the light chains of myosin.

Even if they are not related to myosin, the histones' thiol and phosphate state, and thus DNA, could still be regulated via the A–M system. It has been established that NHCP contain actin and myosin; that histone binding to DNA is influenced by NHCP; and that histones interact with NHCP via SS bridges (Bekhor & Feldman, 1976; Douvas, Harrington & Bonner, 1975).

It can be concluded then that DNA synthesis and transcription is controlled by the redox state of the membrane associated A–M system which, in turn, influences the cytoplasmic A–M system, NHCP and histones; differentiation resulting either by anisotropic arrangement of actin and myosin or by different degrees of actin and myosin interaction or both. In its turn DNA regulates protein synthesis. Thus a feed-back mechanism exists between the A–M system and DNA. The problem then is how mitotic agents effect the A–M system.

6. Carcinogens' Effects on A–M

The immediate effect of carcinogens on muscle is induction of contraction (Puszkin & Zucker, 1973; Bacq & Alexander, 1966). Initiation of cellular transformation leads to a decrease in cellular myosin and actin concentration, whereas differentiation and reversion to normal lead to an increase. This process is metabolically controlled and does not require protein synthesis (Wickus *et al.*, 1976; Ash, Vogt & Singer, 1976; Shizute *et al.*, 1976; Weber *et al.*, 1975; Pollack, Osborn & Weber, 1966; Duprat *et al.*, 1975). When uterine extract is treated with the mitotic agent oestrogen and then incubated with $NADPH_2$, a transfer of SH from an acid insoluble to an acid soluble fraction takes place, with a concomitant detachment of the acid soluble protein from a larger protein (Scott & Pakoskey, 1962). The above data taken in conjunction with the conclusion section 3(e) will suggest that the immediate effect of mitogens on the A–M system is the induction of contraction (actomyosin formation).

The changes in actin filament concentration at transformation and some changes in tubulin have been proposed as test for malignancy (Brinkley & Fuller, 1978). However, although tubulin and actin are considered to be two independent entities there does seem to be some connection between tubulin SH and the actomyosin system. Thus myosin appears to be a catalytic partner for microtubules in cell motility. Moreover, for tubulin polymerization SH are necessary and there is also some homology between

tubulin and actin (Hayaski, 1979; Nishida & Kobayaski, 1977; Mann *et al.*, 1978).

Although the above evidence is relatively new, the effect of carcinogens on the acid soluble SH has been known for half a century. In 1930, Vivario and Lecloux, in their work on germination, came to the conclusion that one of the factors which plays a role in germination is an increase in GSH, which could result from the hydrolysis of a more complex polypeptide. Hammet (1929) considered the SH–SS redox of utmost importance in cell division. Shift to the left could lead to division; to the right to retardation of growth.

Hopkins & Morgan (1943) and other workers reached the same conclusion. Thus it was believed that for division to take place an absolute increase in GSH is necessary (Stern, 1956). During division cells are independent of a direct energy supply from glycolysis or respiration, the energy being built up in advance in the form of SH (Swan, 1957). For division to take place a "division enzyme" is necessary to reduce the disulphide bond of the cell wall protein component (Nickerson & Falcone, 1956). Mortenson & Beinert (1953), studying bacteria, observed an increase of SH in the log phase which was preceded by a decrease in the lag phase. They concluded that "possibly the cells continue to age before initiating a new growth cycle".

One of the first to study the relationship between SH and carcinogen was Crabtree (1947), who put the hypothesis that a co-operation of carcinogens and SH-containing cell constituents is an essential first stage of carcinogenic action. The fixation of the carcinogen, through free SH groups to cell constituents, produces an alteration of the biomechanical potentialities of cell enzymes. Inhibition of tumour induction could be achieved by removal of SH groups necessary for combination with the carcinogen. Calcutt (1949), studying the effect of 3:4 benzopyrene on skin tumour induction, found an increase of SH a few days after the application of the carcinogen and postulated that tumour growth can be inhibited by inhibiting the SH increase.

It was generally agreed then that an increase in the acid soluble SH prior to division is a general phenomenon, the increase being observed in normal and abnormal cells and in subcellular constituents such as nuclei and chromosomes (Smirnova, 1973). These lead to the use of electrophilic agents for cancer treatment. However, although all the above workers observed the initial decrease in acid soluble SH after the application of the mitogens, no importance was attached to this phenomenon. The matter became even more confused by the fact that the acid soluble SH were considered to be glutathion SH and, although Sakai and Dan (1959)

had shown this not to be the case more than twenty years ago, with few exceptions this idea is still prevalent today.

At present there is ample evidence to show that carcingoens are oxidizing agents and that mitotic agents as diverse as insulin, partial hepatectomy, oestrogen, radiation, sperm and even smoking induce this cyclic variation in acid soluble SH groups and the associated changes in transport and metabolism (Scott & Pakoskey, 1962; Miller, 1970; Fraser & Cater, 1967; Czech, 1977; Harrington, 1967).

It can be concluded that

(a) the primary action of carcinogens and other mitotic agents is on the A–M system—by their electrophylic nature they induce charge transfer from myosin to actin and thus contraction;

(b) when contraction is neither so high as to induce osmotic cytolysis due to the very high increase in permeability, or to make the cell dormant (contracted), nor so small as to leave the cell in G_0, the cell will proceed to G_1;

(c) the contraction in G_1 will lead to an increased substrate uptake and metabolism which, in turn, will lead to a greater relaxation in S than in G_0; this, in turn, leads to minimum permeability and metabolism late in S, and thus to a maximum contraction and division in M;

(d) once the cell is activated it will continue to divide unless the daughter cell finds itself in a relatively strongly reducing or oxidizing environment.

These conclusions are illustrated in Fig. 1.

It can be seen that carcinogens induce a change in the amplitude and period of the G_0 thiol cycle. These changes and the associated changes in substrate transport and metabolism eventually lead to division.

Assuming that the G_0 thiol cycle is indispensable for cellular survival and the activated thiol cycle illustration in Fig. 1 is indispensable for division, the effects of oxidizing and reducing agents at different points in the thiol cycles can be predicted. As far as cellular death and mitotic delay are concerned, the expected effects of different doses of reducing and oxidizing agents along the activated thiol cycle are summarized in Tables 1 and 2 respectively.

7. Cancer Prevention and Treatment

It follows from the hypothesis that prevention of cancer can be achieved by using antioxidants to keep the cell in G_0. On the other hand, cell destruction may be produced using either high doses of alkylating and oxidizing compounds (carcinogens) which induce cytolysis, or by using high

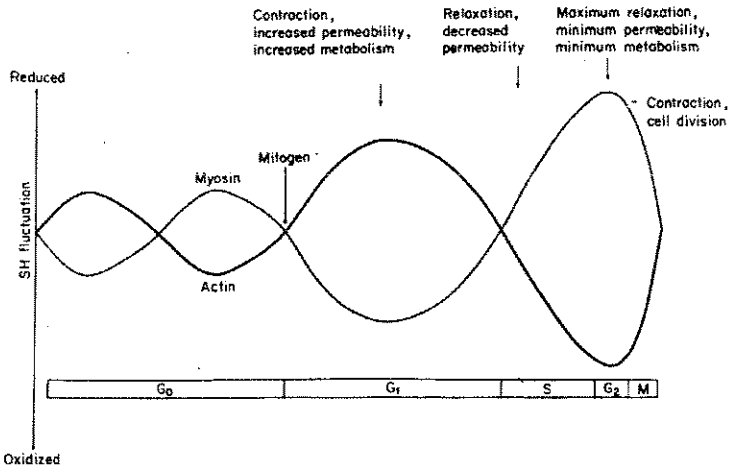

Fig 1.

doses of antioxidants which cause reduced membrane permeability and eventual starvation.

Although the use of antioxidants for cancer prevention and treatment has, so far, been very limited, there are some data which suggest their usefulness. Thus, antioxidants as diverse as butylated hydroxyanisole, butylated hydroxy toluene, ethoxyquin, yeast, cystein, cysteamide, vitamin E, 2,3-dimercapto propanol, vitamin A, heparin, vitman C, have been shown either to prevent carcinogenesis or inhibit cancer growth (Lusky, Braun & Woodard, 1947; Harisiadis *et al.*, 1978; Wattenberg, 1978; Leuchtenberger & Leuchtenberger, 1977; Rosen & Stich, 1978; Pauling, 1980; Cameron, Campbell and Jack, 1975; Regelson & Holland, 1958; Elias & Brugarolas, 1972; Apffel, Walker & Issarescu, 1975; Campbell, Reade & Radden, 1974; Slaga & Bracken, 1977; Marguardt, Sapozink & Zedeck, 1974).

Reducing agents have also been shown to revert the properties of the cancerous cell back to normal. For example, cell adhesiveness has been shown to be minimum in G_1 (Couchman & Rees, 1979); to be SH dependent (Grinnel, Milam & Srere, 1972; George & Vasudeva, 1975); and has been proposed to be regulated by the A–M system (Jones, 1966). Cell adhesiveness of cancerous cells is decreased but is returned to normal by reducing agents (Gosalvez, Vivero & Alvarez, 1979).

TABLE 1

Effects of reducing agents on different phases in the cell cycle

	G_1					
Time	Early	Mid	Late	S	G_2	M
Small doses effect	Lengthening of G_1, return to G_0	Accelerated S entry	Accelerated S entry	Accelerated G_2 entry, killing by starvation	Delay in M entry, killing by starvation	Division delay
High doses effect	Return to G_0, killing by starvation	Accelerated S entry	Accelerated S entry, killed by starvation	Killing by starvation	Killing by starvation	Division delay, increase in daughter's G_1 or return of daughter to G_0, some killing by starvation

TABLE 2

Effects of oxidizing agents on different phases in the cell cycle

	G_1					
Time	Early	Mid	Late	S	G_2	M
Small doses effect	Decrease in G_1	Osmotic killing	Delay in s entry dormant cell formation	Delay in S entry	Accelerated M entry	Accelerated division, decrease in daughter's G_1, dormant cell formation
High doses effect	Osmotic killing, dormant cell formation	Osmotic killing	Osmotic killing, dormant cell formation	Dormant cells, osmotic killing	Accelerated M entry, dormant cells, osmotic killing	Osmotic killing, dormant cells

It can be concluded then that antioxidants and diet manipulation, such as increase of magnesium intake and decrease of sodium, may prove to be a more effective regime of cancer treatment than current treatments.

This hypothesis, however, also predicts that relaxing agents, when given in small doses for a short duration, could activate the dormant cancer cells (cells stuck in G_1 due to lack of reducing power) present in advanced cases and especially in the interior of solid tumours. In this case, a treatment regime of surgery, followed by any of the A–M system relaxing agents, could be indicated.

8. Conclusions

The evidence presented supports the conclusion that the A–M system and its redox state appears to be the unifying factor in muscle function, impulse transmission, transport, metabolism, cellular division, and indeed the basis for biological function. The redox state of the A–M system appears to be periodic. This periodicity may be described in terms of a "thiol" cycle, which involves charge exchange between actin and myosin. Each tissue is characterized by a specific thiol cycle. Different changes in the thiol cycle will lead to different pathological states. Carcinogens are oxidizing agents and by this property they produce a characteristic thiol cycle which leads to cell division. This carcinogen induced thiol cycle, and thus division, can be inhibited by using relatively high doses of either oxidizing or reducing agents.

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