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Force, Development, and Neoplasia: Development from Another Perspective as Illustrated through a Study of in vitro *Plant Development from Neoplasm*

Abstract. *Differentiation from the neoplastic state can be a dynamic adaptation to the localized stress of increasing cohesive forces in tissue. Repulsive forces, occurring within and between cells, are seen as leading to de-differentiation into the neoplastic state or neoplasm. During early development, especially where and when mitosis occurs frequently, cohesive and repulsive forces may necessarily co-exist in oscillating degrees. Correspondingly, cohesive-force and repulsive-force generating metabolites may co-exist in oscillating concentrations. Cancer or neoplasia occurs, according A. Szent-Gyorgyi, when cohesiveness breaks down locally, probably thru the conversion of methylglyoxal into lactic acid. Cancer may also occur due to the accumulation of such putatively, repulsion-generating factors as lactic acid. Plant tumors in vitro respond adaptively to cohesion-generating chemicals, such as ascorbic acid and methylglyoxal, by generating buds, embryos, and plantlets.*

1. FORCE AND DEVELOPMENT

Physical forces of various types are essential for the complex structure, pattern, and function of living matter. The very integrity or unity of a living organism, essential for its survival, and the enhancement of that integrity through development, require forces, especially cohesive forces. The creation, specificity, and precision of that integrity would necessarily involve and require the generation of diverse forces of changing, non-uniform vector configurations thru time and space.

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As manifested in biological development, this generation would not be random. In accord with an universal principle governing force in natural phenomena (P. Lieber [1969]), it would be an adaptively necessary or directed enhancement of the uniformity of force configuration within and by means of a matrix of non-uniform force, a dynamic stress. Implicit in this increasing dynamical uniformity would be an increase in dynamical unity. Such a growing unity would be based upon the generation of an increasingly uniform cohesiveness within increasing dynamical diversity or non-uniformity, this generation utilizing the very dynamical non-uniformity. Such non-uniformity of force would be manifested as a dynamical imprinting or stress, opening-up dynamical avenues for globally increasing uniform cohesiveness or the uniformity of cohesive forces. Dynamical equilibrium would be a limiting or special case of such increasing dynamical uniformity. This increased uniformity within diversity, having its source in emerging cohesive forces, would have definition or manifestation in an increased, cohesive geometry of increased organizational complexity.

Such a dynamic, cohesive geometry, patterned via imprinting by non-uniform forces implicating both genome and environment, would necessarily be involved in the evolution and development of living organisms. Through development, these dynamics would confer on the organism an increase in adaptiveness vis-à-vis its dynamical nitch to which it is connected by forces. The very dynamics of the development would use the stress of its non-uniform, force connections to its environmental and internal nitch in order to generate the organism's adaptation to internal and external dynamic environments: Development would be the means for the dynamic adaptation to stress, using the very dynamic non-uniformity of the stress to generate itself, and thereby, the adaptation.

Molecular phenomena have been seen as playing an important role in development. However, molecular phenomena, such as biochemical reactions and their products, cannot in themselves account for the unity or cohesiveness within the complexity of specificity that goes to make up the dynamical geometry of the organism. The ultimate role of biochemical, molecular processes in a living organism may be their involvement in the creation of critical forces or force-configurations at particular regions and periods throughout the protoplasm, and so

generate critical, functional geometries during development. These forces rendered thru biomolecular phenomena would be an important dynamical means through which development would achieve increasing organismal integrity and hence the adaptation of a high degree of organization. Neoplasia or cancer could be the result of a breakdown of, or a major decrease in, the cohesiveness on which such integrity is based, and there is much experimental support of this.

With regard to such forces, A. Szent-Gyorgyi ([1979], [1980]) presents a new perspective on the causation of cancer. Based on ample experimental data, he maintains that methylglyoxal (MG) is the major regulator of cell division and growth, the barrier to neoplastic reversion. According to Szent-Gyorgyi, electrical conductivity of proteins is necessary for cells to perform their normal functions, and MG attached to protein molecules makes them more conductive by removing electrons from the protein valence bands, thus promoting movement of the remaining electrons along the valence bands of protein molecules. This process of electron removal or transfer is referred to as electronic desaturation. In a neoplastic situation, there is no room in the electron orbitals for the movement of electrons along protein molecules or to other types of complex molecules. When there is no or only a very small amount of MG available, as when it is converted by the enzyme glyoxalase to lactic acid, there cannot be electron-charge transfer from proteins, and the cells revert to and stay in the neoplastic state. His research also indicates that ascorbic acid synergistically influences the action of MG by attaching to MG and conveying electrons to oxygen. This process of electron transfer and mobility thru desaturation promotes in effect the generation of complex electromagnetic fields, including van der Waals forces, and it is through such cohesive fields that a high cohesion between and within cells is developed. "K. Laki and J. Laki have shown that the electronic desaturation of protein leads to a strong increase of interactions and enhances cohesive forces by orders of magnitude" (Szent-Gyorgyi [1980]). In neoplastic tissue, cohesive forces are of very low degree, if at all present (Szent-Gyorgyi [1979]). This would imply that dynamic connections in the form of cohesive forces are needed to maintain the differentiated integrity of an organism and are most likely necessary in various degrees during the developmental process itself; neoplasia in the differentiated state ensues when such cohesive

forces become greatly reduced or cease to exist.

Though these principles with regard to ascorbic acid and MG are universal to life, according to Szent-Gyorgyi, generally, only mammalian systems have been investigated in this regard. The emphasis had been on inhibiting the growth of tumors, and this was successfully accomplished (Szent-Gyorgyi [1965]; Egyud and Szent-Gyorgyi [1968]). Until recently (e.g., Langdon and Hickman [1987]), the question of reverting the neoplastic state in mammals through the initiation of differentiation was not even addressed. Furthermore, there had been no investigations as to how such principles would apply to *in vitro,* plant tissue culture research in which neoplasms of some species have been induced to regenerate, under given culture conditions, buds and plantlets, and in some cases, embryos. In this regard, I proposed (Lieber [1979]) to investigate the effects of MG and ascorbic acid on plant tumors grown *in vitro* with the aim of promoting organogenesis (or development) in the undifferentiated, neoplastic tissue of certain plants, such as pine. In pine, organogenesis could not be induced by particular concentrations of plant growth hormones (or growth regulators) in culture medium, as had been the case with some other plants such as tobacco.

In theory, organogenesis in such situations could be promoted by applying MG and ascorbic acid in the culture medium to increase cellular or tissue cohesion within many regions or foci, but, not increasing it to the degree where too much cohesion would inhibit or repress differentiation. The neoplasm was seen not as being uniform in its response to increasing cohesive forces, or stress. Some parts would respond adaptively by having their growth reduced or limited, while others would respond adaptively by each generating an internal, increasingly uniform cohesion and becoming differentiated. Such differentiation would be using the very dynamic stress of the increasing cohesive forces in the adaptation. This adaptive differentiation would lead to the completed development of a bud or plantlet originating from the plant tumor or neoplasm *in vitro.* These plant tumors, known as calli, can be derived through the use of plant growth hormones in culture media, be maintained aseptically on such growth media, and then be subcultured onto bud/plantlet regeneration medium containing MG and ascorbic acid. These substances can be added in various concentrations to a basic plant culture medium called

MS (Murashige and Skoog [1962]) or variations of it.

2. MG AND ASCORBIC ACID PROMOTE PLANTLET DEVELOPMENT

With this new theoretical approach as a possible means of promoting developments from plant tumors, many pine tumors were derived *in vitro* from needle fascicles of the southern pine, *Pinus taeda.* Three to four weeks after subculturing such tumors onto plantlet-regeneration and control media, MG at 1.38 mM and ascorbic acid at 10 mg/L promoted the *in vitro* and frequent development of bud primordia (and possible embryos) from the neoplastic tissue, the growth of the latter being inhibited by the MG and ascorbic acid in the medium (Personal Communication to A. Szent-Gyorgyi [1980]). More recent studies were undertaken with another pine species, *Pinus muricata.* It was found that an increased concentration of MG with ascorbic acid promoted composite bud and embryonic plantlet development from needle callus. The embryonic plantlets were exceedingly small and in various stages of very early development (see Figure 1). Some had produced needle primordia.

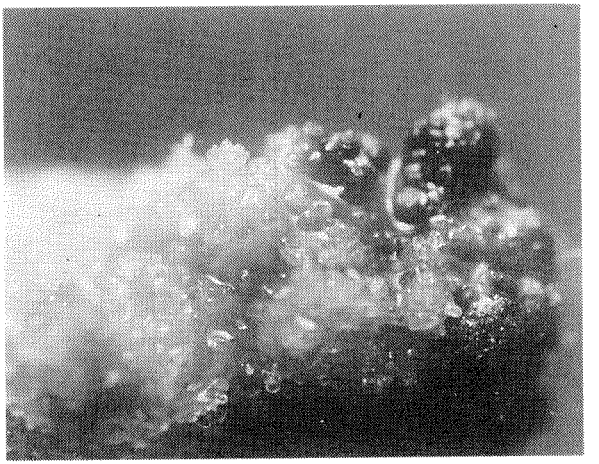

Fig. 1 – Pine embryos of different developmental stages emerging from brown, inhibited needle-callus (neoplasm) cultured on growth medium containing methylglyoxal (MG) and ascorbic acid. Note the very small, embryonic plantlet in top-center. Callus was cultured on this medium for 23 days at 25°C. Photoperiod was 16 hours. (Magnification at 20X).

Additional investigations of this type were undertaken from 1992 to 1994 on a plant species in which *in vitro,* induced regeneration of buds and plantlets from neoplastic tissue has hitherto proved very difficult. In such studies pertaining to a plant species of this type, the green bean, *Phaseolus vulgaris,* MG and ascorbic acid, present in regeneration medium, repeatedly promoted, with the growth hormone, benzylaminopurine (BAP), bud and plantlet development at high frequency from compact, meristemic callus produced by and adjoined to somatic tissue (e.g. apical explants of shoots) and also from compact callus produced by and adjoined to immature embryonic tissue (Figures 2, and 3). In one experiment, the mean number of plantlets (or buds-into-plantlets) generated per neoplasm was 83, with one neoplasm generating as many as 110 plantlets. In some situations, possibly related to a lower sucrose concentration, MG and ascorbic acid also promoted the regeneration of embryos, many with emerging shoots, from somatic callus (See Figure 4). Such somatic embryogenesis had not previously been observed in this species.

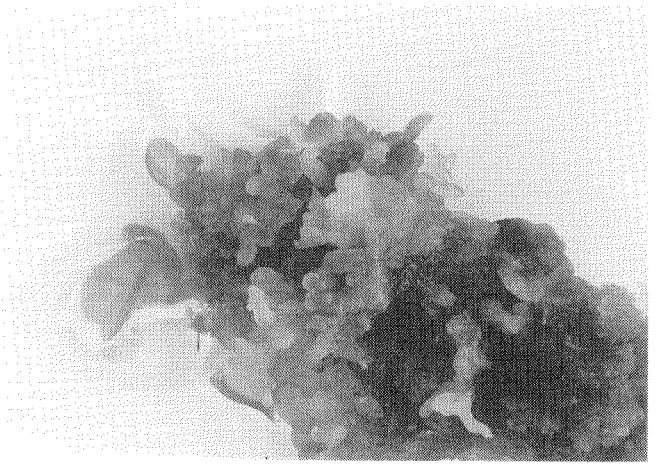

Fig. 2 – Green bean plantlets and buds emerging from callus (having an immature embryo source) on MG and ascorbic acid containing medium. Culture period during which buds/plantlets arose was six weeks at 25°C, photoperiod being 16 hours. Medium contained 0.1 mM MG, 10 mg ascorbic acid/L, 0.383 mg BAP/L, and 0.05 mg IBA (an auxin)/L. pH of culture medium was 5.9.

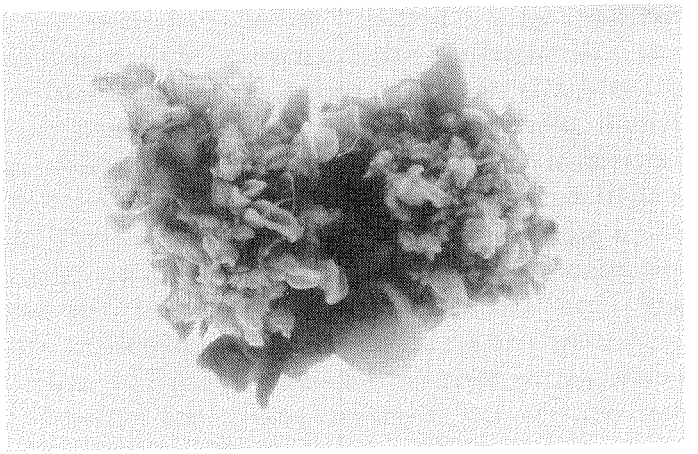

Fig. 3 – Regeneration of bean plantlets from somatic callus derived from a shoot-apex, cultured on MG and ascorbic acid containing medium. Culture medium contained 0.1 mM MG, 40 mg ascorbic acid/L, 2 mg BAP/L, 0.2 mg NAA/L, 3% sucrose, and a K_2 Citrate PO_4 buffer. Culture period was for one month at 25°C. Photoperiod was 16h.

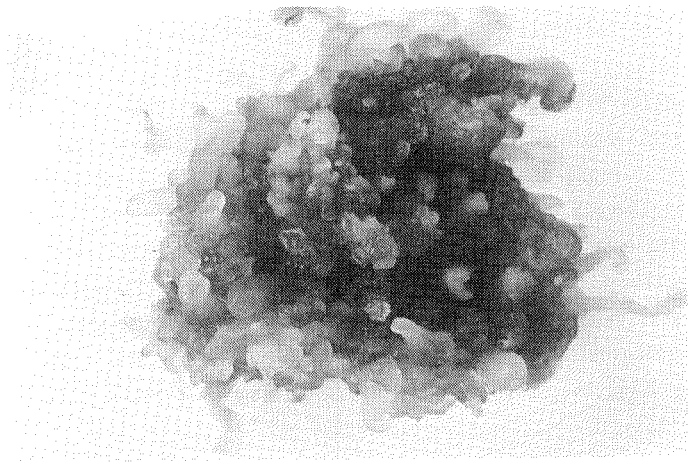

Fig. 4 – Bean embryos regenerated from somatic callus derived from a shoot apex. Many embryos have produced plantlet-shoots. This example of somatic embryogenesis occurred on a growth medium containing 0.1 mM MG, 10 mg ascorbic acid/L, 1 mg BAP/L, 0.1 mg IBA/L, and 0.6% sucrose. pH was 5.9. Culture period was for six weeks at 25°C. Photoperiod was 16h.

In the case of bean, 0.1 mM MG appears to be the optimal concentration with regard to frequency and rate of development. However, there is the suggestion that this may vary during development, where 0.1 mM MG can, after a period, become inhibitory of early bud-primordia development, possibly by accumulating in tissues, or regions thereof, at concentrations far greater than 0.1 mM. Concentrations of 10 mg/L to 40 mg/L ascorbic acid appear most effective with MG in promoting uniform plantlet developments from neoplastic meristem, though higher concentrations are not ruled out in this regard. There is indirect evidence from this (and other data) that MG and ascorbic acid act synergistically in promoting such bean-plantlet development. Relatedly, MG is very much associated with the production of a very deep or emerald green colour in plantlet tissue, strongly suggesting that MG is involved in chloroplast development. Chloroplasts are very much needed for the absorption of electromagnetic energy used in plant development.

These studies with bean also suggest that there are cases where concentrations of MG less than 0.05 mM would be sufficient along with 15 mg/L to 40 mg/L ascorbic acid for the promotion of high frequencies of bud and plantlet developments from neoplastic tissue during long periods. Moreover, there is the indication that the frequency of development from the stage after the bud-primordia and on thru plantlet maturation, i.e., later development, is greatly increased or promoted through the contribution of MG and ascorbic acid; but, increased concentrations of MG, inferred to be accumulating in given tissue regions, appear to be very inhibitory in that regard. Various increasing concentrations of ascorbic acid do not appear, however, to be inhibitory during any period or in any tissue region throughout much of development. In fact, ascorbic acid at a concentration of 40 mg/L, as opposed to concentrations of 2 mg/L and 4 mg/L, and without MG in the growth medium, can also promote a high frequency of bud/plantlet development from neoplasm, even from neoplasm maintained in culture for five months through subculturing. This does not mean, however, that MG is not present in the plant tissue, where it would have been present naturally to some extent. It would only be needed in lesser concentrations, in some developmental situations, when ascorbic acid is present in necessary concentrations for a high frequency of development. An increased concentration of

MG with ascorbic acid seems, however, to be necessary in bean for the uniform completion of many bud-into-plantlet developments, and for the completion of somatic embryogenesis. Namely, an increased concentration of MG (with ascorbic acid) may be necessary, beginning at a critical developmental stage, for the uniform completion and stabilization of the later stages of bean development. The concentration so needed might very well be species dependent, especially so, if one also considers the investigations of *in vitro* tobacco-plant development from neoplasm.

In such, related investigations, I studied the effect of MG and ascorbic acid, present in the growth medium, on plant tumors derived from tobacco leaves. Unlike pine calli, calli from the tobacco plant can produce buds and plantlets under given hormonal conditions *in vitro.* Thus, it was thought to be a more amenable biological system for studying the functional effects that reverse the neoplastic process. Perhaps, in this case, the functional effect of MG and ascorbic acid would be to increase the frequency of organogenic development from undifferentiated, neoplastic tissue.

The investigations with tobacco gave rise to the following results. MG acting synergistically with ascorbic acid inhibited the growth of the tobacco neoplasms while greatly enhancing the frequency of differentiation (or organogenesis) within or from regions of such inhibited neoplasms. This differentiation (or completed differentiation) was expressed, as in the case of bean, as the number of plantlets emerging from non-growing neoplasms or calli relative to different controls where MG and ascorbic acid were not in the same culture medium or present separately (e.g. Table 1 and Figures 5a and 5b). The rate of development of these plantlets was also enhanced by MG and ascorbic acid. A concentration of 1 mM MG appears to be the optimal concentration with regard to frequency and rate of development in this species. This enhancement of developmental frequency and inhibition of neoplastic growth points to a differential effect of MG acting with ascorbic acid. Namely, where mitosis is inhibited in neoplastic tissue by these chemicals, mitosis involved in organogenic tissue is allowed or enabled by these very same chemicals.

Though lower concentrations of MG enhanced the frequency of development, this development was incomplete. Regarding the lowest concentration tested, MG at 0.05 mM with 40 mg/L ascorbic acid

only induced the production of bud primordia at high frequency. With concentrations of MG much higher than 1 mM, no or very little development of any type ensued, with the growth of the calli being completely arrested. However, it is important point out that the inhibition of development at higher MG concentrations depended on the initial size of the callus explant. For example, with an initial callus size of 3-5 mm in diameter, inhibition of development by 2 mM MG was generally the situation. With a larger initial callus size of 1 cm-2 cm, the frequency of development was greatly increased, but such

Table 1
The effect of methylglyoxal (MG) and ascorbic acid (C) on the generation of tobacco plantlets from calli (neoplasms)

Culture medium	Exp. (code n°)	N° of tested calli	Plantlets per callus (mean n°)	Comments
M4	1	28	3.0	Plantlets pale green
	2	39	3.9	Less complete in development
	3	24	2.9	
M4+MG+C	1	50	29.0	Planlets green, generally
	2	31	20.7	uniform at complete development
	3	25	24.1	great variation in frequency (up to 50 to 30-40 plantlets/callus)
M4+MG	2	34	2.2	Most calli with no buds-plantlets; two with 9-11; most calli brown*
	3	23	9.9	Plantlets greener; one callus brown
M4+C	2	34	10.4	Plantlets greater than on M4
	3	24	9.3	

M4: MS medium with B vitamins, sucrose 3%, glycine, K_2 citrate, $P0_4$ buffer; pH 5.8
6-benzylaminopurine 2mg/L; a-naphthaleneacetic acid 0.2 mg/L; agar 0.8 %
MG: methylglyoxal 1mM
C: ascorbic acid 40 mg/L
32 days cultures: no significant changes in plantlet freq. with extended incubation.
*According to Szent-Gyorgyi [1979] a higher conc. of MG can give tissues a brown color.

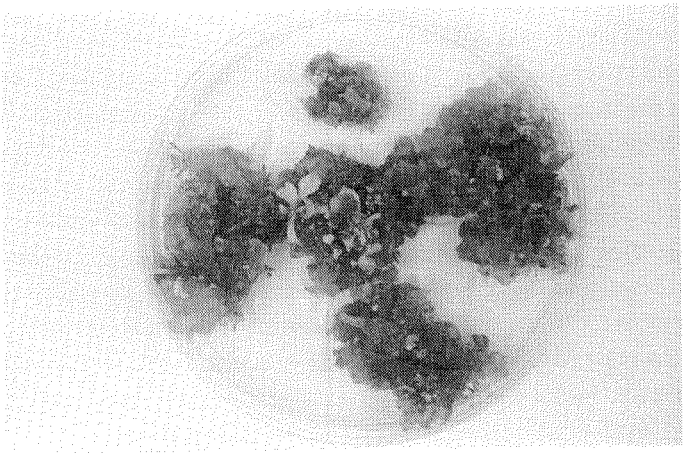

Fig. 5a – Tobacco calli (neoplasms) cultured on a control medium (M4) lacking ascorbic acid and methylglyoxal. Culture time was one month at 25°C, with a 16 hour photoperiod.

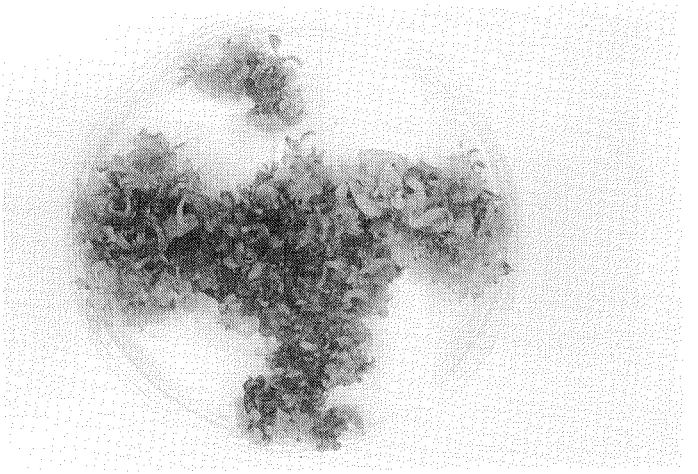

Fig. 5b – Green tobacco plantlets emerging from neoplasms cultured on M4-MGC medium containing 1 mM methylglyoxal and 40 mg/L ascorbic acid for one month at 25°C, with a 16 hour photoperiod.

plantlet development was generally incomplete. In some cases, there was also evidence that MG could accumulate in callus-tissue regions in high concentration, and, in so doing, inhibit organogenesis, even on culture medium containing 1 mM MG (Table 1, Experiment 2, M4-MG). Smaller, initial callus-explants on medium containing 1 mM MG (with 40 mg/L ascorbic acid) appeared, however, to result in a further increase in the developmental frequencies of plantlets.

Regarding frequency, increasing the concentration of the plant-growth regulator, BAP – which is generally used to promote somatic organogenesis in a relatively lower concentration – while the concentrations of MG and ascorbic acid remained 1 mM and 40 mg/L respectively, had a significant inhibitory effect on callus growth and plantlet/bud development. Very few buds and plantlets developed. The auxin NAA is a plant growth hormone or growth regulator used in culture media in given concentrations to induce and maintain callus or neoplastic growth from differentiated, plant tissue. When present in a particular high concentration relative to BAP, callus growth will ensue from organized plant tissue. NAA was used to initiate the callus or neoplasm used in this study. However, when MG and ascorbic acid were also present in the medium, such attempts at callus initiation from organized, plant tissue, using an high auxin concentration, were repeatedly unsuccessful. Relatedly, when auxin was not present in the culture medium, but BAP was present in normal concentration, the frequency of plantlet development from tobacco neoplasm significantly increased. With the addition of MG and ascorbic acid to this medium, the frequency of these developments increased far more. (Data not tabulated). Such developments were generally complete.

3. METABOLITES AS AVENUES FOR THE GENERATION OF THE FORCES NECESSARY IN DEVELOPMENT AND NEOPLASIA

These investigations have clearly shown that in diverse plant families MG and ascorbic acid are necessarily involved in generating and completing developments from neoplastic tissue, most probably in synergy with plant growth hormones such as BAP. However, the previous results with tobacco also indicate that BAP at very high concentration relative to auxin, can also inhibit plant development or

organogenesis, possibly by acting synergistically with MG and ascorbic acid. Relatedly, the neoplastic, inducing effect of the auxin, NAA, can also be inhibited by MG and ascorbic acid. As these two growth regulators, NAA and BAP, were used along with MG and ascorbic acid in these investigations pertaining to the induction of organogenesis, these results suggest a profound relationship or interaction between effects of these chemicals in that regard. These results may also point to classes of chemicals which respectively have different, but profound dynamic effects necessary for development. BAP, MG, and ascorbic acid, though chemically unrelated, may nevertheless be representative of a larger group of chemicals that synergistically enhance or generate organogenesis by promoting the dynamic of cohesion. In too much concentration, however, the agents of cohesion could inhibit the high frequencies of mitosis, involved during the earlier stages of development, by promoting too much cohesion within and between cells, thereby inhibiting development. As might be predicted from this, various, polar organic solvents were found, at particular concentrations, to induce differentiation from neoplastic cells, regardless of the solvents' chemical structure (Langdon et al. [1987]). These solvents were found to have a cytostatic effect on cells at concentrations greater than those needed to promote differentiation.

In contrast, the auxins such as NAA could be members of a chemically diverse group of chemicals that promote, in given concentrations, disorganized, neoplastic growth by reducing or cancelling out the forces of cohesion between and within cells thru the creation of repulsive, electrical forces. The auxins are known to cause a loosening within cell walls. A deeper implication is that for normal and enhanced development, precluding neoplastic induction, the concentration of these particular chemicals must be in particular concentrations relative to one another through time and space for the developmental-generating, dynamical configurations to be existent between and within cells. The cohesive, dynamic effect of BAP, MG, and ascorbic acid would be to counter or balance the dynamic, repulsive effect of too much auxin by enhancing just enough net cohesive forces within tissue so as to enable the coherent regulation of mitosis involved in and necessary for organogenesis.

The auxins would serve to generate just enough of a counter force to the excessive cohesive effects of chemicals such as MG, which,

through too much cellular cohesion, mitosis could not occur at all. In order to allow for the recurring and controlled process of mitosis in a developmental situation, there would necessarily be the periodic enhancement of the repulsive effect of the auxins, while, during the completion of mitosis, and between mitotic cycles, there would necessarily be an increase in, or a re-establishment of, the cohesive effect of MG, ascorbic acid, and BAP-type growth factors, as well as that of any cohesion-generating chemical. During development, especially its earlier stages, there would be a periodic alteration between greater cohesion within tissues and a diminishing of cohesion thru, in large part, the generation of repulsive forces. This would mean a recurring alteration between cellular cohesion and repulsion. The dynamic alteration between increasing and lessening cohesion within the developing organism would be a periodic, dynamic non-uniformity or non-equilibrium occurring thru and necessary for development. Continually, too much repulsive force via too much auxin – or other, repulsive-force generating chemicals – would lead to the neoplastic, implicated mitosis of uncontrolled growth. On the other hand, continually, too much dynamic cohesion generated by means of MG would lead to the cessation of mitosis, hence growth and development. Particular degrees of cohesive force in neoplastic tissue thru space-time would be necessary for, and thereby allow, the maximum degree or frequency of organogenesis to occur after such cohesive forces are generated.

The later or final stages of development and the stabilization of differentiation would require less frequent or no mitosis, and this would be based on the generation of a very high degree of cohesion within and between cells. As we have seen, MG and BAP at much higher concentrations (or accumulations) inhibit development, and thus they may serve in the role of agents which stabilize the final developmental state or stages by being involved in ever increasing, global cohesion. To overcome this cohesive, dynamic effect and so induce neoplasia in the form of tumors, a large amount of auxin – or repulsive-force generating chemicals in general – would have to be produced *in vivo* or added to the culture medium. As one will recall, auxins in high concentrations, with relatively much less BAP, are used to generate calli from organized plant tissue, and yet, it is not understood developmentally why this is the case. Relatedly, as implied by

earlier data, MG with ascorbic acid generated cohesive forces of such degrees that the addition of auxin at a concentration normally neoplastic-inducing was not sufficient enough to counter the cohesive force, leaving a net degree of cohesion to maintain the continuation of the differentiated state. In this regard, Szent-Gyorgyi (1979) argues that the removal of MG from mammalian tissue, through its conversion by the enzyme glyoxalase to lactic acid, results in the cancerous state. In Douglas fir needles, a highly differentiated tissue, MG was found to be present with no active glyoxalase, whereas in callus or neoplasm derived, via auxin application, from such needles, active glyoxalase was present in significant concentration, and no MG was evident (Smits et al. [1981]).

However, even the continual presence of MG in differentiated tissue may not always be sufficient to counteract a potent source or avenue of repulsive force leading to or maintaining neoplasia. In this regard, a catabolite of MG, lactaldehyde, produced through the glyoxalase-enzyme system, was found *in vitro* to counteract the MG-initiated, deleterious effect on the growth and survival of mouse and human carcinomas (Ray et al. [1991]). One can speculate that it does so by generating or conducting a high degree of repulsive forces, negating the extreme, cohesive effects of MG on neoplastic tissue. One can also speculate that the related catabolite, lactic acid, also does so, and thus may indirectly contribute, along with the loss of MG, to the generation of the Douglas fir callus (tumor). Based on his earlier research, Spirito [1995] shows that lactic acid is in fact implicated in the generation of neoplasia in plant and animal tissue.

According to Spirito, the accumulation of lactic acid leads to an inflammatory process in higher mammals which, evidence suggests, could promote and maintain tumorgenesis. Normally occurring as a response to tissue damage in higher animals, inflammation involves regenerative, cellular proliferation, in which, a very low degree of cohesion could be existent. In a similar manner, when a higher plant *in vivo* is injured, the generation of scar tissue in the form of callus at the site of injury is the normal response thru a controlled, increased production of auxin. Neoplasia might thus be an extreme variation of a normal, adaptive healing process in which repulsion-generating agents are involved.

In view of these phenomena, lactic acid and lactaldehyde may thus

be additional and potent representatives of a class of chemicals or metabolites which contribute to neoplasia in the developed organism thru the generation of high degrees of repulsive forces. This would be without the cohesive effect of metabolites such as MG that could counteract such repulsion in many situations through and after development.

In his investigations with MG and ascorbic acid, Szent-Gyorgyi did not completely address the question of organogenesis and the role such chemicals could play throughout development, leaving important questions unanswered in that regard. Certainly the phenomenon of plantlet regeneration from neoplasm or callus was not addressed in the theoretical context of his research. The investigations of this author suggest, much more completely, ways in which cohesive-force generating chemicals play in plant development, and by extension, mammalian development and point to classes of chemicals, which, by altering degrees of cohesion with degrees of repulsion, may play a general role in the development of all organisms and in the generation and inhibition of neoplasia. As suggested earlier, chemicals completely unrelated in structure or in apparent function may nevertheless serve on a deeper, dynamical level the same dynamical function of enhancing cohesion between cells, and thereby, precluding the generation of neoplasia. These chemicals, such as MG and BAP, may in chemical combination serve as even greater sources of cellular cohesion in humans, and thereby, be powerful anti-carcinogenic agents.

If BAP, a very likely cohesive-force, generating agent in plants, could have, at given concentration, an anti-carcinogenic effect in mammals, then one can predict that an auxin such as NAA would have the opposite effect in mammals; namely, it would have a carcinogenic effect in mammals by virtue of its presumptive cohesive-reducing or repulsive-generating dynamic. Another plant growth regulator, the auxin 2,4-D, capable of inducing neoplasia in plant tissue, and chemically similar to NAA, is possibly carcinogenic in humans (Ibrahim et al. [1991]).

As we have seen in this study, not only can neoplasia be inhibited in plants by MG and ascorbic acid, far more importantly, it can be reversed in plants through the induction or generation of organogenesis by those chemicals acting synergistically with one another, possibly through these metabolites being avenues of a periodic, dy-

namic cohesive-field. Relevantly, the use of a polyamine-biosynthesis inhibitor arrested the growth of Datura callus and led to its differentiation. In this situation, it was found that the level of glyoxalase was low as well (Deswal et al. [1993]). This would suggest that a consequential accumulation of MG in the callus tissue – and its cohesive effects – was also implicated in its differentiation. The inhibition of polyamine biosynthesis, and its metabolic consequences, could have contributed a pervasive, cohesive stress to which MG-mediated differentiation was a dynamic adaptation. In a related situation, N-methylformamide, a polar solvent, induces *in vitro* the differentiation of promyeloctic leukaemia cells into neutrophils and that a high concentration of MG was not present during the differentiation (Hooper et al. [1988]). These same studies, however, also suggest that MG is needed or present in much higher concentration during the later or ending stages of leukocyte differention to neutrophils *in vivo.* It is possible, if not unlikely, that N-methylformamide is a cohesion-generating chemical, especially if it were to be chemically bound to MG, creating a particular dynamic, cohesive field involved in the adaptive reversal of leukaemia thru differentiation. By MG being bound to N-methylformamide, only MG in free form would thus be detected in low concentration during differentiation, and thus may very well have been utilized in higher concentrations in bound forms for differentiation. Only with the necessary presence of bounded MG, might N-methylformamide be sufficient for the induction of this *in vitro* differentiation. The addition of ascorbic acid might have hastened the process. In this regard, ascorbic acid and the vitamin B6 group stimulated the terminal differentiation of preadipocytes into adipocytes (Kawada et al. [1990]).

In my investigations with tobacco, the incompletion of organogenesis, when MG was much less than 1 mM, would suggest important information regarding the changing concentration of MG during development. In probably bound form with ascorbic acid and protein, MG in a critically higher concentration, as opposed to a relatively low concentration, is necessary during the later stages of development or differentiation, as opposed to early development, and MG is probably necessary in relatively very high, though differing, concentrations for the stabilization of the completed development in different species. On culture medium without MG and ascorbic acid, but containing

BAP, most bud primordia in tobacco and bean did not develop into plantlets, even upon extended incubation.

Perhaps, in view of this, the different types of metabolites, implicated in the generation of cohesive force fields, must behave in that regard in particular combinations and concentrations, or singularly, only during certain stages or periods of development. If not, for example, BAP alone might be responsible for creating a degree or configuration of cohesion such that only a few undifferentiated regions develop completely, whereas with MG and ascorbic acid in addition to BAP, there could be cohesion of such a significant degree and of dynamic configuration so as to enable development to be completed throughout many regions.

If particular cohesive fields between cells are necessary for the completion and integrity of development, one would predict that there are also chemicals on cellular surfaces or in membranes which also mediate such cohesive forces. Cellular adhesive molecules (CAMs) are glycoproteins found on cellular surfaces in mammals, and these have been found to play a critical role in mammalian differentiation, especially in neurogenesis, with their temporary absence in embryonic budding resulting in a dedifferentiation (Bondi et al. [1994]). Apparently, according to these authors, the degree of adhesion between cells, necessary for development, can be modulated or changed during development through the removal of part of the sugar moiety from the CAMs. This would indicate that the degree of cohesive force generated through a cohesion-mediating chemical, during and for development, can itself change and be contigent on – and hence be relative to – the internal dynamical milieu of the protoplasm. Such a milieu would include other sources of dynamic cohesion and repulsion. In this regard, electronic desaturation of such CAMs by MG and ascorbic acid could very well contribute to the very high degree of dynamic cohesion necessary for promoting and stabilizing more complex developmental stages.

In contrast, a dynamic milieu might ensue in which such CAMs could become cellular avenues of repulsive forces. In so doing, they could generate repulsive forces between cells, negating cohesion, and so lead to the neoplastic state. A variation of such a situation could involve protein kinases. These are enzymes that are produced by oncogenes. Such enzymes phosphorylate the structural protein, vinculin,

among others. Vinculin makes up the structure of the adhesion plaques that help bind cells to one another. Researchers speculate that increased phosphorylation of these plaques in cancer cells could decrease their adhesion to one another (see Mange and Mange [1990]).

Thus, depending on dynamic milieu, particular chemical/molecular avenues of cohesive force could become mediators of repulsive force or means for the reduction of cohesion. On the other hand, chemical agents, normally mediators of repulsive force, could become mediators of cohesive force in another dynamic milieu. Auxin can promote neoplastic growth in the organized tissue of a plant, as we have seen. However, it is well known that auxin, when applied in given concentration at the base of a plant, can promote roots from the base of the developed plant. Roots are like the mirror or complementary image of a plant, and thereby, in a different, complementary, dynamical spatial-temporal milieu, auxin could become an agent of cohesive forces, as opposed to repulsive forces, necessary for and leading to root development.

The neoplastic situation promoted in somatic plant tissue by auxin, in a given dynamic milieu, does not mean the complete loss of cohesive forces from other sources. Even the long-term maintenance of callus or neoplastic tissue *in vitro* may require some degree of cellular cohesion, otherwise the necrosis of the tissue could ensue. Callus of *Pinus taeda* derived from various, somatic tissue sources – such as needles, stems, and buds – cannot be maintained beyond one or two subcultures, each of three weeks duration, without necrosis. However, with 40 mg/L ascorbic acid in the culture medium containing a potassium-citrate-phosphate buffer, green pine callus on this medium can be maintained indefinitely over many subcultures in a healthy state (Lieber [1980]). It is possible that ascorbic acid, acting synergistically with the buffer, can enhance cellular cohesion to such a degree where necrosis – the complete breakdown of the viable integrity of the neoplastic tissue – is prevented.

It was also found that the *in vitro* maintenance of conifer callus is tissue and species dependent. For example, pine callus derived from embryo tissue in *Pinus taeda,* as opposed to somatically derived callus in that same species, can be maintained indefinitely without the addition of ascorbic acid to the culture medium; where, in contrast, the somatically derived callus of another pine species can be maintained

indefinitely on standard culture medium without ascorbic acid. These results may suggest that variation in dynamical cohesion required for viability, organogenesis, and completed development have epigenetic and genetic parameters. In this regard, 1 mM MG is probably the concentration present in and necessary for healthy, non-neoplastic, mammalian tissue (Szent-Gyorgyi [1979]). This probably means the concentration of MG needed to maintain completely developed mammalian tissue and organs. In contrast, as we have seen, 1 mM MG and 0.1 mM MG appear respectively optimal for developing plant organs, as opposed to completed development, in at least two respective plant families, and higher, respective concentrations of MG are probably necessary in these plant families for the stabilization of the completed development. The very incidence of cohesion-promoted developments seems to be related to taxonomic family or genetic/epigenetic history.

Further evidence of this species or family dependency resides in the fact that in using standard culture media and conditions, one can induce organogenesis in somatically derived tobacco callus but not in somatically derived pine callus, the pine being a very different genetic or taxonomic group from tobacco. However, as recalcitrant organogenesis can be overcome in one genetic group and the frequency of such greatly enhanced in another thru the application of chemical factors that appear to enhance tissue cohesion, it would seem that the genetic role in dynamic cohesion can be significantly influenced.

4. THE ROLE FORCES PLAY IN DEVELOPMENT AND MUTAGENESIS ILLUSTRATES AN UNIVERSAL PRINCIPLE OF FORCE

We have seen the critical role that cohesion can have in development and hence in the integrity of the developing organism. During development, the degree of cohesive forces would have to vary in a periodic manner in order to allow for mitosis. In so doing, such cohesive forces would appear to be in periodic, dynamic equilibria – or in periodically, uniform dynamic configurations – with the forces of repulsion. Development would appear to involve the periodic disruptions of these dynamic uniformities. Each disruption would be a dynamical non-uniformity or internal stress, a dynamic imprinting via

cohesion- and repulsion-generating chemicals, and it would serve as the dynamic means for the global generation of a greater dynamical uniformity composed of increasingly cohesive forces within a context of repulsive forces. On a higher level of order, this uniformity itself would be a type of complex coherence, as it would have the dynamical properties of integration and coordination over diverse domains. With each dynamic disruption of dynamic uniformity, a greater dynamical uniformity or higher order of cohesiveness in non-uniformity would globally ensue or generate as an universal, dynamical and adaptive necessity to the resolution of dynamic stress.

Development, using dynamical, cohesive stress, would be the globally adaptive solution to such stress. In effect, through periodic, dynamic non-uniformity, uniformity of force configuration becomes progressively maximized within an increasing diversity of force. This changing yet coherent, dynamic structure, including its intersecting sub-structures, gives coordination, direction and organization to the cellular and tissue systems of the developing organism. As the chemical and other sources of repulsive forces become reduced and then depleted and the sources of cohesive forces increase more and more, development comes to an end. The completion of development would be the establishment of a maximum of dynamic coherence within a field of diverse or non-uniform forces. Biochemical processes would be the mediators or avenues of this maximization of dynamic coherence. (For example, enhanced cohesive forces within cells could imprint conformational changes within enzymes, thereby affecting their catalytical activity.) These processes would be dynamically subsumed in a complementary relationship to a dynamic generation eventually leading to dynamic uniformity.

The maximization of dynamic uniformity in non-uniformity within an organism and within the diverse dynamical connections that tie the organism to its dynamical nitch would enable the dynamic structure in the form of the organism to achieve maximum adaptation, and hence stabilization of its integrity, vis-à-vis its nitch. Organogenesis, involving the phenotypic or epigenetic level of organization, would be one mode expressing or defining this adaptation. Mutagenesis involving the genetic level of organization would be another, dynamical mode contributing to such dynamic adaptation.

Genetically controlled mutagenesis is seen ultimately as a dynamic

response to stress. Stress would be a dynamical non-uniformity imprinting on the genome via the epigenome, such as cellular membranes, which connect the genome to the external environment. As in organogenic domains, such an imprinted, non-uniform force configuration cannot remain in any natural system, genomic or otherwise, but must be resolved if the integrity of the system is to be maintained. This resolution entails generating a new, increased uniformity of force in the system by means of the very forces in non-uniformity. Hence, in a genomic system, a genetically controlled mutagenesis, utilizing the very forces of the imprinted, dynamical non-uniformity, would be the necessary generation of a greater dynamical uniformity in this non-uniformity within the genome than existed before the imprinting, giving thereby, a greater cohesiveness (or coherence) to the genome. Dynamically connected to this enhancement of dynamic coherence within the genome would be the eventual enhancement of dynamic coherence – thru dynamical non-uniformity – between the genome and the cellular systems, and ultimately between genome and its dynamic environment. This would be an overall, dynamic resolution of the stress. In this context, mutagenesis is thus seen not as being disruptive, but as a dynamic directed to overcome or resolve, via genetic mutators, a disruptive situation; namely, an imprinted non-uniformity of force within the genome, potentially lethal, if severe and not resolved. A classic version of this dynamic resolution would be the process of genetic repair.

The preceding dynamics leading to enhanced dynamical uniformity or coherence would confer an increased adaptation on the part of the organism, as an integrity, to the stress, that is, the change in environmental dynamics which led to dynamic imprinting. Such uniformity could be defined or expressed through an increased dynamical coherence from that of the original differentiated state. This would be through a further development – hitherto not normal to the organism – occurring until a greater dynamical coherence is further achieved in the organism. This development would be through transitional and necessary dynamical non-uniformities. In this situation, incipient neoplasia might also be transitory dedifferentiations leading to a far more, adaptive development.

Development would require a dynamical coherence of differing degrees between genome and protoplasm, and within developing tis-

sues. Species probably differ as to the degrees of internal, dynamic coherence required, and this would be due to the adaptive degree of dynamic cohesion which has been evolving through the epigenetic/dynamic history of each species. A completed, adaptive development would demand the highest degree and order of cohesion throughout genome and protoplasm, though this may also vary – for purposes of adaptation – from species to species, or from situation to situation. In view of this, one can predict that cohesion-implicated chemicals such as ascorbic acid would also be involved with the genome. There is in fact much evidence that ascorbic acid does interact with the genome and is generally involved *in vivo* plant development (Chinoy [1984]). In this connection, MG, possibly with ascorbic acid, may also have an indirect role in the mediation of photo-electromagnetic energy in plant development. This is based upon the earlier suggestion that MG plays a role in the development of chloroplasts. These are plant organelles, containing complex electron transport systems, that are very much needed for the absorption and utilization of photo-electromagnetic energy in plant growth. Such developmental, electromagnetic energy, countering entropy, would necessarily involve cohesive forces and would contribute to coherence.

5. PRACTICAL IMPLICATIONS OF THESE INVESTIGATIONS

The new perspective or approach, theoretically and experimentally illustrated throughout this article, has important practical implications or benefits with regard to medicine and agriculture. For example, it is clear that a neoplastic state can be reversed through the induction of differentiation or organogenesis utilizing ascorbic acid and MG. Such induced reversal, using various, cohesion-generating chemicals, has the potential of becoming a very powerful therapeutic approach in the treatment of cancer. With regard to the application of MG and ascorbic acid in the inhibition of neoplastic growth, Szent-Gyorgyi, as we have seen, did not illustrate how this would relate to developing tissue, only to post-developmental tissue that has undergone a neoplastic transformation after the completed differentiation. However, because of their role in cohesive-force generation, he does point out that MG, ascorbic acid, and free oxygen – which receives the electrons

from protein via MG and ascorbic acid – were necessary for the evolution of highly differentiated organisms (Szent-Gyorgyi [1979]).

As one will recall, 1 mM MG is the concentration of MG in non-developmental, mammalian tissue. This is most likely the concentration responsible for maximum, dynamic cohesion in non-developmental, mammalian tissue, the degree of cohesion necessary to maintain the highly differentiated state. In this connection, ascorbate stabilizes the differentiated state in mammalian-cell culture and reduces the ability of the Rous sarcoma virus to transform such cultures into neoplasm (Schwartz [1991]). In considering such phenomena, it is important to theoretically understand, and so artificially create, the various means to generate the cohesive fields that would lead to such highly differentiated states. This is especially so in agricultural applications.

In this regard, the *in vitro* induction of differentiation or organogenesis within the neoplasm of plant tissue is also quite relevant to the *in vitro* propagation and breeding of new plant lines or types that are important to agriculture and forestry. The new biotechnology of plant breeding *in vitro* requires the use of viral and bacterial/plasmid vectors for the introduction of beneficial genes into plant tissue cells, such as those of leaf sections. Such cells are referred as transgenic cells, and plants derived from such tissue are referred to as transgenic transformants or transgenic plants. For these new techniques to be successful, however, the plant tissue having the transgenic cells must first produce a transgenic, meristemic callus, from which, the desired transgenic plantlets must be induced to develop. Procedures that induce or increase the frequency of this development increase the number of new transgenic plants that can be recovered.

Using a culture medium containing 40 mg/L ascorbic acid, this author in 1990 was able to increase the frequency of recoverable, newly transgenic plantlets regenerated from transgenic callus of tobacco (such plants were transgenic for disease resistance). Compared to controls, these transgenic plants of tobacco, having been cultured on medium containing ascorbic acid, also developed more quickly. This shows how the approach and theory described here defines procedures that can increase the frequency of new transgenic transformants of plants. Relatedly, bean plants, possibly transgenic for disease resistance, were frequently recovered using tissue culture

methods based on the conceptual approaches involving MG and ascorbic acid. As one will recall, these approaches, in contrast to earlier approaches, repeatedly led to the high frequency regeneration of bean plantlets via meristemic callus from different types of somatic tissue. Such regeneration was very difficult to obtain before, and, as such, this points to a situation where MG and ascorbic acid were involved in a situation where recalcitrant organogenesis was overcome. Were it not overcome, such recalcitrant organogenesis would preclude a very important avenue by which transgenic plants, such as bean, can be generated and isolated.

The creation of transgenic plantlets involves recombinant-DNA techniques. However, there is nothing in the conceptualization or theory underlying such techniques that would predict the particular means of increasing the frequency of recoverable, transgenic plantlets in a tissue culture situation. Such was predicted by a completely different body of theory illustrated in this article, and thus points to the limitation of the concepts underlying the approaches of molecular-biology, while illustrating the importance of the biodynamical, structural approach in grasping the deeper meaning of development and mutagenesis. This is not, however, to devalue the recombinant-DNA approach but to put it in a larger perspective. For such an approach to be effective, especially in medical and agricultural applications, it must be used in complementation with other, non-molecularly oriented paradigms.

6. CONCLUDING REMARKS

Using more than a molecular paradigm, these studies have indicated that cohesive forces are necessarily involved in the generation of organogenesis from neoplasm in various plant species. With regard to neoplasm, one class of chemicals or metabolites, possibly including the auxins and lactic acid, may universally act as the mediators of repulsive forces, and, in so doing, giving rise to a virtually non-existant cohesion leading to de-differentiation or neoplasia in plants and mammals. While, in contrast, another class of metabolites may universally mediate the generation of those cohesive forces necessary for differentiation. Metabolism would thus become subordinated to the generation

of such forces. In development, this generation of cohesive forces appears to be cyclical in terms of their degree, especially during mitotic periods, with later cycles during later development consisting of cohesive forces effectively of increasing degree compared to earlier cycles. These cohesive forces of enhanced degree and order are seen as being needed to stabilize development's later stages and completion. This cyclical generation of cohesive forces in space-time would be in the form of a dynamic-helix or a complex of intersecting dynamic-helices. The regions dynamically defined by such curvilinear intersections would be the regions of impending sub-differentiations. A complex of such intersections could be the vortical locus of a bud developing from neoplasm. On a micro-physical scale, these helical intersections could define an universal physical constant, the quantum of action.

These dynamic intersections would also be a dynamic non-uniformity in uniformity, and such would be a dynamic stress. Development – and any mutagenesis involved in such development – would be seen as a progressive and adaptive means of reducing this stress by globally generating, in an helical manner, an increasing, dynamical cohesive uniformity in non-uniformity. The stress, itself, in the form of non-uniform cohesive forces, would be the dynamic avenues to achieve such, and hence would be necessary for development from the neoplastic or undifferentiated state.

As there is a very low degree of cohesion in neoplastic tissue, the degree of dynamic uniformity or of dynamic unity in such tissue would be very low. The cessation of such neoplasm thru a cohesion-induced re-differentiation can have both medical and agricultural value. To effect this development, such unifying, cohesive-force fields could either be generated through certain types of chemicals or be imprinted upon the neoplastic tissue from outside electromagnetic sources. In this connection, whole organs or organ-systems can be regenerated in certain amphibians thru the application of certain electric fields (see Becker [1991]). This would provide further indication that emergent cohesive-force fields are universally involved in, and necessary for, the development and evolution of complex organisms, whether they be plants or animals. "The process of reducing the [dynamical] non-uniformities in nature's space-time manifold is here envisaged to be the ultimate aspect of all adaptive phenomena in na-

ture. Evolution becomes then a word labelling this universal adaptive process. An aspect of evolution that is both essential and universal is *force,* and its nature we evidently do not grasp more in physics than in biology" (P. Lieber [1969]). Through the study of force in biology, the underlying unity and pattern of the diverse forces in the universe may be revealed.

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Michael M. Lieber

FORZA, SVILUPPO E NEOPLASIA: UN'ALTRA PROSPETTIVA LO SVILUPPO VEGETALE DA NEOPLASMA *IN VITRO*

Riassunto

Il differenziamento dallo stato neoplastico può essere un adattamento dinamico all'impatto locale di forze coesive nel tessuto. Si considera in generale che lo sviluppo richieda una classe universale di metaboliti generanti forze-coesive. Forze repulsive, operanti entro o tra cellule, condurrebbero al de-differenziamento verso uno stadio neoplastico o neoplasma. Un'altra classe universale di metaboliti potrebbe agire da mediatrice di tali forze repulsive.

Durante lo sviluppo precoce, specialmente dove e quando la mitosi è frequente, forze coesive e repulsive potrebbero coesistere in intensità oscillanti, ma sempre con un netto grado di variabilità. Corrispondentemente, metaboliti generatori di forze-coesive e forze-repulsive coesisterebbero in concentrazioni oscillanti. Il metabolismo avrebbe un ruolo nel dirigere la generazione di tali forze di sviluppo, specialmente

quelle coesive. Procedendo lo sviluppo verso una più alta complessità e verso stadi tardi, il grado delle forze coesive aumenterebbe globalmente, ma sempre in modo oscillante. Il cancro (o neoplasia) si forma, secondo A. Szent-Gyorgyi, quando tale coesività si spezza localmente, probabilmente per conversione di metilgliossale in acido lattico. Il cancro può anche formarsi per l'accumulo di presunti fattori repulsivi come l'acido lattico. L'implicazione dell'acido lattico nella generazione di neoplasie in tessuti vegetali e animali è stata sostenuta da A. Spirito (*Riv. Biol.*, 1995), nell'ambito della sua teoria flogistica della tumorogenesi. I tumori vegetali in vitro rispondono adattativamente ai composti generatori di coesione, come l'acido ascorbico e il metilgliossale, attraverso la generazione di gemme, embrioni e piantine.

La generazione delle forze coesive sembra essere ciclica e aumentare di intensità nella crescita tarda, onde stabilizzare gli ultimi stadi dello sviluppo. Questi cicli assumerebbero la forma di un'elica-dinamica o di un complesso intersecantesi di eliche-dinamiche. Lo sviluppo di una gemma da un neoplasma sarebbe il luogo di un vortice di tali intersezioni. I campi di forze-coesive che producono il re-differenziamento da neoplasma possono essere generati da certi tipi di prodotti o essere imposti nei tessuti neoplastici da sorgenti elettromagnetiche esterne. L'emergenza di campi di forze-coesive sarebbe necessaria nello sviluppo e nell'evoluzione di organismi complessi, siano questi animali o piante.