Cancer as a consequence of the rising level of oxygen in the Late Precambrian

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The origin of multicelled animal life required collagen-family molecules whose own formation depended on the availability of molecular oxygen. Cancers, by contrast, are characterized by their low use of oxygen. In discussing the relationship between the origin of multicelled life and the origin of cancer, it is useful to think in terms of tissues rather than individual cells or complete animals. When animal tissues are disturbed, their constituent cells may be partially released from the constraints of multicellularity. This permits or obliges cells to reactivate anaerobic metabolic ways used by their single-celled ancestors in the oxygen-deficient Precambrian seas. Inhibition or loss of cell respiration under such circumstances may cause reversion to glycolytic fermentation, a less efficient metabolic style that generates waste products that are retained, thereby producing excess cell-growth. Distortion of tissue architecture may ensue with impairment of cell-to-cell adhesion, thereby liberating individual cells. Cells freed from tissue constraints undergo Darwinian variation which leads to loss of differentiation and produces cell types that are incompatible with the normal functioning of tissues. These steps, which may manifest themselves as carcinogenesis, are not reversible by restoration of oxygen and in effect constitute a demergence from the metazoan state. The existence of cancer among diverse phyla and especially among domesticated animals, suggests that the risk of cancer may be an initial condition of complex multicellular life and that it remains preferentially associated with newly modified designs. If so, there would be therapeutic strategies that have not yet been adequately considered. □ *Cambrian explosion, cancer, cell differentiation, collagen, glycolysis, hard parts, metazoan origins.*

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Cancer is meaningful only in reference to complex multicelled life. A single-celled creature cannot get cancer. Thus, when the 1931 Nobel Laureate Otto Warburg demonstrated that healthy cells used far greater amounts of oxygen than cancer cells, the results were necessarily tied to the world of multicellular life. Decades later, Nursall (1959) became the first of many to argue that complex multicelled life could not have emerged until the oxygen level of the oceans had surpassed some critical threshold.

In this paper we propose that Nursall's ideas can be combined with Warburg's results to situate the origin and nature of cancer within the early history of metazoan life. In addition, we reaffirm Graham's contention that 'evolutionarily significant events that occurred in the deep past were more momentous than more recent events because the number of descendants … affected by the event was immensely larger' (Graham 1992, p. 46).

The Cambrian Explosion and the origin of the major animal groups

Fossils indicate that multicelled animals containing specialized cells did not appear until some 80% of the way through the history of life on Earth. Unambiguous fossils of metazoan animals dated to 543 Myr are preceded by fossilized tracks, trails and burrows and by very small soft-bodied animal-like forms datable to ca. 600–580 Myr (Chen *et al.* 2004). Whether metazoans emerged abruptly in the course of the Cambrian Explosion around 543 Ma, or from a cascade of events commencing around 600 Myr or even before, one thing is sure: multicelled animals have been around for only a relatively small part of the history of life on Earth.

The metazoans, all of which began as marine creatures, can be classified in accordance with their body plans, distinct geometrically-defined designs

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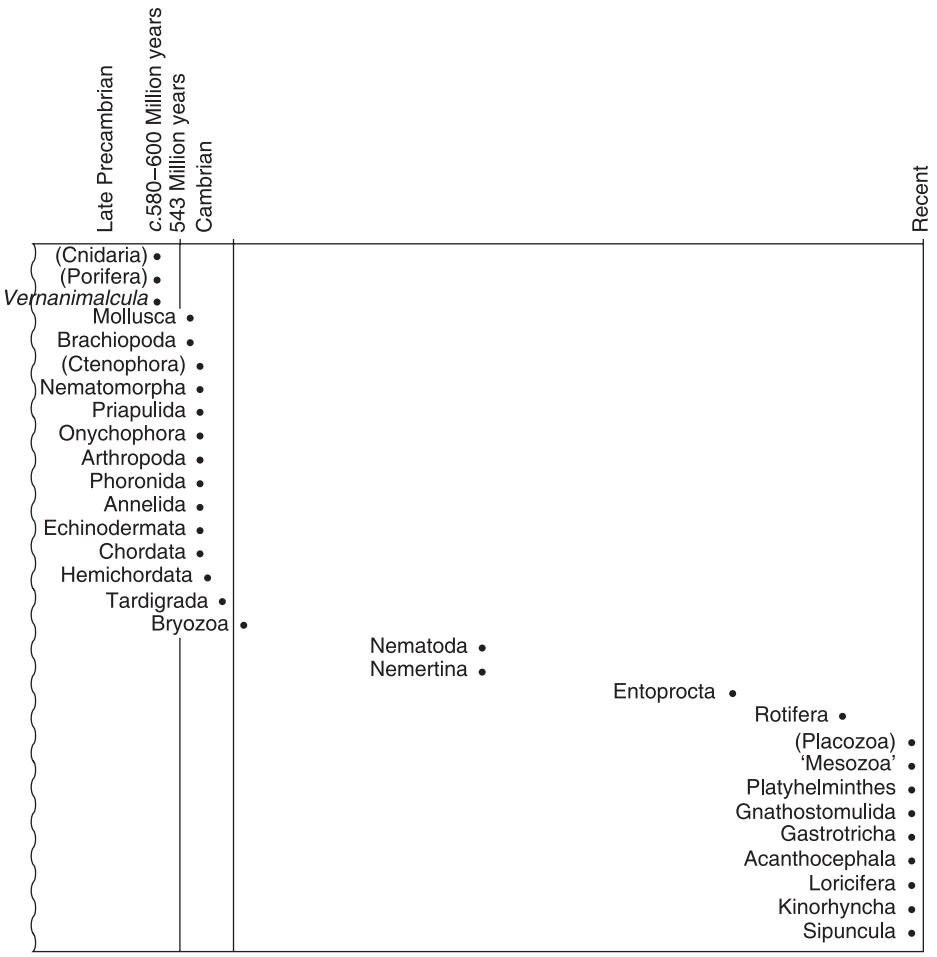

Fig. 1. Relative ages of oldest known members of individual phyla. (*Vernanimalcula* has not been assigned to a phylum (Chen *et al.* 2004)). Most of the phyla known from Cambrian times include animals with readily fossilized hard parts. Those known only from later times generally lack easily preserved anatomy but are nevertheless believed to have had long unrecorded evolutionary histories. One clear exception is the phylum Bryozoa, fossils of which are first recorded from Ordovician rocks, well after the Cambrian Explosion. But the Bryozoa, which possess hard parts, are remarkable for their secondary embryology during which their body plan is redesigned. Phyla lacking bilateral symmetry are shown in parentheses, following Valentine (2002).

that are limited in number. These body plans define the 30–35 recognized phyla, virtually each of which has also had its own separate evolutionary history *at least* as far back as their oldest known fossils, which in many instances means back to the Cambrian Explosion (Fig. 1).

Here we propose that, on passing some threshold shortly before 580 Myr, changes in the chemistry of the oceans had suddenly permitted complex multicellular life to emerge as a new phenomenon. A novel biochemical mechanism came into being that allowed the formation of tissues, i.e. it permitted the continued adhesion of eukaryotic cells which, although presumed to have been identical at the outset, subsequently differentiated and became specialized. For reasons we indicate, we believe that the threshold in question may have possessed a fine structure made up of a number of closely spaced sub-steps.

Tens of millions of years after this event, continued change in ocean–water chemistry permitted the formation of animals with hard (skeletal) anatomy. Due to the existence of hard parts and (as we shall argue) the concurrent increase in the strength of cell-to-cell adhesions, such creatures were easily fossilized. Their sudden appearance in the geological record at 543 Myr corresponds to the Cambrian Explosion.

In this view, Parazoa (sponges), radially symmetrical metazoans, and metazoans with bilateral symmetry could have emerged successively as oxygen became increasingly available or as new oxygen-dependent molecular species began to interact. We compare this to the way the elements emerged separately but similarly once the universe cooled to the point where

protons and electrons could come together to form atoms. The usage of François Jacob is followed here in which 'emergence' refers to a condition whereby new rules suddenly come to apply without, however, repealing the old, for example, in the way the laws of chemistry subsumed those of physics once atoms had been formed (Jacob 1977). Treating the origin of the metazoans as an emergent phenomenon owes little to Darwinian thinking (and nothing to Creationism).

The distribution of cancer across the metazoan phyla

By definition, there is no such thing as an animal – living or fossil – which falls between two phyla (provided the phyla in question have not been improperly defined). This does not imply that humans and, say, fruit flies or other arthropods are unrelated; similarities in their DNA show an unambiguous long-distance relationship.

Cancer is known in animals belonging to several very different metazoan phyla. John Harshbarger, former head of the Smithsonian's Registry of Tumors in Lower Animals, accepted cancer in four phyla: chordates, molluscs, arthropods, and flatworms. He reported cancer in all eight classes of chordates (J. Harshbarger, personal communication, 2003), though common only in the 'upper five'. And among invertebrates, he reported cancer as abundant in only one class of the Mollusca, the Bivalvia, where it is documented only for farmed shellfish (J. Harshbarger, 2003). Elaborating, Harshbarger added that 'cancer in Bivalvia clusters in those groups farmed and/or consumed by humans but it is likely an artifact. Those commercial species (several oysters, several clams, a scallop and a cockle) are the ones that are studied histologically. I know of no funding for histology on chitons, limpets, octopods, squid, freshwater clams, moon snails, etc'. He also noted that '… neoplasms have been reported in Cnidaria, Sipuncula and Annelida but I do not accept the latter two [phyla]. However, some of the lesions in Cnidaria [whose symmetry is radial] might be benign neoplasms' (J. Harshbarger 2003).

The phyla for which Harshbarger accepts the occurrence of cancer represent great subgroupings of metazoan animals: coelomates, acoelomate flatworms (Harshbarger & Gibson 1982), and Radiata. (Sponges are classified as Parazoa because of their lack of organized tissues.)

Given that each phylum has had its own developmental history, this distribution of cancer through diverse phyla suggests that precursor conditions for cancer already existed prior to the Cambrian Explosion. If so, cancer might be an inherent risk of complex life, of any animal (Saul 1994) or plant composed of tissues.

Later we briefly discuss groups of animals in which cancer is *not* reported, but cancer-like growths in complex plants are not further mentioned because they are normally non-fatal, primarily because metaphytes lack vital organs.

Oxygen in Precambrian oceans

A notable and seemingly rapid stepwise increase in the oxygen content of the oceans occurred somewhat before the observed appearance of the first metazoans (Des Marais *et al.* 1992) (Fig. 2), or coincident with them (Chen *et al.* 2004). Assuming something of this sort to have been the case, Nursall (1959) had proposed that key oxygen thresholds had been sequentially passed, providing the oceans with new molecules essential to metazoan existence.

Oxygen in cancerous tissues

In a series of papers, Warburg (reviewed *in* Warburg 1956) demonstrated that cells in cancerous tissues burn far less oxygen than cells in healthy tissues. He further showed that the low oxygen (hypoxia) that

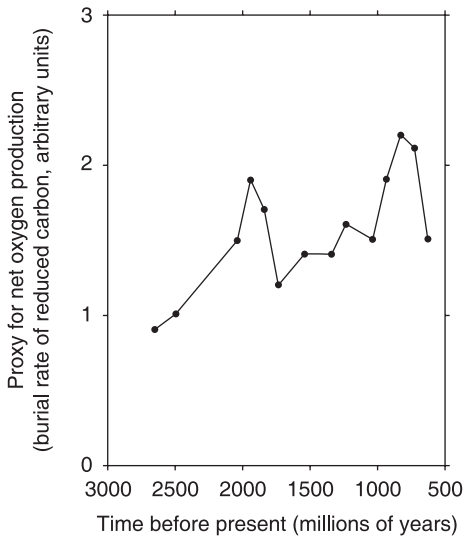

Fig. 2. Indication of rates of net oxygen production from approximately 2500 to 540 Ma. This and similar curves have been constructed using the amount of buried carbon as a proxy for oxygen. Using diverse models and measures, these curves are based on the assumption that for every atom of reduced carbon that is buried in aquatic sediments, one diatomic oxygen molecule must be released; following Des Marais *et al.* (1992). For discussions of other types of data indicating a rise in oxygen near the end of the Precambrian, see Lane (2002) and Towe (1996).

characterizes many tumours is indicative of situations in which normal oxidative metabolism has been partially replaced by fermentation (of sugars; i.e. glycolysis). Fermentation, which is an order of magnitude less efficient at producing energy than aerobic respiration, occurs in oxygen-poor contexts, whether cancerous tissues, wine vats, or garbage heaps. Warburg also showed that simple restoration of oxygen to cancerous animal tissues was insufficient to restore aerobic respiration or to halt or reverse glycolytic fermentation. This, we argue, is because the cells have partially, but irreversibly, reverted to ancestral metabolic mechanisms, while in some cases perhaps also deactivating their mitochondria, essential for efficient aerobic respiration.

Oxygen and collagen

The main phase of the Cambrian Explosion was marked by the appearances of shells and other hard-part anatomy requiring oxygen-rich molecules (Towe 1970). Metazoans of different phyla suddenly began to manufacture hard parts of chitin, phosphates, calcite, aragonite, silica, organic matter, and agglutinated sand (Signor & Lipps 1992, p. 16) and unicells with hard parts also appeared about the same time. Metazoan hard parts appeared in a rough chronological sequence commencing with granules and spicules set in soft tissue, followed by weakly mineralized thin-walled cuticles and shells, and then by more substantial hard-part anatomy (Brasier 1990). This sequence of events has been speculatively attributed to an evolutionary arms race, to the emergence of carnivorous appetites, and to other geological, biological, and environmental causes, but it is sufficient here to insist that it implies the availability of novel molecules requiring more oxygen than previously available.

Taxa that agglutinated sand (*Platysolenites*, *Onuphionella* and the debatably agglutinating *Volborthella*) are particularly intriguing. Among the earliest was the single-celled *Platysolenites*, a foraminifer that appeared in latest Precambrian time around 545 Myr, followed by other agglutinating organisms by ca. 542–540 Myr (Lipps & Rozanov 1996; J. Lipps, personal communication, 2004). Available sources do not make it clear why certain animal cells suddenly became stickier at just this time.

A part explanation proposed here following the work of Towe (1970, 1981, 2003) is that the increase in available oxygen permitted the production of collagen (a substance formerly used as glue). For whereas members of the collagen family of fibrous glycoproteins are essentially unknown in today's protozoan world, collagen (or closely related molecules) is ubiquitously present in all metazoan groups. There it has what Towe termed a 'tape and glue' function for which there is no substitute (Towe 1981, p. 299). But an absolute prerequisite for the production of molecules of the collagen family is the availability of molecular oxygen (Towe 1981). And given that there are slight differences between one collagen-family molecule and another, there should have also been corresponding differences in the oxygen thresholds required for their formation.

The main phase of the Cambrian Explosion – with the initial appearances of collagen-dependent bilaterally-symmetrical animals with hard parts – was preceded at around 570 Myr by the first appearances of spicule-bearing marine sponges (whose symmetry, if observable, is often poorly defined) and then, perhaps slightly later, by corals or coral-like creatures exhibiting radial symmetry (Fig. 1). These two phyla utilize spongin and gorgonin respectively, two varieties of collagen which Towe characterizes as 'phylum-specific' (K. Towe, personal communication, 2004). It thus appears that a common precursor to spongin, gorgonin and more familiar types of collagen had been in production in the pre-dawn of Cambrian times (also see Towe 2003), and it would be instructive to know whether spongin and gorgonin require quite as much oxygen as do other collagens.

Numerous types of fossil tracks, trails and shallow burrows are of comparable age (older than 555.3 ± 0.3 Myr; Martin *et al.* 2000) and many clearly seem to be the work of bilaterally symmetrical creatures active in the late Precambrian (Martin *et al.* 2000). Yet we do not find the corresponding body fossils. In our view this is because the production of collagen in these times had been more severely limited in quantity or quality by the still lower amount of available oxygen, thus prohibiting the production of well-mineralized hard parts. We further suggest that due to metabolic limits imposed by the oxygen-deficient marine environment in the times running up to the Cambrian Explosion, bilaterally symmetrical metazoans may have been weak as well as soft-bodied. As evidence, we contrast the deep burrows that appear in the fossil record just before the collagenizing main phase of the Cambrian Explosion with the older shallow burrows of the immediately preceding late Precambrian. The deep burrows were apparently made by creatures with systems of body-wall muscles that enabled them to dig by peristaltic locomotion, whereas the older shallow burrows may have been made by creatures lacking such muscles and the energy to make them function.

Collagen accumulates only intercellularly (Towe 1970), but it is not known how and where it had been

manufactured, and why it should have become preferentially concentrated on the exteriors of certain marine unicells prior to the formation of the first soft-bodied metazoans. An approach to such problems was devised by Israël (2004), who focused on the role of the mitochondria, energy-producing organelles that engage in aerobic respiration, and which are found in all animal cells. Israël (2004) started with the idea championed by Lynn Margulis since the early 1970s that the mitochondria had originally been free-living oxygen-respiring bacteria that had taken up residence within relatively primitive eukaryotic unicells some 2 billion or more years ago. At the time, the host eukaryote had already added a rudimentary oxidative metabolism of its own to its primordial mechanism for glycolytic fermentation. Made redundant by incorporation of the mitochondria, the oxidative system of the host eukaryote could be partly co-opted for other purposes and, according to Israël (2004), its ATP synthase began to work in the opposite direction, forming acidic compartments. These became cellular factories from which were secreted oxygen-rich molecules responsible for cell connections and communications within subsequent metazoans (Israël 2004).

In these circumstances, certain novel oxygen-rich molecules would have accumulated in the extracellular matrix and we speculate that such molecules included the precursors of collagen (see Towe 2003). These may have been useful for sticking to food particles. But whether initially useful or not, cell stickiness among unicellular protozoans did come into being and certain cells did become stuck to one another.

In the absence of evidence to the contrary, it is reasonable to assume that the cells in question were both, or all, of the same type because this assumption provides answers to later questions arising from the fact that all cells in the body of a given metazoan carry the same DNA. But if they were indeed all of the same type, it then follows that the cells in question had probably not come together as the result of some random process or happenstance. Instead they may have become stuck to one another during cell division, with the parent plus the daughter generations remaining attached to one another (E. Sercarz 2003 and J. Bergström 2006, personal communications).

Life in a sticky situation

The somewhat oxygenated seas of the very late Precambrian contained populations of identical single-celled creatures, some of which were stuck to one another as pairs, filaments, clusters, or perhaps as hollow balls. Although the actual geometries preferred by such groupings of cells are not known, they may perhaps be deduced from observations of modern-day ciliate unicells that clump together when exposed to toxic concentrations of oxygen (Lane 2002, p. 51). We may also make the simplifying assumption that the shape of the individual cells was cubic, with physical, chemical, and biological properties about the same in all directions. (While indeed simplifying, this assumption also deflects charges of special pleading.)

Filaments, clusters or balls, anchored or not, these cell *ensembles* would not have been metazoans, just groups of cells stuck together, unable to pull apart, with each individual cell struggling for survival. Metazoans contain specialized cells (as a matter of definition) but the cells of the *ensembles* described here would have been identical to one another, with no specialization or differentiation. The inside of each cell would have contained the same biochemical soup, hence there would have been no chemical gradient to pump anything from one cell into another.

Subsequently, as the early varieties of collagen became more and more sticky and as cell groups became larger and larger, new factors would begin to acquire importance, geometry, for example.

Cell differentiation and the first metazoans

Aerobic respiration is efficient because reactions go to completion. Water and CO_2 are the only end products. By contrast, anaerobic cell metabolism (fermentation) is inefficient. Fuel is incompletely burned, with some waste molecules retained within the cell, some spilled into the intercellular environment, and some winding up stuck to the outsides of cell walls. Single-celled creatures learned to treat these waste molecules as resources for cell growth and cell division by an early date, even before the incorporation of mitochondria (Schwartz 2004).

As a consequence of geometry alone, individual cells within a ball or cluster would have been in somewhat different situations from one another. Differing geometrical and physical circumstances could then have translated into variable access to oxygen, different chemistries of fermentation, and different chemical end-products. With time, there might develop electrochemical gradients sufficiently strong to pump molecules from one cell to another, traversing the outer membranes of both.

Conditions within the larger cell-groupings would not have necessarily been conducive to life and the cells deepest inside might have been in the worst situations. In such configurations, which may evoke

the blastula stage of embryonic development prior to gastrulation, significant electrochemical gradients could be established, leading to considerable molecular exchange. Then as diverse molecules within individual cells activated or suppressed particular genes at various times and in various ways, cells with specialized properties would come into being, a step towards the emergence of the first metazoans.

Within sufficiently large (but still microscopic) *ensembles*, individuals belonging to a single type of protozoan could have been obliged *by geometry alone* to differentiate in a great variety of different manners while retaining ancestral molecular similarities across the metazoan phyla. In this view, a single type of protozoan, all on its own, could have been the ultimate ancestor of more than one phylum. The geometry of each phylum's microscopic founding member would have been a critical initial condition.

Judged by today's standards, the physical and biochemical construction of the earliest metazoans could not have been particularly stable. Their collagen would have been limited in both quantity and quality and neither their collagen, nor their DNA, nor anything else about them would have yet been winnowed by the forces of selection within the context of metazoan fitness and survival. But these unstable conditions no longer prevailed by the time of the Cambrian Explosion around 543 Myr when not just the rare metazoan, but multiple species, well-populated habitats, niche partitioning, and food chains become apparent in the fossil record (Zhuravlev & Riding 2001).

Members of the collagen family of molecules have repetitive structures with periodically recurring anchor points that are variably spaced according to extremely local geometric, physical and chemical circumstances and constraints. At the time of the Cambrian Explosion, particular metazoan characteristics could have arisen from the mix of collagen-type molecules. Under diverse conditions, these would later be the midwife molecule for the formation of chitin, phosphate, calcite, or aragonite and later, of tendon, ligament, bone, nail, hoof …

Tissues, healthy and cancerous

Following the emergence of the first self-replicating metazoans, the individual evolutionary interests of each of their component cells came to depend on cooperation. Yet cooperation in the context of metazoan tissue would have necessitated overcoming ages-old patterns of unconstrained proliferation and variation (Saul 1994), a newly required metabolic demand that depended on the maintenance of a balance of forces.

The normal internal accumulation of molecular resources within individual cells permits them to grow. Augmentation of their mass then enables them to divide. That is part of the Darwinian heritage of free-living uni-cells. Yet once incorporated within, say, metazoan epithelial tissue, growth and division are physically constrained by compressive forces exerted by laterally connected neighbouring cells, all anchored to the basement membrane. In healthy tissue, lateral compression prevents cells in the epithelial monolayer from dividing beyond the tissue's requirements for cell renewal, while the basement membrane (itself composed of collagen) maintains geometric integrity in the depth dimension (Schwartz *et al.* 2002).

In healthy epithelial tissues, a constant contest of opposing forces takes place as cells attempt to grow and divide in accordance with their unicellular inheritance despite constraints imposed by multicellular reality. In almost all cases, the tissue succeeds. But if the tissue has been weakened – whether by malformation, disease, chemical insult, fibrosis, or intrusively embedded foreign bodies such as asbestos fibres – interference with mesenchyme–epithelium interactions and defective cell-to-cell adhesions may result, releasing an individual cell from some of its metazoan tissue-constraints. Lacking adequate access to its normal metazoan sources of oxygen and molecular signals, such a cell may then revert to fermentation in order to survive. It thereby becomes sufficiently massive and strong to overcome collagen-derived and other forces exerted by its home tissue. Additional disturbances to tissue architecture may then result (Schwartz *et al.* 2002; Fleury & Schwartz 2003).

Let us imagine an exceedingly simple and generalized two-dimensional model of the tissue lining or the surface cells of a generalized organ, i.e. a 2-D model of any organ of any metazoan with individual epithelial cells laterally attached to their neighbours by gap junctions (Fleury & Schwartz 2003). Aside from the gap junctions, this model resembles a nicely aligned set of smiling teeth. As in a mouth, these teeth are not symmetrical. They possess tops and bottoms and somewhat less definite lefts and rights, and they are fixed onto the basement membrane as a sort of gum line, below which lies the mesenchyme. These 'teeth' represent living cells that will grow and divide until prevented from doing so by the constraining forces exerted by their neighbours. But if a tooth-like epithelial unit is geometrically displaced – up, down, left, right, back, forward or twisted – normal metazoan constraints may be relaxed (Fleury & Watanabe 2002; Fleury & Schwartz 2003). Fermentation may follow, and the balance of forces thereafter altered by concurrent tissue inflammation caused

by the increased size of individual cells (Fleury & Schwartz 2003).

An immediate effect of inflammation may be to retain potentially wayward cells in their correct positions during the healing process. Yet severe chronic inflammation results in the stiffening of the extracellular matrix and of the tissue as a whole. Possible outcomes of tissue stiffening include irregular adhesion, disruption of the underlying basement membrane, and deeper physical and geometrical disturbances. Darwinian considerations and experience with healing processes suggest that in almost all cases, the cells in damaged or diseased tissue will be pushed back into position by the inflammation, or pushed or pulled back by other restoring forces, or else they will die by apoptosis or necrosis.

Restoring mechanisms are particularly likely to fail or to be inadequate once the structural problem has affected the tissue's underlying scaffold-like mesenchyme, or in cases where the disturbance originated within the mesenchyme itself (Sonnenschein & Soto 1999; Maffini *et al.* 2004). When failure occurs, cells may continue to divide but they may have lost their polarity, a loss whose upstream cause is fermentation followed by inappropriate cell growth (Schwartz *et al.* 2002; Fleury & Schwartz 2003; Schwartz 2004). As determined from a literature search, *loss of cell polarity, i.e. loss of functional orientation, correlates with a decrease in cellular respiration* throughout a broad range of examples (Schwartz 2004).

Loss of polarity does not necessarily affect the viability of individual cells (Hasan *et al.* 1998). But cell division in such circumstances occurs in an inappropriate geometric plane (actually a curved epithelial surface). Inflammation in such instances may not lead to healing and cell-to-cell connections may fail to control the orientation of subsequent daughter cells, especially at joins between different tissues and at anatomical bends and angles. Such cells will be poorly constrained by the host tissue, to which they may or may not remain attached, or into which they may grow intrusively (Fleury & Schwartz 2003). Conditions permitting, individual cells involved in such growths might continue to divide more or less as free-living unicellular creatures (Saul 1994), given that the 'default state' (Sonnenschein & Soto 1999, Ch. 2) of living cells – prokaryotic, eukaryotic, plant, animal, fungal, unicellular, cancerous or healthy – is proliferation (Saul 1994; Sonnenschein & Soto 1999, Ch. 2).

By itself, unconstrained proliferation might not produce irreversible tumours. But *the default condition of any cell is not only to proliferate, it is also to vary* (Saul 1994). Variation is favoured by multiple mutations such as those facilitated by the acid conditions associated with fermentation, and with high oxygen gradients, variation is poorly constrained. Cell types are then produced, whose shapes, sizes, surface properties, metabolic preferences, and products will be incompatible with the structure and functioning of metazoan tissue.

Loss of cell-to-cell communication and variation through a range of subnormal oxygen concentrations may produce cells that have reactivated archaic metabolic mechanisms and pathways. This may be irreversible and such cells may be unable to revert to metazoan-style cell respiration even after restoration of oxygen. Such cells have lost the novel metabolic abilities that had emerged during the run-up to the Cambrian Explosion; in the words of Sonnenschein & Soto (1999, p. 80), they have 'demerged'. Organized tissue structure may then disappear and the functioning of organs lost. (Cancerous breast tissue does not produce milk; cancerous testes do not produce sperm; etc.)

In addition to mutations, other genomic disturbances commonly attributed to cancer – such as aneuploidy and the silencing or overexpression of genes – may also be the consequences of metabolic reversion to glycolysis (Prehn 1994; Reynolds *et al.* 1996).

Although free from many of the constraints of multicellularity, cancer cells nevertheless exist within a biochemical environment provided by a living metazoan. Such environments are exceedingly rich in molecular signals, many of which cannot be properly read by cells detached from their home tissue. In this chemically noisy context, cancer cells will on occasion respond to imperfectly received chemical messages. We suggest that their defective ability to interpret messages might be yet another cause of their extreme variation.

One reason why advanced and metastatic cancers may be difficult or impossible to treat is that they may have disactivated their mitochondria (Lane 2002, p. 273), perhaps simply by natural selection in an environment that is oxygen-poor. Such selection may help explain Warburg's still poorly understood observation first made in the 1920s that simple restoration of oxygen to cancerous animal tissues was insufficient to halt or reverse glycolytic fermentation and to restore aerobic respiration (reviewed *in* Warburg 1956).

An evolutionary role for cancer and the consequent unlikelihood that it can be eliminated among humans

The great question is why cancer, which is commonly fatal, should even exist. Logic would seem to dictate

its elimination via natural selection. In addressing this matter, two broad categories of cancers must be distinguished: (1) juvenile, which includes pre-natal cancers through those of puberty, and (2) adult, which frequently means cancers among individuals past the age of reproduction. These categories occur in contrasting patterns: cancers in long bones during the adolescent growth spurt, for example, are very different from cancers of the prostate among older males.

Another contrast of patterns is between the low incidences of cancer among wild animals and the very much higher rates among humans, pets, laboratory and farm animals, and for fish raised on fish farms. A compilation initiated by Fritz Anders (Graham 1992; A. Anders, personal communication, 2002) has domesticated trout, hybrid ducks, laboratory mice, Lipizzaner horses, domestic cats, boxers and other large dogs as particularly susceptible to tumour formation. The sharp contrast between wild and domestic has remained unexplained even after accounting for the peculiar foods given to domesticated animals, early deaths in the wild from causes other than cancer, and our own peculiar habits ranging from smoking to sunbathing. The contrast is particularly strong between recently domesticated creatures – Lipizzaners were first bred in 1580 – and groups such as sharks, little changed over great spans of evolutionary time. Combining this information with Harshbarger's data (J. Harshbarger, personal communication, 2003), we find that cancer is most prevalent among more complex animals, especially those that have evolved most recently.

Addressing the contrasting patterns of cancer between juveniles and adults and across species and breeds, James Graham, a specialist in manufacturing and quality control, identified some fundamental facts concerning animals constructed with bilateral symmetry (Graham 1992). With reference to personal experience, Graham noted that for all mass-manufactured products – whether copper tubing, lawn furniture, or soap – those responsible would set out precise specifications for the raw materials to be used, the parts and sub-assemblies and the finished product (Graham 1992, p. 66), the purpose being to produce a uniform product adapted for a particular market niche. Quality would in all cases be controlled by sampling, with items such as electronic devices requiring more stringent sampling than, say, common nails (Graham 1992, pp. 66–67). Graham envisaged a parallel between mass manufacturing and the biological world in which animals are also 'mass manufactured', but asked how quality could be controlled in animals without sampling. The problem was that for a bilaterally symmetrical animal to be viable, '… *every* part (cell) of *every* product (animal) had to be monitored to ensure compliance with the master specifications' (Graham 1992, p. 68).

Referring to aircraft manufacture during World War II, Graham reported that whenever design modifications were introduced, more errors were made, though only for a while (Graham 1992, pp. 39–40). As workers advanced along the learning curve, they would make fewer errors. For Graham, errors in manufacturing newly modified airplanes correspond to errors in manufacturing newly modified trout, dogs and laboratory mice.

Graham contended that without product sampling, animal lineages could not 'have climbed evolution's learning curve' unless errors in construction had been totally eliminated. This absolute requirement demanded 'the prompt death of the animal and all its genes' (Graham 1992, p. 40) whenever unacceptable imperfection occurred. He insisted on the fact that not a single one of our ancestors, or the ancestors of any other living animal, had died before reaching the age of reproduction.

Graham saw juvenile cancer as assuring that, by the age of reproduction, each animal is individually constructed in a viable manner, a view supported by the common association of juvenile cancers with malformations. Children born with malformed reproductive organs of the Denys–Drash syndrome, for example, have a greatly elevated risk of Wilms tumour, a cancer of the kidney almost never encountered among adults, as well as cancers of the malformed tissues themselves. And juveniles suffering from hemihypertrophy, in which one side of a body grows faster than the other, are particularly susceptible to cancers of the liver and to Wilms tumours. Broadly speaking, those molecules that cause fetal malformations (teratogens) are also carcinogens.

Cancer selection implies *survival of those manufactured within acceptable tolerances whose viability is maintained into the age of reproduction* (Graham 1992), a task that is increasingly more stringent with increasing complexity and increasingly more fallible with novelty. A reason cancer has not been eliminated among sufficiently complex animals, and is likely to remain prevalent in humans and other recently modified metazoans, is that juvenile cancer is an aspect of natural selection that is normal among new forms. Eliminating cancer at an early stage of development might be paramount to undoing a half-billion-year heritage of selecting for fitness. In this view, cancers of the reproductive years may simply be instances of the imperfect nature of natural selection, while cancers of old age are an aspect of

diminishing fitness once we have lost our Darwinian usefulness as potential parents, grandparents, or nurturers.

The lack of cancer in lower bilaterian phyla reported by Harshbarger may be partly due to their relative simplicity, hence the shorter learning curves needed to master their construction. Another factor would be the rarity of substantial biological novelty among invertebrates in the wild, with farmed shellfish providing a counter-example (J. Harshbarger, personal communication, 2003). Creatures such as jellyfish whose tissues are able to accommodate aberrant cells without disruption of tissue-function might also be exempt from cancer.

Cancers in flatworms may be attributable to their tissue-filled body plan that lacks a secondary body cavity. This acoelomate body architecture, combined with flatworm-style respiration via diffusion through the external body wall, may render the tissues of flatworms especially susceptible to structural disturbance.

Recent evolution and complexity correlate with the prevalence of cancer. But whereas the first of these factors seems to be potentially quantifiable, complexity is a more elusive concept and may require value judgements. We nevertheless note that within the deuterostome phyla, chordates are arguably the most complex and that, as noted earlier, cancer is present in all eight classes of chordates, though common only in the five highest; furthermore, the arthropods are perhaps the most complex among the protostomes. These observations, if properly formulated and valid, may indicate that cancer provides a sort of limit or lid on the amount of complexity and/or rate of innovation allowed at any given evolutionary moment by the deuterostome and protostome (and perhaps acoelomate) ways of constructing animals. This notion is reinforced by the observation that 'advanced insect and vertebrate embryogenesis are derived processes' (Davidson 1991, p. 2), which may be reformulated as a statement that the two taxa that are especially subject to cancer selection are the same two taxa whose manufacture includes additional levels of complexity.

Among the numerous phyla in which cancer has *not* been reported are the micrometazoan phyla Loricifera, Rotifera, Tardigrada and Nematoda. Members of these phyla exhibit a style of development called eutely in which a fixed number of cells are produced in each individual, not only as adults, but also throughout each stage of development. We propose that eutely may be an anti-cancer strategy and we wonder if lineages employing this mechanism can ever develop additional complexity. Their evolutionary journeys may have ended.

A necessary element in the management of cancer?

In some respects, cancer is a metabolic disease, a consequence of undue cell proliferation caused by unrelenting fermentation. Effective treatment may depend on decreasing fermentation by targeting cells whose metabolic activity favours glycolysis (which includes cells with disturbed polarity and cells not smoothly attached to their substrate). Since cell growth is essentially halted by glucose deprivation, molecules that block the uptake of glucose may be of therapeutic value. These include substances akin to 2-deoxy-D-glucose (2-DG), a well-tolerated non-metabolizable molecule that differs very slightly from glucose itself and that binds preferentially to cells with highly anaerobic glycolytic metabolisms, a property used diagnostically by spiking 2-DG with a radioactive tracer, thereby permitting the imaging of tumours by PET scan.

Cancer, a property of tissues

Cancers associated with, say, asbestos fibres lie outside Graham's treatment, and asbestos does not interact with oxygen either. But when lodged between cells, asbestos fibres of certain sizes and shapes may trigger cancers. Sonnenschein & Soto (1999) interpret such foreign-body cancers as further evidence that cancers commence as architectural defects of tissues. They also reiterate that, aside from advanced cases, it is normally impossible to identify an individual cancer cell removed from its histological context. This is because primary cancer is not a pathology of cells but of tissues (Sonnenschein & Soto 1999).

Conclusions

An increase in the availability of oxygen led to a broad stepwise collagenizing event (Towe 2003) that permitted the assembly of animalian tissues and allowed metazoan life to emerge. If tissue architecture is disturbed, individual cells may be freed from their tissue constraints, causing them to revert to primitive glycolysis. Inappropriate cell growth may then result in cancer. To this we append the recent observation by Teodoro *et al.* (2006) that multiple collagen-derived fragments are shed at tumour–host interfaces.

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