Origin of the phyla and cancer

JOHN M. SAUL

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Multicelled animals with specialized cells (metazoans) emerged shortly after rising oxygen levels in the seas permitted formation of collagen-family molecules. Certain unicells then formed 3-D clusters, some with disc- or ball-like shapes that happened to resemble blastulas. These became unstable beyond a certain size due to contrasting metabolic styles among their component cells. For whereas cells near their exteriors could employ oxygen respiration, cells closer to the oxygen-deprived interiors were obliged to rely on anaerobic metabolism (fermentation), a process that produces waste molecules that, if retained within cells, cause disproportionate cell growth. Unstable blastula-like forms would either disintegrate or reorganize along surfaces of relative weakness in a process that may be likened to gastrulation. Initial cell-differentiation depended on the quantity and diversity of retained fermentation products and on the pumping of molecules from cell to cell by the consequent electro-chemical gradients. In subsequent contexts, oxygen deprivation, fermentation, excess cell growth, and disintegration or reorganization of tissues produce cancer. □ *Blastulas*, *cancer*, *cell differentiation*, *collagen*, *gastrulation*, *metazoan origins*, *Warburg effect*.

John M. Saul [john.saul@wanadoo.fr], ORYX, 3 rue Bourdaloue, F-79009 Paris, France; *manuscript received on 20/03/2007; manuscript accepted on 10/06/2007.*

Macroscopic fossils of metazoans appear only about 543 million years (Ma) ago, some 80% of the way through the history of life on Earth. Whether metazoans emerged abruptly from the world of unicellular life in the course of the Cambrian Explosion (however defined), or from a cascade of events commencing around 580 Ma when the deep ocean became enduringly oxic (Canfeld *et al.* 2007), or even somewhat earlier (Chen *et al.* 2004), one thing is certain: the oldest recognized ancestors of humans (phylum Chordata), fruit flies (Arthropoda), and oysters (Mollusca) go back to a relatively short interval of time. This observation extends to all 30 to 40 metazoan phyla, each of which has: (1) an origin, whether true or only apparent, within this one window of geological time (with the early-appearing and now extinct 'Ediacaran fauna' as one special case and the late-appearing phylum Bryozoa as another, both discussed later; (2) a separate evolutionary history at least as far back as its oldest known fossil member, which in many instances means back to the Cambrian Explosion; and (3) a distinct geometrically defined body plan.

Each phylum is recognizable and defined by its characteristic geometry or body plan, with the seemingly unbridgeable anatomical gaps between one phylum and another commonly illustrated by the distinction between animals with backbones and invertebrate creatures with exoskeletons or other organic covering. A broadly shared opinion, accepted here, holds that the phyla are natural non-arbitrary categories. This makes them inherently different from the classes, families and genera whose definitions and boundaries may be shifted for the convenience of taxonomists.

Differences in opinion concerning the exact number of phyla arise from poor data, especially among rare soft-bodied marine worms, many of which lack informative fossil records. Although difficulties caused by gaps in the data can usually be left to specialists, problems of broader and more general interest are raised by pairs of phyla (of which there are many) that, while indeed seemingly distinct, give indications of being somehow related or close to one another. This is commonly assumed to be due to a very early branching event. The question then arises whether a phylum-like group should qualify as a bona fide phylum if it had ever branched from another. And if the phyla are natural categories, what is their 'natural' definition, and would it hold following a branching event?

No compelling evidence has been found that any phylum ever branched from another. As put by Valentine (1992, pp. 543–544), it is not a fluke that the phyla of bilaterally symmetrical animals remain obscure in origin 'whether studied from the perspectives of comparative developmental and/or adult morphology, of molecular evolution, or of the fossil record . . . Even though we may eventually learn the branching patterns of the phyla, it would appear that there is something about the origin of phyla that makes this a particularly difficult task . . . Although workers using each sort of evidence can cite special circumstances to explain their difficulties, it is possible that the problems may arise from a common source'.

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The Smithsonian Registry of Tumors in Lower Animals provided additional information of a puzzling nature, reporting the presence of cancer in members of several phyla: Chordata, Arthropoda, Mollusca, Platyhelminthes and Cnidaria (John C. Harshbarger, former head of the Smithsonian Registry of Tumors in Lower Animals, personal communications, 2003, 2007). Yet if the phyla have had separate evolutionary histories as far back as their oldest known fossil members (and if cancer is not contagious across phyla), this might indicate that the natural history of cancer commenced before the phyla were distinct. It might also indicate that cancer is a risk inherent to the metazoan state (Saul 1994; Saul & Schwartz 2007).

Branching versus emergence

With many lines of inquiry already explored (Valentine 1992), it is worth asking whether branching of the phyla could have occurred at an extremely early developmental stage, perhaps at the blastula stage prior to gastrulation when the supposed ur-metazoan had been an essentially hollow thick-walled disc or sphere-like mass of cells. Great difficulties arise from such a hypothesis, however. Two of these are (1) the requirement that blastulas (which lack vascular systems) would have had to give rise to near-identical vascular systems in the nine coelomate phyla that have a dorsal heart that pumps blood forwards; in principle, a vascular system could have many shapes and different flow directions; and (2) derivation from blastulas (which also lack guts) of the distinctive brain with two rings encircling the gut which characterize the six cycloneuralian phyla (Bergström, personal communication, 2007).

In sum, there is no evidence for late branching (Valentine 1992) and there are enormous problems with early branching (Bergström, personal communication, 2007). Something appears to be wrong, and here I propose that problems such as those evoked by Valentine and Bergström might be derived from an unnecessary assumption that branching of one phylum from another had necessarily occurred.

Molecular evidence, including numerous studies that involve DNA or Hox genes, indicates that some of the similarities across the phyla are due to homologies, i.e. to similarities due to a common origin. But '*similarity by homology*' *does not necessarily implicate branching*. By their origin, carbon and silicon, for example, are similar but their similarities were not caused by branching.

Here I argue that there never was a common metazoan (or bilaterian) ancestor and that the phyla all originated separately but similarly within a short period of time. I claim that the increasing oxygen content of the oceans and the consequent production of collagen-family molecules had suddenly obliged a particular type of unicell to form 3-D lumps, and that complex multicelled life emerged as a new phenomenon from certain 3-D lumps whose geometries resembled present-day blastulas. In such cases, each metazoan phylum would have emerged separately but similarly, somewhat as the elements emerged separately but similarly once the universe had cooled to the point where protons and electrons could come together (Jacob 1977). This was rapid but not instantaneous; parts of the universe cooled before others, and some elements are easier to form than others.

The usage of Jacob (1977) is adopted here, with 'emergence' as a condition wherein 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 and elements had been formed (Jacob 1977). Instances of emergence generate multiple results, as with the formation of the elements (or chemical compounds, or languages, or forms of government, etc.), and something roughly similar, appears to have happened in biology with earlier emergences of those phyla whose collagen-family molecules required marginally less oxygen and the slightly later emergences of others.

Collagen

Certain cells suddenly became sticky in the course of the Cambrian Explosion. A part explanation derived from the work of Towe (1970, 1981, 2003) is that an 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 is ubiquitously present in all metazoan groups. There it has what Towe termed a 'tape and glue' function for which there is no substitute (1981, p. 299). But an absolute prerequisite for the production of molecules of the collagen family is the availability of molecular oxygen, O_2 (Towe 1981). And, given that there are slight differences between one type of collagen-family molecule and another, there must have also been corresponding differences in the oxygen thresholds required for their formation. (Sponges and corals make their first appearances in the fossil record slightly earlier than bilaterally symmetrical animals, but it is not known whether spongin and gorgonin, which Towe considers to be two phylum-specific types of collagen, require quite as much oxygen as the varieties of collagen found in bilateria.)

Early development

When exposed to toxic levels of oxygen, free-living modern-day anerobic marine ciliates come together to form groups (Fenchel & Finlay 1990, pp. 1956–1957), and certain unicells may have done likewise in late Precambrian times. Then, once the oxygen threshold for the formation of collagen had been passed, unconsolidated groups of cells could have been transformed into agglutinated lumps that would have formed in a large variety of shapes. Among them, some may have resembled modern-day blastulas, thick-walled discs or near-spheres with a fluid-filled central cavity lined by a blastoderm of tightly-packed undersized cells.

For the sake of simplicity, let us assume that these blastula-like discs and near-spheres were all composed of a single type of unicell (which may have also produced the collagen in the first place).

Among the (presumably) tiny minority of cell lumpings that happened to resemble blastulas, systematic variants would have formed. When the number of cells increased from four to eight, for example (whether by cell division or by the agglutination of new cells), the additional cells may have been set into the grooves formed by the underlying four (stacked like oranges), or they may have been stacked one directly on top of another. Other systematic differences may have been generated if the availability of oxygen continued to increase during the course of the Cambrian Explosion. For, if so, stronger varieties of collagen-family molecules could have been produced as time went on.

Following an increase in size of the blastula-like discs and balls to fifty or a hundred thousand cells, marked differences would have developed between those cells exposed to the external environment and those located deep within their thick walls. Cells bordering on the outside world and those of the blastoderm-like lining of the inner cavity, would have had access to more oxygen than those deep within the walls. In consequence they would have preferentially employed oxygen respiration for their metabolic activities. Meanwhile, those situated within the walls would have existed in surroundings poorer in oxygen and would have been more dependent on anaerobic styles of metabolism. (This 3-D situation has no 2-D biofilm counterpart.)

In aerobic respiration, reactions go to completion with water and CO_2 as the only end products. This contrasts with the far less efficient anaerobic styles of cell metabolism, i.e. the fermentation of sugars (glycolysis), in which 'fuel' is incompletely consumed with a concurrent production of an enormous variety of waste molecules. These are either spilled into the intercellular environment or retained within the cell, in which case they augment cell size (Schwartz 2004; Saul & Schwartz 2007).

Fermentation deep within the walls of the blastula-like near-spheres would have caused cells there to grow disproportionately in size. With internally located cells increasing in size more rapidly than those near the surface, the blastula-like configurations would have eventually become unstable. Some might then break apart. But in others, unable to fully disintegrate due to the restraining presence of the glue-like collagen, groups or layers of cells might shift position until a newly stable geometric cell-configuration was attained. I liken this shifting of cell positions to gastrulation, with the hollow near-spheres and discs transformed into layered configurations or rearranged so that cells originally located at depth obtain access to oxygen while not unduly depriving those originally located near the surface. (In some or perhaps all cases, incipient layering of the blastula develops before gastrulation, possibly as a consequence of a stepwise gradient in cell size; such layering may provide surfaces of slippage and its existence may also encourage or guide asymmetrical and tangential cell cleavage.)

There were many ways in which members of a diverse population of blastula-like near-spheres could have opened up or been rearranged. Critical considerations would have been dictated by the exact geometrical, physical and biochemical characteristics of the surfaces of relative weakness or incipient layering upon which separation, gliding, or folding of groups or layers of cells might occur.

Many of these blastula-like forms would have disintegrated or withered without reorganizing. Others might have produced viable results that were not self-reproducing. But in a very few cases, a gastrulation-like cell rearrangement may have produced a viable self-reproducing metazoan. Reproduction, however, requires specialized cells, as do many other metazoan functions.

Cell differentiation and later development

Prior to their reorganization, the blastula-like near-spheres and discs had been composed of (1) cells favouring fermentation surrounded by (2) cells for which respiration had been the main metabolic mode. This had produced differences in cell sizes. At the same time, the contrast in metabolic styles had produced differences in the internal chemistries of diverse cells. Cell differentiation commenced once the consequent electrochemical gradients had become sufficiently strong to pump molecules across

membranes from one cell to another. And if genes of the Hox family had been present in the original type (or types) of unicell, as they are in all groups of living metazoans (excluding sponges, which are classified as Parazoa because they lack organized tissues), their ability to switch other genes on and off under different conditions could have facilitated the production of an enormous variety of proteins and eventually of subsequent metazoan cell types.

As suggested, the specific initial chemistries of fermentation, and hence of later cell differentiation, would have differed from case to case, both as concerns the types of molecules and their concentrations. In addition, the surfaces of weakness along which successful gastrulation-type reorganizations occurred would have differed from case to case, *though perhaps only very slightly*. In these circumstances, parallel development could have occurred among phyla that had been very similar or had had very similar cell-cleavage patterns from the outset. A developmental history of this nature could account for many of the similarities between pairs of phyla, and do so without invoking branching.

Many additional factors affect cell differentiation and these include the presence of molecules of the collagen family themselves, recognized since the 1960s to possess qualities that help induce differentiation (Hay 1984, p. 1). To some extent, this is due to the near-ubiquitous gels in which extracellular collagen floats. Gel contraction aids in maintaining cell-to-cell contacts, hence facilitating molecular exchanges and consequent differentiation (Hay 1984, p. 13). From the late Precambrian, collagen had thus been available as an essential tape-and-glue protein as observed by Towe (1981), and *also* as an important physical support, i.e. as tape and glue *and* vice.

Accounting for the exceptions

As best we know, no new phyla have come into existence since Cambrian times, with the exception of the Bryozoa, a late arrival whose fossils are first recorded in rocks of Ordovician age. But the Bryozoa are a special case, remarkable for their distinctive and perhaps unique secondary embryology during which their body plan is redesigned.

I provisionally assume that in the times running up to the Cambrian Explosion, oxygen had been less abundant than towards the end of the Explosion itself. If so, collagen-type molecules produced during pre-Explosion or early Explosion times would have been rare and/or of inferior quality, i.e. not particularly effective at sticking one cell to another. Yet despite the probable scarcity of good quality collagen in late Precambrian times, substantial life-forms had flourished worldwide, some of them over a half-meter in diameter. Their body plans were pillow- or quilt-like, constructed as though to assure that all parts of their bodies received more-or-less equal access to oxygen. 'Ediacaran fauna' was the name they were originally given, but after decades of debate whether they should be classified as animals, plants, fungi, or 'other'; the term 'Vendian biota' has been adopted. Here I suggest that members of the Vendian biota may have been neither animals, nor plants, nor fungi, nor even fully 'other'. Instead, they may have been collagen-deprived 'animal-like' creatures that had grown directly from blastulas without undergoing full (or familiar) gastrulation-style cell rearrangement.

By the time of the main phase of the Cambrian Explosion, the Vendian biota was nearly extinct, perhaps because the Vendians had been unable to compete with true metazoans. Yet, no metazoan phylum has become extinct in post-Explosion times. For whatever reasons, there always seems to be refuge at the phylum level, whether in a protected niche or by a lifeboat adaptation. Thus, a different or more complete explanation may be necessary to explain the total disappearance of the Vendian forms around the time of the Cambrian Explosion.

The notions of closely spaced oxygen (and collagen) thresholds have been used here in explaining the origin of today's phyla, and of the Vendian biota as well. Yet, these concepts do not account for the observation that no additional phyla have come into existence since the Cambrian Explosion (broadly defined), the special case of the Bryozoa excepted, nor do they address the exceptional extinction of the Vendians.

Along with stepwise thresholds, it may also be useful to think in terms of an 'oxygen window' and a 'collagen window'. For as the seas became more and more oxygenated, collagen-family molecules with stronger molecular bonds would have emerged. The cell-to-cell adhesions produced by these superior quantities or varieties of collagen may have eventually become too strong to be broken by the forces exerted by anaerobic cell-growth within blastulas *except* along already-established 'gastrulation-friendly' surfaces of weakness.

Such surfaces may have been inherently weak from the outset, and selective forces may have caused them to evolve towards further weakness (or slipperiness) in order to keep up with the gradual increase in the strengths of the collagen bonds with which they had to contend. The stronger varieties of collagen in post-Explosion times may have been too weak to anneal established 'paths of gastrulation' but too strong to permit new gastrulation-type cell rearrangements from coming into existence. A

window may have shut, preventing the formation of new phyla evermore.

In this view, worldwide habitat destruction would have been responsible for the extinction of the Vendian biota, a worldwide increase in oxygen availability that caused the disappearance of the weak varieties of collagen required by the Vendians.

Cancer, a two-step reversion, first of tissues, then of cells

When living tissue is insulted, inflammation results. If chronic, the inflammation eventually causes weakening of collagen bonds. If tissue architecture then degrades, individual cells are partly or fully released from normal metazoan tissue-constraints, including their normal oxygen supply. In order to survive, such cells may partly revert to ancestral anaerobic metabolic modes, an irreversible process (Warburg, reviewed *in* Warburg 1956) which is characteristic of cancer ('the Warburg Effect').

The behaviour of tissues under conditions of oxygen deprivation is reminiscent of events during gastrulation (and also embryogenesis) in at least one respect: outsized cells that favour anaerobic modes of metabolism break loose from their previous positions and become mobile. If only partly released from cell-to-cell connections and other tissue constraints, such cells may proliferate, grow in size, and form *in situ* tumours. If fully released from tissue constraints, they may produce metastases. In keeping with their Darwinian heritage, individual cells freed from normal metazoan tissue constraints will also vary. The resultant cell types may then be incompatible with the functioning of tissues and, more broadly, with metazoan life (Saul 1994; Sonnenschein & Soto 1999; Schwartz 2004; Saul & Schwartz 2007).

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