A HISTORICAL PERSPECTIVE ON CANCER *

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Abstract

It is proposed that cancer results from the breakdown of universal control mechanisms which developed in mutual association as part of the historical process that brought individual cells together into multi-cellular communities. By systematically comparing the genomes of uni-celled with multi-celled organisms, one might be able to identify the most promising sites for intervention aimed at restoring the damaged control mechanisms and thereby arresting the cancer.

More or less by definition, a cancerous cell is one that grows and reproduces uncontrollably. Of course, this characterization presupposes that the cell in question lives within a multi-celled organism — a community of cells. The identical behavior would appear perfectly normal for a cell existing in isolation.

But there is more to cancer than uncontrolled growth; for this behavior occurs in association with another trait which — in itself — would not seem to be related to growth at all: loss of differentiation. Why should a "histologic" characteristic like (lack of) differentiation be correlated in this way with a "dynamical" characteristic like growth rate? I believe that, far from being necessary for reasons of biochemistry or cellular dynamics, this association is *historical* in origin.

Let us try to imagine the transformation that took place when the first multicellular organisms coalesced from collections of cells living in relative isolation from each other.

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* Although the main idea exposed herein occurred to me some 20 years ago I was never able to get it published. After some hesitation, I am posting it to the "arXiv" in the hope that the historical viewpoint it puts forward may still be useful to people trying to understand cancer.

Aside from the mutual "solidarity" of its members, such a community of cells has the advantage that different cells can specialize in different tasks and collectively accomplish all these tasks more effectively than any individual cell could by itself. In other words, a division of labor becomes possible (specialized tissues, specialized organs, etc.) But for such an arrangement to function, the relative multiplicities of the cells with different specializations must be suitable, which in practice means controlling their absolute numbers as well. To participate in such a community, then, a cell needs (*at least*) the ability to specialize itself for a range of functions and the ability to regulate its rate of reproduction as needed: precisely the features whose absence typifies the disease of cancer.

It seems clear that, in order to provide these twin abilities, new biological "machinery" would have been required, either at the cellular level, or the supercellular level, or both. Furthermore, since the required mechanisms must have arisen in association with one another as part of the same historical process (a process presumably occupying an extended period of time), it would be natural for them to overlap and share components to a great extent. That is, there should have developed, in some measure, only a single (and universal) mechanism responsible on one hand for regulating growth and on the other hand for producing functional differentiation. Cancer would then result from the breakdown of this mechanism. From this perspective, cancer would not be a disease like measles, caused by the *presence* of some pathogen or some actively harmful abnormality, but a disease of deficiency like scurvy, caused by the *absence* or the failure of some mechanism that is present in normal cells (or normal tissue). It would be the consequent *regression*, on the part of the tumor cells, to an earlier, pre-social form of behavior.

The focus for finding a cure (or for prevention) would thus shift from *removing* the abnormality to *restoring* the missing or damaged machinery, and a strategy of trying to destroy the defective cells would be less likely to succeed than one of providing them with "replacement parts" for their damaged control mechanisms. How this could be done would naturally depend on the nature of the defect, but one might imagine, for example, delivering the replacement parts by means of retro-viruses or similar agents. With luck, such replacement parts would not harm healthy tissue, and hence they (unlike traditional chemotherapeutic agents) could be introduced in numbers sufficient to reach all the cells they needed to reach.

Before it could be repaired, however, the relevant "machinery" would have to be identified. Here a plausible concomitant of the postulated historical transition to communal life becomes relevant, namely the *universality* of the control mechanisms that evolved then. Assuming that the transition to multi-celled organisms was a prolonged process, one would expect the control mechanisms that developed in its course to be shared by all, or almost all, multi-celled forms. Conversely, uni-celled organisms should lack these control mechanisms.

To test this idea, one could compare the genomes of one-celled organisms with those of multi-celled organisms susceptible to cancer, searching for genes, or sequences thereof, that were universally present in the latter and absent in the former. These genes (or sequences) would then be the ones responsible for the postulated control mechanisms. Moreover, the *oldest* such genes (or sequences), would furnish better candidates than the newer ones, assuming that age could be identified reliably. Any attempt to develop a "gene therapy" or diagnostic test for cancer could then focus on the components of the genome identified in this way.

Of course, it might be overly optimistic to expect that the postulated control mechanisms could be identified simply with some well delineated portion of a cell's genome. They might involve non-genetic components whose failure was not occasioned by genetic mutations. On the other hand, one knows that genetic change is involved in cancer and that, in particular, there is a close correlation between mutagenicity and carcinogenicity. Given these facts, it does not seem too much to hope that the required "social skills" are coded into universal portions of the genome which could be identified and catalogued. Conversely, the failure to discover such portions would constitute evidence *against* the historical explanation of cancer put forward in this article.

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