The nature of cancer

New prospects for understanding and treatment

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This essay was first published in April 2008, and is updated regularly by adding information about recent advances. It is meant for readers who seek the truth but do not necessarily have any scientific background. All new thinking put forward is well based on research results, including the last section – an introduction to individualised treatment for cancer; the scientific and ethical problems.

Contents:

1. *Introduction.*

How cells are of the body are organised, and relate to the whole.

After decades of well-funded, clever and industrious research, cancer treatment is still not highly successful. The purpose of this essay is to explain some of the reasons why, as a help in understanding new advances, and you will need some idea of what a cell of the body is like though not at high level. We assume, for example, that you know how the information to run a cell is nearly all –

• stored away in an office, which we call the nucleus,
• in filing cabinets that we call chromosomes,
• as very long strings of DNA units (bases) instead of words,
• and the meaning of each string follows from the sequence of those bases; much like the meaning contained in the sequence of letters, spaces and symbols on this page.

The actual working parts of a cell, the "real economy", is mostly outside the nucleus and includes power stations, builders, factories, warehouses, importers, exporters, mail, telephone, health, police, army, secret service, transport, demolition, waste removal and disposal of the dead. Some real-economy workers are needed in the office too, including to make partial copies of the files on a daily basis for executive functions and to duplicate the whole lot from time to time. Each new cell is given a complete set of files even if most are never looked at again because the individual cell is specialised in its functions and pulls out only the relevant ones for detailed instructions on what to do.

Cells operate like semi-independent cities, linked together to form an empire which is the human body. Generally speaking, the interests of the whole empire should and do outweigh those of the individual city, but in the run-up to cancer one cell begins operating as if its own selfish concerns were the only important thing, seeks to reproduce and grow at the expense of others, consumes resources intended for the common good, eventually attacks its neighbours and attempts to take over the entire territory with disastrous consequences both for the empire as a whole and the descendants of the criminal cell itself. This is only possible if control systems and police forces both inside and outside the city fail to react properly, and we shall see that this is often because the information in the filing cabinets has been lost, destroyed, wrongly copied or locked away in an inaccessible drawer.

How cancer behaves is an excellent example of 'selfish DNA', selfish but stupid.

This fanciful kind of writing can easily be carried too far so we shall henceforth use plain, biological language, only occasionally reverting to the city-state metaphor where it seems likely to help. The first step must be to explain what happens in the earliest stages before changes in how a cell is managed can possibly justify the word 'cancer'. After that we shall describe how a combination of failures is needed, occurring in succession without adequate repairs to put things right, until the loss of control is such that we have no choice.

2. *Essential but risky Functions. Cell Growth and its Control*.

Most cells have specialised functions and in some this goes so far that they no longer grow or divide. In such cells, cancer is nearly impossible; instead it occurs in cells whose role requires them to be perpetually renewed; examples are those on body surfaces (including internal surfaces such as the lungs and intestines, hidden from our eyes), blood cells, and tissues that operate to defend the body against attack or to repair damage. There is a clear predisposition for cancers to start among cells that are already growing and replicating themselves, so our first concern is with how those two processes are directed and controlled; that is to say both stimulated and restrained because it is essential for health that cellular growth does occur when and where it is needed - as is made clear by what happens to people who have some fault in these systems.

Stimulation or restraint can be by way of messenger molecules from a distance (endocrine hormones), or similarly from a neighbour cell (paracrine), or even sent out by itself (autocrine), and then again by pathways that are confined within the cell so that the environment is not involved at all. Characteristically, one step in signal transmission is by way of one protein molecule binding to another so as to make it either more or less active and in many cases involving the attachment of a phosphate group to the second protein. Characteristically too the positive signal is accompanied by an off signal so that the stimulus administered lasts only for a few seconds or hours and is then switched off if

there is no further stimulus. For example in cases where the on switch operates by addition of a phosphate group, the off switch is an enzyme whose job is to remove it.

These control pathways are of almost unbelievable complexity, affecting many different cellular systems such as metabolic activity, response to the extra-cellular world, avoidance of cell suicide (apoptosis) and regulating the replication of DNA. The success story of cancer research in the last 30 years has been the extensive but still incomplete understanding of these pathways. Each sequence of activations and inhibitions may have many steps and branching points, linking to each other sideways as well as down the line, common elements serving several seemingly distinct processes. Just a few are known to be of great importance in many cancers (src, Rb, Ras, p53, myc, etc.) but hundreds of others may be of equal importance if acting in combinations that we do not yet understand, so that although we already know a great deal it is also certain that there is far more out there waiting to be discovered.

Powerful stimulation of cell growth and division is often a necessity (repair of injury, response to infection) but if it occurs without such compulsion we may call that a 'proto-oncogenic' process. The cells or tissues taking part do not yet by any means constitute a cancer, it is still under control so that (even if some of the signalling pathways are already damaged in the ways described below) trouble can in principle be reversed just because of the huge number of interacting, partially overlapping controls - if one is damaged the other systems may be able to compensate. Real trouble comes when several different control pathways are damaged; by some estimates not less than six and perhaps more. Often enough, inappropriate stimulation of growth and division occurs because of an 'oncogene' introduced by a virus or arising by somatic mutation as described below, but overgrowth in itself does not make the resulting cells into a cancer. Overactivity alone is not enough. A single mutation is not enough.

3. Mutations that lead to Failures of Intelligence and Command.

The damage that leads, stepwise, to full-blown cancer is of a critical kind which prevents correct information reaching an executive unit of the cell. In many cases the damage may be at the level of the 'paperwork', the DNA, if for example the base sequence has been wrongly copied so that the instructions can no longer be understood or are plain wrong. In consequence, a messenger molecule or receptor might be wrongly constructed so that it is no longer functional at all and must be bypassed, or permanently switched off or permanently switched on. The original protein is no longer made; the structure of the substitute differs to a greater or lesser degree. We call such a fault a mutation (a change), though here we are not talking about passing a defect on from one generation of a family to the next. It is a "somatic mutation", that is to say confined to the individual animal and passed on only from the cell in which it originates to its 'daughter' cells. Elaborate systems operate at the time when cells are replicating (and therefore making copies of their DNA) to catch bad copies and restore or destroy them, or destroy the cells containing them, and those systems nearly always succeed. We are to be concerned only about the rare escapees.

It turns out that other kinds of error are of importance in cancer about equal to that of mutations directly affecting the sequence of DNA bases. In any given cell, either part of the time or permanently, most genes are switched off, for example by way of methyl groups bonded to selected DNA bases, with or without changes to the histone proteins (which form the scaffolding round which DNA is wrapped). The effect is as if a filing cabinet drawer were locked shut. Interestingly, the instructions about which drawers are to be locked and which open are passed on at the time of cell division (by means still being worked out) so that an error in these instructions has much the same effect on daughter cells as an error in the base sequence itself, and again the correct protein is not made.

Damage of a more extensive kind occurs through break-up, reshuffling or rearrangement of chromosomes: the cell no longer knows which filing cabinet contains which information or sometimes this leads to 'pages' from different cabinets being filed together in the same folder so that completely wrong instructions are given and proteins are made which function differently from any in the normal cell. It is now known that such mutations are very numerous; merely most of them are not visible under the microscope and were missed until, only in 2009, it became possible to examine the whole DNA sequence of a cell line.

Yet another kind of information loss arises because cells normally have two copies of most genes, they are heterozygous; one of each pair of chromosomes was inherited from each parent. This protects the individual, because if one copy is defective, the cell in many cases can function quite well with the single good copy. But at each cell division, the two gene copies are compared with each other: if they are different one may be discarded, and occasionally it is the good one. This is 'loss of heterozygosity'. All the descendants of the affected cell will now have only the defective gene so the eventual functional effect is just like what happens with DNA mutations of the more ordinary kinds.

4. Initiation of Cancer, Key Mutations, Multiple Failures.

The continued overgrowth of a cell lineage and its eventual conversion into a full-blown cancer depend on a succession of somatic mutations (that is, mutations in the broad sense, including these newly-discovered phenomena) so that eventually a sufficient number, or a critical selection, of control mechanisms is disabled and the kinds of control mentioned below are finally lost. The aberrant cells now grow and spread as fast as possible, and they put in place (by yet more mutations, occurring accidentally, not involving intelligent design) all kinds of methods to enable them to do so. Evidently, any mutation that disables the DNA-screening process at the time of cell division will make it more likely that these new mutations will escape uncorrected, and that is obviously how it comes to pass that damage to the p53 protein is present in over 50% of all human cancers. Undamaged p53 would have initiated cell-suicide. Development of the cancer proper had to wait until damage to p53 disabled that function. Note however, that a

cancer can still occur in the presence of a normal p53 if exactly the necessary errors are present elsewhere among the control systems. Likewise mutations to the Ras gene are present in 90 % of cancers of the pancreas and over 50% of colon cancers. Even 90% is not 100% and that is surely very important in showing that neither p53 nor Ras mutations are in themselves essential to cancer, neither of them characterizes a particular cancer or tells us anything about the tissue of origin or causation. In the case of p53, these reservations are confirmed by recent research (*Nature* 468 (2010) doi 10.1038/nature 09535).

Research published in December 2009 (Franovic et al, *PNAS* (106) p.21306) introduces another candidate for a 'universal' cancer gene, more convincing than *p53* or *Ras*. This is *HIF2alpha* (not the *HIF1alpha* variant), which, in the cancer cells tested, controls many of these signalling pathways and might offer a widely applicable route for control of cancer cells. We shall see. As explained below in Section 10, we believe that killing all the cancer cells remains the gold standard for therapy.

We can now see that the key first step in cancer formation is occurrence of a mutation that makes it possible for subsequent mutations to escape detection and destruction. The particular cell concerned is still not yet cancerous, but the required succession of additional mutations is now more likely, or perhaps inevitable if the subject lives long enough.

Somatic mutation is a constant and essential feature of cancer and may be obvious on looking down the microscope in cases where the chromosomes are sufficiently muddled up. That was known over 100 years ago (Theodor Boveri). In general, however, several mutations are required and nearly all are much too small to see. Several different control pathways must be disabled. Just any old mutation or even many mutations will not necessarily lead to cancer and many mutations that occur in cancer cells are irrelevant or of low relevance to the cancer process, as is predictable from the preceding paragraphs and is confirmed by recent research. It is only mutations affecting the control systems that really matter in letting a cancer escape from control and, all too often, these mutations can occur spontaneously. The popular belief, attributing cancer to radiation or dangerous chemicals in food or the environment, is partly true but is not the whole truth. There really are such instances including the obvious ones of lung cancer due to smoking, skin cancers due to excess UV light and mesothelioma due to asbestos, but most cancers will occur anyway and it is doubtful how much diet will help in prevention beyond avoiding certain kinds of salted fish and a few other foods.

5. How many mutations - Irrelevant Mutations - Points of Weakness?

Many mutations in a mature cancer are 'irrelevant', as we suspected several years ago. What was not known until very recently was that there may be tens of thousands of mutations in a single cell, most of which can have no functional effect at all but may nevertheless be a weak point of cancer cells, where an attack might be possible. Though not essential to the development of a mutated cell into a cancer, such mutations could give rise to additional features for distinguishing the cancer cell from surrounding normal cells and therefore allow attack. Since all cells of a given cancer are descended from a

single originator they must also all share a common set of somatic mutations, namely those that were present in the first truly malignant cell and which is named the 'malignant-clone-defining mutation set' (McDMS), although each sub-clone may then go on to acquire its own additional mutations. If the means exist to detect the McDMS, it must be possible to recognise all the cells descended from that first malignant cell. See *Medical Hypotheses* (2009) vol. 73 pp.503-5. There is a link on this website.

For more related to this subject see *Nature* (2007) vol. 446 p.153, (2008) vol. 455 p148, (2009) vol. 458 p.719, vol. 461 p.809*; *Science* (2006) vol. 314 p.268, (2008) vol. 321 pp. 1801 and 1807. Absolute evidence of a cancer adding more mutations as time goes by is given in the paper marked with a star* where the writers show, with perfect precision, 30 mutations in coding regions of the DNA, in a relapsed cancer; and 11 of them were present also in the original cancer that had been removed 9 years previously. How many mutations are needed to make a cancer is a highly technical and controversial question and the argument is muddled by people not being careful about whether they mean ALL mutations or only those known to change the structure of named proteins. In the case just mentioned, the minimum estimate of the real number of the McDMS must be more than the 11 actually found in the original tumour because the 11 were only those in coding DNA and which happen to have been detected.

6. Cancer is a Composite and Complex Tissue; the Matrix.

Just as a city depends on the infrastructure of its surrounding countryside, and the entire country, so the characteristic cells of a tissue interact with other kinds of cell round about, and a non-living framework laid down by those cells, to form a cooperative whole, exchanging materials and messages to keep each other happy and under control. This is a pattern set down during the process of specialisation, mostly by silencing unnecessary genes, and they may not be so easily switched back on again. We can identify a tissue by looking at it under the microscope, taking into account the appearance of both the characteristic cells and the supporting cells; the overall pattern. Much of this is continued in a developing cancer; so that until an advanced stage its tissue of origin may be readily recognizable, and there are many cases where the actual cancer cells form only a small proportion of the whole lump. The normal tissue organization remains to some extent; that is, even the uncooperative cancer cells are partially responsive to their neighbours, and may even exploit them to assist growth (*Nature* (2007) vol. 449 p.557).

Three surprising conclusions follow: a] The appearance, classification and even clinical behaviour of a cancer may depend as much upon the tissue where it began as upon the exact nature of the mutations and the consequent protein alterations that make it cancerous. b] We may have as much success by attacking the supporting tissue as the cancer cells themselves (but see Section 10). c] The cells we see most of down the microscope and think of as representing the cancer may not be the most important in treatment, being partially differentiated and partially cooperative: maybe we should be seeking out cells which have not adapted in that way.

7. Stem Cells.

The important ones to attack for complete cure may be ‘stem’ cells, that is to say cancer stem cells, which have already acquired the really dangerous mutations, but grow slowly and divide infrequently so that they are resistant to chemo- and radio-therapy, yet provide a source of more sensitive successors that form the bulk of the tumour. Even if we kill all these successor cells, the tumour will be renewed by the persistent stem cells; which might explain a lot about the difficulties of treatment. See *Nature Biotechnology* (2009) vol. 27 p.44. The concept remains controversial and may be applicable for only some cancers. Also we have no knowledge yet about the McDMS in stem cells.

8. Invasion and Metastasis. Civil War.

We have talked loosely of ‘invasion’ by cancer cells. For that to occur requires loss of specific structural and control functions so that the cell is no longer tied so tightly to the framework of the surrounding tissue, and then breaks down that framework, allowing growth without the previous restraints, and movement into the vacant spaces. A tumour is generally defined as cancerous by microscopically observing invasion through the fibrous tissue that confines normal cells, or by spread to more distant tissues, called ‘metastasis’, which is not a simple consequence of the cancer invading a blood or lymph vessel. Most cells which spread in that way and lodge in distant sites would die or be inhibited in their growth until they find a way of integrating with the supporting tissue cells in the new environment. But some of them have succeeded. A vicious cycle operates so that these cells are then likely to grow and divide more rapidly and in such a way that their daughters acquire even more mutations of the kinds that in normal cells would lead to cell suicide. Ever more extreme mutations rapidly accumulate, and we observe loss of even the former degree of differentiation so that the cancer can no longer be recognised as to tissue of origin.

(This is the predicted end-result of any cancer that is not extirpated at an early stage and if the patient lives long enough. ‘Selfish’ behaviour of the faulty DNA leads inevitably to its own destruction as well as death of the patient. How selfish DNA acts in evolution of species is different because there we are talking about mutations in the germ-line cells, not somatic cells, so that if a successful mutation occurs it is perpetuated in later generations. At the molecular level, the principles are the same for somatic and germ-line mutations.)

Rather different is detection of metastasing cells in blood, which recent research suggests may be possible. Even if such cells prove unable to lodge and grow in distant sites, they must still all carry the McDMS and therefore offer a route to determining the weak points discussed in Section 5.

9. Immune Response to Cancer. The Gendarmerie.

Part of the body's mechanism for preventing development of cancers is the immune system. Many tumours, probably the vast majority, that begin to escape from the control mechanisms inside the cell itself, are soon thereafter detected by 'killer cells', with or without the cooperation of antibodies, and invited to die. Recent research reveals another mechanism, wherein the immune system holds miniature tumours in check without actually killing them. We can be sure that these things are important because people with impaired immunity die of cancers that hardly matter to the rest of us. The immune system is under difficulties in this area because it is naturally orientated to detecting and attacking things that are definitely abnormal (in particular, small parts of proteins that were either totally foreign to the cell or present in unusual quantities or in unusual circumstances). Cancers, however, originate within ordinary cells, so most of their proteins are wholly normal, and they also evolve ways of suppressing or adapting the immune response (*Nature* (2009) vol. 457 p.102; *Nature Biotechnology* (2008) vol. 26 p.1348). Immune activity against cancers surely exists, yet not one anticancer antibody has ever been made artificially, isolated or studied in detail so as to understand exactly how it might act.

We really cannot see how and why the immune system works even as well as it does.

Therapeutic cancer vaccines have limited success in a few tumours especially by way of stimulating cellular immunity (*Lancet* (2009) vol. 373 p.673) and there are recent suggestions about how this might work better (*Lancet* (2009) vol. 373 p.1033). Antibodies loaded with radioisotopes or toxins and directed towards tumour cells have had virtually no success. Vaccines that prevent infection with tumorigenic viruses are altogether different since they act long before any tumour or any kind of precancerous lesion has begun: they are preventative rather than therapeutic.

10. Treatment Options. What Can We Do?

This essay is all about finding effective treatments for cancer and knowledge is beneficial only if it helps in that. What, in general, are the approaches open to us?

Helping the body to help itself: Thousands of quack clinics thrive on persuading desperate people that they hold the secret to curing cancer by diet, thought-control, etc. None of that works. There is a dream of tricking the immune system into recognizing and attacking cancer cells more efficiently and something may come of it (*Science* 330 (2010) 440-3), the problems being those outlined in Section 9 – cancer cells are so very like normal, and also cancers evolve by mutation to escape immune control. The best hope is that the body's response can help in eliminating cancer cells already damaged by some other means, and indeed that probably happens anyway.

Removal of the tumour: Good, but unless you get it all, the remaining cancer cells may continue to grow. It may be that the body can react successfully against them once the numbers are diminished; occasional cases hint at that; more often the cancer can be seen to re-grow and because of yet more mutations become more aggressive than ever. Miniature metastases including displaced stem cells have been found lurking in remote sites years after the removal of the primary tumour and years before the cancer relapses. One cannot say that this is observed in all cases, but it certainly is a frequent behaviour in some kinds of tumour, and sets a biological limit to the benefits of surgery.

Radiation and chemotherapy: The conventional kinds work because they act against cells that are under stimulation to grow and divide, damaging the DNA as it replicates so that many dividing cells commit suicide, whether cancerous or not. Unfortunately that effect operates upon immune system cells, intestine, skin and hair follicles, so people may feel horribly sick during the treatment, their hair falls out and so on. The greatest successes in treatment of the last fifty years have been through use of these approaches, so no-one is allowed to condemn them, yet everyone concerned would be delighted to see better means made available. In these cases too as with surgery, relapses sometimes occur years after successful treatment, so it must be that a few cells or stem cells survive and re-seed the tumour process.

Restoration of control: Very hopeful new treatments involve putting cellular controls back in place, in the cancer cells themselves or their surroundings, by various clever subterfuges which in future may include gene therapy, putting good copies of a desirable gene back into cells that have lost it. It is too early to judge, but the limitations may prove to be the same as those affecting surgery and radiation. How do you catch all the rogue cells? What happens to the few cells left unaffected? Why should they not re-grow and change even more? The existing treatments of this kind do not involve gene therapy and nor do they repair control mechanisms in a perfect, engineer's way – more like sticking a plaster on a cam-shaft instead of putting in a new one.

Kill all the cancer cells. Better selectivity of antibody and drug therapy. Treatment directed to the individual patient: The standard kinds of chemotherapy and radiation are hardly selective at all for cancer cells, rather they select for actively growing cells. Conventional antibodies have failed consistently in the clinic to kill off cancer cells, but then they have always been directed to targets that are present to some extent on normal cells also; they are not selective enough for cancer. If 'antibodies' could be made to select not for a single target but for several at once, on the same cancer cell, and chosen so as to be representative for the cancer present in a particular patient, then this would be the basis for a new and far better-directed kind of treatment. Such sets must exist, since all the cells of a cancer must have a McDMS.

11. A role for hybrid antibody technology?.

(Super-selective, artificial 'antibodies' of this kind (co-bodies) are expected to be better than ordinary antibodies in many other applications; not only medical treatment, not only cancer; but that is a different story for another day.)

It is known how co-bodies might be made and they have a name. Moreover they can be made in minutes once the constellation of surface molecules present on a particular cancer cell is known and provided that background work had been done so that the source materials are in stock. So why are they not in regular use already?

Answer one: it takes time and money. Working only with patient biopsy samples is impractical (frontal assault rarely works) so a quite different approach is needed and is in hand. A first suggestion of how the correct choice of targets might be made appeared in *Nature* (2007) vol. 450 p.1235 – isolating metastatic cells from the blood of patients. More recent still is the stunning discovery (*PNAS* (2010) 107 p.18769) of a method for isolating, from blood plasma of cancer patients, peptides (protein fragments) that are specific to the individual's own cancer cells. This sounds like the perfect complement to co-bodies, which have the special, additional advantage that their effectiveness is not blunted by the presence of single copies of target molecules free in the body fluids. (Cancers commonly shed a lot of such material into their surroundings as one mechanism to confuse the immune system and evade attack.)

These advances make a stepwise approach practical, and if additional resources are made available this can be accelerated so as to offer real benefits within 5 years.

Answer two: there are ethical and regulatory difficulties to overcome since co-bodies are not like ordinary drugs tested and approved for use in thousands or millions of similar patients. We have seen how the individual cancer cell mutates and changes until it is not like the original tissue cell at all. Worse, it mutates until it is not like any other cancer cell either: it is unique, so its co-body treatment also must be unique and this is impossible to deal with under present-day regulation. The patient would be long dead before approval of his treatment.

If the problem cannot be solved any other way, the whole conceptual framework must be re-cast, and fresh thinking applied as to what is ethically acceptable, just as with the pioneers of *in vitro* fertilization (IVF), 40 years ago. The problem is not confined to co-bodies: other modes of individualised cancer treatment will come in to use whatever happens and the same difficulty applies to them. It is now common to find discussion in serious journals of the need for treatment to be individualised for each patient individually; therefore not capable of regulation in the manner now in vogue. We shall leave the question there, with a few references:- *Nature Biotechnology* (2010) vol.28 p.904; *Nature* (2010) vol. 458 p.131.

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