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A new strategy for cancer

The advent of genetic medicine has so far made little difference in the battle against cancer. In fact, despite advances in treating leukaemia and breast cancer, little overall progress has been made since the early 1970s. A new strategy is needed.

by Michael Baum / February 20, 2002 / Published in February 2002 issue of Prospect Magazine

As susan sontag famously pointed out, the rhetoric of cancer treatment and cancer research is couched in the terms of military conflict. Politicians claim that we are winning the war against cancer and the doctors with the highest profile are described in terms normally reserved for military leaders. At the sharp end, the patient never simply dies of the disease but loses the fight. This metaphor fixes in the public mind the idea that cancer is a foreign invader and therefore the war must destroy every last malignant cancer cell.

This is a false analogy. The cancer cells are simply an undisciplined sub-stratum of our cells. Cancer is an inevitable component of the aging process and all of us at some time in our lives co-exist with latent cancer scattered around the body. Medical oncologists often complain that the differences between the normal cell and the cancer cell are so small that they can rarely be exploited to the patients' benefit. This is why the most aggressive modern treatments can end up killing the person, before killing the cancer. No, we are not winning the war against cancer and the annual aggregate mortality from the disease has barely changed since President Nixon declared war on it with his cancer act in 1971.

Just as Kennedy had promised to land a man on the moon in the 1960s, so Nixon would find a cure for cancer by 1980. I was working in Pittsburgh with Bernard Fisher at the time of the Nixon promise and shared his scepticism about it. When Kennedy told Americans that they would land a man on the moon, we knew with a very high degree of accuracy where the target lay. All that remained was to create the technology based on the rocketry developed in the second world war. By comparison, for cancer, we did not know in 1971 where the target was and the therapies then available were equivalent to firing off rockets in random directions.

With last year's decoding of the human genome it is now naively believed by some people that we know where the targets are and now we need only develop the technology of the smart bomb. But do we really know what we should be targeting?

Genetic medicine not a panacea

The genome will eventually begin to deliver a better understanding of human biology-in health and in disease-and out of that a better understanding of the prevention and treatment of cancer. But knowing the position of a string of amino-acids that can stretch to the moon and back six times will not help us achieve a cure for the common malignancies within the foreseeable future.

It is only in very rare instances that a single genetic defect determines the development of a cancer. Most cancer geneticists believe that the emergence of a malignancy is determined by a minimum of four or five cumulative genetic events, each of which is rare, considering the number of cells in the body and the number of times they divide. In fact, one of the miracles of the human body is the fidelity of the copying of the DNA sequences, so that cancers are truly very rare events, bearing in mind the number of cells in

the human body and the number of times they divide in a lifetime. But each cell division is an opportunity for genetic disorganisation. Once a cell has made up its mind to pursue a malignant route, the evolutionary theory of cancer development suggests that it will eventually find a way to bypass the molecular checkpoints.

The laws governing these phenomena are poorly understood and the biology, mathematics and computing necessary to be able to reconstruct a model of a whole organ in health or in a state of malignancy are at a basic stage. In the same way an archaeologist might struggle for decades to reconstruct an ancient temple from a pile of rubble, the modern molecular biologist is trying to reconstruct the organism from a huge number of building blocks. In the fullness of time, human ingenuity will again decode these mysteries but that decoding will be an achievement equivalent to that of the genome project itself.

Amongst the many reasons for the lay public to confuse activity with progress are the dramatic changes in trends of cancer incidence and mortality across the world. Undoubtedly, there have been dramatic breakthroughs in the treatments of leukaemia, lymphoma (cancers of the lymphatic system) and the childhood cancers. Thirty years ago, all these would have been fatal but today we can expect between 50 per cent to 75 per cent cure rates. This progress followed on the classic experiments with animal models and cytotoxic chemotherapy-the chemical attack on malignant cells-in the 1960s. It turns out that this group of diseases are exquisitely sensitive to cytotoxic drugs. Unfortunately, the diseases that are most responsive to chemotherapy tend to be rather rare and count for less than 5 per cent of the total cancer burden in Britain. Furthermore, the success of chemotherapy in these rare cancers has diverted attention and resources from discovering effective treatments for the more common solid tumours such as colorectal and bronchogenic carcinomas which have stubbornly refused to respond in significant numbers to these very toxic treatments.

Instead of the reductio ad absurdum of persisting with high dose chemotherapy to virtually lethal doses, we should try to understand why rare cancers respond to chemotherapy but common solid cancers do not. We must also acknowledge that the incidence of some cancers falls or rises for reasons that are not understood. For example, at one extreme, stomach cancer, which is very common in Japan, is rapidly disappearing in the west. Between 1979 and 1997, the incidence of stomach cancer in Britain decreased by 34 per cent. The reasons are a mystery, but possibly relate to better methods of food preservation. At the other extreme, malignant myeloma (which affects the bone marrow) is increasing globally, almost as if there is a viral vector.

In contrast, the trends in lung cancer mortality are easy to explain. In Britain and the US, lung cancer mortality for men fell rapidly once there was a clearly established link between smoking and the disease. Tragically, many young women have now taken up the habit and deaths from lung cancer overtook deaths from breast cancer in Britain in 1999. The incidence of lung cancer in men decreased by 34 per cent between 1979 and 1997 but increased in women by 29 per cent.

There is only one of the common cancers that can truly be viewed as a success story of modern treatment-that is breast cancer. Here treatment has contributed to about a 30 per cent reduction in mortality over the last 15 years. This can largely be ascribed to the fact that breast cancer, unlike the majority of other cancers, is peculiarly sensitive to the level of sex hormones in the circulation and we now have safe and effective drugs that can modify these oestrogen levels. As far as the other common cancers are concerned, little in the way of therapeutic advance has been made in spite of the vast sums of money thrown into research and treatment since Nixon's initiative 30 years ago. Why has this been the case and how might we break out of the impasse?

a short history of cancer treatment

The 2nd century AD Roman physician and philosopher Galen, building on Aristotle, considered cancer to be the result of accumulating an excess of melancholia (black bile) within the diseased organ. Therapeutic strategies involved venesection, purgation and dietary modulation in order to rid the body of this excess of a natural humour. Such treatments were commonplace up until the early 19th century and

are still in vogue amongst the neo-Galenic doctrines of new age medicine.

The first serious challenge to the doctrine was the description of the cellular nature of cancer by M?ller in the early 19th century. By the 1840s, Virchow had completed his studies on the anatomy of cancer, which led to a revolutionary anatomical model of the disease. He taught that far from being a systemic disorder, cancer was a local problem of cellular organisation. This led to tumours arising within organs such as the breast, colon and lung, invading locally and centrifugally along tissue planes in the lymphatic channels. The regional lymph glands were thought to act as filter traps providing a line of defence. With exhaustion of these filters the tumour was thought to progress along more distant lymphatic channels and tissue planes ultimately to invade the deep vital organs such as the liver and the skeleton. The therapeutic consequence of this belief had to await the development of anaesthesia and antisepsis in the late 1890s. This then allowed the surgeon off his leash to carry out radical resection of cancers, taking out the organ, the surrounding tissue planes and as many lymphatic channels and lymph glands as were compatible with returning a living patient to the ward.

Although these operations achieved a high degree of local control and palliation of symptoms, the surgical mortality was high. Despite little evidence of improvements in mortality, surgeons stuck slavishly to these approaches, at least until the mid 1970s and some cancer surgeons still naively believe they can achieve a cure by cutting it all away. By the mid-1970s, the majority of thoughtful surgeons accepted the limitations of their technical expertise as new models began to evolve, largely as a result of the work of Bernard Fisher. He stressed that some form of general therapy had to be added to the surgeon's local control of the disease process. So patients recovering from the best efforts of the surgeon were then subjected to the best efforts of the chemotherapist and now, 25 years later, we are in a position to take stock.

Sadly, the common solid tumours in the organs (breast, prostate, colon, lung, ovary and so on) have proved more resistant to cytotoxic chemotherapy than might have been anticipated. Furthermore, the advances in treating breast cancer are predominantly a result of direct or indirect effect on the endocrine system. (It is worth noting that this breakthrough has nothing to do with molecular biology and everything to do with chemistry and endocrinology.) None the less allegiance to a regime of surgery plus chemotherapy, with or without radiotherapy, remains tenacious. Many medical oncologists believe they can cure cancer by increasing the dose or complexity of their cytotoxic regimens.

This belief that non-specific cytotoxic regimens will ultimately lead to the cure for cancer has had a profound influence on the budgets of the cancer research agencies and on the development strategies of the pharmaceutical industry. Because 60 per cent of the expenditure on cancer treatment occurs in the US, which only bears 5 per cent of the world's cancer burden, the pharmaceutical industry's primary target is to develop a drug up to FDA (Food and Drug Administration) approval for sale in the US. Therefore, hugely expensive treatments which can only promise minor increments in survival are rapidly brought to the marketplace. Two recent examples in the field of breast cancer include the use of the taxanes and herceptin. They are fascinating molecules, but they only add a few months to the life of someone who is pre-determined to die of the advanced stages of the disease. This cruel distortion of the R&D programmes of the pharmaceutical companies has indirectly had a profound effect on the development of alternatives that are affordable in the developing world. Similarly, there are some drugs based on unpatentable chemical formulas which might be of value in the treatment of cancer but have insufficient economic value for the pharmaceutical industry to manufacture in bulk. It is argued that the academic community should step into this breach, but the academic research programmes are patrolled by the thought police on the peer review committees, who are stuck in a cancer paradigm overdue for replacement.

a new strategy in the cancer war

It is time for a new start in the "war" against cancer. The contemporary paradigm has served its purpose and we require more innovative approaches to the understanding and treatment of the disease. Politics, finance, industry and academia must all shoulder their responsibilities. We have to recognise that cancer is a global problem and that cancer research should look beyond the egocentric needs of Orange County,

California. One must also be realistic. The wealth of the developed world, and the US in particular, will continue to skew the direction of research but, with political will and relatively modest investment, we could also have a profound effect on the prevention or treatment of cancer in the poorest parts of the globe.

Here are just three examples. First, hepatoma (primary cancer of the liver) is very common in South East Asia, particularly amongst the poor, yet extremely rare in northern Europe and north America. This cancer is one that is clearly linked to a mutation on the P53 gene (a gene known to be associated with DNA repair). This mutation is known to be linked to a common carcinogenic toxin that develops in rice that is stored inadequately, for example, in Philippine villages. When combined with the hepatitis virus which is endemic in those areas the result is a mutation of the P53 gene which kick-starts the liver cell on its route to cancer. The use of fungicides and adequate storage for the rice, coupled with a vaccination programme against hepatitis, could prevent the majority of hepatomas occurring in the rural areas of south-east Asia. Unfortunately, an investment today would be in anticipation of a long-term gain and therefore would not be perceived as politically or economically important. Neither would industry find this an attractive investment. The World Health Organisation (WHO) should be taking up this cause, but it has been crippled by in-fighting.

Second, the commonest cancers in India are cervical and breast cancer amongst women. These are often present in a very advanced stage in the rural communities. The simple expedient of having trained health workers to go to the villages and palpate the breast or inspect the cervix would allow the detection of cancers at a much earlier stage, although not at the latent stage screened for in the west.

Third, women in the poorer parts of the world with operable breast cancer are almost always subjected to a mastectomy, for want of a high technology radiotherapy centre. My own research group at University College London has developed a very simple mobile radiotherapy technique that can go into any operating theatre, anywhere in the world, and deliver radiotherapy at the time of surgery, allowing these women the luxury of breast conservation without the expense or inconvenience of having to live in the city for six weeks after the operation.

We should not, of course, neglect the legitimate demands of patients in the rich world for treatments that can improve on length and quality of life. But we need a new model that can explain the successes of the past, whilst also interpreting the flaws in the current cancer model. The current model assumes that the cancer cell grows in a linear way (one cell doubles to make two which doubles to make four, eight, sixteen and so on) and then in the secondary or metastatic stage gets into the blood stream, attacks other organs and evolves into a tumour which shows the same linear growth. But this model cannot explain why many cancers remain latent for long periods and may disappear rather than move on to the second stage. This is especially true of the thyroid gland of both sexes, the prostate of the man and the breast of the woman. Indeed the high level of "latent" breast cancer means that the present system of screening followed by surgery on the breast is tragically unnecessary in many cases.

When a primary cancer is "switched on," it grows by a process known as angiogenesis. This describes the process by which the cancer stimulates the creation of blood to feed the growing tumour. But according to the seminal work of Judah Folkman, the primary tumour itself secretes anti-angiogenic hormones which can maintain the cancer in a state of equilibrium for long periods. It is thought that the act of surgery or some other major disturbance may sometimes have the effect of disrupting this equilibrium.

To understand and analyse these events needs the help of the new non-linear mathematics, based on chaos and complexity theories. These mathematical models could inform a novel therapeutic strategy which might involve anti-angiogenic agents delivered before or during the surgical act. The drugs industry is now busy developing specific angiogenic agents.

An even more radical model suggests that the source of tumour growth is not necessarily the whole cell. Organs such as the liver and the bone marrow contain pluripotential stem cells with a capacity to develop into any organ (any cell in the body has the genetic coding for any other cell in the body and one

of nature's continuing mysteries is precisely what turns on and turns off the switches for differentiation). I have proposed that sub-cellular particles of DNA interfere with stem cells, which start growing into inappropriate organs at the wrong site. If there is anything in this alternative model of tumour growth then, instead of anti-cancer therapies, perhaps we should be looking at anti-viral therapies.

where next?

Conquering cancer requires concerted action from the public, governments, the UN, the pharmaceutical industry, the basic scientist and the clinical scientist. The public must continue to protest against governments' immoral dependence on the tax revenue from tobacco. Cancer patients themselves must also volunteer in larger number for drug trials. Only about 5 per cent of patients currently enter trials, although the number is growing.

Governments must recognise that there are no quick fixes for cancer and long-term investment for prevention is a mark of a humane society. The current attempt within the NHS to produce better co-ordinated treatment between GPs, radiotherapists and oncologists is a start. Early diagnosis remains vital in the cancer war and, while genetic medicine may eventually lead to breakthroughs in both diagnosis and therapy, it is contributing precious little at present.

The drugs industry must also exercise more restraint. Capitalism has created many benefits, but capitalism and the drugs industry are uncomfortable partners. Industry should consider a dual regime for patents-offsetting the development of cheap drugs for the developing world by increasing the cost of sales in the US for those expensive drugs which produce only modest incremental benefit. This will, of course, create a political backlash, but it can be confronted.

The academics can play their part by freeing their minds and being ready to accept ridicule when pursuing new ideas. Peer review will, I suppose, always be with us, but the grant giving bodies must set aside more funds for blue sky projects. Of course the competing claims of modest incremental progress and conceptual leaps have to be weighed in the balance. But the dominance of peer review thinking means that the latter is largely ignored. I find little comfort in the fact that the two biggest cancer charities in Britain, the Cancer Research Campaign and the Imperial Cancer Research Fund, join forces in February 2002 as Cancer Research UK. Now we have one huge monolithic structure that will further hamper innovation.

It is also the case that what we already know about cancer, inadequate though it is, is not being applied in treatment either in the developed or developing parts of the world. There is an enormous body of knowledge already available, but very few individuals carry this in their head. We need to think more cleverly about how to disseminate it.

The internet can be a useful educational tool, but it can also make matters worse. By marketing expensive anti-cancer drugs directly to patients, it increases inappropriate demands on over-stretched health services and fans the conspiracy between science and the media to inflate patient expectation to levels which cannot be satisfied. We need balance and diversity in our approach to cancer and this must include hard-headed cost-benefit analyses, interdisciplinary research, lifestyle modification and appropriate technology for the developing world, as well as the research which will spin off from the human genome.

The war against cancer is bogged down by undeclared special interests, petty-mindedness, political quick fixes and slavish adherence to outdated paradigms. It is time for the cancer army to be re-equipped.