Medical research

Are we losing the war on cancer?

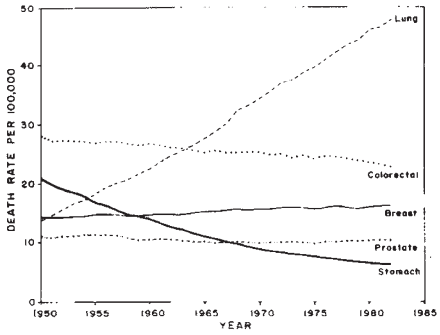
from Marie M. Cohen and Jared M. Diamond

CANCER is the second leading cause of death in the United States, and to defeat it, the government in 1971 declared a 'war' to be led by the National Cancer Institute (NCI) of the National Institutes of Health (NIH). Since then, NCI has spent $15 billion, its current annual budget is close to $1 billion (the largest of any NIH institute), and other government and private agencies devote $1 billion more to cancer. What progress has been made?

There have been impressive advances in curing certain cancers, notably most childhood cancers, Hodgkin's disease and certain leukaemias and testicular cancers. But these cancers are rare compared with those of the lung, colorectum, breast, prostate and stomach. The overall picture in the United States is summarized in NCI publications (see, for example, ref. 1) and in a recent controversial article by Bailar and Smith[2]. Relative 5-year survival rates (cancer patient survival adjusted for deaths from other causes by comparison with a similar age distribution from the general population) have improved slightly from 47 to 49 per cent between 1973 and 1978, the most recent years analysed. Despite this, age-adjusted mortality rates (see figure) have been increasing because age-adjusted incidence rates have increased. Thus, by the least equivocal criterion — mortality — we are losing the war on cancer.

Some disagree with this view. "The national statistics are inevitably a few years behind the times and therefore do not reflect the most recent advances in treatment"[3]. "The implication that the war on cancer is being lost is ridiculous. There are many cures already there. They just haven't come out of the computer"[4]. But this latter view, although often advanced in the past decade, "has never been vindicated by national statistics when these eventually became available"[3]. If predictions of future trends should consider recent advances, they should also consider setbacks such as the long-continuing steep rise in incidence and mortality of lung cancer (see figure), which is likely to leave the overall mortality trend flat or rising in the foreseeable future.

Cancer researchers disagree strongly about how to fight the war. One view is to continue present NCI policy, which puts more money into treatment (especially its biochemical/cellular aspects, which have undoubtedly spawned advances in treatment) than into prevention (see page 184 of ref. 1). Perhaps new drug development, monoclonal antibodies and studies of oncogenes, retroviruses and immunology will produce breakthroughs. It is agonizingly difficult to decide at what stage an expensive, long-term strategy should be considered a failure or whether it requires more time. One guide is to consider whether there are other, undersupported approaches with more promise. Several suggest themselves.



Age-adjusted mortality rates for five of the commonest cancers in the United States, 1950 – 1982. Age adjusted to the US population of 1980. (From ref. 2.)

First, smoking is estimated to cause 30 per cent of cancers. It is the main cause of the rise in lung cancer since 1945 to its current rank as the commonest cancer and also contributes to cancers of the oesophagus, bladder, pharynx and mouth[1,5]. Although NCI spends about $20 million a year in a programme to control tobacco use, the tobacco industry spends $2 billion on advertising and the US government spends $3.5 billion to subsidize the tobacco industry. In Norway a national anti-smoking programme that involved banning cigarette advertisements resulted in fewer people taking up smoking. An end to subsidies and a ban on tobacco advertising would save the US government a sum nearly equal to the entire NIH budget while also promoting the war on cancer.

Second, lung cancer exemplifies a broader, self-evident point: it is better to prevent cancer than merely to try to treat it. As suggested by geographical variation in cancer incidence as well as dramatic shifts in incidence when a human group migrates from one country to another, about 80 per cent of cancers are thought to have environmental causes, including 35 per cent that are influenced by diet[1,5]. Changes in environmental factors, and not changes in treatment, are responsible for the two biggest recent components of change in US cancer mortality: the rise in lung cancer and the decline in stomach cancer (see figure). These facts, as well as elementary common sense, suggest that more money should be spent on cancer prevention than on cancer treatment — the reverse of present policy.

Third, for a prescribed drug to be efficacious, patients must take it. Do they? A recent study by Levine *et al.*[6] monitored patient compliance by measuring blood levels of prescribed drugs and their metabolites after the patient had supposedly taken a dose. Patients claimed to have taken about 35 per cent of their doses, but in fact compliance was only 17 per cent, a value raised to 40 – 50 per cent by intensive educational and supportive programmes. Few oncologists are aware of these astonishingly low compliance rates, and even fewer devote much effort to patient education or to measuring compliance. When MOPP, a multi-drug chemotherapy for Hodgkin's disease, is said to produce a cure rate of 50 per cent, does this mean that the real cure rate is 50 per cent, or that the rate was 100 per cent but only 50 per cent of patients were compliant? Nobody knows, and there is surely a strong case for research on improving compliance with existing drugs rather than inventing new ones.

Finally, physicians tend to treat cancer as a biochemical/cellular process that either kills the patient or is cured, leaving no other consequences requiring professional attention. In fact, 'cancer' has become a group of mostly chronic illnesses in which the new patient must cope with repeated disruption or devastation of personal competence, morale, family relations, friendships, career and income[7]. There is little support for research in this area. There is also insufficient funding for professional personnel to help surviving cancer patients rebuild family relations, career and self-image, although physicians routinely make such referrals for patients surviving heart attacks.

Given the obvious advantage of avoiding cancer, why is more support given to treatment than to prevention? Part of the reason may be a confusion between the goals of basic and applied biology. The goal of applied biology is to solve prob-

1. National Cancer Program. *1983 – 84 Director's Report and Annual Plan FY 1986 – 1990* (NIH, Bethesda, 1986).
2. Bailar, J.C. & Smith, E.M. *New Engl. J. Med.* **314**, 1226 (1986).
3. Cairns, J. *Scient. Am.* **253**(5), 51 (1985).
4. Holland, J. *The Cancer Letter* **12**, 7 (1986).
5. National Cancer Program *NCI Fact Book* (NIH, Bethesda, 1985).
6. Levine, A. *et al. Proc. Am. Soc. Clin. Onc.* **3**, 71 (1984).
7. Cohen, J. *et al. Psychosocial Aspects of Cancer* (Raven, New York, 1982).

Errata

In the article by Velia Fowler (*Nature* **322**, 777; 1986) the figure was incorrectly attributed to ref. 4. In fact it was taken from ref. 6: Byers, T. J. & Branton, D. *Proc. natn. Acad. Sci. U.S.A.* **82**, 6153; 1985.

In the article by R. Letolle (*Nature* **323**, 19; 1986) the start of the second paragraph should read "In 1886 Crookes had just discovered yttrium..."

lems by means of any available knowledge, whereas basic biology currently favours certain types of knowledge (for example, reductionist, molecular and obtained under controlled conditions at the laboratory bench). Research on oncogenes, viruses and immunology is highly rewarded; research on methods of coping, patient compliance and motivating people to stop smoking is scorned as 'soft', eligible for no Nobel prizes and little support. In an infintely rich world, one would increase expenditure on prevention and treatment, but an increase in the large US cancer budget cannot be expected when support for other areas of medicine and science is even stingier. Thus, some reallocation of funds from the biochemical/cellular aspects of treatment towards prevention and broader aspects, seems called for. □

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Retroviral vaccines

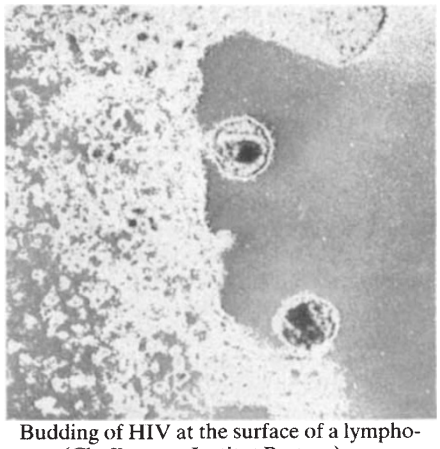
How close is C to D?

from Jerome E. Groopman

PERHAPS the highest octaves in recent meetings in Paris and Cold Spring Harbor, New York were reached in discussions of the development of retroviral vaccines. There has been considerable controversy concerning the optimal approach to the production of a safe and effective vaccine against the human immunodeficiency virus (HIV), the aetiological agent of the acquired immune deficiency syndrome (AIDS), and the significance of neutralizing antibodies. These antibodies are defined by their ability to kill the virus *in vitro* but their role in protection against infection is not clear. Marx, Gardner and their co-workers at the California Primate Research Center in Davis, in collaboration with Syntex Corporation, have now developed a vaccine based on inactivated whole virus that protects monkeys from infection and subsequent immune deficiency related to the simian AIDS serotype 1 virus (Marx, P.A. *et al. J. Virol.* in the press). Although the simian AIDS virus is a type D retrovirus whereas HIV is type C, it may help understand the host immune responses necessary for protection and the significance of neutralizing antibodies.

Lasky and co-workers at Genentech have adopted a different approach to a vaccine against HIV by cloning and expression in mammalian cells of the major viral envelope glycoprotein gp 130 (Lasky, L.A. *et al. Science* **223,** 209; 1986). Immunization of rabbits and guinea pigs with the recombinant gp130 elicits neutralizing antibodies of moderate titre that appear capable of inhibiting not only the HIV isolate used in the cloning but several other isolates as well (R. A. Weiss *et al.*, personal communication). This success in eliciting neutralizing antibodies was repeated by scientists in the National Cancer Institute and Duke University who used gp120 purified from HIV-infected lymphoid cell cultures to immunize goats (Robey, W.G. *et al. Proc. natn. Acad. Sci. U.S.A.* in the press). Similarly, F. Wong-Staal *et al.* (personal communication) have used non-glycosolated HIV envelope fragments expressed in *Escherichia coli* and elicited neutralizing antibodies.

Although these approaches appear to follow the successful development of vaccines for viruses that do not belong to the retroviral family, the significance of the neutralization response as an indicator of success has been questioned. Furthermore, the presence of neutralizing antibodies in patients with AIDS has been taken as evidence of their inability to limit the pathogenic effects of HIV. Cell fusion and syncytia formation, perhaps caused by gp120 interaction with the CD4 determinant on uninfected lymphoctes, is thought to be a mechanism of lymphocyte loss and immune deficiency.



Budding of HIV at the surface of a lymphocyte (Ch. Daguet, Institut Pasteur).

The approach adopted by the Davis group is simple and direct, and is modelled on the Salk vaccine for the poliovirus. Formalin-inactivated simian AIDS virus was used with the adjuvant threonyl muramyl dipeptide to vaccinate six macaques, and a control group received adjuvant alone. Moderate titres of neutralizing antibody were elicited in the vaccinated monkeys. Persistent viraemia was prevented in vaccinated animals and none developed disease, whereas five of six controls were viraemic, with four developing clinical simian AIDS. Although the pathogenesis of simian AIDS resulting from the type D retrovirus may differ from disease related to HIV, the study from California is the first report of a vaccine which prevents spontaneous retrovirus-induced immunosuppressive disease in primates.

Recent data from our laboratory and elsewhere indicate that the humoral neutralizing response in man following HIV infection does not appear until 6–9 months after the primary antibody response. The reasons for this are not yet understood, but it is possible that the presence of neutralizing antibody before exposure to HIV might effectively limit entry and spread of the virus. The ability of human or animal neutralizing sera raised to gp120 to block formation of multinucleated giant cells *in vitro* is being studied in several laboratories. Although it is possible that the configuration of neutralizing epitopes on the viral envelope in the infected cell membrane may differ from those in native or recombinant antigens, it is still unclear whether this is of practical importance in vaccine development.

The direct approach to the development of an AIDS vaccine still has considerable hurdles, most notably strain specificity. It appears that the neutralizing antibodies raised against the recombinant gp130 and the native gp120 will neutralize some but not other geographically distant isolates of HIV (R. A. Weiss *et al.*, personal communication). Again, we can look back to the development of a vaccine against poliovirus where success was achieved after systematic serotyping of numerous strains to give the current trivalent formulation. A polyvalent subunit vaccine encompassing the major serotypes of HIV will probably be required, although how many major strains will be needed is not known.

Other approaches being considered in the development of an AIDS vaccine, such as synthetic peptides related to neutralizing epitopes of the envelope protein and anti-idiotypic antibodies, as well as study of the immune response to proteins other than gp120, should be pursued. Considering that 5 million or more individuals throughout the world are estimated to be infected with HIV, and the continued rapid spread of the retrovirus in the West and in Africa, a variety of approaches should be taken. The next step, trial of prototype HIV subunit vaccines in chimpanzees, will tell us if the direct approach works. This should teach us a lesson in the alphabet of clinical retrovirology. □

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