The war on cancer - failure of therapy and research: discussion paper

N J Temple PhD *Animal Sciences Division, Alberta Environmental Centre, Vegreville, Alberta TOB 4LO, Canada* **D P Burkitt** MD FRS *Hartwell Cottage, Wells Road, Bisley, Glos GL6 7AG*

Keywords: research design; neoplasms therapy; neoplasms prevention and control

A generally-held belief by both the medical profession and the lay public is that therapeutic medicine greatly affects health. Providing more hospital beds, doctors and resources is viewed as the path to improve health.

Therapeutic medicine is of much benefit to sick people. However, with the exception of several highly contagious infections, it has not reduced the incidence of disease. This generalization applies particularly to cancer. Despite this fact most of the expense and effort devoted to the management of cancer is directed towards early diagnosis (screening) and improved therapy. Evidence has steadily accrued that this strategy is essentially a failure: little impact has been made on the toll taken by the major cancers.

The failure of therapy, coupled with the realization that the overwhelming majority of cancer is related to environmental, particularly lifestyle, factors, dictates that prevention should be our foremost aim. It follows, therefore, that cancer research should concentrate on those environmental factors which may cause or prevent cancer. Instead, most research looks at either the detailed mechanisms of cancer formation or else investigates new types of therapy.

Medicine should admit its severe limitations in therapy and redirect itself. Using the fruits of an expanded research programme into such areas as diet and exercise, medicine should strive to apply this knowledge to cancer prevention.

How successful is the war against cancer?

C'est magnifique mais ce n'est pas la guerre

As is well known, there have been major improvements in survival rates for certain cancers of children and young adults[1]. However, since only about 1.3% of cancer cases occur in those under 25 years[2], this has little impact on the overall picture. In other cancers, lymphomas and breast cancer for example, various advances in treatment have been achieved.

Early detection appears to be of value against two major cancers of women. The Papanicolaou smear has apparently cut the mortality for cervical cancer in countries with well organized screening programmes[3]. A total of four randomized screening studies have shown that mammography in women aged about 50 years or over can reduce breast cancer mortality by 20-30%[4-8]. Hewitt[9] and others, however, have questioned the extent of the benefit. Even if one accepts the results of the above trials, they hold no promise for most women destined to develop the disease. Moreover, the large number of false positives associated with mammography causes much trauma. One cancer where early detection may prove to be of value is colon cancer, particularly if screening methods improve.

While these examples do represent success stories, albeit limited ones, when the field of cancer as a whole is surveyed, a generally depressing picture emerges.

In their 1981 study of preventable cancer in the USA, Doll and Peto[10] stated that there may have been no improvement in survival from the common cancers since the early 1950s. More recently Cairns[11] argued that there has been no real advance in survival rates for the major cancers. These claims stand in stark contrast to the 'official' figures for the USA. These indicate that since the 1950s significant progress has been made in the 5-year survival rates for most cancers[1,12]. However, critics have pointed to two major flaws in the way survival rates are calculated[10,11,13,14]. Each of these flaws reflect the greatly increased use of screening to detect several cancers at an earlier stage.

First, we have the problem of lead-time bias[14]. Let us suppose a particular cancer is invariably fatal and that in previous years death always occurred 4 years after clinical symptoms forced the patient to a doctor. Let us further suppose that early diagnosis now causes the cancer to be diagnosed two years earlier, but treatment is never successful. The result of early diagnosis will be that the survival time of each patient (measured from diagnosis) will jump from four years to six. Even more impressive, the five year survival rate will jump from zero to 100%! Something of this has actually occurred.

The second flaw in the survival figures is that screening causes much over-diagnosis[10,11,13]. Many of the early 'cancers' detected by screening and subsequently 'cured' are not, in fact, destined to develop any of the clinical symptoms of a true cancer. This problem applies particularly to cancer of the lung, breast and prostate.

It is important not to lose sight of the harm done by the above two problems (early diagnosis of cancers destined to be fatal and the over-diagnosis of 'cancer'). Each case exposes the patient to much unnecessary emotional distress and unpleasant treatment.

Bailar and Smith[13] took a different approach to the question of whether we are successful in the war on cancer. Rather than focusing on survival rates they looked at the changes in overall mortality since 1950 in the USA. This led them to a similarly pessimistic conclusion: '(The data) provide no evidence that some 35 years of intense and growing efforts to improve the treatment of cancer have had much overall effect on the most fundamental measure of clinical outcome - death. Indeed, with respect to cancer as a whole, we have slowly lost ground, as shown by the rise in age-adjusted mortality rates in the entire population'.

0141-0768/91/020095-04/$02.00/0

A recent study from West Germany came to the same conclusion. The authors reported that there is no real evidence that between 1952 and 1985 improvements in treatment had any significant effect on overall cancer mortality[15].

Overall, therefore, little real success has been achieved in the war against cancer. True increases in survival rates have appeared in only a few cancers. Increases in age-adjusted mortality rates have wiped out any gains.

We also see this by contrasting the meagre improvements in survival rates with the far greater changes in the age-adjusted mortality rates in the USA. Between 1930 and 1985 mortality from stomach cancer fell by about 85% and that from uterine cancer by about 77%[1]. Simultaneously, there was an explosion in lung cancer. Lesser rises were seen for leukaemia and cancer of the prostate, pancreas and ovary. The volatile nature of the different cancers is illustrated by the changing ratio of stomach cancer deaths to lung cancer deaths: 9 : 1 in 1930, 1 : 10 in 1985. The causes of these dramatic changes lie almost entirely in environmental, particularly lifestyle, factors. Clearly, improvements in medical treatment are of little importance compared with environmental factors.

Over the last several decades, then, medicine has waged a major war against cancer, concentrating on earlier diagnosis and improved therapy. The war is not being won. Nevertheless, medicine shows few signs of admitting that its strategy may be flawed. In this it resembles a World War I general who stated: 'Casualties: huge. Ground gained: negligible. Conclusion: press on.'

Cancer: a preventable disease

The enormous differences in the incidence of particular forms of cancer in differing geographical and socio-economic situations, together with the changing incidences following emigration from high to low risk areas, or vice versa, indicate the major role of environmental factors. It is reckoned that the vast majority of cancer is related to the environment, particularly lifestyle[10,16]. These observations suggest that much cancer must be potentially preventable, if the responsible environmental factors could be reduced or eliminated. In many instances causative factors have been identified and preventive action recommended, eg lung cancer from smoking and skin cancer from excessive sunshine.

Breast and colorectal cancers, two of the commonest tumours of Western populations, are rare in populations whose lifestyle is pre-industrial. Each cancer has comparable prevalences in black and white Americans, and increases dramatically in populations that emigrate from areas of low to areas of high prevalence, as in the case of Japanese immigrants to Hawaii[10,17]. Breast cancer is about eight times as common in black American women as in African women[17], and colon cancer is nearly 15 times as common in black Americans as in Africans[18]. This underlines the dependence of these cancers on the environment of Western culture.

Tumours of the lung, colon and prostate are by far the most common cancers in man, while tumours of the breast, lung and colon are the most common in women. These are, if one adds endometrial cancer, the tumours that are characteristic of Western culture and affluence. Because these tumours share epidemiological features, namely geography, socio-economic status and chronological emergence, with a large group of disorders now referred to collectively as Western diseases, they must be assumed to share common or related causative factors[19]. Therefore, the same measures recommended for avoiding diseases varying from coronary heart disease to diverticular disease, from gall stones to hiatus hernia, from diabetes to obesity, to name but a few, should also apply to colon and breast cancer.

Cancer research

For the main thrust of the war on cancer to be prevention, research into cancer must reveal how this can most effectively be done. Unfortunately, most cancer research is misdirected.

In a previous paper by one of us, medical research was divided into two types[20]. Most research is 'complex'; it involves studying intricate body mechanisms in health and disease and attempting to gain a real understanding of the disease process. A minority of research is 'simple'. Here the major activity is to determine which environmental or lifestyle factors cause or prevent diseases. It also includes studies of simple body mechanisms (eg the effect of dietary fibre on intestinal transit time).

The major tools of simple research are population studies, prospective and case-control studies, experimental intervention in humans (eg changing the diet to test the effect on health) or analogous studies on animals. The key feature of simple research is that the results are immediately and directly relevant to our understanding of the disease.

The reason for the inferiority of complex research is that disease processes are immensely complex. The history of medical research over recent decades is not one of understanding disease. Rather it is of finding huge numbers of small pieces of gigantic jigsaw puzzles. Whenever there appears to be light at the end of the tunnel, this nearly always turns into more tunnel where the light should be.

Areas such as immunology, molecular genetics and cellular biology have seen impressive numbers of discoveries. Yet rarely does this knowledge tell us what changes in our lifestyle are likely to help prevent or treat particular diseases. These problems apply particularly to cancer research.

A classic example of the advantages of simple research is the discovery that the great majority of lung cancer patients smoke[21,22]. By further use of simple research (prospective and case-control studies) it was a straightforward matter to establish that tobacco causes a whole group of other cancers.

Not surprisingly, researchers became intrigued as to the mechanism by which smoking causes cancer. Analysis of cigarette smoke revealed some 2000 chemicals. A large effort has gone into elucidating the metabolism of these chemicals and how they cause cancer. However, the research effort has faced tremendous obstacles. To determine exactly how or why this happens will take an army of researchers many decades.

During the last few years simple research also led to the important discovery that passive smoking causes various diseases, including lung cancer[23]. Similarly, the recent finding that cigarettes may be the biggest single known cause of leukaemia was the result of case-control studies[24,25]. Complex research contributed nothing to these discoveries. Indeed, it

undoubtedly had a delaying effect by diverting attention from a full investigation into the effects of smoking on health.

More advantages of simple research are shown by dietary studies. We will concentrate on two examples, though the same lesson is learned from numerous others.

The hypothesis that colon cancer can be prevented by dietary fibre was based on epidemiology and the known effects of fibre on colon function (ie an increase in faecal bulk and a speeding of the transit time)[26,27]. These actions of fibre, it was hypothesized, reduce the exposure of the colon to carcinogens and thereby prevent colon cancer. Here we have an example where mechanisms may be looked at without straying from simple research.

Support for the fibre concept has come from prospective and case-control studies and from determining whether fibre prevents colon cancer in animals[28]. Of course, over the years the hypothesis has had to be modified, but this merely reflects new information coming from simple research.

We do not believe that complex research has significantly contributed to the story. Areas such as identifying carcinogens in the faeces, determining their metabolism and their effects on the colonic mucosa have yielded little useful information.

Beta-carotene is another important protective factor against cancer. This was first proposed by Peto *et al.*[29] in 1981 based on data coming almost entirely from simple research. First, they reinterpreted prospective and case-control studies and pointed out that beta-carotene intake apparently has an inverse relationship to cancer risk. Second, several animal experiments had indicated that beta-carotene is anti-carcinogenic.

Fortunately, the large majority of the subsequent work has been by simple research (ie mostly prospective and case-control studies)[30]. The mostly positive results have indicated that beta-carotene protects against several types of cancer, particularly lung cancer.

Thus simple research into beta-carotene has provided much important information on the prevention of cancer. Had the research been confined to biochemistry and allied techniques (complex research), it seems highly likely that the anti-carcinogenic action of beta-carotene would have been postponed by several decades.

The large body of useful information discovered in just a few years of simple research into beta-carotene should be contrasted with the great 'in' area of modern cancer research: molecular genetics. It now accounts for a sizeable fraction of cancer research: the resources devoted to molecular genetics (even when narrowed just to that directly related to cancer) probably outstrips all research on dietary factors in cancer by a factor of two or three.

Molecular genetics is, in the main, another attempt at producing a 'magic bullet' against cancer. Like its predecessors (eg interferon), it offers great promise, at least in theory. However, the track record of such quests is extremely poor. The reason lies in the inherent flaws in the logic of complex research, as discussed earlier. The fact that it took almost 30 years between the discovery of the double helix and the emergence of oncogenes as a distinct research field (1953 to the early 1980s) suggests that several more decades will elapse before valuable new treatments based on molecular genetics can emerge. It seems highly probable, therefore, that molecular genetics is destined to be the greatest ever Pied Piper of cancer research.

Towards an integrated plan for cancer control

There is need for a major reappraisal of how the problem of cancer is approached. Prevention, rather than early diagnosis and treatment, should be the top priority. Prevention has the great advantage that it entails nothing worse than nicotine withdrawal symptoms. On the other hand, cancer treatment, even when successful, often exposes the patient to much suffering, both physical and psychological. Indeed, some cancer treatments are considered worse than the disease.

An integrated plan for cancer control must also research how cancer can be prevented. This objective necessitates a far greater emphasis on simple research.

For simple research to reach accurate conclusions as to the factors which cause or prevent cancer, it should use several types of investigation in parallel: (1) population comparisons, (2) prospective and case-control studies, (3) controlled clinical trials, (4) analogous studies on animals, and (5) envisaging a plausible mechanism. However, just as guilt can be established in a murder trial without a motive being demonstrated, so a mechanism is not an essential ingredient in proving the hypothesis under test. Indeed, the hunt for a mechanism can quickly enter a quagmire of complex research. Sometimes, however, a mechanism presents itself without loss of simplicity (eg dietary fibre and colon cancer).

Each of the above types of study has its pros and cons. Forming a clear picture is best achieved by combining the evidence from all five types of study.

A crucial area of research which we feel has been badly neglected is behaviour modification. Few people can be unaware that smoking is dangerous, yet a large minority still smoke. Here is an urgent need for research into appropriate anti-smoking strategies. Similar research is needed in other areas, particularly diet.

It would be myopic to view cancer in isolation from other degenerative, particularly Western, diseases. There is a great overlap between the factors which cause or prevent all Western diseases. Moreover, a prevention campaign is likely to be far more successful in motivating people if the goal is the prevention of the diseases that cause 80% mortality (all Western disease) rather than those that cause 21% (cancer only). For these reasons, the prevention of cancer should be part of a major campaign to prevent Western diseases in general. Medicine, it must be pointed out, has a poor ability to cure virtually any of the Western diseases.

Acknowledgment: We are indebted to Dr L E Lillie and Richard Johnson for helpful comments.

References

1 Silverberg E, Lubera JA. Cancer statistics, 1988. *CA* 1988;38:5-22
2 Canadian Cancer Society. *Canadian cancer statistics 1988*. Toronto: Canadian Cancer Society, 1988
3 Kelsey JL, Hildreth NG. *Breast and gynecologic cancer epidemiology*. Boca Raton, Fla: CRC Press, 1983

4 Shapiro S. Evidence on screening for breast cancer from a randomized trial. *Cancer* 1977;**39**:2772-82
5 Tabar L, Fagerberg CJG, Gad A, *et al.* Reduction in mortality from breast cancer after screening with mammography. Randomized trial from the breast cancer screening working group of the Swedish National Board of Health and Welfare. *Lancet* 1985;i:829-32
6 Tabar L, Fagerberg G, Duffy SW. The Swedish two county trial of mammographic screening for breast cancer: recent results and calculation of benefit. *J Epidemiol Community Health* 1989;**43**:107-14
7 Andersson I, Aspegren K, Janzon L, *et al.* Mammographic screening and mortality from breast cancer: the Malmo mammographic screening trial. *BMJ* 1988; **297**:943-8
8 Roberts MM, Alexander FE, Anderson TJ, *et al.* Edinburgh trial of screening for breast cancer: mortality at seven years. *Lancet* 1990;**335**:241-6
9 Hewitt HB. Breast cancer screening: a response to Dr Maureen Roberts. *BMJ* 1989;**299**:1337
10 Doll R, Peto R. The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. *J Natl Cancer Inst* 1981;**66**:1191-308
11 Cairns J. The treatment of diseases and the war against cancer. *Sci Am* 1985;**253**:51-9
12 Schottenfeld D. The epidemiology of cancer. *Cancer* 1981;**47**:1095-108.
13 Bailar JC, Smith EM. Progress against cancer? *N Engl J Med* 1986;**314**:1226-32
14 Kolata G. Is the war on cancer being won? *Science* 1985;**229**:543-4
15 Becker N, Smith EM, Wahrendorf J. Time trends in cancer mortality in the Federal Republic of Germany: progress against cancer? *Int J Cancer* 1989;**43**:245-9
16 Wynder EL, Gori GB. Contribution of the environment to cancer incidence: an epidemiologic exercise. *J Natl Cancer Inst* 1977;**58**:825-32
17 Pike MC, Ross RK. Breast cancer. *Br Med Bull* 1984;**40**:351-4
18 Waterhouse J, Muir C, Shanmugaratnam K, Powell J, eds. *Cancer incidence in five continents*, vol 4. Lyon: IARC Sci Publ No. 42, 1982
19 Trowell HC, Burkitt DP. *Western diseases: their emergence and prevention.* London: Edward Arnold, 1981
20 Temple NJ. Simplicity - the key to fruitful medical research. *Med Hypotheses* 1985;**17**:139-45
21 Doll R, Hill AB. Smoking and carcinoma of the lung; preliminary report. *BMJ* 1950;**2**:739-48
22 Wynder EL, Graham EA. Tobacco smoking as a possible etiologic factor in bronchogenic carcinoma. *JAMA* 1950;**143**:329-36
23 Fielding JE, Phenow KJ. Health effects of involuntary smoking. *N Engl J Med* 1988;**319**:1452-60
24 Kinlen JL, Rogot E. Leukaemia and smoking habits among United States veterans. *BMJ* 1988;**297**:657-9
25 McLaughlin JK, Hrubec Z, Linet MS, Heineman EF, Blot WJ, Fraumeni JF. Cigarette smoking and leukemia. *J Natl Cancer Inst* 1989;**81**:1262-3
26 Burkitt DP. Epidemiology of cancer of the colon and rectum. *Cancer* 1971;**28**:3-13
27 Cummings JH, Southgate DAT, Branch W, Houston H, Jenkins DJA, James WPT. Colonic response to dietary fibre from carrot, cabbage, apple, bran and guar gum. *Lancet* 1978;i:5-8
28 Greenwald P, Lanza E, Eddy GA. Dietary fiber in the reduction of colon cancer risk. *J Am Diet Assoc* 1987;**87**:1178-88
29 Peto R, Doll R, Buckley JD, Sporn MB. Can dietary beta-carotene materially reduce human cancer rates? *Nature* 1981;**290**:201-8
30 Temple NJ, Basu TK. Does beta-carotene prevent cancer? A critical appraisal. *Nutr Res* 1988;**8**:685-701

(Accepted 31 July 1990)