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Special Paper

The Pierre Denoix Memorial Lecture: Nature and Nurture in the Control of Cancer

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PIERRE DENOIX

PIERRE DENOIX, whose work and person I have the honour of commemorating today, was by any criteria a remarkable man. Professor of Clinical Oncology in the University of Paris, Director of the Institut Gustav Roussy, the first specifically designated anticancer centre in Europe and one-time President of the UICC, he led the attack on cancer in France and shared its leadership with very few peers internationally.

Denoix was a visionary with a keen sense of what was possible, so that his visions came to be realised in practice. Appointed to the Paris public hospitals as a surgeon in 1946, he was one of the few to realise the need for specialisation in oncology and to appreciate the wide range of scientific disciplines that the subject required. When, 10 years later, he was appointed Director of the Gustav Roussy he introduced computing and medical physics, which other hospitals had ignored, and he sought and obtained the cooperation of Daniel Schwartz, a non-medical statistician, thus restarting biostatistics in France after a lapse of 100 years. With Schwartz, he conducted the first epidemiological studies of tobacco and alcohol in relation to cancer in France [1–3] and initiated the first French randomised trial of therapy.

Within France his influence was enormous, not only through the directorship of the Institute, an appointment that he held for 26 years, but also through his many other appointments as, first, Director of the Cancer Section of the National Hygiene Institute, then President of the Cancer Commission and finally Director General of Health. In these capacities he played a major part in creating anticancer centres throughout the country.

Internationally, Denoix's influence will be remembered primarily for the introduction of the TNM classification of malignant growths. Criticised, initially, as too simplistic, he defended the method as practicable worldwide. In this he has proved right and its use has enabled oncologists in all countries to speak to each other in a common language. Important, too, was the creation of the UICC's project on clinical trials, which helped to initiate the organisation of the Early Breast Cancer Trialists' Collaborative Group in a meeting chaired by his colleague Robert Flamant and, through the Group's work, the establishment that tamoxifen improves long-term survival [4].

Pierre Denoix had an imposing personality; elegant, good-looking and with an open friendly countenance, he exuded confidence. Within his Institute he associated himself closely with the staff and was always accessible to them. He was not, however, afraid of taking a position counter to the ideas of the time and, having taken it, would defend it vigorously. Pierre Denoix was not only one of the founders of modern oncology, but he also set an example of how leadership can be both democratic and firm.

I met Pierre first at a small international conference in 1952 and thereafter was proud to call him a personal friend. Despite his intense patriotism, which had earned him a Croix de Guerre, he tolerated my poor French and would, after a few polite introductory remarks, slip into English for the rest of our conversation. I am confident that, in the same spirit, he would have tolerated my choice of 'Nature and Nurture in the Control of Cancer' as the subject for the Pierre Denoix Memorial Lecture, recognising that I could not do justice to the more specific subject that was nearest his heart: the aetiology, prevention and treatment of cancer of the breast. The control of cancer by the modification of nurture was, however, of perennial interest to him and I have no doubt that he would have been among the first to enquire how the recent dramatic increase in our knowledge of natural susceptibility to the disease would affect our policies for its control.

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KNOWLEDGE OF NATURE

That knowledge of genetic risk factors, which I call 'nature', will eventually have a profound effect on our ability to control cancer cannot be doubted. In the first place, genetic abnormalities have been identified that increase susceptibility to the development of some types of cancer to such an extent that under all normal circumstances the bearers of the abnormality have an 80 to 100% chance of developing the disease. Those identified by the end of 1997 are listed in Table 1 together with the cancers to which they give rise. To these we must add a few others that give rise to similarly high-risk when they are inherited from both parents and, doubtless, in the course of time many others with lower but still substantial penetrance. The list will certainly grow, but I doubt whether more than a few per cent of the cancers that now occur each year will prove to be accounted for by inherited susceptibility of such a high degree that nurture is essentially neutral. With the discovery of these genetic mutations and of the means to detect them *in utero* or postnatally, the possibility arises of avoiding some cancers by abortion of the affected fetus, by organ ablation in the child or adult, with or without a preliminary period of screening to detect the appearance of pre-malignant change and by personal prescription rather than by general control of the environment or general education to modify behaviour of the community as a whole. But how far prevention by these different means will be socially acceptable remains to be seen.

What could be more important would be the discovery of genetic variations that modify risk to a lesser extent and provide opportunities for the control of a substantial proportion of cases of a particular type of cancer by focusing screening and changes in nurture on that minority of people who are most at risk. We have long had knowledge of variations in the risk of skin cancer with variation in skin pigmentation and of gastric cancer with the ABO blood groups and there have been many claims of variations in risk with variation in the efficacy of polymorphic enzymes that activate or inactivate carcinogens or sex hormones. The latter have often been *post hoc* hypotheses based on small numbers and many of them have not stood the test of time—as, I suspect, may prove to be the case with the suggestion that smoking protects against the development of breast cancer in carriers of the *BRCA1* gene [5]. Now, with the new laboratory techniques that are available the position is altered; some 100 000 variants of polymorphic enzymes have already been discovered and the National Institute of Environmental Health Sciences in the US is giving high priority to a long-term project to assess the relevance of inherited characteristics to human disease. As the new techniques now enable many thousands of affected people to be studied, instead of the hundreds that have been studied in the past, some differences in outcome in different individuals will certainly be found to be due to differences in genetic susceptibility of the sort described. I suspect, however, that the most important result of the discovery of such differences will be the clues they provide to the mechanisms by which the disease can be produced and that this may lead to more effective methods of control.

LUCK

We should not, however, expect such genetic differences to account for all the situations in which, for example, one man who smokes 15 cigarettes a day develops a lung cancer at 60 years of age while another who smokes 25 a day survives without developing it for 80 years. For the development of cancer is a complex process involving several changes in the same stem cell and whether or not all the necessary changes

Table 1. *Cancers attributable to hereditary susceptibility with high penetrance*

Syndrome	Cancer	Gene
Common cancers		
Familial adenomatous polyposis	Colon, rectum	*APC*
Hereditary non-polyposis colorectal cancer		
Type 1	Colon, rectum, stomach, endometrium	*MSH2*
Type 2	Colon, rectum, stomach, endometrium	*MLH1*
Type 3	Colon, rectum, stomach, endometrium	*PMS1*
Type 4	Colon, rectum, stomach, endometrium	*PMS2*
Hereditary breast cancer		
Type 1	Breast, ovary	*BRCA1*
Type 2	Breast	*BRCA2*
Brain and CNS cancers		
Hereditary retinoblastoma	Retina, sarcoma	*RB1*
Li-Fraumeni	Brain, breast, sarcoma	*TP53*
Neurofibromatosis 1	Brain, sarcoma	*NF1*
Neurofibromatosis 2	Brain, acoustic neuroma	*NF2*
von Hippel-Lindau	Brain, kidney, adrenal	*VHL*
Tuberous sclerosis 2	Brain, kidney	*TSC2*
Other cancers		
Hereditary Wilms' tumour	Kidney	*WT1*
Multiple endocrine neoplasia 1	Nasothyroid, other endocrine	*MEN1*
Multiple endocrine neoplasia 2	Medullary thyroid, adrenal	*RET*
Hereditary melanoma 1	Melanoma	*CDKN2a*
Hereditary melanoma 2	Melanoma	*CDK4*
Gorlin	Basal cell carcinoma	*PTC*
Langer-Giedion	Chondrosarcoma	*EXT1*
Peutz-Jeghers syndrome	Multiple	*LKB1*

CNS, central nervous system.

accumulate in one cell is largely a matter of luck. If this were not so, there would be no possibility of curing cancer of any organ by ablation of part of it—or by removing one breast or one kidney—for all the stem cells in an organ have the same genetic constitution and have been exposed to much the same extent to the same environment and, if luck played no part, malignant clones would develop in many of them at about the same time.

Luck, which does not appear in the title of my paper, plays a major part in determining whether an individual develops cancer and, if he or she does, when it appears; but it plays no part in determining the population risk in a large community or, consequently, the differences in risk between communities. If these are not due to nature, as they occasionally are, they are due to nurture.

EFFECT OF NURTURE

By nurture I mean the effects of both the environment and the individual's personal behaviour and knowledge of its effects offers the opportunity for major reductions in the age-specific risks of many of the common cancers. This is nothing new, for the possibility came to be generally accepted some 30 years ago, when it was realised that the incidence of all cancers that were at all common anywhere varied greatly in incidence not only with area and community, but also with time. Hence it followed that ways of living might well be possible that would reduce the age-specific incidence of the disease by some 80–90%. Some of these ways might not be particularly attractive, but even if attention were restricted to practicable changes it was soon concluded that more than half the premature deaths from cancer—by which I mean deaths occurring under about 70 years of age—could be avoided. Analysis of the contribution of different factors has led to various estimates of the proportion of cancer deaths attributable to different types of cause, which have varied from country to country, but which for developed countries have generally been in fair agreement [6, 7] and they have not altered greatly over the last 20 years. An example of the proportions recently estimated for the U.K. is shown in Table 2.

The reliability of these estimates varies greatly. For some (notably the effects of smoking, of consuming alcohol and of exposure to electromagnetic radiation) the figures are unlikely to be far out; for some others (notably reproductive hormones and diet) the range of estimates is wide and even so may not include the true figure.

The total should not, of course, be expected to add up to 100%, because different factors may produce the various changes in a cell that are required before it can give rise to a malignant clone or facilitate the effect of other factors, as in the case of smoking and asbestos in the production of lung cancer and aflatoxin and hepatitis B virus in the production of hepatocarcinomas. Hence the development of any one cancer may be controlled in several ways. If we knew all the causes of cancer I have no doubt that the sum of the proportions in a table like Table 2 would be two or three hundred per cent, if not more.

Table 2. Proportion of fatal cancers attributable to different avoidable factors

Per cent	Factor	Per cent	Factor
29–31	Smoking	20–50	Diet
4–6	Alcohol	2–4	Occupation
< 1	Pharmaceutical products	< 1	Industrial products
10–20	Infection	1–5	Pollution
	parasites		air
	bacteria		water
	viruses		food
5–7	Electromagnetic radiation	1–2	Physical inactivity
	ionizing		
	UV light	10–20	Reproductive hormones
	lower frequency		

Table 3. Cancers largely attributable to smoking [10]

Cancers of:	
Mouth	Lung
Pharynx*	Pancreas
Oesophagus	Kidney, pelvis
Larynx	Bladder

*Excluding nasopharynx.

I cannot in the space available review the evidence that has led to all these estimates and must be selective. I shall, therefore, omit reference to the last five types of cause listed in the table, apart from noting that indoor pollution appears to be responsible for the increased risk of lung cancer in non-smokers seen almost alone in some parts of China [8] and that occupation or pollution of some kind is, or may be, responsible for much or all of the mounting incidence of mesothelioma, testis cancer, and non-Hodgkin's lymphoma.

Mesothelioma is now the most evident occupationally induced cancer in many developed countries and occurs, as Peto and colleagues have pointed out [9], in men employed in a wide variety of occupations, including carpenters, electricians and plumbers exposed unwittingly to amphibole asbestos in buildings. In the U.K. in 20 years time, this one-time rare cancer may account for 1% of deaths in men from all causes. Why the other two cancers are increasing so generally is unknown, apart, that is, from the contribution that AIDS and the immunosuppression associated primarily with organ transplantation make to the increase in non-Hodgkin's lymphoma. There have been many suggestions that the increase in the incidence of both these tumours is due to some form of environmental pollution, but the evidence is weak and inconsistent.

Smoking

Of the other known causes, the first and foremost is the effect of smoking, which is quantitatively the most important and affects the risk of many different types of the disease. The eight types that are listed in Table 3 were recognised to be largely attributable to smoking by the International Agency for Research on Cancer (IARC) in 1986, at least in populations in

*Table 4. Other cancers associated with smoking** [11]

Nature of association	Type of cancer
Causal	Lip, nose, stomach, body of kidney, myeloid leukaemia
Causal and confounding	Liver
Confounding and possibly causal	Large bowel, cervix uteri
Preventive	Endometrium

*Principally or entirely cigarette smoking except for lip cancer, for which pipe smoking is more important.

which cigarette making has long been common [10]. For these eight cancers, prolonged consumption of average numbers of cigarettes per day increases the risk between 3 and 20 times. With further research since the IARC's report it has become clear that several other types are also associated with cigarette smoking [11]. These are listed in Table 4. For some, the mortality in smokers is only slightly greater than in non-smokers, but the consistency of the findings in different countries, the evidence for a dose–response relationship, the lower mortality in ex-smokers than in continuing smokers, the presence of many different carcinogens in tobacco smoke and the lack of evidence of adequate confounding provide grounds for believing that most of the observed relationships are causal. For one, cancer of the liver, the association in developed countries has commonly been attributed to confounding with the consumption of alcohol and consequent cirrhosis of the liver; but two case–control studies show that the association persists after adjusting for alcohol [12, 13] as does evidence from China, where cirrhosis of the liver is largely uncorrelated with the use of tobacco (Liu and Peto, Oxford, U.K.). For two (cancers of the large bowel and cervix uteri) the associations may be wholly due to confounding with, respectively, diet and sexually transmitted infection; but smoking may still play a part in the former indirectly by causing dietary modification and, in the latter, by causing excretion of tobacco specific mutagens in the cervical mucus. For one, cancer of the endometrium, the effect is to prevent the disease by modifying the metabolism of oestrogens and consequently reducing the risk by up to half.

Recently childhood cancers have been added to the list, as a small proportion appears to be produced by parental smoking; not as a result of exposure to environmental smoke after birth or to smoke products in maternal blood *in utero*, but as a result of genetic mutations caused by paternal smoking before the child was conceived. This, to me, surprising finding is strongly suggested by the massive data from the Oxford Childhood Cancer Study reported in three papers by Sorahan and colleagues [14–16] the results of which are summarised in Table 5 and by the combined results of 13 smaller studies, which give a relative risk of 1.20 if the father smoked [15] and Sorahan (Birmingham University, U.K.). A causal relationship is made plausible by Fraga and colleagues' (1996) finding of oxidative damage in the sperm of smokers [17], but I shall suspend judgment until it is confirmed in further independent studies.

Altogether Peto and colleagues [18] and Peto (Clinical Trial Service Unit, Oxford, U.K.) have estimated that smoking was still responsible for approximately 40% of all deaths from cancer in men in the U.K. in 1995, having come down from 52% 20 years earlier, and that the proportion in women was 20%, having gone up from 12% over the same period. The proportions estimated for 14 other developed countries in 1990 are shown in Table 6. The highest proportions in men were found in the Russian Federation and Poland and the lowest in Sweden and Portugal. The highest proportions in women were found in the U.S.A. and Denmark and the lowest in Portugal and Spain, where so few women had been smoking for a long time that no material effect could be detected at all.

Table 5. *Risk of fatal childhood cancer associated with paternal smoking* [14–16]

Father's smoking cigarettes a day	Risk relative to father not smoking		
	1953–1956	1971–1976	1977–1981
1–9	1.03	0.99	1.20
10–19	1.31*	1.33*	1.24
20–29	1.42*	1.30*	1.26*
30–39		1.43*	1.35*
40 or more		1.62*	1.47*
No. of deaths	1549	2587	1641

*$P < 0.05$.

Alcohol

A second agent, whose effects can be estimated with reasonable accuracy, causes a few cancers of the liver: namely, the consumption of alcohol. It also causes a substantial proportion of cancers of the mouth, pharynx, oesophagus and larynx most of which can, however, be avoided by not smoking, as the two agents act synergistically increasing each other's effects [19]. Recently, however, alcohol has also been shown to cause some cases of cancer of the breast. A relationship with alcohol has been suspected for many years, but has commonly been thought to be due to bias or confounding. Now, however, the pooled results of 6 large cohort studies, each reporting at least 200 cases of breast cancer, which have shown a progressive increase in risk with the amount drunk [20] and the evidence that alcohol increases the level of blood oestrogens [21] put the nature of the relationship beyond reasonable doubt. Recently, too, evidence has been obtained that maternal consumption during pregnancy may increase the risk of a specific sub-type of myeloid leukaemia in children under 18 months of age [22] but this needs to be confirmed.

Alcohol, of course, also has many other effects and in considering policies for the control of cancer we have to bear in mind that small and moderate amounts have a substantial effect in reducing the risk of myocardial infarction and several other vascular diseases and that these diseases are so common in many developed countries that the overall effect of moderate but regular consumption is to prolong life for those who have reached middle age, as is illustrated by the recent findings of the American Cancer Society's second cancer prevention study [23]. For cancer prevention, the policy must be to avoid the interaction with tobacco and restrict consumption sufficiently to avoid cirrhosis of the liver and for women to avoid a large increase in the risk of cancer of the breast.

Pharmaceutical drugs

As for other drugs, the more they are studied the more some are found to prevent rather than cause cancer. Apart

Table 6. *Per cent of deaths from cancer attributable to smoking in* 1990 *(Selected developed countries* [18]*)*

Country	Male	Female	Country	Male	Female
Australia	35	11	The Netherlands	48	6
Denmark	39	18	Poland	50	7
France	37	1	Portugal	25	0
Germany	38	4	Russian Federation	52	5
Hungary	49	11	Spain	39	0
Italy	42	5	Sweden	21	7
Japan	27	7	USA	45	23

from those used to treat the disease, several of which cause a small risk of second cancers in patients otherwise apparently cured and those extracted from foodstuffs to which I shall refer later, the most important are listed in Table 7, along with the types of cancer that they either cause or prevent. That aspirin should have a prophylactic effect was surprising, but the idea that the reduced risk (of the order of 50%) seen in cohort studies is caused by the drug is supported by experimental studies in humans with Sulindac, another non-steroidal anti-inflammatory agent [24, 25].

Just how great an effect the combined steroid contraceptives have on the risk of breast cancer has been a source of controversy for many years; but the re-analysis of existing data for over 50 000 cases by the Collaborative Group on Hormonal Factors in Breast Cancer has settled the issue [26]. The risk of breast cancer is increased, but only while the drugs are being used, when the increase is of the order of 20%, and for a few years after stopping, when it is less. Similarly, the risk associated with the use of oestrogenic hormone replacement therapy occurs only while the drug is being used and for a few years afterwards [27] in this case, however, increasing with the duration of use. With both drugs, the increased risks are chiefly limited to tumours localised to the breast and it is possible that there is little or no effect on the mortality rate.

That tamoxifen can prevent cancer of the breast as well as curing it is shown by the fact that when women receive tamoxifen for the treatment of cancer in one breast, there is a reduced incidence of new primaries in the other breast; but it also causes endometrial cancer [28, 29]. The risk is certainly much less than the benefit when the drug is used as adjuvant treatment for women who already have developed breast cancer but the balance of benefit and risk from its long-term use, when given prophylactically, is uncertain.

Electromagnetic radiation

Two other important categories of cause for which we can make reasonably reliable estimates are electromagnetic radiation and infection.

The energy of the types of radiation to which we are commonly exposed, varies by 12 orders of magnitude and until recently it is only the highest frequencies with the highest photon energies that have been thought to constitute any biological hazard. Now, however, public concern has been aroused by suggestions that the fields produced by radio frequency radiation might cause brain cancer in adults and the extremely low frequency fields associated with high power electricity cables might cause leukaemia in children. The former suggestion rests entirely on anecdotes, but there is some epidemiological evidence to support the latter [44]. At present we must suspend judgment, but the risks, if they exist at all, are certainly small.

Ultraviolet radiation and ionizing radiation are another matter. In developed countries, the former is responsible for nearly all cases of skin cancer, now that the occupational causes have been (or should have been) eliminated and the latter is responsible for perhaps 4 or 5% of all cancer deaths, mostly as a result of the natural radiation to which everyone is exposed from radon in air, cosmic rays from outer space, the external radiation from radionuclides in rocks, soils and building materials and the internal radiation from radioactive traces of potassium, lead and polonium in food. Of this natural radiation much the most important is produced by radon and its decaying products which, in the U.K., accounts for about half the total dose received and in some other countries for more. Its effect has, until recently, had to be extrapolated from the effect observed in underground miners who have been exposed to larger doses under rather different conditions to those in which people are normally exposed in their own houses. Now, however, it is clear from ten studies carried out in several different countries that the extrapolation was justified: the doses to which people are normally exposed at home do have the estimated effect, as is shown in Table 8, and consequently it is estimated that radon is responsible for some 5–10% of all lung cancers, the absolute effects being much greater in smokers than in non-smokers, because the two agents act synergistically. The radiation dose received from radon varies enormously from house to house and in many countries is over 100-fold. High-doses can, however, be avoided by installing underfloor ventilation or, in the future, by building regulations that require impermeable sheeting to be included below the floor in new houses in high risk areas.

Infection

Many more potentially avoidable cancers are attributable to infection.

Parasites. Infection with parasites is responsible for many cancers of the bladder, large bowel, liver and bile ducts in parts of Africa and Asia. In all cases, it could be avoided by a combination of hygienic and therapeutic measures, if sufficient public collaboration could be secured.

Bacteria. The most important bacterial infection appears to be chronic life-long infection of the gastric mucosa with *Helicobacter pylori*. Infection commonly occurs in youth, when

Table 7. Pharmaceutical products affecting the risk of cancer

Drug	Cancers	
	Caused	Prevented
Immunosuppressive drugs	Non-Hodgkin's lymphoma Skin	–
Oestrogens, including hormone replacement therapy*	Breast Endometrium	? Large bowel
Combined steroid contraceptives	Breast	Ovary, endometrium
Tamoxifen	Endometrium	Breast
Aspirin	–	Large bowel

*Oestrogen only.

*Table 8. Risk of lung cancer from radon in houses**

Method	Reference	Per cent increase in risk per 100 Bq.l^{-1}
Estimated from experience in miners†	30	9
Observed in case–control studies:		
(i) Meta-analysis of 8 studies	31	9
(ii) West Germany	32	13
(iii) South West England	33	8

*Average in houses varies from 10 to 40 Bq.l^{-1} in different countries and the range from 5–5000 Bq.l^{-1}. †Exposed to small or moderate amounts.

it may cause antral gastritis and lead to duodenal and (less specifically) gastric ulceration, atrophic gastritis, intestinal metaplasia and eventually an approximately doubled incidence of gastric carcinoma. Whether antibiotic therapy that eliminates the infection would eliminate any substantial proportion of gastric cancers remains to be shown; but it would certainly eliminate some gastric lymphomas, as these rare tumours can regress and may even disappear when *H. pylori* infection is treated after the tumour is diagnosed [34].

Other forms of bacterial infection are not known to contribute much risk, except perhaps in the bladder, where chronic infection may be accompanied by the formation of carcinogenic nitrosamines and in the large bowel, where their role in producing carcinogens from bile salts is still a matter for debate.

Viruses. Viral infection is even more important. Chronic life-long infection with the hepatitis B virus (HBV) is a cause of the great majority of the deaths from hepatocarcinoma in Africa and Asia, where the disease is so common that liver cancer ranks eighth in the list of common cancers worldwide. In China, neonatal immunisation reduces by about three-quarters the risk of lifelong chronic infection and elsewhere, where transmission is horizontal rather than vertical, even greater degrees of protection can be achieved. Hence there is good reason to hope that the mass immunisation of children now being carried out in some tropical and semi-tropical countries will lead to a large reduction in the incidence of the disease. Indeed, in many populations HBV vaccination is second in importance only to smoking cessation for the avoidance of cancer. Some hepatocarcinomas, however, are attributable to hepatitis C virus, which is an RNA virus and infection with it cannot be prevented in the same way. Established infection can sometimes be cured by interferon.

Almost as important is infection with certain specific types of the human papilloma virus. They are responsible for the great majority of cancers of the cervix and probably also for most cancers of the vulva, vagina, penis and anus and they may be responsible for some cancers of the mouth, larynx and skin. Immunisation against them with specific gene segments may well be possible. It has been shown to be effective in animals and a similar vaccine should soon be available for testing in humans.

Table 9. *Viral causes of cancer*

Virus	Cancer
Hepatitis B	Cancer of liver
Hepatitis C	Cancer of liver
Human papilloma types 16, 18 and others	Cancers of cervix, vulva, vagina, penis, anus
Human herpes Type 4 (EBV)	Burkitt's lymphoma Immunoblastic lymphoma Nasal T-cell lymphoma Hodgkin's disease Nasopharyngeal cancer
Human herpes Type 8 (Kaposi associated herpes virus)	Kaposi's sarcoma Body-cavity lymphoma
Human T-cell leukaemia type 1	Adult T-cell leukaemia/ lymphoma
Simian virus 40-like	Ependymoma Choroid plexus tumours Mesothelioma Bone tumours

Four other oncogenic viruses are listed in Table 9. The roles of the EB virus (or human herpes virus type 4 as it is now called) and of the human T cell leukaemia virus in causing many, if not most, of each of the cancers listed are firmly established and there is strong evidence to relate the Kaposi-associated herpes virus (human herpes virus type 8) to all types of Kaposi's sarcoma, the classical East European type, the tropical type and the type associated with AIDS. The association of simian virus 40-like viruses with four mostly rare types of cancer is, however, still tentative.

As with nearly all other causes of cancer, the viruses are not associated with every case of the specific cancer and they often require other factors to be present as well before they exert an evident carcinogenic effect, such as intensive infection with malaria parasites in the case of Burkitt's lymphoma, asbestos in the case of pleural mesothelioma and aflatoxin to cause a high incidence of liver cancer. With so many newly discovered virus-associated cancers it would be surprising if there were not more waiting to be discovered; but how many it will be practicable to prevent by immunisation remains to be seen.

Diet

Last in my list, but certainly not least in importance, is diet. Its effect on the incidence of cancer has been the subject of intensive research for many years, but the extent to which such major components as meat, fat and fibre contribute to the effect is still unclear. A pooled analysis of five cohort studies of vegetarians has, for example, shown no reduction in the incidence of colorectal cancer compared with that in meat eaters [35] despite the suggestion in many case–control studies that meat increased the risk. Nor could the International Agency for Research on Cancer (1993) find any human evidence of a harmful effect of cooking, despite the production of many products that were carcinogenic in the laboratory [36].

Five relationships have, however, been established sufficiently clearly to justify intervention. Two have little relation to life in the developed world: namely, that of liver cancer with aflatoxin, a metabolic product of fungal contamination of oily foods stored under hot and humid conditions, and that of nasopharyngeal cancer with a peculiar type of decomposed salted fish typically consumed in south China. A third has little relevance in most countries now, but used to be important worldwide: namely, that of gastric cancer with salted and salt preserved foods. The two other aspects of diet for which relationships have been established that are highly relevant in many countries are over-consumption leading to obesity and a relative deficiency of vegetables and fruit.

Dietary restriction is a powerful means of reducing cancer incidence in laboratory experiments. In humans, in the wild, restriction in youth leads to diminished growth, delayed sexual maturity in both sexes and consequently a diminished risk of both breast and testis cancer. It is not a practicable means of reducing risk, but the avoidance of obesity is and will reduce the risk of cancers of the endometrium and gall bladder and of breast cancer after the menopause.

Precisely what is meant by a relative deficiency of vegetables and fruit is unclear, but has been interpreted by the National Cancer Institute in the US and the British Department of Health to be anything less than 5 servings a day. Investigators have mostly estimated odds ratios for different types of cancer in people whose consumption of fresh fruit

Table 10. *Relationship between food consumption and risk of cancer: cohort and case–control studies* [37]

Food	No. of studies	Relationship in studies: per cent of total		
		Inverse	Null	Positive
Vegetables, any	68	81	6	13
Vegetables, raw	39	85	10	5
Vegetables, green	79	77	6	17
Vegetables, cruciferous	54	70	15	15
Vegetables, allium	34	79	9	12
Legumes	36	39	17	44
Carrots	64	78	11	11
Tomatoes	50	70	10	20
Fruit	46	63	26	11
Citrus fruit	40	65	20	15

and vegetables was in the highest third, fourth, or fifth category compared with people whose consumption was in the lowest such category and they have found reductions in risk with high consumption of the order of 50%. The results reported for different types of vegetable or fruit are summarised from a review by Steinmetz and Potter [37] in Table 10. Inverse relationships have been observed most consistently with cancers of the lung, stomach and oesophagus, less consistently with cancers of the mouth, pharynx, colon, breast, pancreas and bladder and not at all with cancer of the prostate.

On this evidence, trials of some of the potentially anticarcinogenic compounds found in vegetables and fruit would seem to be justified. Until recently, most attention has been focused on beta-carotene, high blood levels in cohort studies consistently predicting reduced risks of cancer, most notably lung cancer (see [38] for review). No benefit has, however, been shown in three controlled trials. Two even suggested that beta-carotene might increase the risk of the disease [39, 40] but this was not borne out in the third and largest study continued for longest, in which 22 000 US doctors took beta-carotene or a placebo regularly for 12 years [41]. Most current interest now centres on vitamin E.

Other components of food that may be specifically beneficial are calcium and vitamin D, which, in relatively large amounts, may reduce the risk of colorectal cancer. The most recent results of the cohort study of nurses being carried out in the US suggests that the vitamin D intake is likely to be the critical factor, though it may of course act by facilitating the absorption of calcium [42] and this explanation would fit with Yang and Chu's observation of a reduced risk in Taiwan in areas with relatively high levels of calcium in the drinking water [43]. The current evidence, however, falls far short of proof that these or any other micronutrients are of any material relevance.

CONCLUSION

I note, in conclusion, that it is sometimes said that progress in the control of cancer has been disappointingly slow. Indeed the relative stability of the total incidence of cancer and the continued increase of a few types of cancer that is still unexplained makes it understandable that this might be thought to be so. In fact, of course, we have made substantial progress in learning how the risk of the disease can be reduced: the difficulty has been in getting the knowledge applied. Recent developments now encourage us to believe that progress will be much faster in the next few decades. The enormous increase in knowledge of the role of nature will not, I think, make much difference directly, except for a very small proportion of the population, but it should help us elucidate the mechanisms by which the disease is produced and hence to identify the aspects of nurture that we need to control.

Meanwhile, we know that a large reduction in the age-specific incidence rate can be obtained by refraining from smoking and, in some countries, by immunisation against the HBV and we have reason to believe that further substantial reductions may soon be achievable by immunisation against some types of the human papilloma virus. We have learnt too of the potential benefits that may be obtained by chemoprevention using both man-made drugs and micro-nutrients extracted from food, the scientific study of which has only just begun—benefits which must, however, be validated in control trials before they can be generally recommended.

If, in this conclusion I am accused of over optimism, I can say only that no-one who was influenced in any way by Pierre Denoix, his rational enthusiasm and his zeal for oncology could be anything other than optimistic.

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