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A CONFERENCE ON
MALIGNANT DISEASE

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Research on Aetiology

Within the limited environment of the Royal Marsden Hospital and Institute of Cancer Research, there are some who are troubled because they see a deep gulf between the clinicians and research workers. They are worried that basic research into cancer problems has cut adrift from urgent clinical needs, that facilities are being used to answer questions which at best have low priority, and at worst are quite irrelevant to clinical cancer. Whilst I would not for one minute pretend there is no room for improvement in the liaison between the clinic and the research laboratory, I should like to emphasise that the present situation stems primarily not from poor administration but from a fundamental gap between interests. Evidence both from epidemiological studies in man and from experimental studies in animals indicates that it takes a long time to induce cancer. With potent carcinogens such as the soot to which the infantile chimney sweepers of Sir Percival Pott's time were exposed, or the industrial bladder carcinogens of our own era, minimum induction periods measured in years are involved. Exposures of 20-40 years seem to be involved in the induction of lung cancer by cigarette smoke. Even these periods are not maximal, for the rate of lung cancer in smokers continues to rise right up to the end of the period during which it can be measured, i.e. up to the end of the natural life-span. Similarly it is possible, as we know from our own experiments, to expose an animal to a carcinogenic chemical on the first day of its life and to see tumours attributable to this exposure at a time when the animal is preparing itself for the grave at the end of its natural life span.

It follows that the general practitioner and the consultant in a Cancer Hospital, encountering cancer as they do, as a problem in treatment, are separated in interest by decades from the cancer research worker concerned primarily with aetiology and prevention.

This long induction period is not part of the layman's image of cancer. He, helped by superficial journalism, regards cancer as a single disease with a single cause, the latter operating a few days, weeks, or possibly months, before the start of symptoms. It is regrettably true that I have encountered numerous medical colleagues who share this image: who ask lightly (perhaps whilst drawing deeply on a cigarette!) "Have you found *the* cause yet?"

I do not doubt that one day a common thread which links the mechanisms of cancer-induction by these widely different agents will be found. In the meantime I am certain that the search for this thread is not the only laudable aim in basic cancer research. Furthermore, I doubt very much whether knowledge of the thread will have any practical value. Is it not enough to know that a man who is drunk is liable to cause a car accident? Must we know, in addition, why he drinks before we take precautions?

The following tables will give some indication of the array of viral, physical, genetic and chemical agents which are known to cause cancer, and following them I have compiled a table of some of the more recently recognised carcinogenic factors to be found in our everyday environment.

May I draw your particular attention to asbestos, for I am commenting later in the paper on this, and also to the query raised by treatment with INAH. The last group in this table is, of course, the well known insecticides.

CARCINOGENIC AGENTS

Terminology

Complete carcinogens	}	Initiating agents
Incomplete carcinogens		Promoting agents
Co-carcinogens		

Types of Agent

VIRUSES (both DNA and RNA)

PHYSICAL AGENTS (e.g. wounding, burning,
X-radiation, UV-radiation)

INHERITED GENETIC ABNORMALITIES

(absent chromosomes, deficient or mutant genes)

CHEMICAL AGENTS

- (a) Endogenous (e.g. hormones, cholesterol)
- (b) Exogenous

VIRAL CAUSES OF CANCER

Avian leukoses (many types)	Chicken
Rous sarcoma	Chicken
Shope papilloma	Rabbit skin
Shope fibroma (related to myxoma virus)	Rabbit
Lucke's agent	Kidney of Leopard Frog
Papillomatosis (skin and mucous membranes)	Man
	Dog
	Horse
	Cat
	Rat
	Cattle
	different virus
	unrelated antigenically
*Bittner milk factor	Mammary cancer in mice
* Murine leukaemogenic agents (e.g. Gross' agent, Friend virus, Graffi's agent)	Mouse
* Polyoma virus	Tumours of many sites in mouse. Kidney tumours in hamster.
(?) Agent from Rhesus monkey kidney	Tumours at injection site in Hamster.
(?) Agents from cases of human cancer	Leukaemia in mice

PHYSICAL AGENTS

X-rays

High rate of cancer and leukaemia amongst:—

- (a) Radiologists and Radiotherapists (NB X-ray martyrs)
- (b) Hiroshima victims
- (c) ??? children of mothers who had X-ray pelvimetry during pregnancy.

UV-radiation

1. Skin cancer especially in white people living under conditions of high UV-radiation.
2. Xeroderma pigmentosum.

Wounds and burns

Tendency for cancer to arise in scars both in men and experimental animals (? = co-carcinogenic factors).

EXOGENOUS CHEMICAL AGENTS

- I Aromatic Polycyclic Hydrocarbons and related Heterocyclic Compounds (with substitution of Nitrogen, Oxygen, or Sulphur for Carbon)
- II 4-Nitroquinoline Oxide
- III Aromatic Amines
- IV Azo Compounds
- V Urethane (ethyl carbamate) and closely related compounds
- VI Alkylating Agents
- VII Nitrosamines
- VIII Polymers

ENDOGENOUS CHEMICAL AGENTS

HORMONES

- (1) Tumours of ovary
adrenal gland
mammary gland
uterus
kidney
pituitary
Leukaemia } Induced
by
oestrogens
- (2) Tumours of thyroid gland induced by prolonged treatment with thyroid suppressant drugs (e.g. thiouracil, aminotriazole)
NB Cranberry Scare
- (3) Influence of hormones on induction of tumours by other agents
- (4) Influence of hormones on tumours already present (e.g. prostate, breast)

CHOLESTEROL (???)

Work of Hieger.

SOME ENVIRONMENTAL CANCER HAZARDS

1. Aflatoxin (from the mould *Aspergillus flavus*) in groundnuts and certain cereals
2. Cycads and cycasin
3. Safrole
4. Tannins
5. Cadmium
6. Nickel
7. Arsenic
8. Iron—especially as Iron-dextran
9. Asbestos
10. Creosote
11. Isonicotinic acid hydrazide (INAH)
12. Insecticides (DDT, Aldrin, Dieldrin, Aramite)

I hope that I have built up a picture which shows man's environment and his very existence as carcinogenically hostile. We must get used to the idea that agents which cause cancer lurk in every part of our environment, at home, at work, in food, in the air we breathe, in our pleasures (tobacco smoke, sun-bathing, exhaust fumes of our cars) and in our medicine chests. We expose ourselves to carcinogenesis when we have our chests X-rayed to see if we have lung cancer. We cannot escape ionising radiation, even by living in the deepest hole in the ground. Man didn't create all carcinogens, some of the most potent such as aflatoxin occur naturally. Carcinogenicity is easier to recognise when the effect is potent: the incidence amongst those exposed is high and the minimum induction period short. It is the weak carcinogens, the agents which take most of a life-time to produce their effects, and even then only do so in a small proportion of those at risk, that are difficult to recognise.

So far I have been speaking as though most cancer is due to exposure to carcinogens, physical, chemical or viral, with the exception only of those whose occurrence is genetically determined (as in familial polyposis, xeroderma pigmentosa, von Recklinghausen's disease, etc.). The truth is that we neither know that it is nor that it isn't. Germ-free animals kept under carefully controlled conditions still develop cancer. Whether this is of truly spontaneous origin or the result of some influence in the external or internal environment, it is not possible to say. Even if it was,

it is obviously impracticable to imagine that all cancer can be prevented through environmental control. It is then interesting to speculate as to the proportion of cancer which could be prevented. The commonest type of cancer in males in Britain is lung cancer; its alarming increase has recently reversed (in males but not yet in females) a trend, begun at the end of the last century, of increasing longevity. It is an almost entirely preventable disease. Bladder cancer, which is also increasing in incidence, is largely preventable.

Cancer of the uterine cervix is, for the main part, environmentally determined, and it is possible that most gastro-intestinal and liver cancers are attributable to environmental factors. Rapid advances in the field of mammalian tumour viruses is bound, in my opinion, to lead to the recognition of viral determinants of human neoplasia. The leukaemias, lymphomas and reticuloses, and possibly some tumours of glandular origin, may well be shown to be due primarily to viruses. In the case of mammary and ovarian cancer and neoplasms of hormonally-controlled tissues in general, it is probable that attention has to be paid more to the internal than to the external environment. Some recent evidence suggests that tumours of the central nervous system may be due to exposure to chemical agents. A conservative estimate of the proportion of cancer due to environmental factors could well be in the region of two-thirds.

The possibility of exposure to carcinogens begins at the moment of conception. X-ray pelvimetry seems to have some effect. Administration of drugs during pregnancy, or smoking during pregnancy, may also be important, though this is not known. Slight exposure to this, and minimal exposure to that, throughout life may, in the unfortunate individual, build up to a critical exposure at one site. The site may be especially susceptible for genetic reasons, or especially exposed for metabolic reasons. There is abundant experimental evidence that the effects of different carcinogens may be additive. In some cases synergism occurs, or one substance strongly magnifies the carcinogenic action of another. This phenomenon, known as co-carcinogenesis, is probably involved in the induction of human lung cancer. It seems likely that tobacco smoke contains both carcinogens and co-carcinogens, and that the latter materially enhance the effect of the former. Moreover, the co-carcinogenic element probably enhances the effect of carcinogens acquired in other ways, e.g. inhaled from polluted air. Such a mechanism could explain the high incidence of lung cancer among emigrants from Britain to New Zealand and South Africa, compared with native-born whites indulging to the same extent in smoking.

Before I close I should like to return to the point at which

I began, namely, the long latent interval between exposure and the development of the disease. May I put the following simple hypothesis before you. The great variety of carcinogenic agents do not produce in cells the same initial event, but they have in common the property of giving rise to cells which are both changed and unstable in the way in which they divide. In other words, the effect of exposure is to give rise to a population of cells which differ both from the normal cells from which they were derived, *and from each other*. Under these circumstances the forces of natural selection are bound to operate. More vigorous variants—cells which divide most frequently and are least subject to homeostatic influences—will constantly take up the running, and as each generation passes the lesion as a whole is liable to be more rapidly growing and more autonomous. In fact the changes may take place in sudden, infrequent steps, or gradually and insidiously. This process has been described by Foulds as tumour-progression, when referring to the changes from more-benign to less-benign, to low-grade malignant, to highly malignant. I am suggesting that essentially the same process is going on throughout the long latent interval. Co-carcinogens act either by shortening the generation time or by increasing the pressure of natural selection, e.g. by killing off the less vigorous cell variants and giving the rest a clear field.

Of course the nature of the initial event is fascinating and much important work has been done in relation to particular types of carcinogen such as the polycyclic hydrocarbons and alkylating agents. But it is difficult to believe that all agents act in the specific ways in which these act. At the other end of the line there seems to be, as one would expect if the above hypothesis of progression through natural selection were true, nothing specifically characteristic about cancer cells. No two cancers induced by the same agent in the same animal are identical in their biological or biochemical characteristics.

Unfortunately, knowledge concerning homeostatic mechanisms is scanty. Hormones, cell surface properties, contacts between cells and tissue-specific antigens are undoubtedly involved, but we by no means have the complete picture. Therefore, we know little of the circumstances under which cells can escape from homeostatic control. But one thing is certain, namely, that in most cases *the cells which actually break away from homeostatic control and give rise to a tumour are not the cells which were exposed to the carcinogen*. At the same time, many of the immediate effects of carcinogenic agents on cells are irrelevant to carcinogenesis and that many of the characteristics of cells of which cancers are composed, are features acquired by cells many generations after the one in which the carcinogenic insult was

received. Recent developments in the virus field, however, promise to bring the two ends of the process closer together. Tumours may be induced by viruses after only short latent intervals, and, in the test tube, normal cells may be transformed instantaneously to cancer cells by viruses. A similar effect by some chemical agents has been claimed, but is less certain.

What of the future? Basic research is pushing forward pretty well as fast as the available facilities permit. Full practical use has yet to be made of existing knowledge of causative factors. The role of hygiene and circumcision in the genesis of cancer of the penis and uterine cervix receive little attention. Anti-smoking campaigns are half-hearted. The Rubber Industry had recently to be bludgeoned into cooperating in an attempt to reduce exposure to bladder carcinogens. Finally, I give as my opinion, that we are still only at the beginning of a golden age of epidemiological studies in relation to cancer. In these, I am sure that the College of General Practitioners has an important part to play.

FEATURES OF CARCINOGENICITY

1. Irreversible.
2. Cumulative.
3. Additive (A + A or A + B).
4. Synergism and cocarcinogenicity.
5. Long latent interval.
6. Inapparent exposure
7. Theoretical and practical thresholds.

