Geographical Aspects of Cancer Research

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Before considering some of the geographical and epidemiological aspects of cancer research, I would like to make a few general comments on the classification of tumours and its importance in assessing data from cancer registries. Tumours are classified according to their anatomical site, cell of origin and biological behaviour. Each of the many tumours that can be derived from these axes of classification must be investigated as an entity in order to elucidate its pathogenesis and aetiology (Templeton and Hutt, 1973). Different histological types of tumour arising at one anatomical site may be due to a single or several different carcinogens. For example, there is good evidence to suggest that liver-cell carcinoma has a different aetiology from carcinoma arising from the intrahepatic bile ducts, though such tumours are usually classified together in cancer returns.

In Ugandan Africans 60 per cent of all malignant tumours of the bladder are squamous cell in type, whereas in England only 6 per cent are squamous (Anthony, 1973). These histological differences are a strong indication that the aetiological factors causing bladder cancer are dissimilar in these two countries. Epidemiological evidence also indicates that adenocarcinoma of the lung should be regarded as a different entity from squamous- or oat-cell carcinoma.

There is an increasing recognition that most tumours are multifactorial in aetiology, even in those cases in which a specific carcinogen has been identified. This has been demonstrated by the separate use of initiators and promoters in experimental situations, but may also involve many, and often complex, subsidiary factors, both endogenous and exogenous.

The great majority of human tumours are mainly due to aetiological factors of environmental origin. In narrow terms the 'necessary' causative agent may be a virus, an endogenous or exogenous chemical substance or physical. In wider terms the cause of each tumour is to be sought in the interaction of the geographical, socio-economic, and cultural environments on an individual or population. The importance of environmental factors is shown by the changing pattern of cancer in groups of individuals who migrate to new situations or lands. The American of African origin has today a pattern of tumours similar,

in nearly all respects, to that of the white American. Conversely, it is different in many respects from the pattern in West Africa whence his ancestors came.

Although very few tumours have a major genetic component in their aetiology, genetic factors may play a subsidiary role in some tumours, due to environmental influences. For example, the carcinogenic effect of ultra-violet rays on the skin, producing solar keratosis, followed by basal- or squamous-cell carcinoma, is modified by the degree of skin pigmentation. This ranges from the extreme susceptibility of the albino, through the moderate susceptibility of the fair-haired Caucasian, to the almost complete resistance of skin in black ethnic groups. It is of interest that the only place in which Africans develop solar carcinomas is the conjunctiva, which is unprotected by pigment. A high incidence of squamous-cell carcinoma of the eye, a very rare tumour in the UK, has been reported from several parts of Africa (Templeton, 1967). Burkitt's lymphoma is another example in which a genetic factor has an indirect effect on the susceptibility of individuals to develop this tumour. The current hypothesis suggests that the curious geographical distribution of this tumour is related to the distribution of endemic malaria, which is, in turn, related to the various geographical factors determining the distribution of the mosquito vectors and their ability to transmit the malarial parasite. On the basis of experimental work in animals it has been suggested that malaria plays its role by depressing immune mechanisms, allowing a virus, possibly EB virus, to have an oncogenic effect (Burkitt, 1969; O'Conor, 1970; Wedderburn, 1973). If this hypothesis is true, any factor that reduces the effect of malaria on individuals living in a malarious area might be expected to lessen the incidence of Burkitt's lymphoma in such individuals. This is borne out by the observation that people who are heterozygous for sickle-cell haemoglobin have a lower incidence of the tumour than those who are AA (Morrow *et al.*, 1971).

The greatest difference in the overall cancer pattern of Europe and North America is found in the indigenous inhabitants of Africa south of the Sahara (Doll *et al.*, 1970); somewhat similar patterns are also found in other parts of the world, such as New Guinea, that share many of the African environmental factors. The tumour pattern of rural Africa has probably been the same for many years, long before there was any Western cultural or technical influence (Davies *et al.*, 1964). This suggests that the aetiological factors causing tumours in this area are to be found in the natural rural environment. As might be expected, changes in the incidence of some tumours are beginning to occur in those areas that are becoming urbanised and industrialised.

Recent figures from Johannesburg (Robertson *et al.*, 1971) show that the incidence of liver cancer in Africans living in the city for long periods is

decreasing, while that of lung and large bowel cancer is increasing. The high incidence of liver-cell carcinoma in Africans is still unexplained but recent evidence points to two possible aetiological agents. The common association between liver-cell carcinoma and a macronodular cirrhosis in Africa led to the suggestion that a hepatitis virus might be involved in the aetiology of the cirrhosis and possibly of the tumour. Support for this idea has come from the finding of Au antigen in a considerable proportion of cases of African cirrhosis and liver-cell carcinoma (Vogel *et al.*, 1972). The discovery of aflatoxin, a powerful hepatocarcinogen in experimental animals, derived from the fungus *aspergillus flavus* which contaminates ground nuts and other cereals, suggested another possible aetiological factor that could explain the overall geographical distribution of this tumour (Hutt, 1971). It is possible that both these agents may be implicated with other subsidiary factors, such as protein malnutrition, in the causation of this tumour; the decreasing incidence in Johannesburg suggests there is a lower exposure to one or more aetiological factors in the urban situation.

There is a low incidence of large bowel carcinoma in Africa south of the Sahara and the increasing incidence with urbanisation or migration to the Western world supports the evidence that relates a high frequency of this tumour with Western influence or affluence (Burkitt, 1971). Several authors have pointed to the strong epidemiological evidence connecting diet and large bowel carcinoma, though the exact aetiological mechanisms concerned are likely to be very complex. The quantity of refined sugar (Cleave *et al.*, 1969), unabsorbable residue, 'fibre' (Burkitt, 1971) and dietary fat (Hill, 1971) have all been suggested as important. It is clear that there are marked differences between Europeans and rural Africans in the physiology of the large bowel. The former have a longer transit time, a smaller stool mass and an increase in the number of Bacteroides organisms. The concentration of acid steroids, neutral steroids and urobilins is greater in the European stool (Hill and Aries, 1971); these workers have also shown that some strains of intestinal bacteria have the ability to produce carcinogens from dietary components or from intestinal secretions (Aries *et al.*, 1969).

Changes in the incidence of a particular cancer with time are often a valuable pointer to aetiology, an obvious example being the current epidemic of lung cancer which is closely related to the habit of smoking. Unfortunately, the aetiology of some cancers, showing marked temporal and spatial differences in incidence, has proved tantalisingly difficult to unravel. Cancer of the oesophagus has a greater geographical variation in incidence than most tumours. A very high incidence has been observed for many years in the Transkei area of South Africa and in Bulawayo, Rhodesia (Burrell, 1962; Skinner, 1967).

The tumour is also common in Malawi and in Kenya near Lake Victoria (Ahmed and Cook, 1969). More recently there appears to have been an increase in the incidence in one area of Uganda (Templeton, 1973). The tumour, initially more prevalent in men, now has a rising incidence in women. Cook (1971) has associated these high rates in Africa with the drinking of beer made from maize. The suggestion that nitrosamines might be the carcinogen concerned has not been confirmed. The highest rate in the world is to be found in a zone around the Caspian Sea, in Kazahstan and Iran. In contrast to most other high incidence areas, the tumour there is more common in women and there is no evidence to link the condition with the drinking of alcoholic beverages; indeed, preliminary investigation of this environment has revealed few positive clues (Kmet and Mahboubi, 1972). It seems probable that the factors producing oesophageal cancer in the Caspian area will turn out to be different from those in Africa, which may be different from another high incidence area, the small focus in Normandy and Brittany.

While cultural factors may be involved in a direct way in the aetiology of tumours, as can be seen in the relationship between smoking and lung cancer, or between betel-nut chewing and oral cancer, they may be involved in a much more indirect way through endogenous mechanisms. The low incidence of carcinoma of the breast in most developing countries has been attributed to the much higher frequency and duration of breast-feeding. However, the important protective factor against breast cancer is the age of the woman at the time of her first pregnancy (MacMahon *et al.*, 1970) and one must presume that this effect is mediated through some complex hormonal relationships occuring at this time. The high incidence of cervical cancer in most poor communities is related to the age of first intercourse and to other factors related to sexual habits and child-bearing. The fertility rate and parity may also play a role in the low incidence of carcinoma of the uterine body and the high incidence of choriocarcinoma in Africa south of the Sahara.

I have attempted to show the value and some of the difficulties of the epidemiological or geographical approach in cancer research. Although it is not always easy to relate variations in incidence to specific aetiological factors, the evidence may be sufficient to suggest new hypotheses for the experimentalist, or public health measures for tumour control. At least in theory, a considerable proportion of tumours that afflict individuals in many parts of the world are preventable.

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