Section of Oncology

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Presidential Address

Comparative Oncology: The Veterinary Contribution

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Implicit in the title of this Address is the concept that comparative oncology is wider in scope than veterinary oncology. A working definition of comparative oncology could be formulated on the lines of that given for 'comparative pathology' by Leader & Leader (1971) who, in their fascinating 'Dictionary', define it as 'that branch of pathology which emphasises comparisons of disease phenomena between various species, usually with the ultimate objective of learning more about the diseases of man, but at the same time with an intrinsic interest in diseases of anomen [the plural of anoman, the Leaders' acronym for animals other than man]'. It is clear that comparative pathology embraces more than veterinary pathology, which is, however, along with experimental pathology, one of its two major non-medical components. Veterinary pathology I take to mean the study of spontaneous diseases of animals for their own sake and, in discussing the veterinary contribution to comparative oncology, I shall largely restrict myself to a consideration of spontaneous tumours in domesticated mammals, although tumours have a very much wider zoological distribution (Lombard 1964).

The comparative method has of course long been recognized as an essential, indeed inescapable, approach to the study of human disease, and, by nature of their particular knowledge of human diseases, medically-trained workers are especially qualified to notice those aspects of animal diseases that are likely to prove relevant in the struggle to understand human disease. Shope (1959), the discoverer of the viral fibroma and papilloma of rabbits, in his address on the occasion of the 75th anniversary of the School of Veterinary Medicine in Philadelphia, quoted some characteristically penetrating remarks made by Theobald Smith to the Pathological Society of that same city in 1900:

'Man frequently attempts the conquest of problems from the least accessible quarter. This is true of that stage in the development of medical science when the human species was the chief object of study. Within the past two or three decades medicine has been gradually and almost unconsciously drifting towards animal pathology as the chief, if not the sole, means of clearing up the greater doubts which a broader science inevitably brings with it. We have lately definitely reached this second stage, the study of the more accessible, more varied diseases of animals. The preparations for this stage date well back, and the most conspicuous investigators of human pathology have always had a yearning towards the rich fields of animal pathology.'

The earliest triumphs of the comparative method were in the field of infectious disease, to which, characteristically, medical, veterinary and other scientists were all contributors – the names of Koch, Salmon and Pasteur are sufficiently illustrative. There came something of a lull after this first flush of success, but the search for animal diseases as models of human disease (Cornelius 1969) is now becoming increasingly recognized as of major importance in other fields such as toxicology, hereditary and congenital defects, immunological abnormalities and chronic degenerative diseases.

It seems, from the detailed survey of nineteenth century cancer research by Triolo (1964, 1965), that the first real interest in animals in relation to cancer was in studies, from the late 1700s, of their possible susceptibility to transplantation of

human tumours. Not unexpectedly, such attempts at transplantation failed to produce significant results.

One extraordinarily bright, though transient, lightening of the investigational darkness came in 1802 when, in London, the Medical Committee of the Society for Investigating the Nature and Cure of Cancer (1806) formulated their 13 questions, which show a remarkable penetration of thought. Perhaps significantly, one member of the Committee was Everard Home, an Examiner at the London Veterinary College. Their '10th Query' is: 'Are brute creatures subject to any disease resembling cancer in the human body?' An explanatory note attached to this Query reads:

'It is not at present known whether brute creatures are subject to cancer, though some of their diseases have a very suspicious appearance. When this question is decided, we may inquire what class of animals is chiefly subject to cancer: the wild or the domesticated; the carnivorous or the graminivorous; those which do, or those which do not, chew the cud. This investigation may lead to much philosophical amusement and useful information; particularly it may teach us how far the prevalence or frequency of cancer may depend on the manners and habits of life. As establishments are now formed for the reception of several kinds of animals, and as the treatment of their diseases has at length fallen under the care of scientific men, it is hoped that the information here required may be readily obtained. If animals which live only on herbs, and never drink any liquid other than water, prove to be the least or not at all susceptible to cancer, such proof may, in many cases, become a guide in practice.'

It is interesting to see foreshadowed here what has come to be the salient fact about the occurrence of tumours in different species in animals – their variable occurrence in one species as compared with another, even allowing for the fact that some are killed young for food, and also the hint that epidemiology is likely to be one of the most rewarding disciplines for the approach to comparative oncological studies.

However, there was only sporadic interest in animal cancers during the nineteenth century, although some tumours that are still prevalent were well known then, e.g. the common mammary tumour of the bitch. In mid-century, Leblanc (1858, 1859) gave a thoughtful review of what was known about tumours in animals at that time. He again drew attention to one of the most important factors in determining the incidence of neoplasms in different species – that is, whether or not the animals were normally slaughtered young for meat, or whether, like dogs, some at least would have the chance of living out something like their full life span.

A few years later the Russian veterinarian Nowinsky (1876) published his brief papers on what must be about the most extraordinary of all neoplasms – the transmissible venereal tumour of the dog. This tumour, passed at coitus from male to female to male, and so on, behaves as though it is a transplant derived from a single clone of cells for, in whatever part of the world it has been appropriately examined (e.g. Murray *et al.* 1969), it shows an abnormal and virtually specific karyotype (typically of 59 chromosomes, of which 17 are metacentric and 42 are acrocentric, as compared with the 78 of normal canine kidney cells, all of which are acrocentric except two sex chromosomes). The tumour can be readily transplanted subcutaneously into dogs, even by single cell suspension (Yang & Jones 1973). It tends, both as a spontaneous and a transplanted tumour, to regress spontaneously after a while, particularly when transplanted into adult dogs. When transplanted into pups, however, it may metastasize and thus possibly may provide a useful experimental subject for therapeutic trials. It is known to be markedly radiosensitive.

One of the earlier subsequent successful tumour transplantations was reported in 1903 by Jensen, a Danish veterinarian, who made the very significant observation that a mammary carcinoma could be transplanted from one white mouse to another, as well as to grey mice, and that the new tumour was derived from the original.

The studies of the virus neoplasm, avian leukosis, in the Royal Veterinary and Agriculture College, Copenhagen, by Ellermann & Bang (1908) (Bang being a veterinarian), and Rous's serendipitous discovery of a filterable agent in his Chicken Sarcoma No. 1 (Rous 1910, 1911) in the Rockefeller Institute in New York[1] foreshadowed the intense activity in virus cancer research that we see today. Even so, these observations perhaps received less attention than they deserved. This was partly for technical virological reasons, partly because human cancer does not behave like an infectious disease, but also partly because the fowl was outside the bounds of comparative oncology at that time – whereas now, neoplasia in any Order of animals is thought worthy of attention. There was also some doubt about the truly neoplastic nature of the Rous sarcoma, and there is of course still a respect-worthy body of investigators that needs to be convinced of the relevance of much of the work on viral tumours to human carcinoma.

[1]Thelma Dunn (1975) wonders at the fact that the old farmer, and his fowl, managed to get through the doors of the august Institute, and that he could speak directly to a distinguished scientist who took time to listen!

Despite the individual efforts of some veterinary pathologists – in England, for example, by M'Fadyean, Principal and Professor of Veterinary Pathology in my own College and sometime Chairman of the Scientific Committee of the Imperial Cancer Research Fund – the underdeveloped state of veterinary oncology as late as 1932 is reflected in the words of the American veterinarian W H Feldman (lately an Honorary Fellow of this Society) in his pioneering monograph (Feldman 1932, p 7):

'Little attention is given to neoplasms in various veterinary Colleges. Tumours are usually studied near the end of the course in general pathology, and as a consequence adequate time for a proper consideration of them is not available. The professor of pathology is usually not particularly interested in tumours, and, as a result, little, if any, effort is made to collect material and to obtain the necessary clinical and statistical data so essential for teaching purposes. The urge of other matters of greater pedagogic and economic interest, together with an almost invariable shortage of funds, have retarded the development of really comprehensive collections of tumours for teaching and museum purposes. Furthermore, interest in microscopic pathology is not particularly great among many comparative pathologists.'

The situation as Feldman described it had changed very little by 1948 when Willis wrote (Willis 1948, p 93): 'Much of value for human pathology is yet to be learned from the study of animal neoplasms. More use should be made of the material passing through the hands of veterinarians, breeders and slaughtermen, most of which is wasted.' There was so limited an amount of published information on tumours of domesticated animals twenty years ago that it was possible for me (Cotchin 1956) to survey in a small compass, and indeed personally to read or at least consult, virtually every relevant paper that was available in the UK up to that time. The task of updating that review today would be much more daunting.

There are some interesting reasons for the growing interest of veterinary pathologists in the tumours of domesticated animals, as shown by the great increase in published papers that has been evident in the past two decades. First, with the expansion in the number and size of veterinary colleges in the USA and elsewhere, there has been an upsurge in veterinary pathological investigations in general. The increasing interest and concern of animal owners in the non-infectious conditions of animals has been reflected in a call for greater use of and accuracy in histological and other methods of diagnosis. Again, there is the fact that, in many countries, dogs and cats, which are the principal source of animal tumours, and are also the species which are generally allowed to live out their life-span, are doing so more regularly because of vaccination procedures available against diseases that would otherwise lead to an early death. Veterinary clinicians have thus become more closely involved in diagnosing and treating animal neoplasms, and this in turn has compelled veterinary pathologists to make closer studies of these tumours, with a view to improving diagnosis, and by careful follow-up studies, such as those of Bostock and Owen at Cambridge (Owen *et al.* 1975), of providing a sound base for prognosis.

There can be no doubt, then, that the study of spontaneous tumours in animals is fully justified for its own sake. There is also a slowly growing appreciation amongst cancer research workers in general of the significance of comparative studies. This has been exemplified by the interest taken by WHO in convening meetings of medical and veterinary investigators, one tangible result of which has been a histological classification of animal tumours that tallies as far as possible with that of human tumours (World Health Organization 1974).

However, it might be worth while setting out some of the reasons why spontaneous tumours in animals are still not being investigated from the comparative aspect with the attention that they probably deserve. First, one must accept that there is a natural feeling amongst many cancer research workers that an understanding of the really basic biological mechanisms of the neoplastic process must inevitably facilitate the prevention and cure of cancer in man. (It is, however, a pragmatic fact that the prevention and cure of a disease does not necessarily have to await the elucidation of its pathogenesis.) Secondly, there is a well-founded belief that successful laboratory work on cancer demands the use of inbred strains of experimental animals. However, the question must be asked, how immediately relevant are tumours, spontaneous or (especially) experimental, occurring in inbred strains of animals to the spontaneous cancers occurring in largely outbred human populations?

Thirdly, it is an unfortunate fact that there are sometimes no animal model tumours readily available for study. For example, cancer of the uterine cervix is rarely recorded as a spontaneous tumour in animals, and the common form of human lung cancer has no obvious animal counterpart. (However, this absence of an animal model, if confirmed, could be a profoundly significant fact, and point to some essentially human connotation of the tumour in question.)

Fourthly, there are some practical problems in studying tumours in domesticated animals which are difficult to overcome: the animals are much larger than mice, they are more expensive to feed, trained investigators are few, there is little information available about the background population, and so on.

Against these considerations, there are some quite powerful arguments which could be used to justify an increasingly intensive study of spontaneous tumours in animals. The main argument is that the fundamental significance of a spontaneous tumour must surely just be that it is indeed spontaneous. This means that it may be a truer model of a human tumour than is an experimentally induced tumour, in respect of its etiology, pathogenesis, biological (including immunological) behaviour, epidemiology, and response to treatment. Again, although some tumours show species or even breed susceptibilities, many tumours of animals typically occur in outbred populations. They may occur in considerable numbers, and allow substantial epidemiological and other investigations alongside a human population (Dorn *et al.* 1966, Dorn 1972*a*).

Another feature of animal tumours is that they may sometimes be very large, and provide ample material for chemical analysis. Further, they may be accessible and even visible at all stages of their development, and provide suitable cases for therapeutic studies (Owen *et al.* 1975, Roga *et al.* 1971).

There is always the possibility that animals may act as monitors of environmental and dietetic risks to which human populations may be exposed. One intriguing example (Anon. 1974) has been spotlighted by Priester (1975), who drew attention to the report that the Chinese have found a very high incidence of human œsophageal cancer in some districts, with a correspondingly local high incidence of œsophageal cancer in fowls. Mulligan (1975) has suggested that the incidence of mammary cancer in dogs should be investigated in countries with high (USA) or low (Japan) risk of human mammary cancer.

Moving from these general considerations to a closer look at veterinary oncology, I propose to bring forward a few examples of spontaneous tumours in animals on which a fair amount of work has been done. To provide a clue through the somewhat labyrinthine amount of information available, I shall deal with them on the basis of their known or suspected causes. Those who would like a broader survey might be interested in articles in the WHO Bulletin (Cotchin 1962, World Health Organization 1973) and in papers by Owen *et al.* (1975) and by Dorn (1972*a*).

Extrinsic Causes, Living

Virus: Jarrett and his colleagues in the Glasgow Veterinary School (Jarrett *et al.* 1973, Mackey 1975) made a most significant contribution to comparative oncology when they found in 1964 that the common lymphosarcoma of the cat, with its three main pathological forms – alimentary (1/2 cases), multicentric (1/4) and thymic (1/6) (Mackey & Jarrett 1972) – is due to a feline oncornavirus. There is epidemiological, immunological and experimental evidence that horizontal transmission of the virus is important (Jarrett *et al.* 1973, Essex *et al.* 1973). The virus is much more widely distributed in the cat population, especially in urban areas, where cat-to-cat horizontal transmission would be easy, than is the tumour itself. The virus produces immunosuppression with consequent diseases (Rogerson *et al.* 1975). The normal response of a cat to a small dose of virus appears to be antibody production, while repeated and overwhelming dosage may result in tumour formation. Prevention by vaccination is feasible.

The final demonstration of a causal virus in at least the endemic form of bovine lymphosarcoma, which on the Continent and elsewhere behaves like an infectious disease, is probably imminent. The proof of the viral etiology of lymphosarcoma in the horse, sheep, pig and dog may well follow.

Another virus tumour of the cat is feline fibrosarcoma (Snyder & Theilen 1969). Jaagsiekte of sheep (pulmonary adenomatosis) is a herpesvirus-associated infectious disease, the malignant status of which is uncertain, but which in some cases at least is a form of metastasizing pulmonary adenocarcinoma. One form of mast cell tumour in the dog is due to a virus. Other tumours that might also be worth closer study for virus origin are the nasal adenopapillomas of sheep in Germany, France, USA and Canada, the turbinoethmoidal carcinomas of cattle in Brazil, Portugal, India and Hong Kong, and the similar tumours of pigs in Brazil, India and in Portugal (Teoh 1971, Rajan & Sivadas 1972).

Metazoan parasites:

(1) *C. fasciolaris:* Infestation by the bladder-worm, *Cysticercus fasciolaris*, the intermediate stage of the cat tapeworm, *Tænia crassicollis*, may lead to fibrosarcoma formation in the liver of the rat, but apparently not in the liver of the mouse. The tumour (Tuceck *et al.* 1973) merits renewed study, especially now that a virus fibrosarcoma of the cat has been identified (Snyder & Theilen 1969) of

which the virus has been adapted to rats but which failed to induce fibrosarcoma in mice (Theilen 1976, personal communication).

(2) *Spirocerca lupi* infestation in dogs is sometimes responsible for the development of granulomas, which may eventually become fibrosarcomas or even osteosarcomas, in the œsophagus (Bailey 1963). The lesions are sometimes accompanied by a striking degree of spondylitis and acropachia. The oncogenic agent needs identifying.

(3) *Fasciola hepatica:* While liver fluke lesions are common in cattle and sheep, it is not clear whether they are the origin of hepatocellular carcinomas, although Vítovec (1974) has noted a possible significant relationship between the lesions and tumour formation. He found a tendency for the left lobe of the liver to be the predominant site of both lesions. The liver fluke itself, or the lesions it produces, might act indirectly by providing a base for the action of some oncogenic agent.

Extrinsic Causes, Non-living

Physical: Ultraviolet light (Anderson & Skinner 1961) appears to be the major, if not the sole, cause of 'cancer eye' in cattle, vulval skin cancer in cows (Wettimuny 1974), skin cancer in sheep (Lloyd 1961) and skin cancer, especially of the pinna, in white cats. Especially worthy of mention is 'cancer eye' in cattle (Banks & England 1973), which is a very common tumour in tropical and subtropical countries where exposure to UV light is great. The tumour, which is a squamous cell carcinoma of the eyelid, conjunctiva or cornea, is especially common in Herefords, which are both common and unusually prone to the condition. It bears some morphological resemblances to human xeroderma pigmentosum, but no fibroblastic DNA-repair deficit has been detected (Cleaver *et al.* 1972).

An analogy has also been drawn with human cervical cancer (Van Kampen *et al.* 1973), which lends interest to the reported successful treatment of the bovine tumour with tissue vaccine.

Breeding Hereford cattle for pigment around the eye seems to be protective. The possible concurrent action of a virus remains unproved, although an infectious bovine rhinotracheitis virus has been recorded (Cleaver *et al.* 1972).

Chemical, superficial: Skin tumours are very common in dogs, but it is not known whether dirt or other contaminations are responsible for any of these tumours. The skin of the dog is apparently resistant to carcinogenesis by tarring.

Penile carcinoma occurs from time to time in castrated male horses. It might be worth while identifying the carcinogenic agent present in horse smegma, which has been shown to be carcinogenic when applied to the skin of the mouse (Plaut & Kohn-Speyer 1947).

Chemical, ingested: Stomach cancer and liver tumours can be produced experimentally in dogs by nitrosamines (Fujita *et al.* 1974, Hirao *et al.* 1974). Spontaneous stomach cancer occurs occasionally in dogs (Lingeman *et al.* 1971, Sautter & Hanlon 1975), and a search for possible geographical variations in incidence is indicated.

Chemical causation of bladder cancer by an ingested carcinogen is exemplified by the production of such cancers in cattle by the ingestion of bracken fern (*Pteridium aquilinum*). This plant also causes intestinal carcinoma when fed to rats (Pamukçu & Price 1969) and to Japanese quail, and it is believed to be responsible for some (though by no means all – Simpson & Jolly 1974) cases of intestinal cancer in sheep. The possibility that bracken fern as a food item may be the cause of the high incidence of stomach cancer in man in Japan is raised by Pamukçu & Price.

It is of interest that Döbereiner *et al.* (1967) in Brazil have recorded the angiomatous and carcinomatous lesions of the urinary bladder which are found in chronic hæmaturia cases in cattle, in association with papillomatous and carcinomatous lesions of the upper alimentary tract (UAT). The UAT lesions might occur alone, but the bladder lesions were always accompanied by the UAT lesions.

We may also have to look for ingested carcinogens (possibly of atmospheric origin) as the cause of UAT carcinoma in the dog (especially of the tonsil) and cat (especially of the tongue and œsophagus). Over several decades, squamous cell carcinoma of the (faucial) tonsil of the dog has been one of the most important specific carcinomas we have seen in London. It is less commonly reported elsewhere, although it occurs with some frequency in Paris and in Philadelphia. The tumour, which is sometimes bilateral, is prone to metastasize early to regional nodes and lungs. In the cat, the most specific localizations of UAT carcinoma are on the ventrolateral surface of the tongue, and in the middle third of the œsophagus, just behind the two first ribs.

It will be of interest to see whether these dog and cat UAT tumours disappear with the introduction of smokeless zones in London and elsewhere.

Intrinsic Causes, Genetic

Melanomas occur in most ageing grey horses, especially in the perineal region, but are very rare in horses of other colours. These 'greys' are born dark brown or black, but with age there is a gradual loss of hair pigment, so that they become white. The tumour has been extensively studied by Levene (1971), and it could provide ample material for the study of disturbed melanoblast function.

Melanomas are common in the skin and not rare in the mouth of the dog. They often occur in pigmented breeds, but it is not known whether there is definite genetic influence. Such an influence is, however, clear for the melanomas of the miniature pig (Flatt *et al.* 1972, Manning *et al.* 1974).

Osteosarcomas of the dog are of interest because of their rather specific localizations when they affect the limb bones of larger dogs (which they mostly do) – upper humerus, lower radius and lower femur being favoured sites. The fact that they are commoner in large breeds of dog, such as Irish Wolfhounds and Great Danes, may point to a breed susceptibility. Cohen *et al.* (1974), in their study of the age distribution of tumours in dogs, found that while the general rule was for increasing risk with increasing age, osteosarcomas (and lymphosarcomas) showed a pronounced peak in the 6–10 years age group, followed by a sharp decline. They suggest the possibility of a viral origin for osteosarcoma (and for lymphosarcoma), possibly activated by physical (size) and genetic (breed) factors.

General: In a more general sense, there are apparent genetic susceptibilities (or insusceptibilities) to tumours in breeds of dog which might be worth subjecting to immunological or other analysis. The Boxer dog, for example, is prone to a variety of tumours (Howard & Nielsen 1965); while notably prone to mastocytoma of the skin, it also shows an unusually high incidence of osteosarcomas and lymphosarcomas, but on the other hand fewer than expected cutaneous adnexal, mammary and circumanal tumours (Cohen *et al.* 1974).

Intrinsic Causes, Hormonal

Hepatoid (circumanal) adenoma of the dog: This very common tumour is confined to Canidæ, as are its parent cutaneous glands. It is largely restricted to old male dogs. Its cells show androgen receptors (Evans & Pierrepoint 1975) and testosterone administration to immature pups will cause development of the gland to adult size and appearance (Maita & Ishida 1975). Stilbœstrol has long been used to cause some regression of the tumour.

Mammary tumours in the bitch: The formation of mammary tumours (Hamilton 1975, Strandberg 1974) in the bitch is prevented more or less completely by oophorectomy before two œstrus cycles have been completed (Schneider *et al.* 1969). Such tumours show signs of possessing œstradiol-binding receptors (Evans & Pierrepoint 1975). Whether their incidence is related to parity or to pseudopregnancy needs clarification. The tumour is quite often a mixed one, and in this form is not a good model for human mammary cancer – a better model seems to be the mammary carcinoma of the cat, in which incidentally virus-like particles have been reported (Feldman & Gross 1971, Bomhard & Wettimuny 1974). The canine mixed mammary tumour may instead be a better morphological model for the human mixed salivary tumour, and its great content of proliferating myoepithelium is thus of interest.

The chief medical interest of the bitch mammary tumour at the moment is the development of mammary nodules and tumours in dogs used in the studies of the toxicity and carcinogenicity of oral contraceptive preparations for human use (e.g. Nelson *et al.* 1972, Nelson *et al.* 1973). In interpreting these findings, the differences between the bitch and the human in respect of their œstrus cycles, and their response to œstrogens and progestogens, must be borne in mind (*see* Hill & Dumas 1974). Mammary tumours in the bitch have long been suspected of being related in some way to progesterone, and so what these tests have shown may best be interpreted as throwing light on the possible etiology of mammary tumours in the bitch, as a possible species-specific response to progestational stimuli (Capel-Edwards *et al.* 1973), possibly working through growth hormone (Tucker 1970).

In this connexion, the use of dogs in long-term experiments to test possible carcinogens, such as those in the environment, needs very careful appraisal (Bonser 1969).

Conclusion

One problem of comparative oncology which particularly intrigues me is how to account for the differing spectrum of tumour incidence (or, just as important, lack of occurrence) in the different species, including man. The factors involved must be very complex but, as a theoretical basis for devising investigations, I would put forward the following argument: If we assume that a tumour arises because of the action of a

tumorigenic agent on a particular tissue (and I realize that this is not universally applicable), then the observed species differences in tumour incidence must be related to one or more of the three factors concerned – the tissue, the agent and the tumour:

(1) The *tissue* must of course be present, it must be exposed to the tumorigenic agent, and it must be susceptible to the agent.

(2) The *agent* must be present (or be produced as a proximate agent), and in sufficient quantity; it must act for a sufficient time, and it must have the support of any essential co-carcinogens.

(3) The *tumour* must survive the body's anti-tumour mechanisms, and it must have time to develop.

The testing of these factors in particular cases would be an exacting, but worth-while, project.

In general terms, I think that the future of comparative oncology, in its comparative aspect, will turn more and more to epidemiological and etiological studies on the one hand, and to immunological and therapeutic studies on the other. There will be a continuing need for careful histological analyses of tumours, but these studies will be looked on more and more as essential handmaidens to the others. Already, registers of tumours in animals, including lower animals, are established in Washington, and analytical surveys of tumours in veterinary college clinics are well developed in North America (Priester & Mantel 1971), and are being promoted here and on the Continent, and comparisons with human populations are being made (Dorn *et al.* 1968, Dorn 1972*b*). I think there would be justification for a graduate course in comparative oncology, and I would not be surprised if a journal of comparative oncology were to be established. This Section of Oncology, too, is likely to be used more and more as a forum for communication. Much good comparative oncological work has been done, and there is a good prospect of still wider developments. Nature seems to have been almost provocatively lavish in scattering her clues to the cancer problem, but she has at the same time made the problem perhaps still harder to solve. As Thelma Dunn (1975) points out in her delightful monograph, any theories on cancer must recognize the multitude of facts that have been gathered from studying cancer in animals. Here indeed is a suitable subject for philosophical speculation. To quote Dunn again, few people outside cancer research appreciate the magnitude and complexity of the cancer problem, and we must surely be prepared to follow any promising clue wherever it may lead.

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