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A Brief Comparison of Lung Tumors in  
Man and Laboratory Animals

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There are many differences between tumors of the lung in man and in lower animals. These differences are manifested in such gross anatomical and clinical features as the number of primary tumors, the location of the tumor within the lung, the sex of the affected individuals, the progress of the disease, and the frequency with which tumors are found in different species. The histologic differences are also striking, and must be taken into account in the evaluation of any studies on lung cancer with experimental animals. Finally, confusion in diagnosis may arise from inflammatory reactions and non-neoplastic lesions of the lung.

In man most cancers of the lung manifest themselves clinically as a single localized tumor. If one divides the lung into a central zone that extends to segmental bronchi, an intermediate zone that extends from segmental to smallest visible branches of bronchi and a peripheral zone that includes only minute distal bronchi and bronchioles then central growths account for 45% to 50% of lung cancers. It has been estimated that 30% of squamous cell cancers, 75% of adenocarcinomas, and 20% of oat cell carcinomas in man arise at the extreme periphery of the lung. Most lung tumors in many species of lower animals are likely to be multiple, multicentric in origin and peripherally located within the lung. Primary multicentric lung cancer in human beings is rare. In man most cancers originate from major bronchi, whereas in animals they are likely to arise from small bronchi, bronchioles and alveoli. More pulmonary cancers occur in men than in women, whereas in animals the sex ratio is more nearly equal. Indeed orchietomized rats fed 2,7-FAA

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develop more lung tumors than intact males fed this carcinogen indicating that the absence of the male hormone may actually favor lung tumor development in this species. Pulmonary cancer is a rapidly fatal disease in man but may progress slowly in animals and mice in particular may live for a long time even with multiple tumors of the lung. The frequency of lung tumors in man and in animals also differs. In most animal species lung tumors occur considerably less frequently than in man but in the mouse nearly 100 percent of the members of some strains develop the alveologenic pulmonary tumor in old age. By comparison only one in 300, 500, or 1000 or more Syrian hamsters may have a lung tumor. Likewise both the rat and the domestic fowl have a negligible incidence of spontaneous lung tumors. Canine pulmonary tumors however are being found with increasing frequency because dogs are being protected from fatal infections by vaccination and are living to a ripe old age these days.

The histologic differences are also striking and are an important in comparing lung tumors from man with those in lower animals as any other feature perhaps even more so. The most common histologic types of lung cancer in man are squamous cell carcinoma and oat cell carcinoma where in animals the glandular type of pattern prevails. Of the glandular type tumors, those in man are likely to produce mucin whereas those in animals do not. For practical purposes the oat cell tumor, so common in man, does not occur spontaneously or by induction in animals. The only example of an oat cell tumor I ever saw in a lower animal was in a Java sparrow from the Philadelphia Zoo. I regret that I could not

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tell whether this bird had Cushing's syndrome which is seen so frequently in human beings with oat cell tumors. Pulmonary carcinoid tumors are by no means rare in man but they have not been reported to occur in laboratory animals and the only carcinoid tumor that I know of in animals occurs in the Mastomys. A very high percentage of old Mastomys develop malignant argyrophilic carcinoids of the glandular stomach. Other so-called "bronchial adenomas" with distinctive histologic patterns have been seen and described in man but have not been seen in untreated animals. Under experimental conditions proliferations and cancers of the submucosal bronchial glands can be induced in at least some species that possess such glands as for example the rat. The common pulmonary tumor of the dog closely resembles the pulmonary tumor of the mouse in histologic appearance, peripheral location within the lung, multiplicity and expansive in contrast to infiltrative type of growth. The canine tumor is thought by those with experience to arise from terminal bronchi and alveoli.

A common error in both man and laboratory animals is the misidentification of metastases as primary pulmonary tumor. There is a frequently repeated pattern of metastasis of pulmonary cancer in man, to the adrenal glands and brain especially, but I knew of no such pattern in laboratory animals.

Thus far I have discussed tumors of the lung that are chiefly found in untreated animals but by different methods of experimentation it has been possible to induce squamous cell carcinoma, adenocarcinoma and

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undifferentiated cell carcinoma of the lung in several species. These include the mouse, rat, Syrian hamster and dog and mixed histologic types are not infrequently seen following experimental procedures. In hamsters it is as easy to induce tumors of the trachea as of the bronchi whereas in man primary tracheal tumors are exceedingly rare. Pulmonary hemangioendothelioma can be easily induced in mice and rats but I have never seen this histologic type of neoplasm in man. Thus some similarities but also many differences emerge when the varieties of induced lung tumors in animals are compared with those occurring naturally in man.

The problem of lesions that need to be distinguished from genuine neoplasms exists in many animals including those commonly used in laboratory experiments. Pulmonary adenomatosis and keratinizing and non-keratinizing squamous metaplasia of alveoli and bronchi may be especially perplexing in laboratory rodents. These lesions along with associated pulmonary infection which may be common in rats and mice, but rare in the hamster, adds to the confusion of separating the lesions of non-neoplastic reactions from genuine neoplasms. These conditions may be seen in untreated laboratory animals and in those subjected to experimentation. A notorious mistake was made by Fibiger who diagnosed islands of squamous metaplasia in bronchiectatic cavities as metastasis from what he thought was squamous cell carcinoma of the forestomach of rats. These gastric lesions were in reality mucosal hyperplasias caused by the ingestion of cockroaches infested with tape worms. Since then many similar blunders have been made by overly enthusiastic and incautious investigators but none subsequently won the Nobel Prize.

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