

The Incidence of Cancer in Mice of Known Age.

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The opportunity of obtaining accurate information of the frequency of spontaneous cancer in mice at different age-periods has presented itself in the course of a prolonged inquiry into the possibility of hereditary transmission of a liability to cancer. We have approached the question of heredity experimentally by breeding systematically from mice spontaneously affected with malignant new growths, and propose to determine the frequency of spontaneous cancer in mice in whose ancestry the disease has occurred with varying frequency. This investigation is still in progress and cannot be reviewed profitably for several years, but the data which have so far accumulated are of sufficient interest, in their bearing upon the statistical and biological importance of the age-incidence of the disease, to warrant a preliminary account being published; although the small numbers at present available still render the greatest caution necessary.

The method by which the data have been obtained is as follows: Mice spontaneously affected with cancer are not killed when brought into the laboratory, but the tumours are excised and used for transplantation. The clinical course, the microscopical examination, and the results of transplantation of the tumours, together with the *post-mortem* examination of the animals, give the best security for the correctness of the diagnosis of cancer. It is only under these precautions that the breeding experiments have proceeded. Each spontaneously affected mouse, or pair mated for breeding, has been housed in a separate cage. The cages have been sterilised and changed at regular intervals. In the first instance, the males mated with these spontaneously affected females were the offspring of spontaneously affected animals received pregnant. Later, males bred in the laboratory from cancerous parents were used, so that the pedigrees constructed for the later litters show some strains with a relatively enormous preponderance of cancerous ancestors. When a litter is born each young mouse receives a number, the date of birth is entered in a list, and the sex and colour or other distinguishing marks noted against each. So soon as they are able to look after themselves the litters are separated from the mother, and the males and females segregated in fresh cages. It is thus possible to distinguish each animal born in the

laboratory by reference to an index, which at once gives the ancestry, the date of birth, and the age of the animal in question. The mice have been systematically examined daily.

There is difficulty in obtaining offspring from mice suffering naturally from cancer, and the breeding experiments began to be regularly successful in January, 1907. The first case of cancer was found in a female mouse in March, 1908, the animal being nine months old. Since that date 18 additional spontaneous malignant new growths have been obtained. Every case has been subjected to careful microscopical examination, and only undoubted cases of malignant new growth are reckoned. So far all have occurred in female mice, and with two exceptions have affected the mamma. The exceptional cases were one of generalised malignant lymphoma, and one of melanoma or melanotic sarcoma of the external ear. The remainder were carcinomata of the mamma in which the adenomatous character was present in varying degree; in two of them small areas of keratinisation were found in the sections examined.

It was of interest to determine at what age the tumours were *first observed*, and to determine the number of animals of the same age under observation. As no cases of new growth have yet occurred in the males* bred, these are excluded from the present purview. The females were distributed by means of a card index into five groups differing in age from each other by intervals of three months. Animals under six months old have been excluded because of the high mortality in the first six months of life from infectious diseases of all kinds (pneumonia, enteritis, septicæmia), and because the youngest mouse in which a true malignant new growth occurred was exactly six months old. It will be noted from the table given below that no female animal attained the age of two years. On April 26, 1909, a census of the females was taken, and all those which had died over six months old, since the beginning of the experiment, were added to the corresponding age-groups. The mice which were then still living, after developing cancer, and those which had died from the disease, appear in the age-group corresponding to the age at which the disease was first discovered in them. The percentages of the following table are therefore not strictly comparable with death-rates, but are to be read as giving the liability to cancer at different age-periods.

The progressive increase shown in the table presents a remarkable correspondence with the facts long familiar to students of the incidence of cancer in the human subject. It furnishes a striking confirmation in the

* Of the first 1145 mice bred, 588 were males and 557 females. The preponderance of cancer in the female is due to the great liability of the female to cancer of the mamma.

mouse, of the conclusion we advanced in 'Roy. Soc. Proc.,' vol. 73, January, 1904, and in the First and Second Scientific Reports of the Imperial Cancer

Age.	6—9 months.	—12 months.	—15 months.	—18 months.	—21 months.	—24 months and over.
Total	135	110	94	21	6	—
Cancer	3	4	7	3	2	—
Per cent.	2·2	3·5	7·4	14·2	33·3	—

Research Fund, that, in animals as in man, the *recorded* frequency of cancer varies with the opportunities for examining a large number of adult and aged individuals.

Account was taken of the age-incidence of cancer in the human subject in the hypotheses of Thiersch* and of Cohnheim,† which were formulated for man only, and are untenable to-day. The general biological significance of the age-incidence of cancer, for which we have so often argued, has been ignored, or, when mentioned, minimised by most pathologists, and, in recent years, also by those engaged in the experimental study of the disease. It is, perhaps, not too much to hope that the foregoing presentation of the facts will henceforward impress on those engaged in the investigation of cancer the urgent necessity for precise knowledge of the ages of men or animals in whom the incidence of cancer is being studied. In particular, the difference between mice 15 months old and 21 months old in their liability to cancer at once invalidates completely all statements of the relatively greater frequency of cancer in one group of mice than another, when the exact age of the animals is not known. The same objection must be raised to assertions of the occurrence of epidemics in other animals. Such statements have been frequently made, and have received wide currency since experiment demonstrated the possibility of the artificial transmission of cancer from one animal to another of the same species, but only, however, by implanting living cancer-cells, and also demonstrated that this form of transmission could not be made responsible for the great frequency of malignant disease. The above criticism therefore applies with destructive force to all statements which have appeared up to the present on the occurrence of epidemics of cancer in mice and rats. Until it can be shown that the conditions of experiment have altered the normal age-incidence of the

* Thiersch, 'Der Epithelialkrebs, namentlich der Haut,' Leipzig, 1865.

† Cohnheim, 'Vorlesungen über allgemeine Pathologie,' Berlin, 1877, 2nd Edition, 1882.

disease, the theses which have found such ready acceptance must be regarded as not proven.

As in the case of other communities of mice in outside breeding establishments, our stock, at present under consideration, is a highly in-bred one. It is not profitable at present, considering the small number of tumours which have been obtained, to analyse the cancerous and non-cancerous individuals with reference to this factor or to the ancestry.

The positive value of these observations lies in the statistical confirmation they bring to the results of the comparative histological and biological studies of the Imperial Cancer Research Fund, which have shown the close parallel, amounting in many particulars to complete identity between malignant new growths in man and other vertebrates. They demonstrate that the law of the age-incidence of cancer holds also for the shortest-lived mammals as it holds for man. Since the facts accord with the imperfect data we have elicited for other vertebrates, they make the general applicability of the law of age-incidence probable, and therefore any explanation of the etiology of cancer must accord with the circumstance that, when considered *statistically*, cancer is a function of age, and when considered *biologically* is a function of senescence.
