GENETICAL SOCIETY OF GREAT BRITAIN

ABSTRACTS of Papers read at the NINETY-FIFTH MEETING of the Society, held on TUESDAY, 6th APRIL 1948, in the BOTANY SCHOOL, Downing Street, Cambridge

AN UNUSUAL ABIOTROPHIC FUNDUS LESION, WITH LATE ONSET AND DOMINANT MODE OF INHERITANCE

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A fundus lesion having the following features has been observed :—

(i) The early stages consist of œdema and hæmorrhages at the macula ; this progresses to form an atrophic pigmented scar in the macular area. Subsequently there is extension peripherally, ultimately finishing in a total or sub-total atrophy of the whole of the retina and choroid.

(ii) The affection begins at about the age of forty with loss of central vision, and progresses steadily leading to total blindness by about the age of seventy.

(iii) Two complete family pedigrees extending over five generations, with observed cases over three generations, are available ; there is tentative evidence in two further families.

Clinically the significance of this affection, apart from its late onset and mode of inheritance, is the polymorphism of the intermediate stages readily leading to mistaken diagnosis of inflammatory reactions.

INTRA-SEXUAL SELECTION IN *DROSOPHILA MELANOGASTER*

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In *Drosophila melanogaster* it can be demonstrated that males are more variable in their contribution to the next generation than are females. The variability of male fertility is more than can be accounted for by a greater sensitivity to controllable genetical and environmental factors. This sex difference is analysable into two parts—a greater sensitivity of the fertility of the males to frequency of insemination, and a greater variability between individual males in number of mates.

The former is shown to be not merely a result of the ability of females of this species to store sperm, but also a direct result of the primary sex difference. This explains why over a large range of organisms intra-sexual selection is predominantly intra-masculine. The greater variability of males in number of mates merely demonstrates the existence of intra-masculine selection in *D. melanogaster.*

THE NUMBER OF MOLECULES INVOLVED IN THE SYNTHESIS OF BETA-ALANINE

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McIlwain has suggested that each step in the synthesis and further metabolism of vitamin-like substances in bacteria may be catalysed by one or a few molecules of enzyme per cell.

The origin of beta-alanine, a presumed intermediate in the synthesis of one of these substances (pantothenic acid) has now been investigated. Non-proliferating cells of *Escherichia coli* produce beta-alanine by decarboxylation of aspartic acid at a rate adequate to account for that of synthesis of pantothenic acid from beta-alanine observed by McIlwain.

We have thus information on the magnitude of a second step in the synthesis of pantothenic acid. The rate of production of beta-alanine from aspartic acid *in vivo* is about thirty molecules per cell per second, and more than half this activity has been recovered in *in vitro* preparations. This rate of production is compatible with the assumption that one or a few molecules of enzyme catalyse the decarboxylation of aspartic acid to beta-alanine.

THE INHERITANCE OF STYLE LENGTH IN THE TRIMORPHIC SPECIES *OXALIS VALDIVIENSIS*

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In repeating, with *Oxalis valdiviensis*, Fisher's (1943) method of investigation into the inheritance of style length in *Lythrum salicaria*, the hereditary mechanism was found to differ from that in *Lythrum*. Darwin and Barlow showed that the long-styled form is genotypically recessive, that Short and Mid are controlled by two different genes—Short being epistatic to Mid.

Twelve short-styled plants were crossed with Longs to find those Shorts carrying the mid factor. All the progenies gave a good 1 : 1 Short to non-short ratio. However, six gave Mids, but in the proportion of one Long to fourteen Mids instead of one Long to one Mid as expected. This suggested that the Mid and Short loci are linked, that the Shorts tested were in the repulsion phase, and that the Longs represent half the crossovers. The percentage of Longs was 6·8 of all not short.

Short daughters of these mid-carrying Shorts are being backcrossed with a view to seeing if any carry mid, and if so, to obtaining a plant in the coupling phase.

ANALYSIS OF SEXUAL ISOLATION BETWEEN *DROSOPHILA PARANAENSIS* FEMALES AND *D. PARAREPLETA* MALES

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Sexual preference. Five days' old animals were used in experiments without, as well as with, multiple choice. At least with young flies, the conspecific females are the first to be fertilised, and in the absence of conspecific females the males fertilise sooner than the alienigen females. In " without choice " experiments using 10 males to 10 females, two inseminations were obtained and not a single one in " multiple choice " experiments with a ratio of 10 males to 1 alienigen female.

Influence of time of contact for flies in contact since birth. Experiments were made using animals from seven to twenty-five days in " without choice " as well as in " multiple choice " crosses. There seems to be a positive influence of time of contact on the frequency of insemination in " multiple choice " experiments. In " without choice " experiments the results are rather complex.

Influence of maturation and time of contact. What matters for the frequency of the insemination is the time of contact and not the age of the flies.

Amount of sperm in the spermatheca. There is usually less sperm in the receptaculum in heterogamic crosses. In these the sperm sometimes goes, not into the receptaculum, but into other organs.

ABSTRACTS of Papers read at the NINETY-FIFTH MEETING of the Society, being a Symposium on the *Genetics of Cancer* sponsored jointly by the British Empire Cancer Campaign and the Society and held at the ROYAL SOCIETY OF MEDICINE and the MEDICAL SOCIETY OF LONDON on 24th and 25th June 1948.

ROLE OF GENES AND THEIR RELATIONSHIP TO EXTRA-CHROMOSOMAL FACTORS IN THE DEVELOPMENT OF MAMMARY GLAND TUMOURS IN MICE

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The paper is a general survey to show that genetic constitution, hormones and the milk agent are influential in controlling the probability of mammary tumours in mice. Evidence is presented that hormonal stimulation is under genic control, and experimental proofs are given to show that the difference in the ability of various strains in mice to propagate and transmit the milk agent must also be attributed to genetic differences. New data are presented which show that it is possible to induce mammary tumours in the absence of the milk factor, by combination of certain genetic and environmental factors.

GENETICALLY DETERMINED DIFFERENCES IN HORMONE PRODUCTION A POSSIBLE FACTOR INFLUENCING THE SUSCEPTIBILITY TO MAMMARY CANCER IN MICE

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The paper is a preliminary report of experimental data, which indicate that in the high-cancer strain males the quantity of testosterone produced exceeds that of the low-cancer strain males, and correspondingly in the females the production of oestrone is higher in the high-cancer strain than in the low-cancer strain. It is suggested that at least part of the genetically determined disposition to mammary cancer in certain strains of mice is caused by an overproduction of gonadotrophic hormone.

MAMMARY TUMOUR-INDUCING FACTOR AND GENETIC CONSTITUTION

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Experiments, showing the interaction of mammary-tumour-inducing factor or milk factor and genetic constitution in the development of breast tumours in certain high- and low-breast-cancer strains of mice, are described.

Differences in the quantity and/or quality of the milk factor derived from various high-breast-cancer strains are shown and referred to differences in the genetic constitution of these strains.

The influence of genetic factors on the degree of susceptibility or resistance of breast tissue cells of mice to the milk factor is shown. While large quantities of the milk factor can break down the resistance of mature susceptible female mice and induce a high incidence of breast cancer, similar amounts of milk factor combined with forced-breeding fail to induce breast tumours in mature low-breast-cancer strain mice.

Experiments are described in which the part played by genetic factors in the propagation and transmission of the milk factor is shown. The presence of two sets of genetic factors, one controlling the susceptibility of breast tissue cells to the milk factor—the other controlling the propagation of the factor, both in high- and low-breast-cancer strains of mice is stressed.

The possibility of the development of breast tumours in susceptible mice without the milk factor taking part is shown.

In conclusion, it is suggested that only the study of all factors, with the possibility of existence of other factors in mind, can elucidate the origin of breast cancer in mice.

SIGNIFICANCE OF STUDIES WITH TRANSPLANTED TUMOURS

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Studies with transplanted tumours are significant for general biology and oncology. The antigenic basis of tissue transplantation was first demonstrated with tumours. Linkage of one of the antigens with " fused " has been found. All mammals appear to be polymorphic for antigens. In mice some of the genes appear to have a high mutation rate. Antigens differ widely in potency and tumours may grow in the presence of antibodies. Transplantation by itself does not give an accurate picture of the antigenic structure of a growth. Some antigens are present in greater amounts in malignant cells than in normal ; others may be diminished or even eliminated. Malignant tumours apparently depress the activity of the reticulo-endothelial system.

GENETIC STUDIES ON LEUKÆMIA IN MICE

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The paper is a brief account of studies on the frequency and age distribution of mice that died from leukæmia in the different generations of a crossing between the Aka-strain of mice with 63 per cent. leukæmia and a resistant B-strain. It is concluded that the inheritance of the disease is dependent on one single dominant gene. It was furthermore demonstrated by means of transplantation experiments that the pathological features of the leukæmias are partly dependent upon hereditary factors.

THE INDUCTION OF MUTATIONS BY A CARCINOGEN : A CRITICAL EVALUATION OF THE PRESENT STATUS OF THE PROBLEM

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The somatic mutation theory of the origin of cancer is discussed and supported.

MUTATIONS INDUCED BY CARCINOGENS

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By exposing Drosophila males to aerosols of certain chemicals, it is possible to induce genetic changes in their sperm. Experiments conducted with aerosols of oil solutions of 7 carcinogens and 9 chemically related non-carcinogens indicate a close correlation between mutagenicity and carcinogenicity. Of the 7 carcinogens

tested (4 hydrocarbons, 3 azo compounds) 6 were found mutagenic and of 9 non-carcinogens (5 hydrocarbons and 4 azo compounds) only 2 were mutagens and one is still classified as doubtful.

It was observed that different males treated at the same time quite frequently showed different results ; that is, genetic changes could be induced in some males more readily than in others. A semi-dominant gene was found responsible for this behaviour. That gene determines whether or not an individual will be sensitive to induction of genetic changes by certain chemicals.

THE PLASMAGENE THEORY OF THE ORIGIN OF CANCER

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Tumour development is a contradiction in the nature of individuals and we can understand it only in terms of cells and particles. How we can do so has been made clear in the last five years by our increased knowledge in three directions :—

(i) The induction of cancer by chemical agents is now seen to be a genetic mutation, although outside the nucleus and inherently outside the germ-line.
(ii) Between the hereditary plasmagenes and the naturally infectious viruses an intermediate class, the proviruses, is now seen to lie.
(iii) These three classes of particle are conditional and interchangeable. Cancer-producing particles fall into all three.

The origin of cancer can therefore be ascribed to mutations in cytoplasmic determinants, indifferently infectious or non-infectious, which make themselves visible by causing the resumption of growth.

Further the study of plasmagene and virus inheritance in relation to differentiation reveals a competitive propagation of cytoplasmic particles. This explains both the genetic control and the secondary development of cancer with its potential dedifferentiation, change of protein character, and metastasis.

" INFECTIVE " TRANSFORMATION OF CELLS

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Just as Mendelian genetics is technically restricted to the study of *differences* between individuals, so the study of somatic cell heredity is in effect an analysis of cell transformations, *i.e.* of the origin of inherited differences between the phenotypes of cells. In the differentiated adult organism, cells of a histologically definable genus (*e.g.* of epidermal epithelium) can be further subdivided into a variety of distinct true-breeding " species," *e.g.* the epidermis of body skin, sole of foot, tongue, claw, vagina and cornea. Cells of each such type preserve their cell specific properties indefinitely on heterotopic grafting. The study of " infective " cellular transformations is of peculiar interest because it gives direct evidence of the type of difference that must exist between them. Infective transformations, such as are secured by endogenous or exogenous viruses or virus-like bodies, have two distinctive features : (*a*) the maintenance of the transformed state depends upon the continued presence in cells of the transforming agent or an exact replica of it ; and because of this, (*b*) a cell infectively transformed can in its turn transform another. Such transformations give direct evidence of the *particulate* nature of somatic cellular heredity. Infective behaviour by cell particles cannot be anything but a rarity. A colour transformation of the cells of guinea-pigs' skin, of which the authors have made a particular study, is made manifest only by the coexistence in one and the

same individual of a semi-syncytial system of cytocrine cells (viz., dendritic cells) divided into two distinct species by a trivial but phenotypically conspicuous character difference—pigmentary function in the one, and its absence from the other. It is therefore an oddity. But what is odd about it is not the evidence it gives of the particulate nature of cell inheritance, but the fact that, in defiance of what normal developmental processes must conspire to prevent, the determining particles behave infectively and so reveal themselves as instruments of cytoplasmic heredity. In the same way, the infective propagation of tumours cannot but be a rarity. Their rarity does not justify the refutation of the hypothesis that malignant cells differ from their normal homologues by the multiplication within them of viruses or virus-like bodies of exogenous or endogenous origin ; the limiting factor is not the material existence of such particles but their unwillingness to display infective behaviour. Infective propagation of tumours may nevertheless occur in situations where it is not at present suspected.

THE CARCINOGEN-VIRUS RELATION

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No understanding of the mode of action of chemical carcinogens is likely to be sufficiently comprehensive if it fails to take into account the tumour-producing viruses. If future work continues to support the significance of the mutagenic properties of chemical carcinogens, we shall then have the picture, so far as cancer is concerned, of two types of mutafacient agent :—

(i) A large number of relatively simple organic substances, mainly synthetic in origin, of low molecular weight, belonging to different chemical classes, stable, relatively slow in action, of low specificity in that mutation is effected in a wide range of biological material and in a wide range of characters, and of low specificity in that a wide range of tumours can be induced in nearly all the tissues and in most of the species tested ; although initiating malignant change, these substances are unessential to the continued growth of the tumour.

(ii) A group of highly complex protein-containing substances, probably endogenous, labile, embodying extreme specificity in structure, and exhibiting corresponding specificity in their biological action, affecting only one cell-lineage in closely related avian species, and transforming the affected cell, very often rapidly if not immediately, into the image of the malignant cell from which the agent was derived ; these substances appear to play a vital part in the continued growth of the tumour, in the course of which they may undergo multiplication to an enormous extent.

The hypothesis on which work is at present proceeding, is that these two classes of agent typify the carcinogenic process at its least and most specific levels respectively, the relatively indifferent chemical carcinogens effecting the first insult to the cell which induces it to change its characters, and the virus being the actual carrier or determinant of the altered characters themselves. Since the first suggestion that the Rous virus might be regarded as a modified cytoplasmic determinant under nuclear control, electron microscopy of the Rous tumour cell has in fact given evidence of the existence in the cytoplasm of bodies of which the size is exactly comparable with the dimensions of the Rous agent as estimated by filtration and centrifugation. So far, insufficient work has been carried out to permit a useful comparison of the nature of the cytoplasm in cells of the Rous tumour, in cells of other non-filterable avian tumours, and in normal chicken fibroblasts and macrophages.

CHEMICALLY INDUCED MUTATIONS

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The first clue to the existence of carcinogenic chemicals was derived from the observations on industrial cancer. Recently, two synthetic hydrocarbons have been shown to induce germinal mutations in mice. This suggests that there is a risk of industrially-acquired mutations appearing in man, and the author's animal experiments are discussed in relation to this risk.

A high incidence of mutations occurred in mice injected with 1 : 2 : 5 : 6-dibenzanthracene. In a later test of 62 chromosome sets from animals injected with dibenzanthracene, at least six months previously, no recessive mutations appeared, but one abnormal F_1 mouse appeared. This suggests that the effect of the treatment was lasting. Drosophila males raised on food containing phenolic metabolites of 3 hydrocarbons (2 mg. in 5 ml.) showed a mutation rate of 1·1-2·0 per cent. (controls 0·4 per cent.), many of the mutations appearing after removal from the food, again suggesting permanent derangement of the genes of the reproductive track.

ELECTRON MICROSCOPE STUDIES OF NORMAL AND MALIGNANT TISSUES OF HIGH- AND LOW-BREAST-CANCER STRAINS OF MICE

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Extracts of normal and malignant tissues from mice of C3H, Strong A and R III high-cancer strains and of C57 black and CBA low-cancer strains were prepared in the following way.

Fresh tissues were finely minced and desiccated rapidly over phosphorous pentoxide, ground with sand and petroleum ether to remove fatty substances, and the residue extracted with distilled water. The watery extract was trypsinised, filtered through Berkefeld N candles and the filtrate, after suitable dilution, examined under the electron microscope, after shadowing with metallic gold or chromium.

It was observed that all tumours and normal lactating breast tissues of the high-cancer strain mice presented spherical particles of 200-350 Å in diameter. While these sizes predominated some particles of larger dimension were also present.

In the extracts of lactating breasts and induced tumours of the low-cancer strains similar particles were not observed or were, at most, represented by an occasional particle.

The milks of the respective strains yield comparable results.

The particles can be removed by ultracentrifugation at a speed equivalent to 120,000 times gravity.

Concurrently all extracts were inoculated into C57 × R III hybrid mice susceptible to the development of breast cancer.

While it has yet to be established if the particles are related to the milk factor, it can be stated that the extracts in which the milk factor is known to be present contain the particles, and in those in which there is no milk factor no particles are to be found. The outcome of the biological tests is awaited.

INDICATIONS OF THE HERITABLE NATURE OF NON-SUSCEPTIBILITY TO ROUS SARCOMA IN FOWLS

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An investigation of the differing response to tumour inoculations of the inbred lines of Brown Leghorn fowl maintained at the Poultry Research Centre, Edinburgh, has been in progress for a number of years. Annual losses from spontaneous neoplastic and allied conditions are extremely low. When most of the inbred lines were tested it was found that one in particular showed an obviously high resistance to the production of fatal cancer by the Rous No. 1 virus.

The distribution of the responses in groups of chicks from individual matings makes an interpretation based on a simple genetic situation unlikely and suggests considerable variation due to non-genetic causes.

A resistant male mated to fairly close relatives enabled a non-susceptible line to be established rapidly, and breeding from progeny showing complete lack of tumour growth resulted in offspring which gave only minor variations in the degree of resistance in subsequent years.

The particular inbreds from which the line non-susceptible to Rous No. 1 virus has been derived had shown itself earlier (Greenwood and Peacock, 1945) to be the most resistant to chemically induced tumours. The lack of a seasonal difference in response to Rous inoculations suggests that the factors operating in respect of these two distinct types of induced tumour cannot be entirely the same.

THE SUSCEPTIBILITY TO CARCINOGENS OF ADULT AND EMBRYO TISSUES

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The liability to malignant transformation of adult and embryo tissues was compared because of the reports of the unusually short latent periods of tumours produced by carcinogens in grafts of embryo tissues. Methylcholanthrene was injected into *C* mice together with grafts of adult or of embryo skin. Squamous cell carcinomas derived from embryo grafts were found at autopsy after 54 to 118 days. The growth curves of the tumours indicate that the epitheliomas arise generally earlier than the sarcomas derived from the stroma, but that they may also appear as late as the latter tumours. The growth curves failed to show the earliest date of malignant transformation in the embryo cyst, as the latter may reach a considerable size before the onset of malignancy.

Grafts of adult skin did not become malignant, probably because of their small size and of their frequent failure to take in the presence of methylcholanthrene. However, injection of methylcholanthrene alone into the dermis of *C* mice produced epitheliomas in addition to sarcomas, and an invasive epithelioma was already observed on the 29th day after injection. Many carcinomas were also obtained from embryo skin in Aka mice, but they were produced less frequently in C57 black mice.

Thus embryo skin is not more liable to malignant transformation than adult skin, but both types of epidermis can become malignant earlier than connective tissue. It is suggested as a working hypothesis that mitosis may represent a phase susceptible to the carcinogen.

THE ESTIMATION OF TUMOUR SUSCEPTIBILITY OF PURE LINES

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The problem of estimating the tumour susceptibility of pure lines has been approached in the past by a number of methods though usually in a rather empirical manner. One of the most widely used measures is the percentage of cancer deaths in a group of animals. Although this fraction has the advantages of great simplicity in computation and an easily calculated sampling error it is not a very satisfactory index of tumour susceptibility since its value can be much disturbed by fluctuations in the non-tumour death rate, even though the true tumour susceptibility is unchanged. Other indices have been proposed which are usually weighted averages of the cancer death rates at each age, or of some function of the cancer death rates.

The fundamental information on tumour susceptibility is provided by the cancer death rates regarded as a continuous function throughout life. Estimates of these can be made mathematically and life tables constructed for tumour mortality alone independently of other causes of death.

The application of this method to the assessment of tumour susceptibility gives results which are in some cases at variance with those indicated by percentage tumour incidence. For instance the susceptibility of the dba strain appears to be as high as that of C_3H though its percentage tumour incidence is lower.

A simple index number which gives results in agreement with the tumour life table data is Iball's index of carcinogenic activity. This is calculated by dividing the mean age at death from tumour and non-tumour causes into the percentage tumour incidence.

HEREDITY IN HUMAN CANCER

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The various tumour-causing factors are presented, based on the results of six years of investigation.

I. Endogenous factors

(i) Hereditary predisposition.
Tumours of different forms, types and sites differ in their genetical behaviour.

- (*a*) General predisposition (gen. blastoma tendency).
- (*b*) Tendency to localisation (localisation genes, organ factors, similar histological structure) :—
  - Dominance (irregular), recessivity (?).
  - Polymeric or multifactor inheritance.
  - Homologous polymeric factors.
  - Later and less frequent when heterozygous.
  - Variation in manifestation, penetrance and expressivity. Twin investigation. Age correlation.
  - Variation in susceptibility or refractoriness to tumour formation or tumour transplantation.
  - Genes with the character of viruses. Cytological changes.

(ii) Somatic mutation (induced or spontaneous).
(iii) Cytoplasmic inheritance (maternal effect).
(iv) Internal milieu (partly environmental).

2. Environmental factors

(i) Internal milieu (adaption to individual, type, race or variety and species). Internal carcinogenic environment.
Hormonal unbalance, metabolic disturbances.
Modification of internal milieu caused by transplantation of eggs or embryos, milk factor (maternal inheritance ?), nutrition, age, radiation (decreased resistance), carcinogenic agents (acceleration), intoxication.

(ii) External milieu (*exogenous factors*).
Irritation by trauma, chemical, thermal or ray influence, parasites, bacteria and viruses.

3. Hereditary tumours

Benign and malignant.
Neurofibromatosis. Tuberous sclerosis. Lipomata. (Phakomatosis.) Adiposis dolorosa. Exostoses. Enchondroma. Enostoses. Dermatofibrosis. Fibroma plantæ. Fibroma molluscum. Onychogryphosis. Atheroma. Sebaceous tumours. Xanthoma. Myoma. Cheloid. Hyperkeratosis. Adenofibroma. Adenoma. Struma. Teratoma. Melanoma.

Nævus. Angiomatosis retinæ et cerebelli. Angioma cavernosum, Telangiectases (Osler and Sturge-Weber). Renal cysts (multiple cysts in several organs). Hypernephroma (malignant). Hypertrophy of prostate.

Precancerous conditions, precursors to cancer : Xeroderma pigmentosum. polyposis intestini. Achlorhydria.

Neuroblastoma retinæ. Glioma. Cancer mammæ, uteri, œsophagi, ventriculi, recti. Cylindroma. Sarcoma. Leukæmia. Lymphosarcoma. Reticulosarcoma.

INHERITANCE OF XERODERMA AND ITS CHROMOSOME MECHANISM

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Xeroderma pigmentosum is marked by roughening, dryness, pigmentation and ulceration of the skin, which consequently leads to malignant transformation. According to Haldane, it depends on an incompletely sex-linked gene. Three family histories are presented, in which one or more members of the family are affected with xeroderma. In two families, the usual pathological symptoms were observed, while in the third, the condition was manifested in a mild form. Furthermore it was found that the segregation of xeroderma in this family, does not conform closely to expectations. This behaviour suggests that the condition in this particular family may be due to an independent autosomal gene, or to position effect ; *i.e.* the gene is transferred to a more distal region of the pairing segment of sex chromosome.

TWIN STUDIES IN THE DANISH CANCER REGISTRY

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There is a greater tendency to a higher incidence of cancer among partners of identical cancerous twins than among partners of fraternal twins with cancer, but the deviations from the expected values are not statistically significant if the

age distribution of the material is taken into account. However, there is a clear tendency for tumours in identical pairs to affect corresponding organs in both partners, whereas this is not the case among fraternal twins.

FAMILY HISTORIES OF BREAST CANCER PATIENTS

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Four hundred and fifty-nine patients with cancer of the breast were questioned as to their family history. Most of the stories given have not yet been confirmed by the hospitals concerned or the Registrar-General's department, so that the analyses presented represents essentially what these patients could remember of what they once knew about the medical history of their relations. It is probable, however, that the figures represent an under-estimation rather than an over-estimation of the cancer incidence in these families.

Of the 459 families analysed no evidence of a family history of cancer was obtained in 292, and cancer was reported in 167. Of the 167, 76 were said to have had cancer of the breast ; in 54 cases a history of cancer in more than one member of the family was obtained. Cancer was reported on the maternal side only in 68 ; on the paternal side only in 44, amongst brothers and sisters in 33, and on both paternal and maternal sides in 12. Of 459 mothers, 66 died of cancer ; of these 25 had cancer of the breast. Of 459 fathers, 30 died of cancer, none of cancer of the breast.

There were 1008 sisters, 288 of whom had died—59 in infancy, another 200 of causes believed to have been other than cancer, 29 of cancer—11 of whom had had cancer of the breast. There were 11 sisters living who had received treatment for cancer of the breast. There were 1059 brothers, 425 of whom had died, 75 in infancy and 332 of causes believed to be other than cancer. Eighteen had died of cancer, but none of cancer of the breast and one was alive following treatment for cancer.

An analysis of the patients by age at the time of diagnosis did not show that those with a family history of cancer were in a younger age group as found by Jacobson. Those reporting cancer in sisters had a higher average age than those reporting cancer in older generations, presumably because the brothers and sisters of the younger patients were less likely to have reached the " cancer age."

Preliminary analysis of the data suggested that there was a significantly high death rate from cancer of the breast in the families of patients with that disease, but no higher death rates from other forms of cancer than would be expected in the general population.

Charts were presented showing the occurrence of cancer in relatives in three families with a high cancer incidence.

A GENETIC STUDY OF HUMAN MAMMARY CANCER

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The family histories of a series of 510 cases of mammary cancer in females were analysed. Comparison with official mortality statistics by a new method showed that the proportion of deaths due to mammary cancer in the patients' relatives was significantly increased. The rates for other types of malignancy were unchanged.

It is concluded that a specific genetical agent is responsible for human mammary cancer. Evidence concerning the nature of this agent was obtained from studying incidence in paternal and maternal relatives, laterality, age of onset and history of breast feeding in the patient's own infancy. There is some indication that the specific agent might be cytoplasmic and probably not transmitted through milk.