CANCER

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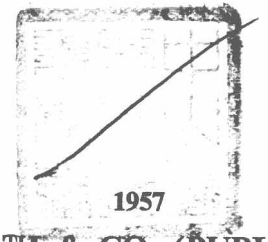
PART I

RESEARCH INTO CAUSATION



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PREFACE TO THE WORK

THE CONTROL of cancer is one of the important problems requiring urgent solution for it is a major threat to life of all nations and none is excluded from its effects. The mortality from the disease rises annually and a concerted effort is required to attain our object. There is need for a close partnership of all who are engaged in different aspects of the work and the facilities for quick access to information concerning advances being made in fields other than their own. These volumes will help to fill this need, for they are planned with the object of including many of the relevant aspects of the subject. "He alone can conceive and compose who sees the whole at once before him."[1]

In planning this synthesis of knowledge care was taken in the choice of subjects and to show each in its right perspective. "To try and approach truth on one side after another, not to strive or try, nor to persist in pressing forward on any one side with violence and self-will—it is only thus, it seems to me, that mortals may hope to gain any vision of the mysterious goddess . . . . He who will do nothing but fight impetuously towards her on his own, one, favourite, particular line, is inevitably destined to run his head into the folds of the black robe in which she is wrapped."[2] It is recognized that some of the subject-matter is in a state of flux, that knowledge is still imperfect and further progress will occur. For instance, when Volume 1 concerning research was planned, the main avenues leading to the goal, as I see it, were chosen. When more progress has been made it is likely that one or more of these subjects will become prominent, or a new line of approach may be developed. In this connexion it is felt that the subject of cellular enzyme reactions in relation to malignant disease is still in its infancy and a separate chapter is not assigned to it. Such new subjects will require detailed consideration as knowledge concerning them matures and it is essential to keep the work up to date by the publication of regular supplements. Although each chapter concludes with a list of references, mention is made only of those authorities whose work is considered in the text. The Index volume—in itself of great value—will also contain a carefully selected bibliography which, in the main, has been suggested by the contributors to the work, and will embody references to the up-to-date papers on every aspect of the disease. In the descriptions given concerning treatment it will be noticed that details of surgical technique are deliberately omitted for they are described in contemporary literature. The present publication forms a strong foundation on which a superstructure can be erected in the future.

To execute the plan, the presentation of the various subjects was entrusted to a team of authors who have given liberally of their talents and time. A certain amount of overlap and repetition may at times be apparent to the reader; it is pointed out that these focal points are important and worthy of further study. It is in these conjoint areas that important clues may be found which will lead to further advances being made.

[1] Fuseli. Quoted by John Ruskin. *Modern Painters* (1896).

In my work as Editor I have been helped and encouraged by a number of my friends to whom I tender my thanks. It is with great pleasure I record my indebtedness and gratitude to all the authors; without their work and co-operation all would have been null and void. In the solution of a number of problems I was advised by G. M. Timmis, M.Sc. and J. W. Whittick, B.Sc., M.B., Ch.B., and I wish to thank them for their co-operation. Throughout my arduous task I have received constant help from Joan Gough-Thomas, M.A., to whom I express my gratitude for all she has done.

The final responsibility for this work is mine. It is offered as a contribution towards the solution of the cancer problem. I trust that my generation will experience the joy of entering the promised land and not die in the wilderness: "but to have desired to enter it, to have saluted it from afar, is already, perhaps, the best distinction among contemporaries, it will certainly be the best title to esteem with posterity."[2]

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[2] Matthew Arnold. *Essays in Criticism* (1865).

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CHAPTER 1

HISTORICAL ASPECTS OF CANCER

W. R. BETT

INTRODUCTORY

THE word "carcinoma" is derived from the Greek καρκίνος, meaning a crab. Its latinized form is "cancer", which occurs in Old English and was reintroduced into Middle English in the astronomical sense to denote the constellation situated between Leo the Lion and Gemini the Twins. It was used in the medical sense about 1600 as a more technical and definite term than "canker", which was loosely applied to corroding ulcerations. This medical usage was probably inspired by the large veins surrounding a malignant growth, which to the ancients suggested the claws of a crab, as witness the following quotation from Galen.

> "As a crab is furnished with claws on both sides of the body, so, in this disease [? cancer of the breast], the veins which extend from the tumour represent with it a figure much like that of a crab".

Paul of Aegina (A.D. 625–690) four centuries later repeats this comparison, but modifies it by adding the following.

> "However, some say that cancer is so called because it adheres with such obstinacy to the part it seizes that, like the crab, it cannot be separated from it without great difficulty".

In support of Paul's view Haddow (1936) mentioned the application of the term "crab" to various grasping tools whose invention was prompted by the crab's powerful chelae, but also recalled an intriguing alternative explanation, advanced by Louis Westenra Sambon, in the frequent parasitic association between crabs and the tumour-like *Sacculina carcini*. This parasite in the Cypris stage attaches itself to the body of a young crab and, after shedding "every part of its economy save a small bundle of all-important cells", enters the host and becomes the *Sacculina interna;* which proceeds to absorb nourishment by means of branching suckers extending like roots to every portion of the crustacean's anatomy.

Echoes are still heard of the fantastic superstition that there is a connexion between Cancer, the sign of the Zodiac, and cancer, the disease, for some people still believe that those born under that sign are predestined to die of cancer.

ANTIQUITY

Cancer is older than the literature of medicine. Its evil signature has been found on palaeopathological remains in distant parts of the globe. According to Moodie (1923), Esper of Erlangen in 1774 described in a cave bear of the Pleistocene (Glacial) period a lesion which he believed to be an osteosarcoma of the femur; later investigators diagnosed it as callus formation around a badly infected fracture.

Though the erudite German historian of medicine Karl Sudhoff doubted whether the ancient Egyptians were familiar with what we know as cancer, certain descrip-

tions in both the Edwin Smith Surgical Papyrus and in the Papyrus Ebers are suggestive of this disease. The former, written between 3,000 and 2,500 B.C. and published in 1930 in facsimile and hieroglyphic transliteration, with a translation and commentary by Breasted, records eight cases of "tumours or ulcers in the breast", which were treated by cauterization with the fire-drill, but gives the warning that there is no treatment for "bulging tumours". The Papyrus Ebers (1500 B.C.) likewise describes a tumour which must not be touched, for treatment might prove fatal. Smith, Elliott and Dawson (1924) refer to two cases of sarcoma of the head of the humerus found in the cemetery of the Gizeh Pyramids (Fifth Dynasty) and give an illustration of a large osteosarcoma of the femur.

The external manifestations of cancer were described by Hippocrates and his School, and their attempted classification of neoplasms still persists. Celsus (53 B.C.–A.D. 7) clearly differentiated malignant tumours from benign neoplasms and from inflammatory swellings.

AETIOLOGY

For centuries progress in the treatment of cancer was retarded by the doctrine of the four humours, with which the name of Galen will forever be ignobly linked. This bizarre genius, who even in his lifetime was regarded as infallible, continued from his grave to paralyse all original thought. He taught that people in whom black bile predominated were liable to develop tumours, as the bile tended to solidify in certain elective sites such as the lips, the breast, and the tongue. Cancer was thus an internal disease which had to be treated internally with purgatives. This theory was unchallenged for over a millennium. The Renaissance heard the first sound of the trumpet of revolt, but the time for Galen's dethronement was not yet. It remained for the Paris surgeon Henri François Le Dran to don the mantle of iconoclast. In a memoir published two hundred years ago (1757) he boldly rejected the humoral doctrine in favour of the theory that in its earliest stages cancer is a local lesion, that it spreads along the lymphatic vessels to the regional lymph nodes, and that it tends to recur. His teaching was based on personal observations in the post-mortem room, and his new lymphatic theory was a logical consequence of Harvey's discovery of the circulation of the blood and of Olaus Rudbeck's description of the lymph vessels.

To Bernard Peyrilhe (1735–1804) belongs the credit of being the first to conduct a systematic experimental investigation of the causation of cancer, in which he attempted to identify its toxin, to trace the spread of the disease, and to devise methods of treatment.

The eighteenth century also witnessed an important development in the history of cancer in England: in 1775 Percival Pott gave the first account of an occupational (chimney-sweeps') cancer when he published his *Chirurgical Observations Relative to the Cataract, the Polypus of the Nose, the Cancer of the Scrotum, &c*". At the turn of the century (1802) the foundation in London of the Society for Investigating the Nature and Cause of Cancer reflected the increasing attention being given to the disease. Four years later—by then the Society had ceased to exist—the *Edinburgh Medical and Surgical Journal* (1806) published the thirteen questions embodied in a list circulated in 1802 by the Society's medical committee. This list affords and interesting glimpse of contemporary ideas on the disease. The first question asks, "What are the diagnostic signs of cancer?" The others deal with

alteration in the structure of affected parts; whether cancer is a primary disease; hereditary aspects; whether it is contagious; "Is there any well-marked relation between cancer and other diseases"; "May cancer ever be regarded as a local disease?"; "Has climate or locality any bearing on its incidence?"; "Are brute creatures subject to any disease resembling cancer?"; "Is any period of life exempt from attacks of the disease?"; "Are the lymphatic glands ever affected primarily in this disease?"; "Is cancer, under any circumstances, susceptible of a natural cure?"

GROWTH OF PATHOLOGICAL KNOWLEDGE

In 1801 Xavier Bichat, without the aid of the microscope, clearly distinguished between the non-cancerous stroma and the cancerous parenchyma of a tumour. Récamier in 1829 drew attention to the tendency of cancer to develop in naevi, described invasion of the veins by cancer cells, and introduced the term "metastasis", which he applied to a nodule in the brain secondary to cancer of the breast. The microscope was used in the study of tumours by Sir Everard Home; whose book *A Short Tract on the Formation of Tumours* (1830) was the first to include illustrations of microscopic sections of cancer. His researches, however, failed to shed any light on the problem of malignant disease. Infinitely more fruitful were the investigations of Johannes Müller whose monumental work *Über den feinern Bau und die Formen derk krankhaften Geschwülste* appeared in 1838. Müller showed remarkable knowledge, far in advance of his time, of the various types of tumours, which he distinguished microscopically, and he described anaplasia as a frequent feature of malignant cells. His awareness of the importance of the cell theory to cancer research made his book one of the most stimulating contributions to the subject, and helped to clear the way for later investigators, who began to appreciate that cancer is fundamentally an abnormal growth of abnormal cells. Adolph Hannover coined the word "epithelioma", which he used in his book *Das Epithelioma* (1852), but failed to recognize its malignant character and thought that metastases were produced by cancer cells travelling along the blood stream.

Rudolf Virchow was only 26 years of age when he founded the famous *Archiv* that bears his name, and to the first volume published in 1847 he contributed an important article on cancer, in which he suggested that its exciting cause was local irritation. In his three-volume work on tumours, *Die krankhaften Geschwülste* (1863–67), he propounded his theory of the connective-tissue origin of carcinoma. In 1865 Carl Thiersch of Erlangen in his book *Der Epithelialkrebs namentlich der Haut* disproved this theory by producing evidence in favour of the epithelial origin of cancer, and his findings were confirmed 2 years later by Waldeyer-Hartz (1867). So overwhelming, however, was Virchow's reputation at the time that it was not until the publication of Waldeyer-Hartz's second paper in 1872 that the connective-tissue theory was finally accepted as erroneous. In 1877 Julius Cohnheim advanced the theory of misplaced embryonal rests, of which Ribbert (1905) became the modern protagonist.

Experimental work

The nineteenth century saw much experimental work. In 1851 Joseph Leidy of Philadelphia reported the first experimental transplantation of a malignant tumour.

Arthur Nathan Hanau in 1889 was the first to transplant cancer in rats successfully. This technique was developed by Carl Oluf Jensen who in 1903 succeeded in carrying a mouse cancer through nineteen generations of grafts without any alteration in its microscopic structure and who discredited the theory of the infectivity of cancer.

Bacteriological research on cancer was conducted by Russell (1890) who described small spherical fuchsin bodies ("Russell bodies"), which are now known to possess no aetiological significance. In 1910 Francis Peyton Rous demonstrated the transmissibility by cell-free filtrates or desiccates of chicken sarcoma ("Rous sarcoma"). In 1907 Johannes Fibiger began to suspect an association between tumours in the stomach of rats and a nematode, which he named *Spiroptera neoplastica*. He found these papillomas to be common among rats infesting a Copenhagen sugar refinery abounding in cockroaches feeding on the rats' excreta. The cockroaches swallowed the eggs of the parasitic maggots which developed into larvae; the rats ate the cockroaches, and the late stages of the maggots' development were completed in their bodies. Fibiger then fed the larvae-containing cockroaches to healthy rats and was able to produce tumours in their stomachs. His claim that organically sound cells can thus be changed to cancer cells and that maggots are the cause of cancer is today of historic interest only.

CARCINOGENS

In 1912 Bayon produced cancer experimentally by injecting tar into the ears of rabbits, and 4 years later Yamagiwa and Ichikawa repeated this demonstration by painting the skin of rabbits for a number of months with tar products. In 1925 William Ewart Gye submitted evidence which suggested that the combination of an intrinsic chemical factor with an ultra-microscopic virus was concerned in the development of the Rous sarcoma. His theory was supported in the same year with the aid of photomicrographs by Joseph Edwin Barnard.

Carcinogenic compound in coal tar

The account of the identification of a carcinogenic compound in coal tar is given by Kennaway (1955). He first attempted to identify the cancer-producing compound in coal tar in 1922, when he joined the staff of the Research Institute of the Cancer Hospital (Free), now the Royal Marsden Hospital. Two years later he showed that gasworks pitch, heated to 500°C, gave a strongly carcinogenic distillate, and he obtained cancer-producing products by heating to 700–900°C in an atmosphere of hydrogen petroleum, isoprene, acetylene, cholesterol, yeast, and human skin, hair, and muscle. Mayneord (1935) discovered a characteristic spectrum of the fluorescent light of various carcinogenic products, chiefly derived from coal tar, and later was joined in this work by Hieger. They obtained the identical spectrum from a carcinogenic mixture of wholly different origin, namely the products of the action of aluminium chloride on tetralin, and a very similar spectrum from one only of a large number of hydrocarbons—1 : 2 benzanthrace. This was the key which opened the way to the eventual solution of the problem. In 1929 Goulden prepared the first synthetic carcinogens—1 : 2 : 5 : 6-dibenzanthracene and its 3′-methyl derivative.

Hieger carried out a very laborious fractionation of distillates obtained from 2 tons of pitch, using the fluorescence spectrum as the guide in the gradual concentration of the active constituent, the process being checked by tests on mice. Hieger and Hewett made a series of fractional crystallizations of the picrates prepared from the distillate of pitch, and Cook isolated two essentially pure crystalline products, which were hydrocarbons rich in carbon. Cook and Hewett showed that synthetic 3 : 4-benzpyrene was identical with the strongly fluorescing major component of the crystals obtained from pitch distillate, that the synthetic preparation was also highly carcinogenic, and that the synthetic 1 : 2-benzpyrene was identical with the minor component of the original crystallate.

HORMONES AND CANCER

Much attention has been given in recent years to the relation between hormones and cancer. In 1916 Lathrop and Loeb demonstrated that spaying of newborn mice belonging to a strain highly susceptible to cancer of the breast almost completely abolished their liability to this disease. Lacassagne in 1932 and Burrows in 1935 showed that persistent administration of oestrogen produces mammary cancer in mice. The neoplastic effects of oestrogen are fully discussed by Burrows and Horning (1952). Hormonal therapy of malignant disease was born in the fertile brain of the great John Hunter who noted that castration resulted in progressive atrophy of the prostate—an observation on which subsequent attempts at curing prostatic enlargement by castration were based. The idea, long abandoned, was successfully revived in 1940 by Huggins in the treatment of prostatic cancer. In 1896 Sir George Beatson of Glasgow introduced bilateral oophorectomy and the administration of thyroid extract for the treatment of advanced cancer of the breast. Raven (1950) recounted the experience of early and recent workers with this treatment and pointed out that Beatson had shown real insight when he said "we must look in the female to the ovaries as the seat of the exciting cause of cancer, certainly of the mammae". Oophorectomy is now an important method of treatment in cancer of the breast.

The history of cancer chronicled thus far is the history of errors, of illusions, of disappointments, of occasional triumphs. The smile of the Sphinx continues inscrutable.

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CHAPTER 2

THE INCUBATION PERIOD OF CANCER IN MAN

E. L. KENNAWAY

THIS chapter is intended to suggest questions rather than to answer them. We do not know many simple things about cancer as it occurs in man and these questions are not yet elucidated by the physical and chemical investigations which are in progress upon the fundamental nature of malignant growth, which is a problem of cell division.

No attempt has been made to collect all the scattered data in the literature, but the following notes may suffice to show the wide range of the incubation period.

CANCER OF THE PENIS IN RELATION TO CIRCUMCISION

Cancer of the penis is unknown among Jews who circumcise on the eighth day (Kennaway, 1947); it occurs among Moslems who carry out the operation chiefly between the third and fifteenth years, but we have no information about the time-relations of these cases, namely the interval between circumcision and the development of cancer. These data are available only from cases of surgical circumcision, of which sixteen are represented in Fig. 1 (Dean, 1935; Lewis, 1931; Lenowitz

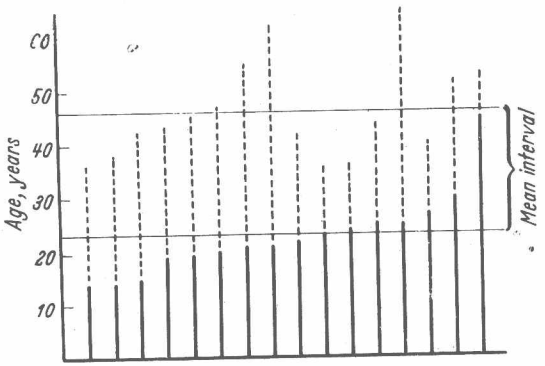

FIG. 1.—Sixteen cases of cancer of the penis following surgical circumcision, in ascending order of age at the time of this operation. The interrupted lines represent the interval between the operation and the diagnosis of cancer.

and Graham, 1946). The figures show a wide range; the average age, from 14 onwards, at circumcision is 23, and the average age when cancer develops is 46, or 23 years later.*

* Henry (1946) recorded a case of occupational cancer of the scrotum in which the time intervals happen to be the same as these mean figures—"a managing director of a cotton mill for 23 years who had been a cotton mule spinner previously for 23 years".

Our ignorance of the changes in progress during the incubation period of cancer is expressed very well by Dean's comment: "In the years following circumcision none of these men had cause for thinking that anything was wrong until a tumor began to grow" (Dean, 1935).

Table I gives the data which are shown graphically in Fig. 1. Those of Dean, and of Lewis, are separated from those of Lenowitz and Graham. The averages of the two series are very similar, which suggests that the cases, though only 16 in number, provide a reasonable basis for study.

TABLE I

INTERVAL BETWEEN CIRCUMCISION AND APPEARANCE OF CANCER OF THE PENIS

Author	*Age at time of circumcision*	*Age when cancer appeared*	*Interval (years)*
Dean	14	38	24
	19	43	24
	20	47	27
Lewis	21	62	41
Dean	23	36	13
	25	65	40
	25	44	19
	45	53	8
Average	24	48·5	24·5
Lenowitz and Graham ..	14	36	22
	15	42	27
	19*	45	26
	21	55	34
	22	42	20
	24	36	12
	27	40	13
	30	52	22
Average	21·5	43·5	22
Average of all cases	23	46	23

* Negro.

As none of these cases would have occurred if the operation had been carried out in early infancy, as in the Jewish method, it must be inferred that the train of events leading to malignant growth was set going in earlier life, and that removal of the cause did not avert the appearance of cancer at a much later age. This may hold good also for other forms of cancer. Thus cancer of, for example, the stomach, arising after the second 25 years of life, may be predestined to occur by factors to which the body was exposed during the first 25 years after birth. The juvenile death-rate draws attention only to the children who die, whereas others may survive injury by adverse conditions of which the effects appear later in life.

Stocks (1953) describes such a process in a study of cancer of the stomach and states "These cohort death rates can be arrived at mathematically by supposing that a total of 5 years with exposure to some carcinogenic substance or influence

is necessary to initiate the cancerous process, that the average risk of such exposure occurring in England and Wales in any year is about 1 in 30 for males and 1 in 37 for females, and that after such exposure about 18 years elapses on the average before death occurs, with considerable dispersion around that interval for individuals".

LATENT CANCER AND CARCINOMA *IN SITU*

The term "incubation period" presupposes a definite beginning, whether we can or cannot ascertain when this occurs, but in some forms of cancer even this "beginning" is difficult to define. Thus before the concept of "carcinoma *in situ*" was developed, cancer of the cervix uteri was regraded as an invasive disease and an irreversible one. Now, it is established that early intra-epithelial, or pre-invasive, stages may exist for years before the lesion either invades, or reverts to normal.

"Undoubtedly all intra-epithelial lesions do not progress to invasive cancer. The average age of patients with carcinoma *in situ* is about 10 years less than that of patients with invasive cancer, the average age varying from 38·7 to 46·9 years. The greatest number of cases of carcinoma *in situ* occur at about age 40." (Payne, 1955). Similar pre-invasive carcinomas occur in the prostate, and have been described recently in the mammary gland and in other organs.

The literature relating to latent prostatic cancer has been summarized by Edwards, Steinthorsson and Nicholson (1953) who recorded their observations upon the occurrence of these cancers in two series of autopsies on males aged 40 years and over, the incidence being 14·8 per cent in 81 cases, and 16·6 per cent in 173 cases. These percentages are similar to those found by many earlier observers.

This incubation period of cancer is by no means an academic subject. The same problem is presented by a person who, having smoked say, 30 cigarettes a day for 30 years, asks whether his chance of developing bronchogenic carcinoma is affected by abstention from smoking now? The great range of variation in such biological matters makes it impossible to give a satisfactory answer to this question.

INDUSTRIAL CANCERS AS A SOURCE OF DATA ON THE INCUBATION PERIOD OF CANCER

Every form of industrial cancer presents two subjects for numerical study: (1) the incidence upon those exposed, and (2) the duration of exposure, and the whole incubation period before cancer begins. The term "incubation period" (Table IX) is used here to denote the time of exposure, and of any interval after it, before neoplasia begins (see also Fig. 1).

Cancer of the skin due to tar and pitch, and to mineral oil

The pioneer work on the incubation period was that of Henry (1928) on mule-spinners which in 1946 was expanded into a monograph embodying the results of 30 years' experience of factory inspection. These figures are summarized, as far as cancer of the skin is concerned, in Fig. 2. The data, from a total of 3,054 cases, included innocent and malignant tumours; this is the best method as the exact time of the transition from the former to the latter is never likely to be known. The numbers show a very wide range; the maximum development of tumours due

to pitch and tar occurs in the quinquennium 20–24 years, and of tumours due to shale and mineral oil 50–54 years. Hence the selection of any one period to represent the incubation period of cancers in general in man is very arbitrary.

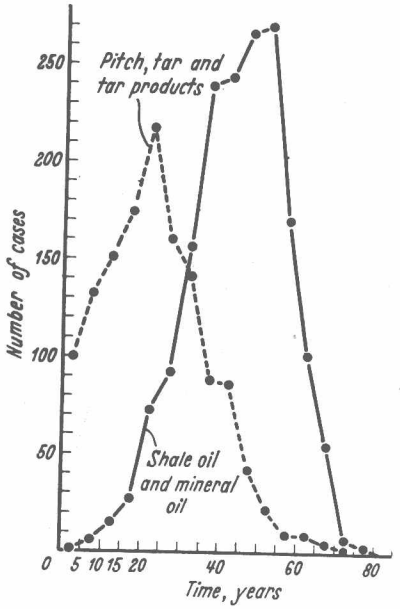

FIG. 2.—Time elapsing from the onset of employment to manifestation of a cutaneous papilloma or epithelioma in 1,335 persons in contact with pitch, tar, or tar products compared with 1,719 in contact with shale oil, or mineral oil (Henry, 1947).

The data quoted below are not of very recent date but cases of the same type occur today. Thus the Annual Report of the Chief Inspector of Factories for 1954 records three fatal cases of cancer due to pitch and tar, as follows:

Nature of occupation and duration in years	*Age at death*	*Length of retirement before death (years)*	*Site of lesion*
Gas works labourer for 28 years	78	6	Face
Gas works labourer for 15 years	79	2–3	Left thigh, scrotum and face
Gas works retort-house stoker for 45 years	78	13	Scrotum

Henry comments upon the data collected in Fig. 2, as follows: "The shortest recorded time elapsing after starting work in pitch or tar was approximately 1 year, or even less for a papilloma, the longest being 73 years (including 25 years after retirement). The shortest time elapsing after starting work in mineral oil was 4 years and the longest 75 years, including many years of retirement." In the case of long intervals of more than 70 years, the possibility that the neoplasm is not occupational in origin must be considered.

Cancer of the scrotum in mule-spinners

Henry (1946) collected about 1,200 cases dating from 1887 onwards. In the early years boys started work in the mule-room at the age of 8 or 10 years. One man who had begun in 1866, at the age of 6, developed cancer of the scrotum when aged 75 and after 10 years of retirement. The graph (Fig. 3) represents the years of exposure in 893 of these cases which occurred since 1920, when mineral oil had been on the market for 60 or 70 years. The greatest number of cases occurred

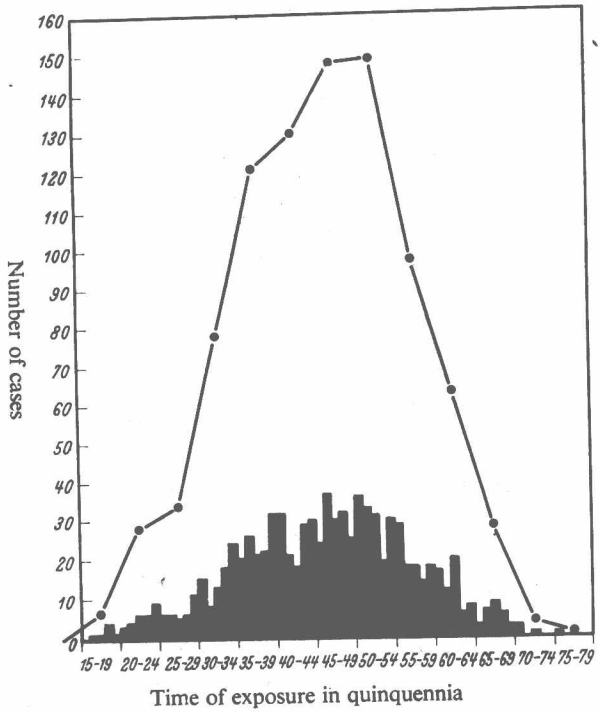

FIG. 3.—Time in quinquennia from beginning of employment to appearance of a papilloma or carcinoma of the scrotum after 1920 in 893 cotton mule-spinners (Henry, 1947).

about 50 years after beginning work; 92 men had retired or been out of work for periods of up to 20 years after from 20 to 67 years in the mule-room. The minimum period of exposure was 16 years in 2 men aged 28 and 30 years respectively. The longest interval after exposure was in the case of a man who, after 28 years in the mule-room, became a trade-union secretary for 44 years when the disease appeared 3 years before death.

Occupational cancer of the bladder

Gross (1940) reported upon 82 cases of bladder cancer occurring in his experience in 60 years in the employees of the I.G. Farbenindustrie in Germany. The number of such cases at a later date was between 300 and 350 (Goldblatt, 1949). Gross summarized his data as is shown in Table II.

TABLE II

OCCUPATIONAL CANCER OF THE BLADDER

(*Gross*, 1940)

Number of cases exposed to—	
Aniline 33 β-Naphthylamine 36 Aniline + β-Naphthylamine 13	82
Shortest exposure	6 months
Longest interval between cessation of exposure and beginning of illness	34 years
Other such intervals—	
One case	33 years
Nine cases	over 15 years
Nine cases	10–15 years
Maximum incidence at age	50–55 years
Youngest patient, age	25 years

Goldblatt (1949) reported upon 100 cases of tumour of the bladder occurring in two factories in Great Britain in the period 1934–47. The data are shown in Table III.

TABLE III

PERIOD BETWEEN EXPOSURE AND DEVELOPMENT OF OCCUPATIONAL BLADDER TUMOUR

(*Goldblatt*, 1949)

Period of years from first entry into industry till first discovered tumour	*Numbers*
1– 5	1*
6–10	12
11–15	26
16–20	27
21–25	20
26–30	7
31–35	3
36–40	1
41+	3
	100

Mean period : 18·95 years. Mean age at recognition : 50·5 years.

* Worked with β-naphthylamine 2 years only, developed papilloma of bladder 2 years later, recurrence 20 months ater after fulguration.

Cancer of the bladder occurred in one third of those who worked with β-naphthylamine for more than 5 years, yet the age at death is lowered in comparison with that of the population in the neighbourhood (presumably from cancer of the bladder) "by only a few years". Evidently this is the phenomenon referred to on p. 13.

CANCER DUE TO X-RAYS

Carcinoma of the skin

The year of Röntgen's discovery (1895) sets a limit for exposure to a new carcinogen which is lacking in the case of cancer of the scrotum in mule-spinners, where the time of transition from animal to mineral oils is uncertain (Henry, 1947).

Hesse in 1911 collected from the literature records of 94 cases of carcinoma of the skin following exposure to x-rays; from these he selected 54 as certainly of the nature in question (4 in patients, 26 in physicians, 24 in technicians). The numerical data are summarized in Table V.