Translated from Danish
by
A. Rousing.

HEREDITY IN CANCER UTERI

A Genetical and Clinical Study
of 200 Patients with Cancer of the Cervix Uteri and
90 Patients with Cancer of the Corpus Uteri

BY

OLAF BRØBECK

UNIVERSITETSFORLAGET I AARHUS
1949

Denne afhandling er af det lægevidenskabelige fakultet ved Københavns Universitet antaget til offentlig at forsvares for den medicinske doktorgrad.

København, den 3. oktober 1949.

J. Engelbreth-Holm,
h. a. dec.

Printed in Denmark
by
Aarhuus Stiftsbogtrykkerie A/S

PREFACE

The investigations presented here were carried out during the years 1943—47 at the University Institute for Human Genetics, Copenhagen, in collaboration with the Danish Cancer Registry.

I am greatly indebted to the head of the University Institute for Human Genetics, Professor *Tage Kemp*, M.D. He inspired this work and helped me greatly with his unfailing interest, encouragement, and by provision of the excellent working facilities at the Institute. I also wish to express my appreciation to the office staff of the Institute, especially Misses *Krebs*, *Ulla Nielsen*, and *Bente Jørgensen*, for their prompt and amiable assistance.

I owe a great debt of gratitute to the Director of the Danish Cancer Registry, *Johs. Clemmesen*, M.D., who in numerous profitable conversations has given me invaluable advice and assistance both in theoretical and practical problems.

I am also greatly indebted to the statisticians of the Cancer Registry, *Th. Busk*, Actuary, and *Arne Nielsen*, cand. act., who with great patience assisted me in the preparation of the statistical section of this volume and made helpful criticisms with regard to the tables.

I wish to express my appreciation and thanks to the head of the Radium Centre in Copenhagen, Dr. *Jens Nielsen*, for his kind permission to make use of material from his hospital, from which the majority of my patients has been taken. My gratitude is due to the chiefs of some of the hospital departments of Greater Copenhagen, from which the rest of my patients has been collected, and to Professor *E. Dahl-Iversen*, M.D., and Professor *S. Kjærgaard*, M.D., from whose departments in Rigshospitalet the control persons collected by me were chosen.

I wish to express my obligation to *Aa. Videbæk*, M.D., for his kind permission to make use of his control series, which he had collected for his investigations on heredity in leukemia.

The confidence and understanding which the patients and their relatives have shown have greatly surpassed my expectations.

My investigations have been aided by grants from the Danish National Anti-Cancer League, for which I offer my heartfelt thanks.

Finally, I wish to give particular thanks to my wife, *Karen Brøbeck*, for her great help with the vast amount of correspondence and for her irrepressible optimism — even when attainment of the aim seemed farthest away.

Århus, december 1949.

Olaf Brøbeck.

CONTENTS

INTRODUCTION

While a number of exogenous factors has been mentioned as possibly significant in the development of *uterine cancer*, few previous publications have been aiming at ascertaining to which extent and in which way hereditary factors may influence the development of human uterine cancer.

The object of the present volume has been to elucidate this problem, parallel with similar investigations already published on heredity in breast cancer (*Jacobsen*, 1946), and leukemia (*Videbæk*, 1947).

Relatives of two hundred patients with *cancer of the cervix uteri* and of 90 patients with *cancer of the corpus uteri* and of a corresponding number of control persons in the same age groups have been subjected to a thorough statistical-genealogical investigation comparing the incidences of uterine cancers and other forms of cancer in the groups of relatives in order to ascertain a possible hereditary difference between cancers of the cervix and the corpus. Furthermore, cancer risks have been computed as the basis of an evaluation of the hereditary behaviour of these diseases, and unlike the publications mentioned the present volume gives the cancer mortality figures for the entire Danish population as the basis of comparison.

Corresponding computations for the control groups show that this method gives good results. However, as far as the categories of more distant relatives are concerned, there proved to be some discrepancies, which have necessitated corrections.

Pedigree charts and case records have been lodged at the University Library II, Copenhagen, where they can be inspected.

Chapter I.

EARLIER PUBLICATIONS ON HEREDITY OF HUMAN CANCER WITH A SPECIAL VIEW TO CANCER OF THE UTERUS

For many years both the medical profession and laity have concerned themselves with the familial occurrence of cancer, but after the rediscovery of the Mendelian laws in 1900 cancer research went into a new phase. The road was now open to genetic studies on cross-breeding and transplantation experiments and to investigations of the influence of carcinogenic, hormonal, and other substances on experimental animals with a known genetic structure.

Heredity in experimental animals is rather complex and difficult to disentangle, but the difficulties become far greather when it is attempted to disentangle heredity in man.

As emphasized by *Wassink* (1935), these difficulties are:

a) *There is no possibility of experiments.* It goes without saying that in man it is impossible to obtain conditions similar to those in experimental animals where constant inbreeding may lead to a genetically identical material. Since cancer is predominantly a disease of middle and late life and is not related to other hereditary criteria, there will, as far as tumour characters are concerned, be a completely free choice of partner.

b) *The life span of a generation is long.* Only a few children are born in each family. It will rarely be possible to obtain reliable information of more than four generations.

c) *Most varieties of cancer show a high incidence.* This makes it more difficult to ascertain a hereditary predisposition than if cancer had been a rare disease.

d) *Cancer rarely manifests itself until at an advanced age,* for which reason a number of individuals die from other causes before they reach the cancer age, and several members of a family now alive will develop cancer at a later age.

The methods used in the investigations on heredity in man are the following:

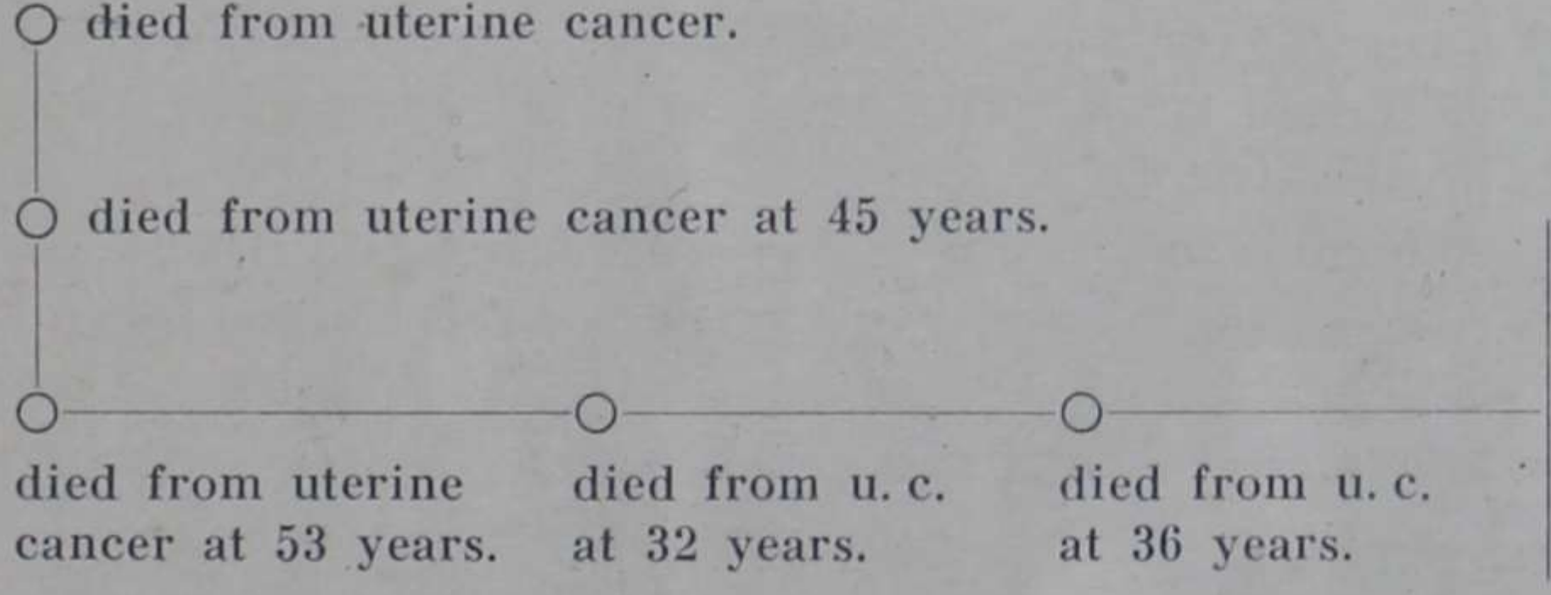
1) Study of family pedigrees.
2) Study of mass and population statistics.
3) Study of propositi (i. e. family histories of patients).
4) Study of twins.
5) Study of multiple tumours.

The study of family pedigrees is the oldest of these methods. Numerous pedigree charts have been published, showing partly tumours of the same variety and localization, and partly different types of tumours. *Jacobsen* (1946) collected from the literature a number of examples of familial occurrence of breast cancer. Most of these investigations are now essentially of historical interest. It is, however, worth mentioning that adenocarcinomata predominate in the studies of pedigrees reported (emphasized by *Schinz & Buschke*, 1935).

A number of reports on familial occurrence of *cancer of the uterus* has been published:

Paget (1851): Uterine cancer in mother, daughter, and granddaughter.

Roger Williams (1898):



In "The Natural History of Cancer" by *Roger Williams* (1908) some older reports are collected:

Athil (1876): A woman (28 years), her mother, and two sisters died from uterine cancer.

Guthmann (1888): Three sisters with cancer of the corpus uteri.

Veith (1902): Two sisters died from cancer of the cervix uteri.

Cullen (1901): Three sisters with uterine cancer.

Pean (1895): Cancer of the corpus in grandmother, mother, and daughter.

Hutchinson (1901): Grandmother, mother, two maternal aunts, and two sisters all died from uterine cancer.

More recent reports:

Auvray (1927): Grandmother, mother, and daughter died from cancer of the corpus uteri.

Purdie (1944): Cancer of the corpus in two sisters, one 34 years, multipara; the other 32 years, nullipara. (The family consisted of 10

siblings; a sister died from meningitis at the age of 10 months; the others are alive and healthy. The mother died from rectal cancer, two uncles from cancer of other organs).

In Denmark *Otto* (1900) found by a review of the case records of 161 cases of uterine cancer information of familial cancer taint in nine patients with cancer of the cervix, in whose family there were three cases of (unspecified) uterine cancer, the two cases in sisters, the third in a grandfather's sister.

In one case of cancer of the corpus it was stated that the patient's mother had died from uterine cancer.

Fibiger & Trier (1910) reported two cases of uterine cancer in the same family, in one instance in mother and daughter, in the other in two sisters.

In both instances the disease occurred in patients who had for a long time lived together, a fact which was taken as suggestive of infection.

A very comprehensive pedigree was analyzed by *Warthin* (1913 and 1925).

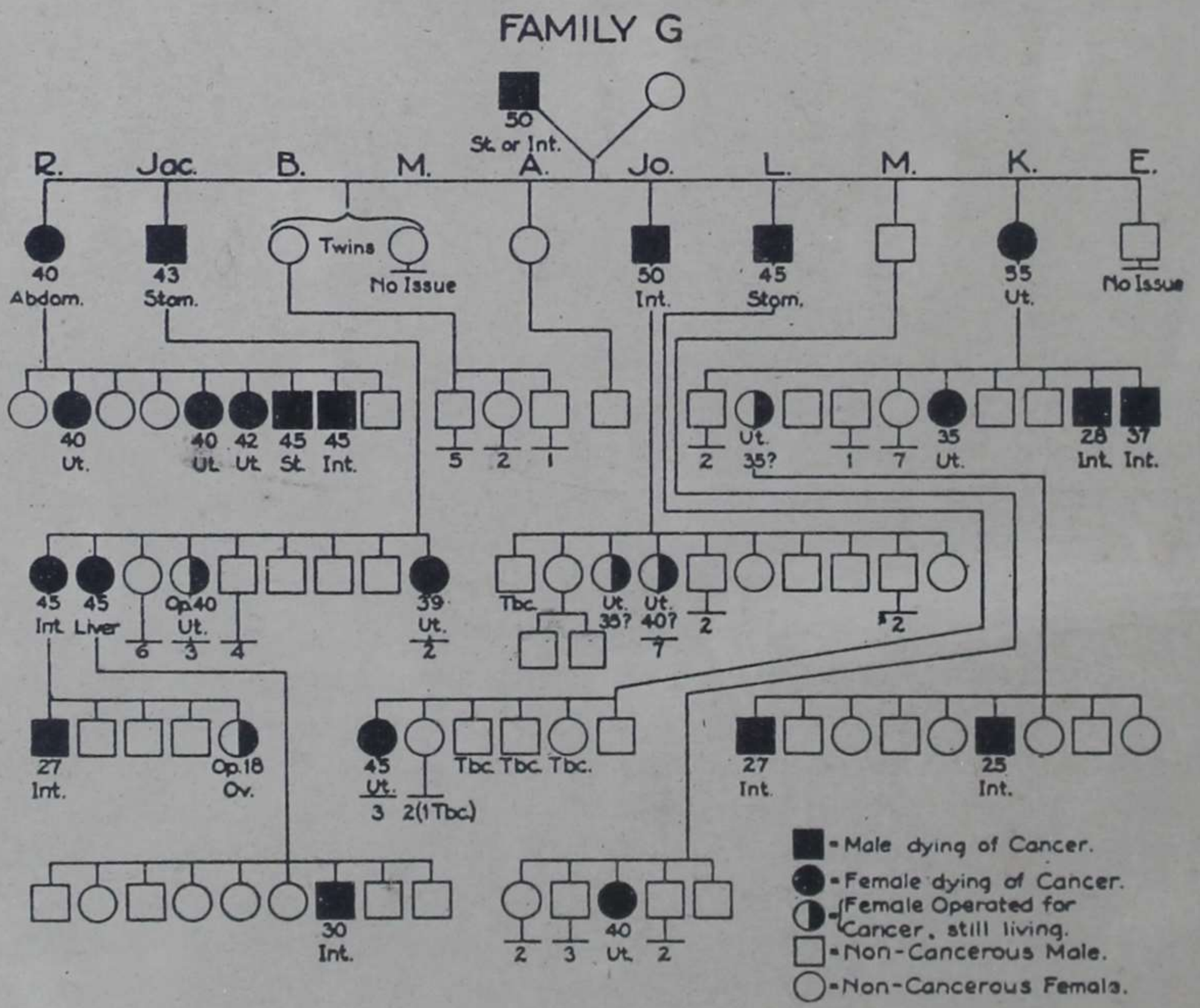


Fig. 1.
Warthin's family "G".

The family "G" was carefully followed from 1913 to 1925. *Warthin* knew the family well, and several of its members were able to give satisfactory information. He examined a large number of the specimens removed by operations and performed several autopsies on members of the family.

The family comprised 146 members, of whom 28 died from cancer, i. e. 19.18 per cent. If 58 children are disregarded, it is 28 out of the 88 that reached the lowest cancer age; this gives an incidence of cancer of 31.81 per cent. Warthin concluded that these findings are in favour of the presence of a recessive familial susceptibility to cancer which in males involves the gastro-intestinal tract and in females predominantly the uterus. The cases of uterine cancer subjected to microscopical examination showed adenocarcinoma.

This family was followed up to 1936 by *Hauser & Weller*. At that time 174 members had reached an age of 25 years or more. There were 43 malignant neoplasms in 41 members, with two exceptions all involving the gastro-intestinal tract and uterus. Twenty cases of male cancers were localized to the gastro-intestinal tract. Fifteen out of twenty-three cases of female cancers were localized to the uterus. All of them were adenocarcinomata of the endometrium, and there was no evidence of cervical origin in any instance.

Warthin's pedigree chart shows that cancer may be transmitted partly direct from generation to generation, partly indirect by skipping a generation.

This is an example of accumulation of carcinomata of different histogenesis and localization.

Attempts at a closer genetic analysis cannot be successfully accomplished, inter alia, because only one of the parents in each generation is known. The chart shows that a pronounced anticipation is present, i. e. the cancer cases occur at an increasingly early age in the younger generations.

Cholewa (1932) has published two family pedigrees showing a hereditarily determined localization of the cancer.

In one of the families the mother had cancer of the uterus, the father cancer of the stomach. They had eight children, two of whom died before the cancer age. A surviving son died at the age of 56 from gastric cancer like his father, three of five daughters died from uterine cancer.

In the other family the mother developed uterine cancer at the age of 70, unilateral breast cancer at 71, breast cancer in the other side at 72, from which she died. At the age of 73 the father died from apoplexy. Two sons were cancer-free; of ten daughters three died from uterine cancer, one from ovarian cancer, all about the age of 55, and two died from breast

cancer. It is thus seen that five of the daughters died from cancer of the same organ as the mother.

By means of pedigree charts for 168 propositi *Schinz, Cocchi & Neuhaus* (1948) have approached the problem of heredity in human cancer. The 168 propositi suffered from the following diseases:

Carcinoma	87	propositi
Sarcoma	15	—
Leukemia	22	—
Hodgkin's disease	20	—

and the following served as controls:

Tuberculosis	12	propositi
Arterial hypertension	12	—

Of the *144 propositi with malignant tumours.*

63 cases were localized to the respiratory and alimentary tracts,
19 to the female genitals (16 to the breast),
20 were carcinomata elsewhere or sarcomata,
22 suffered from leukemia, and
20 from Hodgkin's disease.

The pedigree charts comprise the following categories of relatives: children, grandchildren, parents and their sisters and brothers and offspring, grandparents on both sides, their sisters and brothers, and great grandparents.

These very extentive pedigree charts — often with information of 5—6 generations — comprise 25,469 persons (it was impossible to obtain information of 11.4 per cent. of them). The elaboration of these charts extended over several years and required a detailed study of family registers in which the various data of the members of the families could be found. The causes of death were sought in records from hospitals and pathological institutes, or in death certificates, whereas the propositi and their relatives were not interrogated.

An analysis of the pedigree charts shows:

The frequency of malignant tumours is almost the same among the families of the propositi and the controls. About 50 per cent. of the families of each group were "cancer families", i. e. with malignant tumours. The familial occurrence was almost invariably localized either to the father's or mother's family.

The average frequency of carcinomata in relatives reflects — with the exception of relatives of sarcoma patients in whom the carcinoma mortality is demonstrably lower — the frequency of carcinomata in the population in general.

If *the individual categories of relatives* are considered, it will be found (1) that the frequency of carcinomata is increased only among close relatives (sisters, brothers, and parents) of the propositi with carcinomata, (2) that the frequency of carcinomata is lower among more remote relatives than among the relatives of the controls, and (3) that the frequency of carcinomata is on the whole lower among relatives of propositi with sarcoma. The relatives of propositi with other malignant tumours (sarcomata, leukemia, and Hodgkin's disease) and relatives of propositi with tuberculosis or arterial hypertension show the same frequency of cancer as the population in general.

These facts — so *Schinz* says — militate against the supposition of a general disposition to malignant tumours in man, but are in favour of the presence of a disposition to one type of tumour, i. e. carcinoma. It is impossible to decide whether adenocarcinoma is more likely to be genetically determined than squamous-cell carcinoma. A hereditary localization factor could not be demonstrated. In relatives of propositi with cancer of the female genitals it was possible to demonstrate that the inheritance tended to be transmitted in the maternal line; in leukemia patients the tendency to malignant tumours seems — in contrast to the experience gained in animal experiments — to be transmitted in the paternal line.

Schinz draws rather comprehensive conclusions from his carefully elaborated pedigree charts. He mentions, but scarcely emphasizes sufficiently the difficulties and uncertainty involved in ascertaining the causes of death in the older categories of relatives where an appreciable number of cancer deaths *cannot* be found, and in his comparatively small controll groups he has not attempted to provide a sufficiently convincing basis for comparison*).

Analyses of pedigrees can only be said to be of some importance in the study of cancer if information is available of all the members of the family groups (also with regard to age and sex) together with sufficient registration of deaths due to cancer, preferably accompanied by reports on autopsies and microscopical examinations. These are the ideal requirements which *Wells* (1923) drew up as indispensable for all cancer statistics.

Like the analyses of pedigress, *mass and population statistics* have also been unable to give a satisfactory reply to the question of heredity in human cancer.

---

*) *Otto Lentz* (Fischer, Jena, 1947) has studied 375 genealogical tables of families, among the members of which benign and malignant tumours and hereditarily determined diseases had occurred. He expresses the opinion that the majority of tumours occurs as a result of an interaction of exogenous factors and an impairment of the organism, particularly of its endocrine system, but that a large proportion of cancer cases is due to a hereditary tumour disposition, which is much more frequent than previously assumed.

The first of these often very comprehensive investigations, in which it was attempted to explain the problem of heredity in cancer on the basis of statistics, appeared in the end of the eighteenth century, and a large number of reports has been reported right up to the present time. (*Recamier* (1829), *Velpeau* (1854), *Paget* (1851), *Verneuil* (1884), *Poulsen* (1890), *Fabre* (1892), *Fibiger & Trier* (1910), *Bashford* (1908), *Levin* (1912), *Deelmann* (1931), *Little* (1923), *Waaler* (1931), and *Hanharte* (1943)).

In his monograph on heredity in breast cancer *Jacobsen* (1946) deals with most of these reports.

In his well-known, very comprehensive study *Waaler* arrives at the conclusion that hereditary disposition constitutes part of the etiology of cancer (except for lip cancer) and is conditioned by two mutually independent genetic factors.

Heredity in cancer of the uterus has not been investigated separately, but has been dealt with together with cancers of the breast and ovary. According to *Waaler* it is, however, probable that a hereditary localization factor exists in these diseases, since the same form of cancer is often encountered in sisters of the original patient.

Table 1.

Some older reports on hereditary taint in cancer of the uterus collected by *Wolff* (1911).

Author	Year	Number of cases	Number of cases with taint	Per cent.*)
Lebert	1857	13	2	15
Sibley	1859	135	8	6
Barker	1870	487	36	7
Gusserow	1871	326	34	10
Roger Williams	1884	132	32	24
Cullen	1900			19

*) The percentages have been calculated by the author.

Wolff (1911) collected a number of older reports discussing heredity in cancer of the uterus.

On the basis of 940 cases of cancer of the cervix uteri *Henriksen* (1935) found hereditary taint (close relatives died from cancer) in 14 per cent.; in a control group collected along similar lines and comprising 500 persons hereditary taint was found in 11.5 per cent. *Henriksen* regarded the value of these figures as doubtful because it was difficult to obtain accurate genealogical data.

Crabtree (1941), in an examination of the parents, sisters, and brothers of 152 patients suffering from cancer of the cervix uteri, found 1½ times as many cancers as expected according to mortality statistics. Similar

figures were found for breast cancer; for skin cancer twice the number expected was found.

In 1942 *Hurdon* analyzed the familial taint in 1224 cases of cervical cancer. She found familial taint in 324 cases; in 40 it was (unspecified) uterine cancer, in 41 cases breast cancer. From this analysis *Hurdon* drew the following conclusion: Even though these statistical investigations have only limited value, they suggest a general disposition to cancer, but not the presence of a localization factor, and even if such a localization factor might exist, also other factors seem to be of decisive importance in the development of cancer and in the determination of its site.

These figures are of limited value only, since it has neither been stated in which way information was collected, nor on which diagnostic criteria the material was based.

Study of propositi (i. e. family histories of patients) is of more recent date. An outstanding example is the important study of *Wassink* from 1935. As in breast cancer the number of relatives of patients with uterine cancer ("rendement homotrop") was larger than the percentage of this site of cancer in the population in general (45 and 10—12 per cent. respectively); as far as skin and lip cancers were concerned, the taint in relatives was not increased.

These findings suggest that heredity plays a rôle in the development of mammary and uterine cancers, and *Wassink* presumes that it is a question of predisposing hereditary factors.

One of the most important observations in *Waaler*'s and *Wassink*'s studies is the definite genetic difference between cancers of different sites.

Wassink advances the hypothesis, which cannot, however, be definitively substantiated, that in addition to a localization factor in cancer, which has been distinctly demonstrated in breast cancer, there may in certain families be a disposition of the tissues to cancer, both of squamous-cell and of cylindrical-cell epithelia.

It is possible, *Wassink* writes, that cancer of the corpus of the uterus may be equivalent to cancer of the alimentary tract in men.

While investigations of propositi have been used in the study of heredity in breast cancer (*Lane-Claypon*, 1926; *Wainwright*, 1931; *Martynowa*, 1937), apart from *Wassink*'s investigations, they do not seem to have been employed in the study of heredity in uterine cancer.

A systematic investigation of propositi with breast cancer, coupled with a careful collection of information of all persons in the following categories of relatives: sisters and brothers, parents, grandparents, parents' sisters and brothers, and children, was carrried out by *Jacobsen* (1946) at The University Institute for Human Genetics, Copenhagen, as the first part of an attempt at exploring heredity in human cancer in a co-operation suggested by The Danish Cancer Registry.

Jacobsen examined the relatives of 200 patients with breast cancer (197 women and 3 men) notified to the Cancer Registry. There were 3301 relatives, and he succeeded in obtaining information about all but 171 (5.2 per cent.). Out of 465 cases of cancer he succeeded in finding all 419 theoretically traceable. A group of 200 control persons was used for comparison.

Table 2 shows the principal results obtained by *Jacobsen*.

Table 2.

A survey of the principal results in *Jacobsen*'s investigation of heredity in breast cancer (only near relatives are included).

	Number		Cancer of all sites		Breast canser		Cancer risk calculated on the basis of the cancer incidence in the categories of relatives,
	Patients	Controls	Patients	Controls	Patients	Controls	
			Per cent.	Per cent.			Per cent.
Mothers ..	200	200	55 = 27.5	19 = 9.5	21	2	64.7
Fathers ...	199	199	40 = 20.1	19 = 9.5	1	0	60.0
Sisters ...	381	433	30 = 7.9	8 = 1.8	13	2	60.2
Brothers ..	377	389	16 = 4.2	4 = 1.0	0	0	59.9

It is seen that among the categories of relatives stated (both male and female) the patients show a higher incidence than the control persons both with regard to "endogenous cancer" (i. e. a collective term used by *Jacobsen* to designate all forms of cancer encountered among the families of his patients, except skin and lip cancers, which were practically not represented) and with regard to breast cancer separately. This suggests that a hereditary predisposition is one of the main factors in the development of breast cancer.

Busk, Clemmesen & Nielsen (1948) have analyzed *Jacobsen*'s figures; they find that, as far as the more distant categories of relatives are concerned, *Jacobsen*'s control material is of a questionable value, while they think it fully warrentable to draw conclusions as to cancers of the breast and other sites when it is a question of categories of close relatives such as parents, sisters, and brothers, which categories show a definitely increased incidence both of breast cancer and of "endogenous cancer".

From the taint carried by the various categories of relatives *Jacobsen* calculated *the cancer risk*.

The figures quoted above appear as an expression of the cancer risk for "endogenous cancer". It is concluded that probability favours the view that the development of breast cancer is conditioned by a hereditary factor inherited together with a disposition to development of several forms of cancer supposed to be endogenous and showing a high incidence

in the tainted families of *Jacobsen*, who for brevity designates them as "endogenous cancer as a whole". It is presumed that "endogenous cancers" develop as a consequence of the presence of a general hereditary predisposition, and that the site of the tumour is determined either by genetic or by exogenous factors.

On the basis of the figures representing *the morbidity risk incidence* calculated for "endogenous cancer as a whole" an estimate of the mode of inheritance of the disease is made, and these figures agree approximately with the expected figures for a disease with dominant inheritance at an incidence varying between one and ten per cent. in the population in general. (They are also compatible with an incidence of 22 per cent. as later found by *Videbæk* or with 30 per cent. found by *Brøbeck*).

In a preliminary report by *Smithers* (1948) comprising the families of 459 patients with breast cancer it appeared that also in this series there was a considerably higher familial breast cancer taint than expected from the incidence in the population in general, whereas an increased taint of other forms of cancer could not be demonstrated. However, *Smithers* stresses that only in a few cases of the series he succeeded in confirming the information obtained as to cancer in the family, and he did not apply directly to relatives in order to collect as much information as possible of the family members.

Penrose, Mackenzie & Karn (1948) made an analysis of the families of 510 patients with breast cancer. The information obtained as to cancer in the families was, as far as possible, verified, but in several cases they failed to obtain definite information as to the cause of death.

Also here it was possible to demonstrate an increased incidence of breast cancer in sisters and mothers and more cases of breast cancer in maternal grandmothers and aunts than in paternal grandmothers and aunts.

On the other hand, it was not possible to demonstrate an increased incidence of other forms of cancer in the families (the figures used for comparison were calculated on the basis of the mortality statistics from 1925—1929).

Penrose et al. conclude that their investigations strongly point to the existence of a specific genetical agent as a major cause of mammary cancer, which may possibly be inherited mainly through the maternal line, whereas a general hereditary predisposition to cancer of all sites cannot be demonstrated. They believe that it may be a question of a cytoplasmatic inheritance, presumably not transmitted through the milk.

Neither *Smithers*, nor *Penrose et al.* can confirm *Jacobsen*'s finding that cases of mammary cancer with familial taint commence at an earlier age than those occurring in untainted individuals, but *Busk, Clemmesen*

& Nielsen (1948) explain this disagreement as a consequence of the methods of investigation.

Based on the same principles as those used by *Jacobsen, Videbæk* (1947) investigated heredity in leukemia.

His material consisted of 209 patients with leukemia; as controls 200 healthy persons were used. There were 4041 relatives in the patient material and 3641 relatives in the control material with good agreement between the age distributions of the two groups.

The familial incidence of leukemia was shown to be at least 8 per cent. Several types of leukemia (acute or chronic lymphogenous, or myelogenous, monocytic, or stem-cell leukemias) may occur in the same family. The relative frequency of the various forms of leukemia is the same for the familial cases and for the disease in general. Genetically, leukemia is believed to be an entity. Leukemia as such is not believed to be a heritable condition, but is seems as if a hereditary predisposition to it may be present. Simple dominance and recessivity can be excluded. There is a possibility of failing dominance or polymeria.

A hereditary relationship between leukemia and pernicious anemia was demonstrated, the incidence of pernicious anemia among the relatives of patients being significantly higher than among the relatives of control persons.

The incidence of pernicious anemia in the family histories of patients is of the same order as that of leukemia, and the two diseases are believed to have a common hereditary predisposition. It was also shown that there is a significantly increased incidence of "cancer as a whole" due to high incidence of all forms of cancer.

Also *Videbæk*'s figures have been reviewed by *Busk, Clemmesen & Nielsen* (1948), and it appears that even though the family records of controls have been collected with meticulous care, the incidence of cancer is lower than expected in the categories of more remote relatives, but the calculated frequencies are made the basis of a comparison with those found among the relatives of his patients, there is still a significant preponderance of cancer among fathers and sisters of leukemia patients.

The cancer risk, which was shown to be independent of the type of leukemia, varies between 23 and 48 per cent., with an average of 31 per cent. The figures suggest the inheritance of a dominant gene common to all the different forms of cancer.

The development of leukemia is then believed to be dependent partly on a common non-specific disposition to cancer in general supposed to be present in at least 20 per cent. of the population, partly on one or more genes determining the localization of the cancer to the leukemic. Exogenous — unknown — factors are believed to be decisive for the type of leukemia which develops.

Jacobsen's and *Videbæk*'s monographs will later be discussed together with the report of the author's own investigations.

The study of twins has yielded essential contributions to elucidate the problems of heredity in human cancer.

Cases of concordantly occurring adenocarcinoma of the uterus in monozygotic twins have been reported by *Croom* (1912), *Weitz* (1924), and *Dietel* (1942).

In a dissertation from 1940 *Klotz* published an analysis of 17 pairs of twins, whose hereditary identity was investigated at The Twin Research Institute in Hamburg. One of each pair of twins had been treated for *cancer of the cervix uteri*, and the other member was called upon to present herself for gynecological examination.

There were eight pairs of monozygotic twins, one of each pair having been treated for cervical cancer. In one pair there was concordance; in two pairs the other member had cervical erosion without signs of malignancy. The remaining five pairs were discordant.

Nine pairs of dizygotic twins showed complete discordance with regard to the tumour and its site.

From the Danish Cancer Registry (*Busk, Clemmesen & Nielsen*, 1948) a preliminary survey of cancer in twins has been published. The series comprised 336 pairs of twins (from a material consisting of about 30,000 hospitalized cases of cancer). Several of these pairs had to be excluded, either because the other member had died under five years of age, had emigrated, or was unknown for other reasons, thus leaving 185 pairs for investigation. This analysis suggests a higher incidence of cancer in monozygotic twin partners of cancer patients than in dizygotic twin partners, but the increased incidence is not statistically significant.

In seven pairs of diszygotic twins, in which both members suffered from cancer, there was only one instance of tumour of the same site in both members. In seven pairs of monozygotic twins four pairs had cancer of the same type.

The number of cases of cancer in twins who have been examined to date is too small for definite conclusions. A much larger material will have to be collected and evaluated before it will be possible to obtain statistically reliable information on heredity of the individual forms of tumours.

Statistical investigations on the occurrence of multiple primary carcinomata are also genetically of considerable theoretical interest and must be expected to attract the attention of investigators increasingly as the percentage of cures in the various forms of cancer is rising.

In a publication from 1941 *Lefevre* reviews the literature and concludes that the occurrence of multiple primary carcinomata is more

frequent than previously supposed, and that certain individuals may have a disposition to develop more than one malignant tumour in certain organic systems.

In 1942 *Engelbreth-Holm* published the results of an investigation carried out on the basis of the case records for 1744 cases of mammary cancer treated at the Radium Centre in Copenhagen in the period from 1920—40.

Cancer of two sites was found in 87 instances (5 per cent.); there were 34 cases of bilateral mammary cancer, 19 cases of cervical cancer, eight cases of cancer of the corpus, one case of sarcoma of the uterus, and two cases located in the hymen and vulva, i. e. nearly 75 per cent. occurred in the breast or genitalia.

While the ratio between cancers of the corpus and cervix in the material from the Radium Centre is 1 : 7, the ratio between the two forms of cancer where they occur in association with mammary cancer is 8 : 19 or approximately 1 : 2.4, i. e. showing a considerable relative preponderance of cancer of the corpus. *Engelbreth-Holm* expresses the view that it cannot be the question of a casual coincidence of mammary and uterine cancers, since if this was the case the same ratio should be expected here as in the entire material.

He quotes a number of previous investigators, who found a similar relation between mammary and uterine cancers with a relative preponderance of cancer of the corpus.

On the basis of a material from the Radium Centre in Copenhagen *Andersen & Truelsen* (1942) published morbidity statistics for uterine cancer, in which they showed that both a cancer of the cervix uteri and a new mammary cancer are six times as frequent in patients with cancer of the breast as in other women, and that also cancer of the corpus uteri occurs more frequently than should be expected.

Studying a comprehensive autopsy material *Warren & Ehrenreich* (1944) find that the combination of mammary cancer and cancer of the intestinal tract is almost as frequent as the combination of mammary cancer and cancer of the genital tract.

Schinz (1936) quotes an article by *Regaud* which, unfortunately, I have been unable to trace. In 1009 cases of cancer of the cervix (the patients had been under observation only for a short time) he found nine cases of cancer of two sites, four skin cancers, three mammary cancers, one rectal cancer, and one tumour of the kidney; these nine cases constitute only 0.9 per cent. of all the patients with cervical cancer.

Among 284 patients with cancer of the cervix, free of symptoms for 5—6 years, a new primary tumour was found in six instances, three skin cancers, two mammary cancers, and one rectal cancer, thus constituting

2 per cent. On account of the insignificant number of cancers of two sites *Regaud* rejects the idea of a general disposition to cancer in these women and regards their cancers of two sites as independent of each other with regard to both etiology and pathogenesis.

In this connection it is worth noticing that *Jacobsen* (1946) among the relatives of his patients with mammary cancer could not find a preponderance of cancers of the genital tract (uterine and ovarian cancers).

The study of cancers of two sites has thus given contradictory results. A systematic study of breast cancer patients with complicating tumours is at present carried out at the University Institute for Human Genetics and the Cancer Registry by *Feilberg*. The publication of his results must be awaited with interest.

Even though many different lines of approach to the problem of heredity in human cancer have been attempted, it is obvious that this problem is attended with great difficulties and many factors of uncertainty, and the evaluation of the results obtained is also very difficult.

Kemp (1948) has summarized our present knowledge of the development of malignant tumours, supported by the experiences which have been gained at the University Institute for Human Genetics by clinical and experimental investigations on the genesis of malignant neoplastic growth, as follows:

Table 3.

The genesis of malignant neoplastic growth (*Kemp*).

Endogenous factors.	*Hereditary predisposition.*	Dominance (irregular), recessivity (?), polymeric or multifactor inheritance, homologous polymeric factors. Tumours of different forms, types, and sites differ in their genetical behaviour. Later and more seldom in heterozygous than in homozygous.	
	General predisposition. Tendency to localization (localization genes, organ factors, similar histological structure).	Variation in manifestation. Variation in susceptibility or refractoriness to tumour formation or tumour transplantation. Genes with the character of virus.	
	Somatic mutation (induced or spontaneous).		Extrachromosomal.
	Cytoplasmic inheritance (maternal effect).		
	Internal milieu (adaptation to individual, type, race or variety and species).		
Environments.	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.		
	External milieu (exogenous factors). Irritation by trauma, chemical, thermal, or ray influence, parasites, bacteria, and viruses.		

Chapter II.

METHOD AND MATERIAL

1. *Method.*

As will be seen from Chapter I, none of the methods previously used have been capable of clarifying the problem of heredity in human cancer.

It was obvious that if the problem was to be approached, it would be necessary first to investigate each form of cancer separately, and secondly to use a method in which the incidence of cancer among the families of a suitable number of patients was compared with that of a control group collected along the same lines. As had previously been done in similar Danish studies on breast cancer (*Jacobsen*, 1946) and leukemia (*Videbæk*, 1947), the author used *Weinberg*'s "proband method" (1931) in the statistical-genealogical investigations.

I have used the genealogical table devised for investigations of propositi by the Danish University Institute for Human Genetics. This table comprises four generations with the following categories of relatives: parents, grandparents, paternal and maternal uncles and aunts, brothers, sisters, and children. This must be considered a sufficiently safe basis of a statistical-genealogical investigation, and it was considered unnecessary to extend the examinations to more remote relatives. Information on closer relatives was easily obtained, but the higher up in generations and the further out into the collateral branches one comes, the more difficult it becomes to gather reliable information, and hence I did not attempt to extend my investigations beyond the categories of the genealogical table.

Most of the patients have been interviewed at the Radium Centre in Copenhagen. Usually, I approached the patients when they were out of bed, so that I could speak to them privately, and before asking questions I explained the object of the investigation and generally succeeded in breaking through the obvious scepticism and reserve on the part of the patients.

Only very few patients refused blankly to give information; in most instances they were very responsive in giving information about their families; in some instances interrogation had to be given up at an early stage, because the patient was born out of wedlock or abroad; others had

left home at an early age and lost contact with their family and were thus unable to answer the questions.

I asked careful questions as to each member of the various categories of relatives. First I took down their names, occupations, and marital state. As to relatives still alive I inquired about their age at the examination and their diseases, if any, with a special view to hospitalization and radiation treatment, and as to deceased relatives about their age at death and the cause of death. On no occasion the word cancer was used by me.

Of course, the patient would be quite unprepared for such an exacting interrogation. After having obtained as much information as possible from the patient I addressed in all cases the relatives of the patient, either by correspondence or personally. In nearly all instances where I knew the birth places of the father and mother and their approximate years of birth, I had tried beforehand — often successfully — to find the grandparents and the parents' sisters and brothers by means of the records of the public registration offices. In this way I could often make a complete list of these relatives with statement of birth places and approximate years of birth (exact information as to these points is available from the church registers which, up to 1891, are accessible at the Provincial Record Offices), and on the basis of this list I could ask questions about each member of the various categories of relatives.

In many cases this procedure facilitated work and saved correspondence, since the patients often know at which age their relatives died, but not the year of death. Only patients giving complete information about their children, sisters and brothers, and parents were considered acceptable.

It is obvious that the reliability of the answers to a great degree depends on the questioner, to whom some psychological knowledge of cancer patients is of importance. I have therefore personally questioned each patient and her relatives and carried on the necessary correspondence.

I am under the impression that none of the persons interrogated were unpleasantly affected by the investigations, and the subsequent verification proved that the information obtained was surprisingly exact. Through genealogically interested members of the family several of the patients supplied complete (and much-desired) pedigrees.

It has often been stated that in an attempt at concealing from themselves the severity of their disease, cancer patients may be apt consciously to give incorrect information of cases of cancer in their families. By showing just as much interest in other diseases as in certain or suspected cases of cancer I had, however, no difficulty in averting their suspicion of a special interest in the cancer cases.

2. *Verification of the Information Obtained.*

In order to check the information given to me I tried to verify the cancer cases stated by the propositae.

Only a few years ago most forms of cancer were absolutely lethal. In order to confirm the cancer cases in a family it will therefore very frequently be necessary to trace the death certificate, which is a useful, though not ideal means in this respect. In order to find the death certificate for a Danish person it is necessary to know his name and place, date, and year of death. Not infrequently the information obtained from the patients or their relatives was insufficient or incorrect, and in many instances I had to apply to public registration offices, burial authorities, church registers, and other institutions for assistance, and in nearly all cases I succeeded in finding the relevant data.

Death certificates are accessible at the State Record Office for all parts of the country from 1920 and for the towns from 1850 to 1920.

Some of the death certificates issued in rural district prior to 1920 are kept in the Provincial Record Offices; in a large number of cases I have tried to find these certificates, but many of them have disappeared, and the filing arrangements are so defective that it is very often impossible to trace the certificate in question. (Sometimes several hundred certificates were bundled up quite unsystematically). The importance of these certificates is often attenuated by the fact that at the time they were not infrequently in thinly populated districts issued by laymen appointed for that purpose. Only in very few cases did I succeed in verifying cancer deaths in this way, and broadly speaking it may be said that it is not possible to verify the cause of deaths which have occurred in the rural districts prior to 1920, and that the vast amount of work involved is not in any way commensurate to the degree of certainty obtained. As far as living relatives who have been stated to suffer from cancer were concerned, it was necessary to apply to their physician or the hospital department in which they had been treated.

In 200 cases of cervical cancer I succeeded in obtaining information about 222 cases of cancer in the families. In 90 cases of cancer of the corpus I found 163 cases of cancer in the families.

Table 4 shows the number of verified cancer cases in relatives of patients with cancers of the cervix and corpus uteri and the way in which the verification took place.

Among the relatives of the patients with cervical cancer there were 31 deaths due to cancer occurring in the rural districts prior to 1920. I managed to get a hint of the diagnosis in ten cases, either by death certificates or because cancer was stated to be the cause of death in the

Table 4.

	Number of cases	Verified by death certificate	Verified by hospital record	Died in rural districts prior to 1920	Non-verified cases	Total
					Per cent.	
Cancer of the cervix . .	200	150	34	21 (+ 10)	7 = 3.7	222
Cancer of the corpus .	90	127	11	17 (+ 3)	5 = 3.5	163

The figures given in parentheses under "Died in rural districts prior to 1920" show the number of death certificates actually found.

church register; of the remaining 191 cases, seven, or 3.7 per cent. could not be verified.

Among the relatives of the patients with cancer of the corpus there were 20 deaths due to cancer occurring in the rural districts prior to 1920; here I found three death certificates; five of the remaining 143 cases, or 3.5 per cent. could not be verified.

Under non-verified cases I have included partly cases for which no death certificate could be found, and partly cases in which the death certificate or the hospital record gave a cause of death different from that stated by the proposita but where, nevertheless, the anamnesis pointed so distinctly to cancer that it was thought justifiable to include the case.

The information obtained has been surprisingly exact; of diseases erroneously stated as cancer I should mention the following: peritonitis with perforation of the duodenum, perforating gastric ulcer (for cancer of the stomach), chronic empyema of the chest (for cancer of the lung). I think that nobody can reasonably be blamed for such mistakes.

3. *Control Material.*

As controls for the patients with cervical cancer I used 200 unselected persons with the same age distribution.

Although it would seem far easier to examine the families of control persons than of the patients, as stated by *Videbæk* the reverse is the case, since the control persons do not take quite the same interest in the investigations as do the affected individuals whose disease is being studied.

When therefore *Videbæk*, after having completed his work on heredity in leukemia, invited me to use his control material, I was very pleased to accept. *Videbæk*'s control material had been just as thoroughly elaborated as the families of his patients and comprised propositi from different social classes. I could not exclusively use *Videbæk*'s control material because the age distribution differed from that of my own material, but of his 200 control pedigrees I used 112 as controls for cervical cancer. I

collected the remaining 88 control persons at Rigshospitalet, Surgical Department, C and D, Copenhagen. Like *Videbæk*, I chose individuals who had not at any time suffered from malignant disease. They were mainly chosen among patients admitted to the hospital for fractures, burns, appendicitis, etc.

In this way I succeeded in collecting a control material of 200 healthy persons with the same age distribution and the same social variation as the propositae.

The interrogation took place along the lines described, and since in every single case questions were asked of several members of each family, I have not exclusively used women, although it has been maintained that men are apt to give less complete information about their families than women.

In the control families collected by me (chiefly the younger age groups) there were 89 cases of cancer, of which 55 were verified by death certificate, 17 by hospital record, 13 had died in rural districts prior to 1920, and four could not be verified (5.3 per cent.). In *Videbæk*'s total control material 15 of 181 cancer cases could not be verified, i. e. 8.3 per cent.

Twenty-five of the 88 controls collected by me were used in the investigation of the 90 cases of cancer of the corpus; the remaining 65 came from *Videbæk*'s control material.

It will be seen both for patients and for controls that some relatives had died from cancer in rural districts prior to 1920 (for propositae with either form of uterine cancer 51 persons out of a total of 385). As there was agreement between the cause of death stated by those interviewed and that on the death certificate in approximately 95 per cent., I found it justifiable also to include these cases in both materials.

As in the patient material, the problem consisted in the majority of instances in finding the death certificate; for a minor part the information desired was obtained by application to hospitals or physicians. As is also emphasized by *Videbæk*, the figures obtained for cancer cases in a family are, of course, minima, but it may be supposed that few cases have escaped the attention of the propositae. Cancer deaths in a family will generally be known by the other members of the family, as far as closer relatives are concerned.

During recent years a steadily increasing percentage of cancer patients has been cured of their disease, a fact which makes it less dramatic, and hence less known among members of the family. As far as absolutely curable cancer is concerned, such as skin cancer, the investigation fails completely; in spite of constant questioning about possible radiation treatment of diseases in the family information has been obtained of few cases

only. Both *Jacobsen* and *Videbæk* had the same experience with such diagnoses.

In order to check the reliability of the investigations on this point I have examined death certificates for a total of 300 persons related to the propositae for whom the cause of death was stated to be some disease different from cancer. This examination revealed only two cases of cancer not previously stated. A similar supplementary examination among relatives of the 88 control persons was made, based on 100 death certificates, and only one case of cancer not previously known was disclosed.

At the examination of 387 death certificates for relatives of propositi *Videbæk* found no case, which had not previously been stated as death due to leukemia or cancer, and at the examination of 300 death certificates for relatives in the control material he found only four deaths due to cancer, which had not previously been stated as such. Thus it has been possible to verify the deaths stated by the relatives to be due to cancer in over 90 per cent. of the cases, and only in four instances out of 400 I found death due to cancer, which had not previously been stated (i. e. 0.75 per cent.). Thus the information obtained proved very reliable.

4. *Material of Propositae and their Relatives.*

a. Propositae.

To form the basis of my genetic investigations 296 cases of cervical cancer and 142 cases of cancer of the corpus were collected as propositae. Even though these two forms are cancers of the same organ, they differ with regard to site, age distribution, histology, and in several other respects to such a degree that the only thing they have in common is that they are located to the same organ. After some time spent on studies of cervical cancer, which owing to its higher incidence is more easily accessible, it seemed important also to include cancer of the corpus, as it might be anticipated that, also genetically, the two forms would be different. This supposition was supported by previous reports in the literature, in which it has often been emphasized that adenocarcinoma, which is the commonest type of endometrial cancer, shows a more pronounced tendency to heredity than squamous-cell carcinoma, which is the commonest type of cervical cancer.

The 296 cases of cervical cancer have all been collected at the Radium Centre in Copenhagen, which receives patients from Copenhagen, Sjælland, Lolland-Falster, and Bornholm. Thus all the patients have been hospitalized, but since at present 98 per cent. of all cervical cancers and 92 per cent. of all cancers of the corpus are hospitalized in Denmark (*Clemmensen & Busk,* 1948), no special selection can be said to have

taken place. Of the 296 cases of cervical cancer 96 could not be used. Only a very small number (five) refused blankly to co-operate in the investigation. The remaining 89 were either born out of wedlock, or abroad, or were without sufficient knowledge of their families and thus unable to supplement the information already obtained.

Finally, there were a few instances in which the information obtained could not be verified.

The preparation of the family anamneses began in 1943 and were continued, with some interruptions, until 1946. The investigations of the patients with cancer of the corpus were commenced in 1943 and concluded in 1947.

I have been in touch with 142 patients with cancer of the corpus, of whom 52 had to be excluded for the same reasons as the cases of cervical cancer.

Seventy-seven of the remaining 90 patients with cancer of the corpus came from the Radium Centre in Copenhagen, but as the disease is comparatively rare, I obtained permission to supplement the number with 13 cases from other hospitals in Greater Copenhagen (Bispebjerg Hospital, Department A, three cases; Department D, two cases; Department F, one case; Kommunehospitalet, Department 5, three cases; Sundby Hospital, Surgical Department, one case; Diakonissestiftelsen, Surgical Department A and B, three cases).

The patients from the hospitals of Greater Copenhagen and a few from the Radium Centre, who had not previously been examined, were summoned to report for examination at the University Institute for Human Genetics. Information as to the domiciles of these patients was received from the Cancer Registry.

The selection of all propositae was quite casual, irrespective of age and without any preceding knowledge of possible cancer cases in the family.

I had now 200 acceptable cases of cervical cancer, a number which according to experience is sufficient to form the basis of a genetic analysis. The number of cases of cancer of the corpus, 90, is perhaps smaller than desirable, but I chose to stop at this figure because it would take a disproportionately long time to collect more cases owing to the relative rarity of the disease, and the work involved would have been almost beyond the reach of one investigator.

All the diagnoses have been made by competent diagnosticians and in all instances followed by histological verification.

b. Diagnosis.

In all instances the diagnosis has been made on the basis of a careful clinical examination in connection with microscopical examination of biopsy specimens.

In cervical cancer a distinction between cancer of the cervical canal and cancer of the portio vaginalis has not been made, since such a distinction is often practically impossible. The classification of the various stages of cervical cancer has been carried out according to the principles laid down by The Radiological Subcommission of the League of Nations in 1928.

Histologically, the majority of cervical cancers were solid carcinomata (195 cases), four were adenocarcinomata, and one adenocarcinoma + solid carcinoma.

The 90 cases of cancer of the corpus were distributed as follows: 68 adenocarcinomata, 10 solid carcinomata, 10 adenocarcinomata + solid carcinomata, one sarcoma, and one sarcoma or anaplastic carcinoma.

I have not recorded the clinical and histological examinations in detail as my principal object was to ascertain that each individual case represented an indisputable case of cancer. In the case histories I have therefore briefly stated the stage of each individual case of cervical cancer as the result of the clinical examination and the collective histological diagnosis of the cases of uterine cancer used.

c. Age Distribution of Propositae.

To ensure that the propositae should be representative of the disease as it occurs in the population it was of importance that their age distribution corresponded with that of all cases occurring within the period of collection.

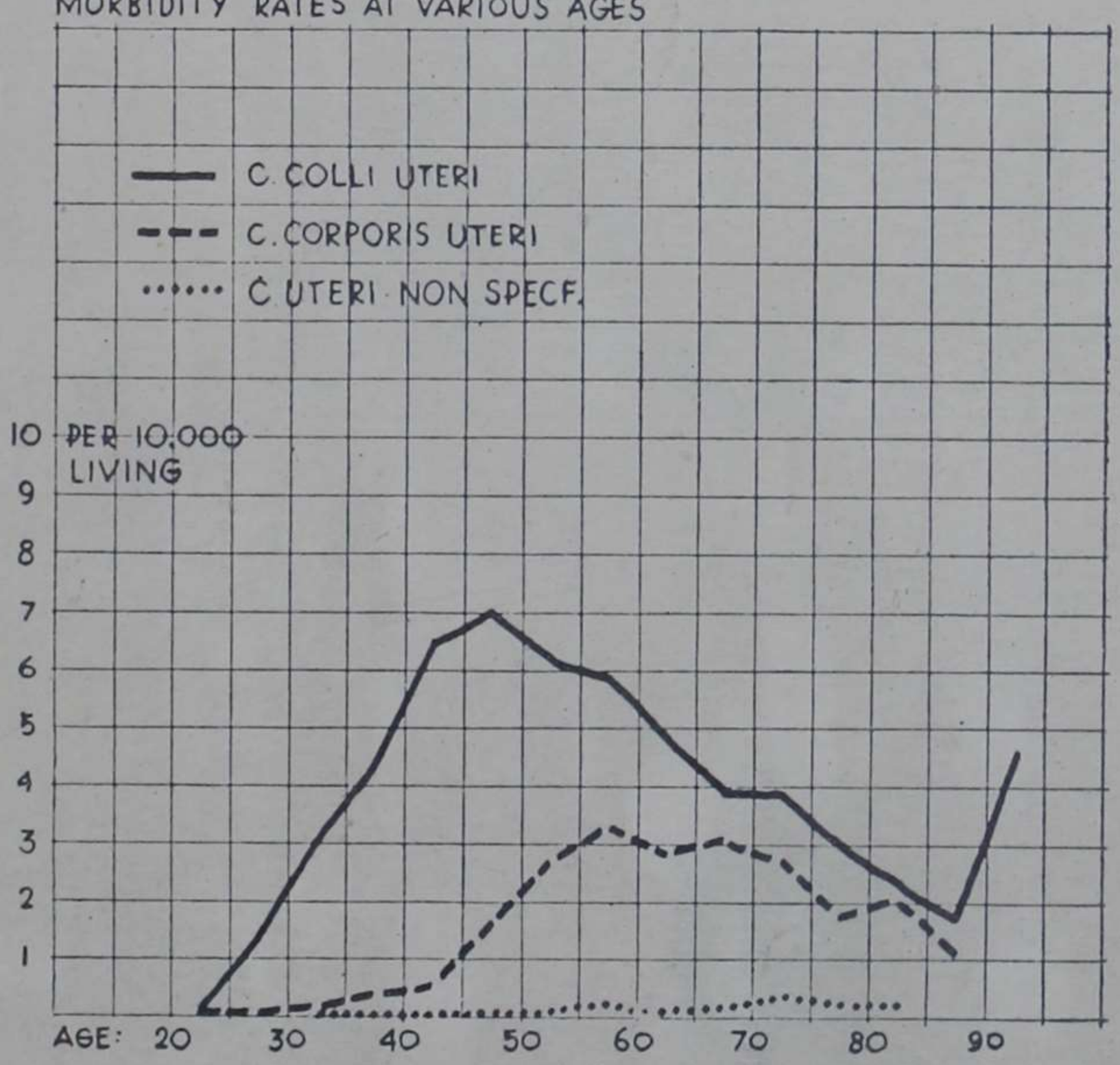
The Cancer Registry (*Clemmensen & Busk*, 1948) has worked out the following diagram of the age distribution of uterine cancer in Denmark for the years 1942, 1943, 1944, comprising 1633 cases of cervical cancer and 504 cases of cancer of the corpus notified to the registry.

It will be seen that the curves differ on essential points. The curve indicating cervical cancer commences at the age of about 25 years, increases steeply to a maximum between 45 and 50 years, then falls less steeply, reaching its minimum between 85 and 90 years, and finally rises a little again. The curve for cervical cancer differs from those of most other forms of cancer — e. g. skin cancer where the curve is constantly increasing — in having its maximum between 45 and 50 years. Incidentally, just in this age group the curve for breast cancer (*Clemmensen*, 1948) shows a temporary fall, which is again superseded by an increase. The common decrease of the curves for breast cancer and cervical cancer

suggests a common cause of the decrease of the frequency, possibly a cessation of carcinogenous influence.

Fig. 2.

Age distribution of uterine cancer in Denmark for the years 1942, 1943, and 1944, comprising 1633 cases of cervical cancer and 504 cases of cancer of the corpus notified to the Danish Cancer Registry (age when first seen in hospital).



Cancer of the corpus occurs at a later age. There are only very few cases before the age of 40, then curve rises steeply, reaching a maximum between 55 and 60 years, and falls again (less steeply) to a minimum between 85 and 90 years. The vast majority of cases occurs after the age of 50, i. e. after the menopause. Both curves show a fairly even course and no two-peaked distribution as found by *Jacobsen* in breast cancer.

The age distribution of the cases of cancer of the cervix and corpus uteri collected by the author was as follows:

Table 5.

Age distribution (quinquennial groups) of the cases of cancer of the cervix and corpus uteri collected by the author.

Age	Cancer of the cervix uteri		Cancer of the corpus uteri	
	Cases used	Cases excluded	Cases used	Cases excluded
25—29	11	4	0	0
30—34	23	8	0	0
35—39	32	14	1	2
40—44	31	16	5	3
45—49	26	16	7	5
50—54	25	6	24	7
55—59	22	8	15	7
60—64	14	14	22	12
65—69	7	6	11	6
70—74	8	4	3	5
75—79	0	0	2	4
80—84	1	0	0	1
Total ..	200	96	90	52

Fig. 3.

Age distribution of the 296 cases of *cancer of the cervix*, of which 200 were used (black areas), whereas 96 had to be excluded (white areas).

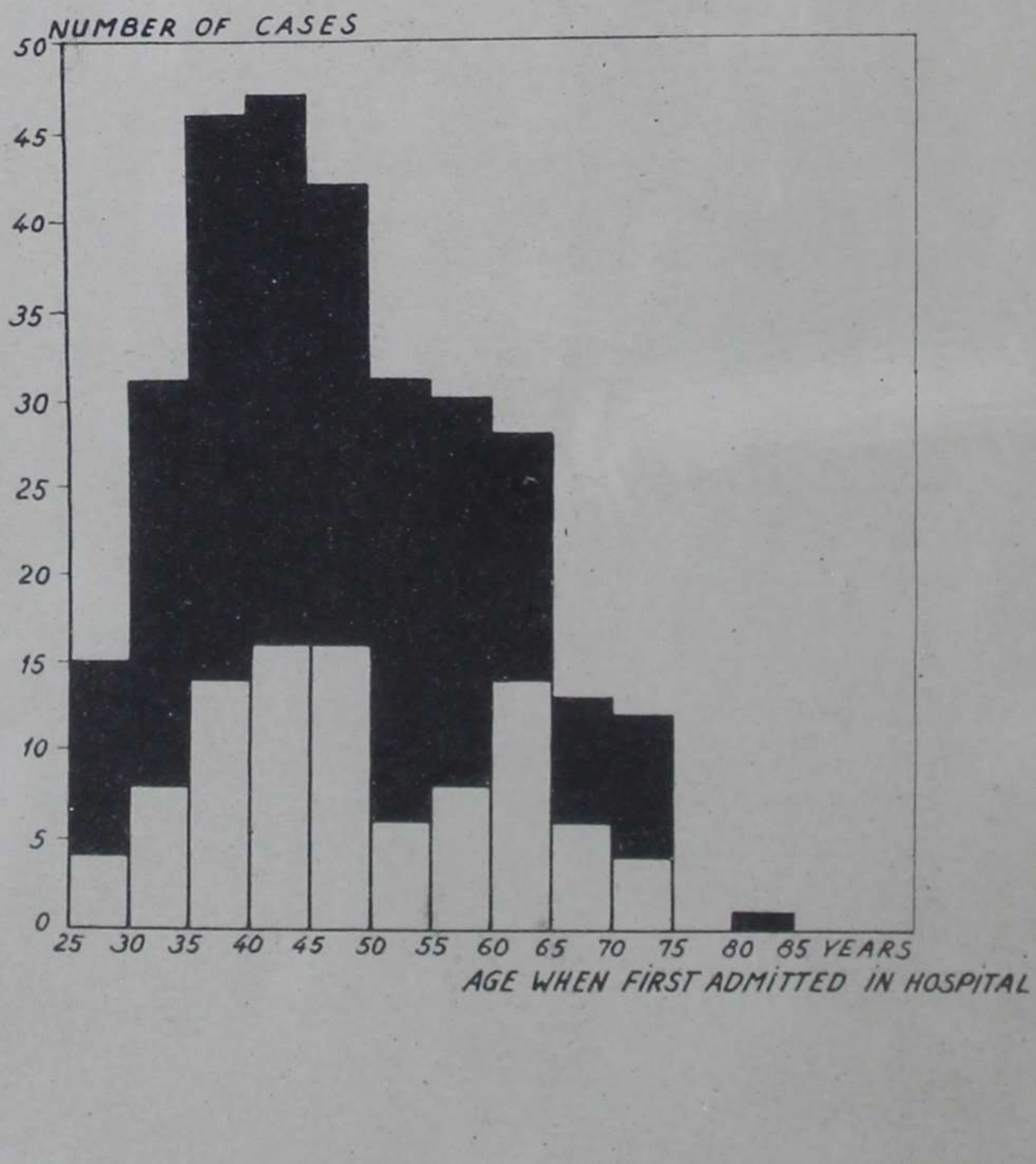
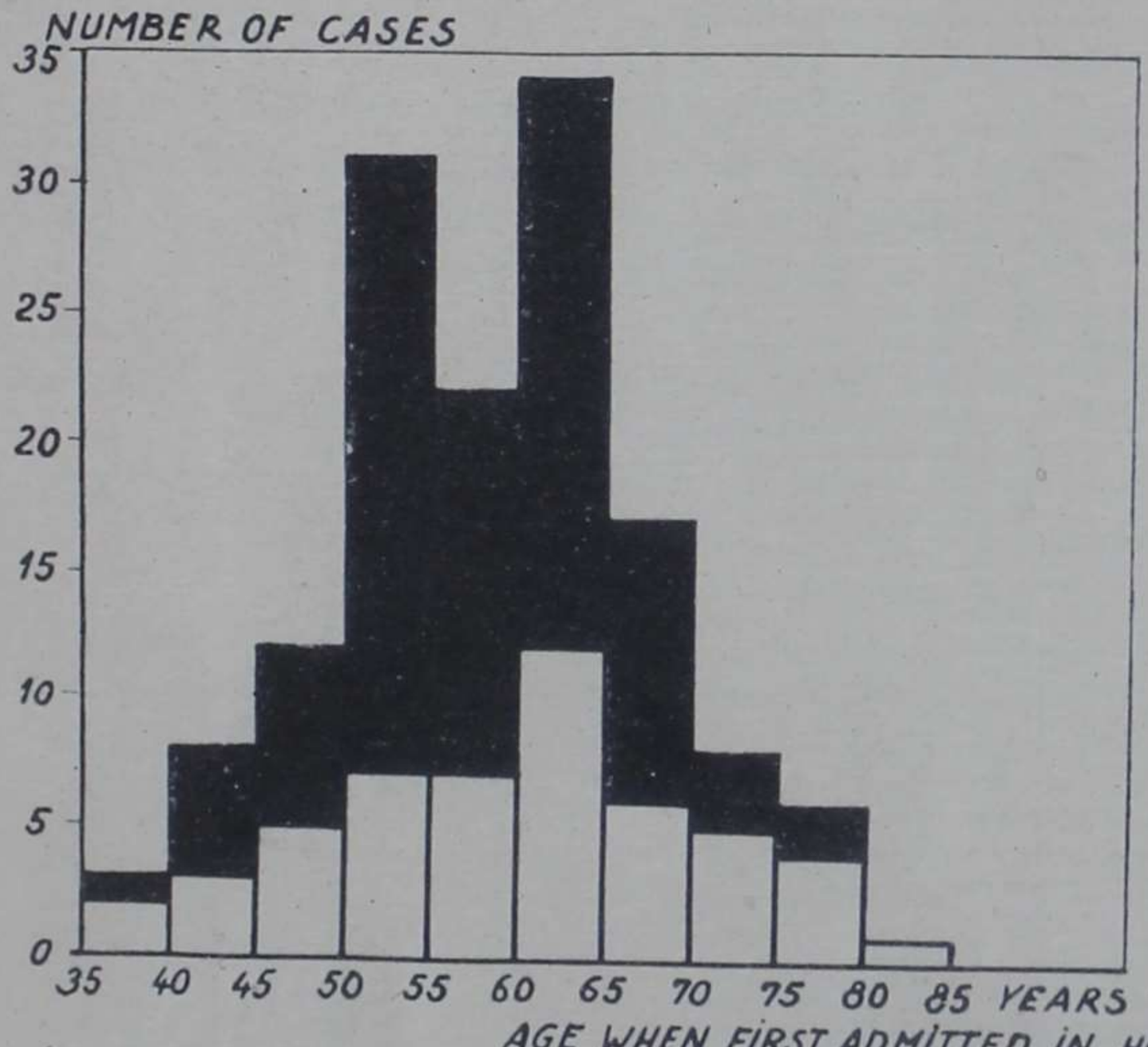


Fig. 4.

Age distribution of the 143 cases of *cancer of the corpus*, of which 90 were used (black areas), whereas 52 had to be excluded (white areas).



It will be seen that there are no cases of cervical cancer below the age of 25 years. After 30 years of age the number increases rapidly, reaching a maximum between 40 and 45 years, after which the curve falls evenly. The maximum for my cases occurs a little earlier than it did in the curve representing the cases of cervical cancer for the whole country.

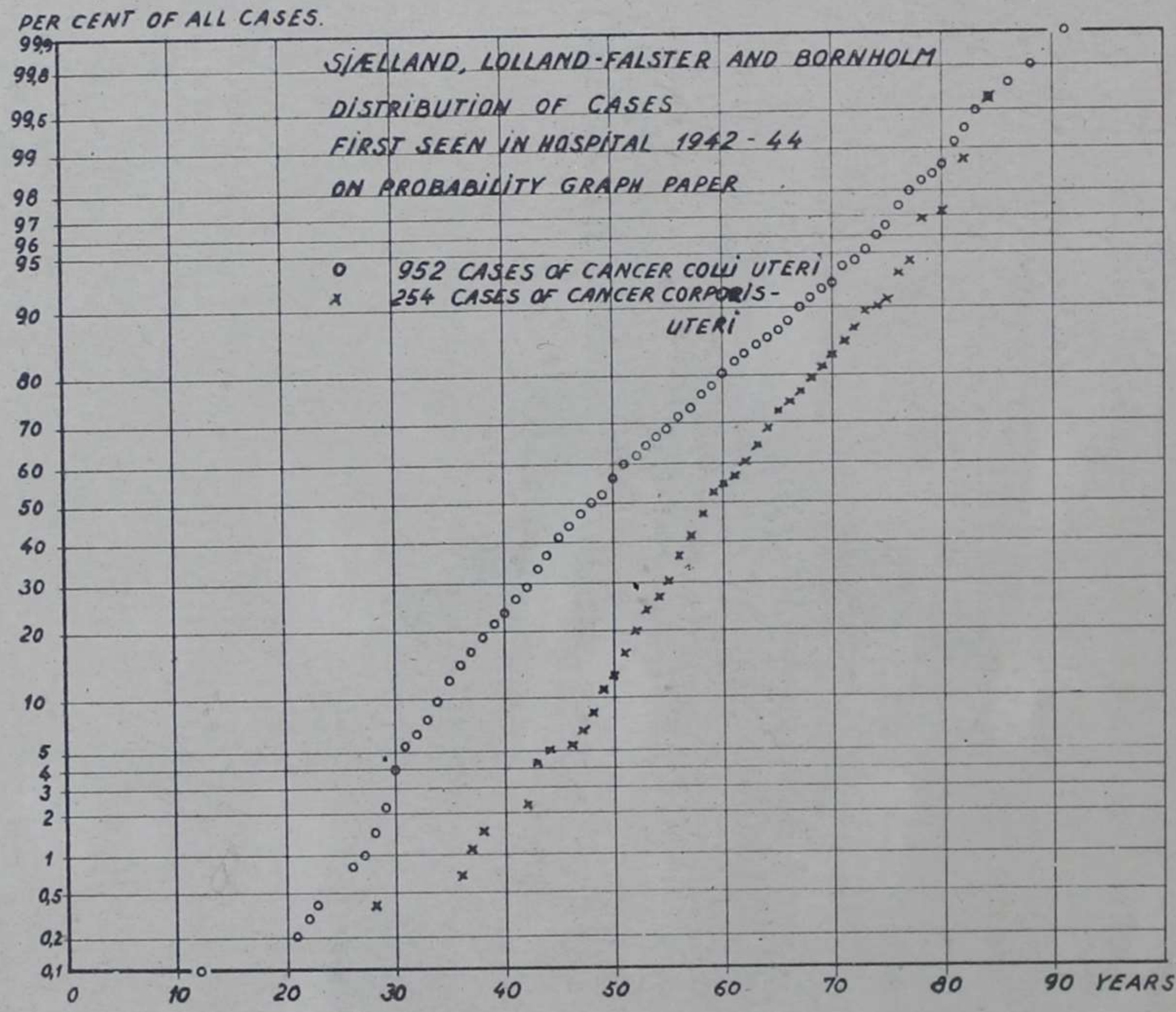
I have not found any cases of cancer of the corpus below the age of 35 years. The maximum occurs between 60 and 65 years, i. e. somewhat later than in corresponding surveys of all the cases of cancer of the corpus for the whole country.

However, the Radium Centre receives its patients only from Copenhagen, Sjælland, Lolland-Falster, and Bornholm. A comparison of the age distributions in this district and the whole country (*Busk*) shows almost complete coincidence of the curves. Yet as far as the younger age groups are concerned, the frequency of cancer of the corpus is slightly lower for the district of the Radium Centre than for the whole country.

Of course, the ideal would be to state the age at the onset of the disease, but as this is impracticable, I have chosen to state the age at admission in conformity with the method employed in the material used

Fig. 5.

Age at first hospitalization of 952 cases of cervical cancer and 254 cases of of cancer of the corpus during the period 1942—44.



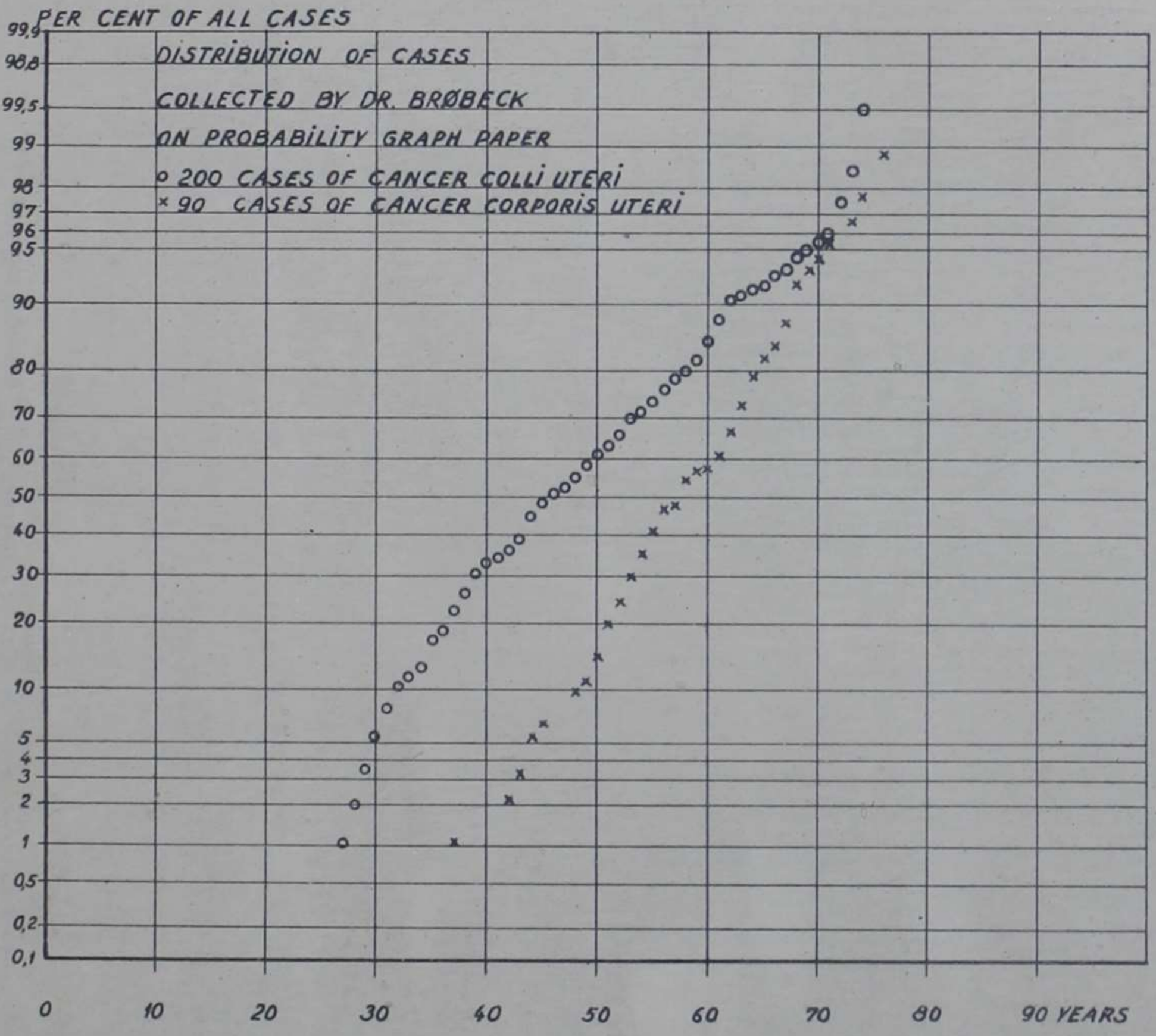
for comparison comprising all hospitalized cases and deaths due to uterine cancer in the period 1942—44 from the district of the Radium Centre. The latter material comprises 952 cases of cervical cancer and 254 cases of cancer of the corpus. The age distribution is shown in the probability graphs in fig. 5 and 6.

It will be seen that as far as cancer of the corpus is concerned, the curves are essentially alike, yet so that there are fewer patients at the more advanced ages than common in the district of the Radium Centre.

The whole course of the curve for cervical cancer shows a small diviation, my patients being, on an average, about 18 months younger than those from the district of the Radium Centre.

On the basis of these findings it may be concluded that with regard to age distribution there is no essential diviation between the material

Fig. 6.
Age at first hospitalization of 200 propositae with cervical cancer and 90 propositae with cancer of the corpus.



from the district of the Radium Centre and that of the author which in this respect must thus be regarded as representative.

d. Age Distribution of Control Persons.

In order to constitute a suitable control group for a disease which does not manifest itself at birth, it must be required that with regard to age distribution it is in conformity with the patient series. It is not only necessary that propositae and control persons are of the same age, but also that there is good agreement between the age distributions of the relatives of the two groups. For this purpose the propositae were divided into quinquennial groups, and in the arrangement of the control material I also divided *Videbæk*'s control material into such groups, and

through a comparison with my series of propositae it appeared that it was possible to use 112 of *Videbæk*'s controls; the others were either younger or older than my propositae.

I have collected the remaining 88 control persons in such a way that agreement between the quinquennial groups in the propositae and control materials was ensured.

The age distribution of the propositae and control materials and the number of persons in the various categories of relatives appear from the following tables.

Key to Abbreviations.

Fathers = F	Mothers = M
Brothers = B	Sisters = S
Maternal grandfathers = MGF	Maternal grandmothers = MGM
Paternal grandfathers = PGF	Paternal grandmothers = PGM
Maternal uncles = MU	Maternal aunts = MA
Paternal uncles = PU	Paternal aunts = PA
Sons = Sn	Daughters = D
	Children = C

These abbreviations are used in the next and some of the following tables.

The genealogical tables for the 200 patients with cervical cancer comprise a total of 3808 persons, of whom more or less precise data were obtained, and 160 persons (i. e. 4.0 per cent.), of whom no information could be obtained.

The genealogical tables for the 200 controls comprise 3581 persons + 134 (i. e. 3.6 per cent.), of whom nothing is known.

The genealogical tables for the 90 patients with cancer of the corpus comprise 1564 persons; there were 72 persons (i. e. 4.4 per cent.), of whom no information could be obtained.

The corresponding control material comprises 1637 persons, and here there were 83 persons (i. e. 4.8 per cent.), of whom no information could be obtained.

It is thus seen that also with regard to the number of persons of whom no information could be obtained there is good agreement between the patient and control materials.

Table 6 a.

Age distribution of the individual categories of relatives of the patient and control groups in cervical cancer.

Men

Age	Patient group								Control group							
	F	B	MGF	PGF	MU	PU	Sn	Total	F	B	MGF	PGF	MU	PU	Sn	Total
—24		72			12	20	153	257		66			17	20	105	208
25—29		29	1		8	2	34	74		30	3		9	4	18	64
30—34	1	50	4	2	6	9	31	103	1	37	7	2	4	3	9	63
35—39	7	58	6	6	8	4	18	107	3	53	3	3	9	9	7	87
40—44	8	61	10	3	10	16	16	124	6	54	5	3	16	11	4	99
45—49	7	53	5	5	13	11	7	101	7	58	8	8	26	15	4	126
50—54	13	65	13	9	30	22	1	153	16	41	8	8	29	18		120
55—59	23	41	19	17	27	27	1	155	21	30	11	9	20	35	2	128
60—64	30	28	17	15	51	38	1	180	33	18	11	11	36	47	1	157
65—69	34	21	16	19	39	37		166	32	22	22	26	44	42	1	189
70—74	29	9	26	35	32	52		183	37	10	35	30	40	54		206
75—79	26	7	19	23	23	30		128	27	3	24	30	37	36		157
80—84	14	1	26	27	16	24		108	9	1	20	27	16	25		98
85—	8		19	14	14	10		65	8		16	19	10	10		63
Total ..	200	495	181	175	289	302	262	1904	200	423	173	176	313	329	151	1765

Women

Age	Patient group								Control group							
	M	S	MGM	PGM	MA	PA	D	Total	M	S	MGM	PGM	MA	PA	D	Total
—24		64			11	15	171	261		64			17	15	109	205
25—29	1	34	2	1	2	3	28	71	4	26	3	4	4	5	26	72
30—34	3	44	6	3	7	3	25	91	1	39	3	2	5	3	10	63
35—39	6	63	5	6	5	5	20	110	5	54		8	6	4	10	87
40—44	5	71	11	2	10	4	11	114	3	63	5	9	12	8		100
45—49	11	65	7	1	18	14	8	124	10	61	7	3	25	17	4	127
50—54	13	60	6	6	33	20	1	139	8	49	2	7	26	23	2	117
55—59	19	32	5	6	30	25		117	18	39	7	4	37	32	1	138
60—64	31	26	14	15	40	35		161	32	20	15	12	27	33		139
65—69	36	14	15	21	56	32		174	37	18	25	32	66	47		225
70—74	25	11	29	34	43	62		204	35	13	39	25	39	55		206
75—79	19	3	24	22	25	28		121	16	3	33	26	36	36		150
80—84	16	1	34	24	22	24		121	13		29	16	21	19		98
85—	15		26	29	12	14		96	18		21	26	15	9		89
Total ..	200	488	184	170	314	284	264	1904	200	449	189	174	336	306	162	1816

Table 6 b.

Age distribution of the individual categories of relatives of the patient and control groups in cancer of the corpus.

Men

Age	Patient group								Control group							
	F	PGF	MGF	PU	MU	B	Sn	Total	F	PGF	MGF	PU	MU	B	Sn	Total
—24				5	6	30	18	59				5	9	40	35	89
25—29	1				2	1	11	15		1	3	4	4	3	15	30
30—34	2	2		1	3	3	9	20			3	1	2	5	12	23
35—39	1			1	6	6	11	25	2	2	3	2	4	9	14	36
40—44	4	5	3	2	1	14	10	39	3	1	3	5	4	21	6	43
45—49	4	4	2	4	4	14	2	34	4	5	2	2	2	27	6	48
50—54	2	9	6	5	7	25	2	56	4	1	2		7	25	2	41
55—59	3	4	4	6	6	29		52	4	2	3	6	6	26	1	48
60—64	7	7	8	15	12	27		76	9	6	7	15	8	20	1	66
65—69	12	5	10	15	17	17		76	11	8	9	21	17	21		87
70—74	16	17	14	28	22	13		110	18	16	12	23	24	10		103
75—79	16	11	11	15	20	2		75	18	11	10	15	26	4		84
80—84	12	12	13	11	17	3		68	12	11	10	12	15	1		61
85—	10	5	6	9	7			37	5	11	11	12	8			47
Total ..	90	81	77	117	130	184	63	742	90	75	78	123	136	212	92	806

Women

Age	Patient group								Control group							
	M	PGM	MGM	PA	MA	S	D	Total	M	PGM	MGM	PA	MA	S	D	Total
—24				6	5	31	19	61				6	4	36	35	81
25—29			2	1	3	4	13	23	1	2	1	4	3	5	19	35
30—34		3	4	1	1	5	14	28	3	2	3	4	3	5	9	29
35—39	2	2	1	3	2	11	12	33	2	3	1		4	5	11	26
40—44	2	3	6	3	1	13	8	36	2	3	1	2	3	16	3	30
45—49	2	3	4		3	24	2	38	2	2	3	1	6	28	1	43
50—54	2		2	6	8	31	1	50	1	3		4	7	33	1	49
55—59	5	1	3	5	3	30		47	1	1	4	8	8	31	1	54
60—64	7	5	2	13	9	19		55	8	8	7	12	6	30		71
65—69	13	9	6	23	16	26		93	10	11	11	12	21	23		88
70—74	16	17	13	26	43	18		133	18	15	13	21	21	16		104
75—79	13	12	14	24	26	5		94	11	8	17	24	29	5		94
80—84	18	17	15	8	26			84	16	9	13	13	16			67
85—	10	9	9	10	9			47	15	8	9	7	21			60
Ialt ..	90	81	81	129	155	217	69	822	90	75	83	118	152	233	80	831

e. Average Number of Relatives.

Per proposita with cervical cancer	19.0
Per control in cervical cancer	17.9
Per proposita with cancer of the corpus	17.4
Per control in cancer of the corpus	18.2

The materials show good agreement; yet there is a certain difference between the patient and control materials in cervical cancer, which is due to the fact that a relatively large proportion of the controls were unmarried, and the two categories sons and daughters are therefore numerically smaller in the control group. Apart from these groups, which for all practical purposes are of minor importance in the investigations presented here, there is good agreement between the various groups.

The control group is thus seen to be in good agreement with the patient group both with regard to the age distribution in the various groups of relatives and the size of the families, and also as far as domicile, occupation, and social conditions are concerned.

Chapter III.

A. CANCER OF THE HUMAN UTERUS

1. *Introduction.*

Cancer of the Uterus. Monographs and More Comprehensive Studies on Cancer of the Uterus.

Cancer of the uterus has been known since Antiquity, and numerous hypotheses have been advanced as to the genesis and causative factors of the disease.

About a century ago *Cruveilhier* wrote in his large *Anatomie pathologique du corps humain* that he had tried in vain to solve the etiology of the disease. He wrote, "Vraiment ai je interrogé les antécédents de la vie des malades pour pouvoir y decrouvrire quelque cause au moins élognée de cette terrible maladie. La vie la plus irréprochable comme la plus dissolue, la stérilité comme la fécondité, les grossesses et les accouchements les plus heureux comme aussi les plus malheureux, l'allaitement comme le defaut d'allaitement, la menstruation la plus regulière, comme la plus irregulière, l'avortement ou le defaut d'avortement, une vie active, labourieuse, comme aussi la vie la plus inoccupée, l'heredite, le temperament, les scrofules, la syphilis, les fluers blanches, les polypes uterin, les tumeurs fibreuses, aucune circonstance appréciable en un mot ne paraît exercer la moindre influence sur le développement du cancer uterin".

As early as 1924 *von Siebold* wrote his little book on cancer of the uterus; he described especially the clinical aspects of the disease, and they are so accurate and complete that they may be read with advantage to this very day. His discussion of the etiology is, however, rather fantastic. He expresses the belief that cancer of the uterus is most frequently encountered in women with many pregnancies and difficult parturitions, and further that the use of pessaries, scrofulous constitution, and reading of novels may play a rôle in the genesis of the disease.

In 1858 *Wagner* published a monograph on the pathological anatomy of cancer of the uterus. It was a fundamental patho-anatomical work,

in which he laid the foundation of the knowledge of the macroscopical anatomy and the extension of matastases in cancer of the cervix uteri.

A fundamental stastistical work on cancer of the uterus was published by *Sibley* in 1859.

Ruge & Veit (1881) were the first to describe cancer of the corpus uteri.

Only after that time a clear distinction was drawn between the two forms of uterine cancer; this was done, e. g. by *Pean* (1895), who gave an excellent description of the clinical picture and histology of both forms.

Schottländer & Kermauer (1912) added further to the knowledge of the pathological anatomy of the disease.

In his large compilatory work from 1911, *Lehre von Krebskrankheiten, J. Wolff* gave a detailed survey of previous publications on uterine cancer. In 1915 *J. L. Faures* published his book carcinomata of the uterus, in which he chiefly discussed the therapy.

Of more recent comprehensive works on uterine cancer *E. Hurdon*'s book from 1942 may be mentioned. (The material of the book has been collected in the Maria Curie Hospital, London).

2. *The Incidence of the Disease in Denmark and the Ratio between Cancers of the Cervix and the Corpus Uteri.*

According to the notifications received by the Cancer Registy during 1942—44 (*Clemmesen & Busk*, 1948) uterine cancers, comprising cancers of the cervix and the corpus, form 17.01 per cent. of all cancers in women and are thus the second largest group of cancers in women. The largest group is breast cancers (19.25 per cent.). The distribution of uterine cancers is as follows: 11.53 per cent. are cervical cancers, 3.83 per cent. cancers of the corpus, and 1.65 per cent. non-specified uterine cancers. (The ratio between cancers of the cervix and the corpus is thus approximately 3 : 1). The distribution of cancers of the cervix and the corpus will, of course, depend on the age distribution within the group of the population being considered (*Clemmesen*, 1946).

Cancer of the two parts of the uterus differs in many ways, and in the following the differences will be discussed and the material arranged accordingly. It is obvious that the study of the relatively small number of patients examined cannot add essentially to our knowledge of the disease as such, but the small number may to some degree be compensated for by the thorough knowledge of the previous life-course of these patients.

3. *Site in Organ and Histology of Tumours.*

Most commonly *cancer of the cervix uteri* arises from the portio vaginalis, less frequently from the endocervix. In both cases a papillomatous or infiltrating variety of cancer may develop. Histologically, it may be a squamous-cell carcinoma arising from the epithelium lining the portio vaginalis or endocervix, less frequently a cylindrical-cell carcinoma from the glands.

The distribution of the 200 cases of cervical cancer in my material was as follows: 195 solid carcinomata, four adenocarcinomata, and one adenocarcinama + solid carcinoma. In 1942 *Hurdon* found among 1296 cases of cervical cancer adenocarcinomata in six per cent. of the cases, whereas the remaining cases were solid carcinomata.

Pack & Lefevre (1930) had 0.42 per cent. adenocarcinomata.

Cancer of the corpus uteri arises from the cylindrical epithelium of the corpus and, with a few exceptions, assumes the form of adenocarcinoma; sometimes a mixture of squamous-cell carcinoma and adenocarcinoma, and in rare cases true squamous-cell carcinomata may be encountered.

The distribution of the 90 cases of cancer of the corpus in my material was as follows: 68 adenocarcinomata, 10 solid carcinomata, 10 adenocarcinomata + solid carcinomata, one sarcoma, and one sarcoma or anaplastic carcinoma.

Hurdon reported that adenocarcinoma was the most frequent variety in her material, a mixture of adenocarcinoma and solid carcinoma was also frequent, while there were only two cases of solid carcinoma. Squamous epithelium is never found in the endometrium in normal adult females (*Hintze*, 1928). How squamous epithelium develops in the corpus in unknown. Sarcoma of the uterus is very rare; according to *Hurdon* it constitutes only 0.5 per cent. of all malignant tumours in the uterus (seven out of 1425 cases).

4. *Etiological Factors.*

a. Age at Onset of Disease.

Cancer of the cervix occurs most commonly before 50 years of age with a maximum between 45 and 50 years, i. e. just before or about the menopause, but it may also occur at any other age, right from early childhood to advanced age. It is, however, very rarely encountered before the twentieth year. In a series comprising 3000 cases from the Mayo Clinic, *Bowing & McCollough* (1941) found only one woman under 20 years of age; *Hurdon* reported one case, aged 18, among 1340 cases. *Ackerman*

& del Regato (1947) had four per cent. under 30 years of age in 453 patients. The Danish Cancer Registry: Two patients among 1633 were 20 years old; the oldest patient was 91 years.

Hurdon had three cases aged 86 years.

The youngest patient in my material was 26 years, the oldest 83 years; 44 per cent. were in the age group 40—55 years.

Cancer of the corpus is most frequent after 50 years of age — usually after the menopause. The highest incidence is found between 55 and 60 years of age. The disease is very rare before the thirtieth year. Among 268 cases *Hurdon* had only one case between the ages of 20 and 29. The Danish Cancer Registry: Six of 504 patients were under 30 years; the oldest patient was 88 years.

The youngest and oldest cases in my material were 36 and 78 years respectively; 70 per cent. were in the age group 50—65 years.

It is noteworthy that adenocarcinoma of the uterus may occur in childhood. The youngest case has been reported by *Lockhart* (1935) in a girl aged two years and three months. The symptoms were vaginal bleeding and discharge and a palpable abdominal tumour. Similar cases have, for example, been reported by *Hirst* (1929) in a 15-year-old girl, by *Morse* (1930) in a 10-year-old girl, and by *Gilbert* (1932) in an 11-year-old girl.

The age distributions of my material are in good agreement with those reported in surveys from other countries. Only one survey from Russian clinics, published by *Parabučev* (1930) shows deviations from the age distributions usually reported. He stated that 24 per cent. af all cervical cancers were found between 25 and 30 years of age. (In the survey published by the Cancer Registry in 1944 3.9 per cent. of all cervical cancers were found in this age group). In his comments on these findings *Parabučev* attributed the large number of cervical cancers in young women to the effects of artificial abortions and to the use of contraceptives.

In analogy with the curve for breast cancer the curves for cancers of the cervix and the corpus have maxima, which differ from those of most other forms of cancer, which usually have their highest incidence about 60 to 70 years or even later. From this *Wespi & Sauter* (1943) conclude that these forms of cancer are related to the normal function of the organ from which the diseases arise.

Even though a high incidence — this applies partially to cervical cancer and particularly to cancer of the corpus — is found after the menopause, the genesis of cancer is nevertheless supposed to be related to the sexual function owing to the fact that through experimentally induced cancers and occupational cancers it has been empirically established that cancer has a prolonged latent period; in human cancers this

latent period may be as long as from 10 to 25 years, which may in turn explain the shift to the more advanced age groups of the highest incidence of cancer.

Wespi & Sauter (1943) find that the curve for cancer of the corpus has a later and steeper fall than the corresponding curve for cervical cancer; in other words, the highest incidence of the former extends over a smaller number of years. The curves made out by the Cancer Registry for uterine cancers show the same tendency. A conspicuous increase of the curve for cancer of the corpus occurs about the age of 40, and 51 per cent. of the cases fall within the age groups from 50 to 65 years. The corresponding curve for cervical cancer shows a considerable rise already at 25 years, and 46 per cent. of all cases fall within the age groups from 40 to 55 years.

b. Marital State.

Practically all investigators agree that an important causative factor in uterine cancer is to be found in the normal and patho-physiological conditions related to pregnancy and parturition. A tabulated survey of the marital state of the patients in series from the literature and my own material is given below in Tables 7 a and 7 b.

Table 7 a.

Marital state of the patients with cervical cancer.

Author	Year	Number of patients	Married (+ widowed and divorced)	Unmarried
			Per cent.	Per cent.
Sibley	1859	135	123 = 91.1	12 = 8.9
Williams	1908	156	146 = 93.6	10 = 6.4
Pack & Lefevre ...	1930	2134	96.5	3.5
Hurdon	1942	1340	1278 = 95.4	62 = 4.6
Brøbeck	1948	200	186 = 93	14 = 7

Table 7 b.

Marital state of the patients with cancer of the corpus.

Author	Year	Number of patients	Married (+ widowed and divorced)	Unmarried
			Per cent.	Per cent.
Norris & Vogt	1924	115	74	26
Lane-Claypon	1927			15.4
Pack & Lefevre ...	1930	233	86.7	13.3
Masson & Gregg ..	1940	730	90	10
Hurdon	1942	268	175 = 65	93 = 35
Brøbeck	1948	90	65 = 72	25 = 28

It appears from the tables that approximately 95 per cent. of the women with cervical cancer were married. The statements with regard to cancer of the corpus are fluctuating (from 65 to 90 per cent. married).

If the propositae are divided according to their marital state and compared with the calculated distributions (calculated on the basis of the distribution according to marital state in Denmark east of the Great Belt (census 1940, V- A- 22) i. e. the district from which the Radium Centre receives its patients, and taking due regard to the age distribution), the results are as shown in Table 8.

Table 8.
Distribution of the patients according to marital state.

	Patients with cervical cancer		Patients with cancer of the corpus	
	Observed	Calculated	Observed	Calculated
Unmarried	14	36.8	25	15.0
Married	143	131.0	38	51.9
Divorced	14	9.4	2	4.3
Widowed	29	21.0	25	17.9
No information ..	—	1.8	—	0.9
Total ..	200	200.0	90	90.0

Table 8 shows the well-known fact that there are fewer unmarried patients with cervical cancer and more unmarried patients with cancer of the corpus than should be expected. For married women the tendency goes in the opposite direction. In both forms there are more widows than should be expected.

A survey of the age distributions in cancers of the cervix, the corpus, and the breast, made on the basis of a Danish material from the Cancer Registry (*Clemmesen*, 1948) and divided according to marital state, shows that in cervical cancer the increase occurs at an earlier age in married women, i. e. married women develop cancer at a lower age than unmarried, while a corresponding difference cannot be shown in cancer of the corpus. In cancer of the breast the reverse is the case. Here the increase of the number of cases occurs earlier in unmarried than in married women. From this it may be concluded that the general disposition to cervical cancer is not very pronounced, but it is appreciably increased when the women marry and bear children. In cancer of the breast child bearing and lactation seem to have a prohibitive effect.

c. Fertility; Influence of Pregnancy and Parturition.

Many investigators have discussed the relation of uterine cancer to fertility. It is generally agreed that cervical cancer is more frequent in

women who have borne children, while cancer of the corpus has the highest incidence in nulliparae. It appears that, on an average, ten per cent. of the patients with cervical cancer are nulliparae, while the corresponding figure for cancer of the corpus is 28 per cent. (*Sibley, Roger Williams, Knack, Pfleiderer, Masson & Gregg, Wespi & Sauter, Ackerman & del Regato, Bowing & McCollough, Hurdon, and others*).

On the basis of tables of the number of pregnancies in Danish women during the period 1936—40 prepared by the Cancer Registry it has been calculated how many births might be expected in the patient materials. A comparison between the actual number and the calculated number of children in the patient materials is shown in Table 9 a.

Table 9 a.

The actual and calculated numbers of births in patients with cervical cancer, cancer of the corpus, and cancer of the breast (*Jacobsen*).

Materials	Actual number of children	Calculated number of children	Ratio between actual and calculated numbers
Patients with:			
Cancer of the cervix	526	401.0	1.312
Cancer of the corpus	142	195.5	0.726
Cancer of the breast (*Jacobsen*)	285	420.7	0.677

Table 9 a shows that the fertility in patients with cervical cancer is higher than in the population in general, whereas it is lower in patients with cancer of the corpus, and in the latter category practically the same as in patients with cancer of the breast.

If the patients are divided according to the actual number of children and compared with the calculated number, a divergency is also apparent.

It appears from Table 9 b that the groups with many children contain more patients with cancer of the cervix than should be expected and fewer patients with cancer of the corpus, for which the figures are similar to those found for patients with cancer of the breast (*Jacobsen*).

The relatively high number of births for patients with cervical cancer is — as *Wespi & Sauter* point out — the more striking because this form of cancer is often found in younger women in whom a smaller number of births should be expected since they often die before the end of the reproductive period.

Cervical cancer in virgins is very rare; however, *Peller* (1922) reports two cases. Among 497 cases of uterine cancer *Knack* (1912) claims never to have seen cervical cancer but not infrequently cancer of the corpus of a virgin uterus. *Knack* expresses the belief that the disposition to cervical cancer increases with the number of births. *Hurdon* claims that child births after the first do not seem to be a predisposing factor, and in agree-

Table 9 b.

Distribution according to the number of children of patients with cancer of the cervix, cancer of the corpus, and cancer of the breast (*Jacobsen*) compared with the calculated number.

Number of children	Patients with cancer of the cervix		Patients with cancer of the corpus		Patients with cancer of the breast	
	Observed	Calculated	Observed	Calculated	Observed	Calculated
0	26	43.8	36	17.5	70	39.0
1	44	50.1	17	21.7	53	47.9
2	44	47.3	13	21.6	31	47.4
3	30	26.0	10	12.3	20	26.8
4	24	13.3	6	6.5	16	14.0
5	12	7.7	6	3.9	2	8.4
6	7	4.2	0	2.2	1	4.6
7	5	2.7	1	1.4	2	3.0
8	2	1.6	1	0.9	2	1.9
9 and over ...	6	3.3	0	2.0	0	4.0
Total ..	200	200.0	90	90.0	197	197.0

ment with this *Deelman* (1920) expresses the opinion that the incidence of cervical cancers does not increase with the number of births. It is, of course, especially obstetrical traumas which have been held responsible for the fact that the cervix is so frequently the site of the cancer in multiparae.

Emmet (1878) maintained that a cancer of the cervix may always be traced back to poorly healed lacerations. Some investigators have expressed the opinion that the cancer should be due to regenerative changes in the laceration, others that the cancer was more likely to be due to the eversions and inflammations in the cervical mucosa arisen from the lacerations. Although unhealed infected cervical tears may be supposed to be precursors of cancer, it is doubtful if a smooth well-healed tear can undergo malignant changes.

In the examination of several hundred cases of cervical cancer *Hurdon* found no evidence that simple trauma was concerned in the production of cancer, and in the cases of healed lacerations there was no apparent relation to the cancer.

That even repeated traumas need not necessarily be concerned in the production of cervical cancer can be seen from the fact that this disease is very rare in cases of prolapse of the uterus (*Craver*, 1935).

d. Influence of Hormonal and Inflammatory Changes on Cervical Cancer.

For many years the changes occurring at childbearing and their sequelae were considered the most important factors in the origin of cervical cancer. Many investigators are now in favour of the view that purely

physiological changes in the cervical epithelium during pregnancy may play a rôle. *Hofbauer* (1931, 1939) has examined sections from cervices in pregnant women and has found downward epithelial proliferations without simultaneous infectious changes. *Hofbauer* concludes, "The cellular changes which occur in the cervical mucosa during pregnancy may perhaps elucidate the problem in as much as pre-existing epithelial proliferation, irrespective its cause, has in recent discussions been given a prominent position as a potential factor predisposing to malignancy".

Hofbauer is thus of the opinion that when cervical cancer pre-eminently affects women who have borne children, this must be attributed to the excessive hormonal stimulation of the cervical mucosa during pregnancy, originating from the ovaries. (*Doisy, Thayers & Veler* (1930) and *Butenant* (1929) have shown that estrogenic substances which are found in the urine of pregnant women have an effect similar to that of the highly carcinogenic 1 : 2 : 5 : 6-dibenzanthracene).

Hofbauer's views are also to some extent supported by pathological studies by *Schiller* (1928), *Hurdon*, and others, who have shown that precancerous changes in the cervix need not necessarily be found in places with cervicitis or cervical lesions, but on the contrary are often found in apparently normal epithelium.

Some recent discoveries shake, to some extent, the foundations of the theory of inflammation as a cause of cervical cancer. As will be mentioned under the section on uterine cancers in experimental animals, it has in some instances been possible to induce malignant tumours in the cervix of experimental animals by estrogenic hormones. Histologically, these tumours are cancers and can infiltrate the rectum and the bladder wall and give metastases to the regional lymph nodes.

As stated by *Taylor* (1944) the main problem must then be to find a satisfactory probability that hormonal conditions in women with these types of tumours resemble those which must be artificially established in order to induce similar tumours in experimental animals.

The methods for investigating ovarian function are still incomplete, and the clinical probability of hormonal disorder with development of tumour is indirect and difficult to evaluate. The difficulties are increased by the fact that secretion of estrogenic hormones at the time when the patient has developed a tumour does not say anything about the conditions when the tumour began to develop — months or years before.

Cancers of the portio vaginalis do not seem to have a tendency to be associated with other changes attributable to an estrogenic causal factor. Such cancers have not been reported in association with granulosa-cell tumours, and they seem to have no connection with hyperplasia. When uterine cancer and breast cancer occur in the same person, the corpus has a higher incidence of involvement than the cervix.

Even though the theory has gained ground during the last 10—15 years that cervical cancers may be produced as a result of hormonal changes, whether physiological or pathological, it does not, however, explain the fact that fortunately it is only a minority of women who have borne children that develop cancer of the cervix. Many investigators are still inclined to believe that abnormal changes of the mucosa of the cervix due to inflammation are concerned in the production of cervical cancer, or that a combination of these two factors must be present.

Cervicitis so common especially in married women is often considered a precancerous lesion. *Orndoff* (1931) regards the pathological cervix as the most common example of a precancerosis, which he defines as follows, "A condition of the tissues in which they have suffered insult from irritation which may affect growth control to such an extent that hyperplasia and malignant tendencies may follow". He emphasizes that cells exposed to irritation may lose all their functions except the fundamental properties, reproduction and growth.

In an investigation on cervical cancer in young women *Schreiner & Wehr* (1934) found that all, except one, had borne children, and all of them complained of leukorrhea.

In a series of 850 infected cervices, *Bailey* (1930) found that chronic cervicitis is an important causative factor in cervical cancer.

Among my 200 cases of cervical cancer there were 22 (11 per cent.), who gave a history of previous hospitalization, and often operation, for inflammation of the genital tract.

After adequate treatment of 2895 cases of cervicitis, followed up for ten years or more, *Craig* (1938) found that no single case developed a cervical cancer, and consequently he believes to have averted this tumour in 112 women.

A careful and adequate therapy of cervicitis must therefore still be considered important to the prevention of cervical cancer.

e. Influence of Hormonal Changes on Cancer of the Corpus.

(Inter alia, the interrelationship between endometrial hyperplasia, estrogen-producing tumours in the ovaries, and endometrial cancer; age at menopause; influence of hormonal therapy).

While the influence of a possible estrin stimulation on the genesis of cervical cancers is not definitely known, these conditions have been more fully elucidated as far as cancers of the corpus are concerned.

The earlier view that cancer of the corpus might be provoked by a chronic endometritis, has now been almost completely abandoned. Chronic endometritis in the corpus is a rare lesion as compared with chronic cervicitis.

Healy (1940) is of opinion that obliteration of the cervical canal with

retention of fluid may possibly irritate the mucosa and give rise to abnormal cellular proliferation and development of carcinoma.

Crossen & Crossen (1941) have emphasized that in women with cancer of the corpus the menopause is often delayed, i. e. occurs after 50 years of age. This means that the endometrium has been subjected to estrogenic activity for an unduly prolonged period. The endometrium is a very sensitive barometer registrating the slightest fluctuations in the ovarian estrogenic activity. While the estrogenic activity up to the time of cessation of normal menstruation cannot with certainty be supposed to have any pathological effect, *Crossen & Crossen* regard a continuation of folliculin stimulation beyond the age at which menstruation should normally end and involution of the endometrium begin, as pathological and capable of creating favourable carcinogenic conditions.

Crossen & Crossen find that most of their patients with cancer of the corpus have a delayed menopause and exhibit signs of an abnormal estrin stimulation, conditions manifesting themselves as endometrial hyperplasia. The histological picture of an endometrial hyperplasia is as follows (*Taylor*, 1944): Glands of varying size, surrounded by non-secreting epithelium. The picture varies from one which is difficult to distinguish from normal proliferating epithelium to changes which may be suspected to represent an incipient adenocarcinoma.

An examination of the age at menopause of my patients with cancer of the cervix and cancer of the corpus compared with corresponding figures from a report of 731 cases of cancer of the corpus published by *Masson & Gregg* (1940) is given in the following table.

In a comparison with 190 women, picked at random as controls, *Masson & Gregg* did not find any definite delay of the menopause in patients with cancer of the corpus.

Table 10.

Age at menopause in propositae with cancer of the cervix and cancer of the corpus and the corresponding figures from *Masson & Gregg*'s report of 731 cases of cancer of the corpus.

	Number of cases	Postmenopausal	Premenopausal	Premature menopause produced by operation or radiation therapy	Menopause before 50 years	Menstruation ceased at 50 or later or continuing at examination after 50 years
		Per cent.	Per cent.	Per cent.	Per cent.	Per cent.
Own cases:						
Cancer of the cervix	200	81 = 40.5	115 = 57.5	4 = 2	55 = 63	33 = 37
Cancer of the corpus	90	70 = 77	15 = 17	5 = 6	37 = 49	39 = 51
Masson & Gregg's cases:						
Cancer of the corpus	731	498 = 68	221 = 30	12 = 2		300 of 498, i. e. 60

Randall (1945) found that 35 per cent. of his cases of cancer of the corpus menstruated up to or after the age of 51 years, while this was the case with only eight per cent. of a control group.

An examination of the age at menopause in 302 women from Copenhagen was carried out by *Clausager-Madsen & Ytting* in 1942. From their report it appears that in 60 per cent. the menopause occurred before the age of 50, 40 per cent. after 50.

My own investigations also point to a delayed menopause in patients with cancer of the corpus; menstruation ceased at a later age than in cervical cancers, and it must be justifiable to conclude that endometrial hyperplasia and, perhaps, cancer of the corpus may be intimately related to an abnormal folliculin production in the ovaries. (Also in cancer of the breast a tendency to delayed menopause has been observed, *Olch*, 1937; *Blank*, 1944).

Herrel (1939) had never seen endometrial cancer in a castrated woman; *Smith* (1941), on the other hand, reported three cases of cancer of the corpus, which had occurred 15 years after bilateral oophorerectomy, which — according to *Ackerman & del Regato* — means that the direct relation between estrogenic hormones and carcinoma is still an open question.

In granulose-cell tumours and theca-cell tumours of the ovaries, which both give rise to intense estrogenic hormone production, hemorrhage from the hyperplastic endometrium will often occur, and there is a close relation between these tumours and endometrial cancer, which has been described by several investigators, e. g. *Clemmesen* (1948). An immediate cure of endometrial hyperplasia can be effected by castration.

Ingraham, Black & Rutlege (1944) reported two cases of endometrial cancer in women with granulosa-cell tumours and one case in a woman with a theca-cell tumour of the ovary.

The relation of endometrial hyperplasia to cancer of the endometrium is thus an important point.

Endometrial hyperplasia is, however, a relatively common disease, and a direct transition from hyperplasia to cancer is difficult to demonstrate; follow-up studies of endometrial hyperplasia have, in fact, shown only very few cases of subsequent development of cancer.

In follow-up studies of 24 patients with indometrial hyperplasia *Hintze* (1929) could not find any transition to cancer.

Nor did *Taylor* (1932) find any transition to cancer in a series of 85 cases of hyperplasia; in 15 of 152 cases of endometrial cancer he found signs of hyperplasia (a figure which must be taken with some reservation because hyperplastic changes may be concealed by an extensive carcinoma).

Taylor & Millen (1938) found endometrial hyperplasia in 15 out of 34 cases of cancer of the corpus, (of 99 non-malignant control cases in the same age group only 11 cases of endometrial hyperplasia were found),

and *Herrel* (1939) found a proliferative type of endometrium in 48 out of 50 cases of cancer of the corpus.

During recent years it has been observed that patients with cancer of the corpus not infrequently also suffer from other diseases which suggest hormonal imbalance. *Ackerman & del Regato* (1947) find a high incidence of obesity, diabetes, and hypertension; *Moss* (in press) has also frequently found diabetes in association with cancer of the corpus — in 15 out of 23 cases —, a family history of diabetes in four cases, and abnormally high blood pressure in 18 cases.

Randall (1945) finds that women with cancer of the corpus are generally of short stature with broad hips and short fingers.

Unfortunately, these statements have been so scattered and appeared so late that I have been unable to make a similar analysis of my series of patients, but I am under the impression that these investigators are right. An investigation of these conditions will be of great interest.

In this connection it will be natural briefly to discuss the development of cancer in relation to treatment with estrogenic hormones. It is a well-known fact that administration of estrogenic substances during the menopause may give rise to endometrial hyperplasia and bleeding (e. g. *Novak*, 1944). While cervical cancer has been induced in experimental animals by means of estrogenic hormones (*Gardner, Allen, Smith & Strong*, 1938), endometrial cancer does not seem to have been produced in the same way.

Gemmel & Jeffcoate (1939) have reported development of cervical cancer in three of 43 patients treated with estrogenic substances for senile vaginitis and kraurosis vulvae.

Fremont-Smith, Meigs, Graham & Gilbert (1946) report a case of endometrial cancer, which developed after prolonged estrogenic therapy.

Clemmesen (1948) found premalignant changes in the endometrium of a patient treated for ten years with large doses of estrogen.

Geist & Salmon (1941) did not find any case of endometrial cancer in 200 women treated through prolonged periods with large doses of estrogenic hormones.

In the opinion of *Twombley & Pack* (1944) a definite relationship between treatment with estrogenic substances and development of endometrial cancer has not been proved. *McLead* (1939) expresses the belief that development of cancer need not be feared in the usual, fairly short courses of treatment with small doses of estrogenic substances. The same applies to *Cramer* (1939), who discusses the problem with a view to cancer of the breast; yet he says that a history of breast cancer in the family should call for care on the part of the physician.

Zondek (1947) never observed the inducing of any malignant uterine tumour during 20 years of clinical experience with estrogenic hormone. In his opinion the fear that estrogenic hormone produces cancer in human

beings is highly exaggerated. "Estrogenic hormone is a harmless drug, although the limits of its dosage must, of course, be strictly adhered to, as with every other drug . . ."

Even though it must be presumed that protracted treatment with large doses of estrogenic substances about the menopause may have some influence on the development of cancer of the endometrium, it is, however, of rare occurrence; with the extensive use of estrogenic substances in gynecology an indisputable causative relation might be expected to be more frequent. Only when substitution therapy, such as the administration of insulin in diabetes, is used for a number of years, the treatment may — in view of the experience gained in animal experiments — be said to involve a certain risk.

Some of my patients have given a history of estrogenic treatment about the menopause, but not in any instance to such an extent that it might reasonably be supposed that the cancer was provoked by this therapy.

f. Social Conditions of Patients.

For a long time it has been well known that cervical cancer has its highest incidence among the lower social classes, while cancer of the corpus is considered more frequent in the higher social classes (see, e. g. *Schroeder* (1886), *Weinberg & Gastpar* (1904), *Johnstone* (1939), and *Hartmann* (1925)).

The 200 patients with cervical cancer and the 90 patients with cancer of the corpus were divided according to the occupation of the husband and, if unmarried, according to their own occupation into the following groups: Employers, salaried employees, workers (skilled and unskilled), and domestic servants, and the result is shown in Table 11.

A statistical evaluation of the figures does not disclose any significant

Table 11.

Social distribution of patients with cancer of the cervix and cancer of the corpus.

Occupation	Cancer of the cervix			Cancer of the corpus		
	Men	Per cent.	Women	Men	Per cent.	Women
Employers	47	25.3	3	23	35.4	2
Salaried employees	40	21.5	1	18	27.7	12
Workers (skilled and unskilled)	99	53.2	3	24	36.9	4
Domestic servants			7			7
Total ..	186	100.0	14	65	100.0	25
Unskilled workers alone ..	41	22.0		9	13.8	

difference between the distributions found for cervical cancer and cancer of the corpus. It is seen that 53.2 per cent. of the patients with cervical cancer are married to workers; the same applies to only 36.9 per cent. of the patients with cancer of the corpus. The remaining cases, i. e. 46.8 and 63.1 per cent., are almost equally distributed on employers and salaried employees in the two materials. Thus these figures provide statistical evidence in support of the theory that cervical cancer has a higher incidence than cancer of the corpus in the lower social classes. It is also seen that the percentage of patients with cervical cancer married to unskilled workers is higher than that of patients with cancer of the corpus, 22 per cent. and 13.8 per cent. respectively.

From the columns showing the number of unmarried women it appears that the cases are evenly distributed, apart from the group of salaried employees. Among 14 unmarried patients with cancer of the cervix there is only one salaried employee; among 25 unmarried patients with cancer of the corpus there are 12. Also among unmarried patients the tendency seems to point to lower social conditions as far as cervical cancer is concerned. Judging from my visits to and interviews with the patients and their relatives I am under the impression that a far greater degree of poverty was prevailing among the patients with cervical cancer than among those with cancer of the corpus. However, the above figures do not fully reflect the actually existing difference in social conditions.

Also *Hurdon* finds a close relation of the development of cancer of the cervix to the social conditions of the patients, but she considers the problem so closely associated with fertility, which is also highest among the lower social classes, that it is impossible to decide which of the two factors has the predominant influence. It is, however, noteworthy that also as far as unmarried women are concerned, there is a relation between cervical cancer and social conditions.

Stocks (1939) has investigated the mortality from uterine cancer (90 per cent. of the deaths are probably due to cervical cancer (*Hurdon*)) in various districts in England and Wales, and he, too, finds a close relation to social standard and fertility, but no indication as to which of these two factors has the predominant influence. However, the great regional differences in the mortality from uterine cancer cannot be fully explained on the basis of these conditions. *Stocks* quotes the Registrar-General's Report on Occupational Mortality from 1930—32:

"Although the resemblance between the gradient of fertility of married couples according to social class and the gradient of mortality of married women from uterine cancer naturally suggests some causative connection, the existence of a similar though not so steep gradient of mortality according to social class amongst single women seems to show that other important factors besides childbearing are involved".

In order to elucidate the problem *Stocks* suggests that comparative investigations of "social stories" and habits of two districts with a high and a low mortality from uterine cancer should be carried out.

Hurdon believes that unhygienic habits may play a rôle. In this connection it is interesting to note that it is a common experience that prostitutes rarely develop cervical cancer. This was pointed out by *Parent-Duchâtelet* already in 1857. He thought that the explanation was that most commonly prostitutes died of pulmonary tuberculosis before they reached the cancer age.

In a report on a case of (syphilitic?) ulceration of the portio vaginalis *Howitz* (1907) states that *Rudolph Bergh* has told him that during the 38 years in which he had been in charge of Rudolph Bergh's Hospital he had never seen a case of uterine cancer. It has, however, repeatedly been reported that a strikingly large number of patients with cervical cancer also has syphilis. *Levin, Kress & Goldstein* (1942) found syphilis in 3.9 per cent. of the cases among 930 patients with cervical cancer. I found syphilis in four cases, or two per cent. of the cervical cancers, and in one case, or 1.1 per cent. of the cancers of the corpus.

g. Nationality.

There are several interesting factors in the relation of uterine cancer to nationality.

An investigation by *Smit* (1941) comprising a series of 3106 women treated at the Memorial Hospital for cervical cancer from 1916—37 shows a strikingly small number of Jewesses among the patients, while cervical cancer forms the largest group of cancer in Italian and British women, and particularly in negresses, in whom the incidence shows an increasing tendency. He shows that the fertility among Jewesses is not lower than that in Italien women. Jewesses are not all insusceptible to other forms of cancer. (It is interesting to note that the ratio between cancers of the cervix and the corpus, which in this country is 3:1, is almost the reverse (approximately 1:4) among Jewesses in Palestine (personal statement by *Dr. H. Karplus,* chief pathologist, Tel-Aviv, at a conference on cancer statistics in Copenhagen in 1946, to *Dr. J. Clemmesen*). According to information collected on behalf of the Danish Cancer Registry in Palestine by *Dr. Holger E. Holm* the ratio between cancers of the cervix and the corpus in Jewish women was the reverse of what is found in non-Jewish women in Western Europe. Thus in the Beiliusan Hospital at Petah Tikwa, serving a population of 150—250,000 during the years 1936—46, only one case of cervical cancer and 25 cases of cancer of the corpus were treated. The Municipal Hospital, Hadassah, Tel-Aviv, with a district of 200,000 people, treated one case of carcinoma simplex of the cervix and five cases of carcinoma of the corpus from January 1943 to May 1946).

The circumcision of Jewish males and their extremely low incidence of cancer of the penis may play a rôle, and *Smit* suggests a closer study of the bacillus smegmatis. In this connection the special rules for sexual hygiene provided in the Jewish law may also be emphasized. An orthodox Jewess is not allowed to have sexual intercourse for seven days following the cessation of menstruation, in which period she is considered unclean. Before sexual intercourse is resumed, a cleansing bath and irrigation are recommended. Also after childbirth abstinence is prescribed — after the birth of a boy for 7 + 33 days, after the birth of a girl for 14 + 66 days.

Böhmert (1937), quoted by *Stocks*, discusses the relation of the birth rate in a number of countries to the mortality from uterine and mammary cancers. He shows that the two forms of cancer are closely associated with the birth rate in such a way that the mortality from uterine cancer decreases, while the mortality from mammary cancer increases with a decreasing birth rate. The sum of the two forms of cancer is practically constant. Japan is among the countries which have the highest mortality rates from cervical cancer, while on the other hand, mammary cancer is almost unknown among Japanese women.

(According to *Cramer* (1937) cervical cancers constitute 32 per cent. of all deaths due to cancer among Japanese women; mammary cancers three per cent. — a condition which is unknown in any other country).

It would not seem unjustified to treat comparisons of mortality figures between countries of very different medical standards with some reservation, but even though there may be a considerable difference between the incidences of uterine cancer in different races and nationalities, the conditions are so closely associated with social standards, customs, fertitily, and sexual habits that definite hereditary racial differences cannot be demonstrated with certainty.

(The problem of the relation of uterine cancer to nationality and influence of social conditions has been discussed in detail by E. L. Kennaway in an article: The Racial and Social Incidence of Cancer, Brit. J. Cancer, 2: 177, 1948).

B. CANCER OF THE UTERUS IN EXPERIMENTAL ANIMALS

While mammary cancer is the most frequent spontaneous tomour in mice — in a report on a series of experiments extending over many years *Slye* (1928) says up to 90 per cent. — malignant epithelial neoplasms of the uterus are rare in mice (*Slye, Holmes & Wells*, 1944), but more frequent in rats (*Bullock & Curtis*, 1930).

Lacassagne (1932, 1936) showed that injection of estrogenic substances could produce an increased incidence of mammary cancer in mice, both females and males, and after such injections abnormal epithelial proliferation of the cervix uteri has been observed. Precancerous and carcinoma-like changes in the cervix and the vagina have been described by *Suntzeff, Burns, Moskop & Leo Loeb* (1938). By injections of large amounts of estrodiol benzoate over a long period *Gardner, Allen, Smith & Strong* (1938) succeeded in inducing a large carcinoma in the cervix uteri with metastases of the lumbar lymph nodes.

Allen & Gardner (1941) and *Allen* (1942) induced cervical cancer in up to 62 per cent. of the animals by injection of estrogenic substances. The treatment of the animals extended over more than twelve months. The tumour showed malignant character and was capable of infiltrating the bladder and rectum and giving metastases to the regional lymph nodes. It could also be transplanted to other animals and continue growth without further injections of estrogenic hormones. Neither genetic factors, nor the milk factor, which is so important in the development of mammary cancer, seem to exercise any influence on the development of cervical cancer in the experimental animals. From his experiments *Allen* concluded that since cervical cancer does not occur spontaneously in mice, the high incidence in animals treated with estrogenic substances suggests that endocrine factors are of extremely great importance in the development of this form of tumour.

Recent investigations on experimentally induced tumours of the uterus have shown that direct intrauterine application of synthetic carcinogenic substances may produce a carcinomatous change of the endometrium in mice and rats. Following intrauterine application of 1 : 2 : 5 : 6-dibenzanthracene *Ilfeldt* (1936) observed development of cancer. *Perry & Ginzton* (1937) found development of polypi in the uterus and vagina after cutaneous application of 1 : 2 : 5 : 6-dibenzanthracene. *Pierson* (1934) succeeded in inducing uterine tumours in rabbits treated with ovarian hormones. These tumours were of infiltrative character, but did not metastasize.

In this connection it may be noted that *Engle, Krakower & Hågensen* (1943) did not succed in producing uterine tumours in monkyes with estrogenic substances.

Chapter IV.

ANALYSIS OF RELATIVES OF PATIENTS AND CONTROL PERSONS WITH A VIEW TO HEREDITY IN UTERINE CANCER

1. *The Number of Cancer Cases in Families of Patients and of Control Persons.*

In order to investigate heredity in uterine cancer I have, as described in Chapter II, examined the cancer incidence among the relatives of 200 patients with cervical cancer and 90 patients with cancer of the corpus (3808 and 1564 persons respectively).

a) Cancer of the Cervix Uteri: Cancer among the relatives of the patients was found in 134 instances, or 67 per cent., and among the control relatives in 123 instances, or 61.5 per cent.

A total of 222 cases of cancer was found among the relatives of the patients, 29 of which were uterine cancers, and among the control relatives 223 cases of cancer, 17 of which were uterine cancers.

Taint in father's family was found with 44 patients and 37 controls
— - mother's — — — — 53 — — 45 —
— - both father's and mother's — — — — 24 — — 34 —
— - sisters and brothers alone — — — 12 — — 5 —
— - children alone — — — 1 patient — 2 —

The distribution of the families according to taint is as follows:

Table 12.

Distribution according to cancer cases of families of patients with cervical cancer and of control persons.

	Patients	Controls
Cancer-free families	66	77
Families with 1 case of cancer	78	61
— — 2 cases - —	36	37
— — 3 — - —	11	16
— — 4 — - —	6	6
— — 5 — - —	3	2
— — 6 — - —	0	1
Total number of cancer cases	222	223

From this it will be seen that both the cancer incidence in the two materials and the frequency with which cancer occurs within the families are practically the same.

b) Cancer of the Corpus Uteri: Cancer among the relatives of the patients was found in 70 instances, or 77.8 per cent., and among the control relatives in 60 instances, or 66.7 per cent.

A total of 163 cases of cancer was found among the relatives of the patients, 18 of which were uterine cancers, and among the control relatives 108 cases of cancer, 12 of which were uterine cancers.

Taint in father's family was found with 21 patients and 17 controls
— - mother's — — — — 24 — — 25 —
— - both father's and mother's — — — — 21 — — 12 —
— - sisters and brothers alone — — — 4 — — 6 —

The distribution of the families according to taint is as follows:

Table 13.

Distribution according to cancer cases of families of patients with cancer of the corpus and of control persons.

	Patients	Controls
Cancer-free families	20	30
Families with 1 case of cancer	22	30
— — 2 cases - —	23	20
— — 3 — - —	12	4
— — 4 — - —	8	5
— — 5 — - —	3	0
— — 6 — - —	2	1
Total number of cancer cases	163	108

It will be seen that — unlike what was found for cervical cancer — there are approximately 50 per cent. more cancer cases in the families of the patients than in the control families, and that especially among the patients there are several cases of heavy familial taint (i. e. four cases or more); these conditions point to the existence of a hereditary predisposition to cancer.

2. *Percentage of Cancer of All Sites in Various Categories of Patients' Relatives Compared with Control Relatives.*

a) Cancer of the Cervix Uteri.

Table 14.

Percentage of cancer of all sites in various categories of relatives of patients with cervical cancer and of control persons.

Category of relatives	200 patients with cervical cancer					200 normal controls				
	Number of relatives	Number of cancer cases	Per cent.	Number of uterine cancers	Per cent.	Number of relatives	Number of cancer cases	Per cent.	Number of uterine cancers	Per cent.
F	200	26	13.0			200	22	11.0		
PGF	175	11	6.3			176	11	6.2		
PGM	170	10	5.9	1	0.6	174	12	6.9	0	0
M	200	28	14.0	6	3.0	200	25	12.5	6	3.0
MGF	181	17	9.4			173	23	13.3		
MGM	184	20	10.9	3	1.6	189	24	12.7	3	1.6
B	495	9	1.8			423	4	0.9		
S	488	22	4.5	10	2.0	449	9	2.0	1	0.2
Sn	262	1	0.4			151	2	1.3		
D	264	0	0	0	0	162	1	0.6	1	0.6
PU	302	21	6.9			329	22	6.7		
PA	284	20	7.0	6	2.1	306	26	8.5	1	0.3
MU	289	16	5.5			313	16	5.1		
MA	314	21	6.7	3	1.0	336	26	7.7	5	1.5
	3808	222		29		3581	223		17	
Average ..			5.83		1.52			6.23		0.94

In the table uterine cancer is stated without specification since a division into cervical cancer and cancer of the corpus has been possible only in about 50 per cent. of the cases. This applies also to the following table for cancer of the corpus.

As appears from Table 14, the percentage of cancer of all sites is roughly the same in the two materials for most categories of relatives. In the three categories of close relatives; fathers, mothers, and brothers, the percentage of cancer is slightly higher than in the control families. For sisters the percentage is twice as high as in sisters of normal persons, and it is seen that the increase is largely due to a heavy increase in the group of uterine cancers.

The number of sons and daughters with cancer is too small to allow any evaluation.

For more distant relatives the percentage of cancer in the various categories is somewhat lower for patients than for control persons.

b) Cancer of the Corpus Uteri.

Table 15.

Percentage of cancer of all sites in various categories of relatives of patients with cancer of the corpus and of control persons.

Category of relatives	90 patients with cancer of the corpus					90 normal controls				
	Number of relatives	Number of cancer cases	Per cent.	Number of uterine cancers	Per cent.	Number of relatives	Number of cancer cases	Per cent.	Number of uterine cancers	Per cent.
F	90	18	20			90	10	11.1		
PGF	81	8	9.9			75	3	4.0		
PGM	81	8	9.9	0	0	75	4	5.3	0	0
M	90	22	24.4	6	6.7	90	15	16.7	3	3.3
MGF	77	8	10.4			78	5	6.4		
MGM	81	9	11.1	1	1.2	83	10	12.0	4	4.8
B	184	8	4.3			212	6	2.8		
S	217	17	7.8	6	2.8	233	11	4.7	1	0.4
Sn	63	0	0			92	1	1.1		
D	69	0	0	0	0	80	0	0	0	0
PU	117	15	12.8			123	11	8.9		
PA	129	12	9.3	1	0.8	118	9	7.6	0	0
MU	130	16	12.3			136	8	5.9		
MA	155	22	14.2	4	2.6	152	15	9.9	4	2.6
	1564	163		18		1637	108		12	
Average ..			10.42		2.19			6.60		1.44

It is seen that the percentage of cancer of all sites in all categories of relatives, except maternal grandmothers, is higher for patients than for control persons. The percentage for maternal grandmothers of controls is, however, very high and is exceeded only by that of mothers. Also in this case the number of children with cancer is so small that it does not allow any evaluation.

3. *Percentual Distribution by Site; Totals for Relatives of Patients and of Control Persons, Compared with All Danish Cases.*

a. Cancer of the Cervix Uteri.

Tables 16 and 17 show the total number of cancer cases among respectively male and female relatives of patients with cervical cancer and of control persons distributed according to site, given as per cent. of various sites, and compared with the total of fresh cancer cases notified to the Cancer Registry 1942—44, distributed correspondingly.

Table 16.

Percentual distribution by site of the cancer total among *male* relatives of patients with cervical cancer compared with relatives of control persons and 11.317 fresh male cases, alive or dead, notified to the Cancer Registry 1942—44.

Site of cancer	101 male relatives of patients		100 male relatives of controls		11317 males from the Cancer Registry	
	Number	Per cent.	Number	Per cent.	Number	Per cent.
Genital tract	6	5.9	3	3.0	889	7.9
Breast	1	1.0	0	0	24	0.2
Esophagus	20	19.8	10	10.0	431	3.8
Stomach	36	35.6	44	44.0	2640	23.3
Intestine	6	5.9	9	9.0	1003	8.9
Rectum, anus	7	6.9	8	8.0	1192	10.5
Abdomen	12	11.9	16	16.0	561	5.0
Skin	0	0	0	0	1068	9.5
Lip	0	0	0	0	352	3.1
Upper resp. tract ..	2	2.0	0	0	218	1.9
Upper alim. tract ...	2	2.0	3	3.0	215	1.9
Lung	2	2.0	1	1.0	652	5.8
Urinary tract	0	0	1	1.0	491	4.3
Hodgkin's disease ..	1	1.0	1	1.0	117	1.0
Leukemia	1	1.0	0	0	344	3.0
Nervous system	2	2.0	0	0	315	2.8
Other organs	2	2.0	4	4.0	680	6.0
Sarcomata	1	1.0	0	0	125	1.1
Total ..	101	100.0	100	100.0	11317	100.0

It appears from Tables 16 and 17 that the percentage for most sites is roughly the same for relatives of patients and of control persons.

However, Table 16 shows a surprisingly large number of esophageal cancers for male relatives of patients. But cancers of the esophagus and the stomach together constitute almost the same percentage in the two materials, so that the high percentage of the former may perhaps be explained by the difficulties in distinguishing between the two forms of cancer. Since cancer of the esophagus, being squamous-cell carcinoma, might be supposed hereditarily to be a counterpart to cancer of the cervix, this finding has been taken into consideration in the subsequent statistical evaluation of the figures.

It is a common experience, shared by *Jacobsen* and *Videbæk*, that it is possible only to a limited extent to obtain information of another form of squamous-cell carcinoma — cancer of the skin. Here the method fails. In spite of close questioning I obtained information of only a few cases, and the same applies to lip cancer.

This may presumably be explained by the fact that these forms of tumours, which are often cured after a single radiation treatment, are

Table 17.

Percentual distribution by site of the cancer total among *female* relatives of patients with cervical cancer compared with relatives of control persons and 14418 fresh female cases, alive and dead, notified to the Cancer Registry 1942-44.

Site of cancer	121 female relatives of patients		123 female relatives of controls		14418 females from the Cancer Registry	
	Number	Per cent.	Number	Per cent.	Number	Per cent.
Uterus	29	24.0	17	13.8	2453	17.0
Cervix	16	13.2	3	2.4	1662	11.5
Corpus	2	1.7	1	0.8	553	3.8
Non-specified	11	9.1	13	10.6	238	1.7
Ovary	5	4.1	2	1.6	636	4.4
Genital tract	0	0	3	2.4	154	1.1
Breast	18	14.9	29	23.6	2776	19.3
Esophagus	5	4.1	3	2.4	216	1.5
Stomach	20	16.5	23	18.7	2218	15.4
Intestine	5	4.1	4	3.3	1127	7.8
Rectum, anus	8	6.6	4	3.3	760	5.3
Abdomen	17	14.1	21	17.1	746	5.2
Skin	3	2.5	0	0	810	5.6
Lip	0	0	0	0	34	0.2
Upper resp. tract ..	1	0.8	0	0	80	0.5
Upper alim. tract ...	0	0	2	1.6	167	1.2
Lung	1	0.8	2	1.6	234	1.6
Urinary tract	4	3.3	4	3.3	315	2.2
Hodgkin's disease ..	0	0	0	0	112	0.8
Leukemia	1	0.8	2	1.6	215	1.5
Nervous system	0	0	0	0	313	2.2
Other organs	2	1.7	6	4.9	952	6.6
Sarcomata	2	1.7	1	0.8	100	0.7
Total ..	121	100.0	123	100.0	14418	100.1

not being recognized as cancers, and hence relatives do not know about them.

Table 17 shows that uterine cancer as a whole shows a considerably higher percentage for relatives of patients than for control relatives, and it is seen that the percentage of uterine cancer among the former — unlike what is found for control relatives — is higher than that of mammary cancer.

As to the other sites the breast shows a strikingly low percentage for relatives of patients, but apart from this, the percentage is roughly the same as for control relatives.

Tables 18 and 19 give the site of cancers found in relatives of patients and control persons arranged according to the individual categories of relatives.

Table 18.

Site of 222 cases of cancer found among relatives of 134 patients with cervical cancer and cancer cases in the family.

Site of cancer	M	F	S	B	MGM	MGF	PGM	PGF	MA	MU	PA	PU	C	Total
Uterus	6		10		3		1		3		6			29
Cervix	1		8		1				2		4			16
Corpus			1								1			2
Non-specified	5		1		2		1		1		1			11
Ovary	1		2		1				1					5
Breast	6		1		2	1	1		4		4			19
Prostate		3								2				5
Testis				1										1
Esophagus		8	1		1	3	2	3		4	1	2		25
Stomach	3	6	3	4	6	6	3	7	3	3	2	10		56
Intestine (non-spec.)	1					1						1		3
Colon	1	1	2	1					1			2		8
Rectum	2	2	1	1	2	1	1	1			2	2		15
Abdomen	1	1	1	1	5	2	1		1	1	2			16
Liver	2					1			2	1	1	2		9
Pancreas			1							1				2
Spleen		1		1										2
Skin	2						1							3
Upper resp. tract ..		1							1	1				3
Upper alim. tract ..		1								1				2
Lung	1									1		1		3
Urinary tract	2								2					4
Hodgkin's disease ..													1	1
Leukemia						1			1					2
Nervous system		1										1		2
Sarcomata						1			1		1			3
Thyroid gland										1				1
Cervical lymph nodes		1									1			2
Cancer									1					1
Total ..	28	26	22	9	20	17	10	11	21	16	20	21	1	222

Table 19.

Site of 223 cases of cancer found among relatives of 123 control persons with cancer cases in the family.

Site of cancer	M	F	S	B	MGM	MGF	PGM	PGF	MA	MU	PA	PU	C	Total
Uterus	6		1		3				5		1		1	17
Cervix	1								1					2
Corpus	1													1
Non-specified	4		1		3				4		1		1	14
Ovary					1						1			2
Breast	5		3		7		2		6		6			29
Prostate										1		1		2
Testis						1								1
External genitals									1		2			3
Esophagus		1.				2	2	4			1	2	1	13
Stomach	4	10		2	8	10	4	3	2	10	5	9		67
Intestine (non-spec.)											1			1
Colon	2	4				1	1	1		1		2		12
Rectum	1	2		2	1	1	1	1	1	1		1		12
Abdomen	1	2	2		3	3	2	1			3	3		20
Liver	2	1			1	3			3	1	1	1		13
Pancreas	1								1	1				3
Spleen														0
Skin														0
Upper resp. tract														0
Upper alim. tract		1							1	1	1	1		5
Lung		1	2											3
Urinary tract	1								3			1		5
Hodgkin's disease													1	1
Leukemia									1		1			2
Sarcomata											1			1
Thyroid gland	2								1					3
Gall bladder											1			1
Hip			1											1
Eye						1								1
Cancer						1		1	1		1	1		5
Total	25	22	9	4	24	23	12	11	26	16	26	22	3	223

b. Cancer of the Corpus Uteri.

Analogous with the tables for cervical cancer, Tables 20 and 21 give the percentual distribution by site of the total numbers of cancer cases in male and female relatives of patients with cancer of the corpus and of control persons compared with a material of all fresh cancer cases notified to the Cancer Registry 1942—44.

Table 20.

Percentual distribution by site of the cancer total among *male* relatives of patients with cancer of the corpus compared with relatives of control persons and 11317 fresh male cases notified to the Cancer Registry 1942—44.

Site of cancer	73 male relatives of patients		44 male relatives of controls		11317 males from the Cancer Registry	
	Number	Per cent.	Number	Per cent.	Number	Per cent.
Genital tract	2	2.7	2	4.5	889	7.9
Breast	1	1.4	0	0.0	24	0.2
Esophagus	9	12.3	5	11.4	431	3.8
Stomach	29	39.7	19	43.1	2640	23.3
Intestine	2	2.7	2	4.5	1003	8.9
Rectum, anus	9	12.3	3	6.8	1192	10.5
Abdomen	10	13.7	4	9.0	561	5.0
Skin	0	0.0	2	4.5	1068	9.5
Lip	1	1.4	0	0.0	352	3.1
Upper resp. tract ..	1	1.4	1	2.3	218	1.9
Upper alim. tract ..	1	1.4	2	4.5	215	1.9
Lung	2	2.7	1	2.3	652	5.8
Urinary tract	2	2.7	1	2.3	491	4.3
Hodgkin's disease ..	0	0.0	0	0.0	117	1.0
Leukemia	0	0.0	0	0.0	344	3.0
Nervous system	0	0.0	0	0.0	315	2.8
Other organs	3	4.1	2	4.5	680	6.0
Sarcomata	1	1.4	0	0.0	125	1.1
Total ..	73	99.9	44	99.7	11317	100.0

Table 21.

Percentual distribution by site of the cancer total among *female* relatives of patients with cancer of the corpus compared with relatives of control persons and 14418 fresh female cases, dead and alive, notified to the Cancer Registry 1942—44.

Site of cancer	90 female relatives of patients		64 female relatives of controls		14418 females from the Cancer Registry	
	Number	Per cent.	Number	Per cent.	Number	Per cent.
Uterus	19	21.1	12	18.7	2453	17.0
Cervix	4	4.5	0	0	1662	11.5
Corpus	3	3.3	0	0	553	3.8
Non-specified	12	13.3	12	18.7	238	1.7
Ovary	3	3.3	0	0	636	4.4
Genital tract	0	0	1	1.6	154	1.1
Breast	26	28.9	16	25.0	2776	19.3
Esophagus	1	1.1	1	1.6	216	1.5
Stomach	19	21.1	9	14.1	2218	15.4
Intestine	3	3.3	2	3.1	1127	7.8
Rectum, anus	3	3.3	2	3.1	760	5.3
Abdomen	10	11.1	11	17.2	746	5.2
Skin	1	1.1	1	1.6	810	5.6
Lip	0	0	0	0	34	0.2
Upper resp. tract ..	1	1.1	0	0	80	0.5
Upper alim. tract ..	0	0	0	0	167	1.2
Lung	0	0	2	3.1	234	1.6
Urinary tract	0	0	1	1.6	315	2.2
Hodgkin's disease ..	0	0	0	0	112	0.8
Leukemia	3	3.3	1	1.6	215	1.5
Nervous system	0	0	0	0	313	2.2
Other organs	0	0	5	7.8	952	6.6
Sarcomata	1	1.1	0	0	100	0.7
Total ..	90	99.8	64	100.1	14418	100.1

When due allowance is made for the comparatively small numbers in each individual group, it is seen that the distributions of the three materials are largely in comformity with each other. The deviations are but small; uterine cancer (and mammary cancer) are slightly more frequent in relatives of patients than in control relatives.

Thus the higher incidence of cancer among relatives of patients does not fall on cancer of a single site, but is distributed on several forms.

Tables 22 and 23 give the site of cancers found in relatives of patients and control persons, arranged according to the individual categories of relatives.

Table 22.

Site of 163 cases of cancer found among relatives of 70 patients with cancer of the corpus and cancer in their family.

Site of cancer	M	F	S	B	MGM	MGF	FGM	PGF	MA	MU	PA	PU	C	Total
Uterus	6		6		1				5		1			19
Cervix	1		2						1					4
Corpus	1		2											3
Non-specified	4		2		1				4		1			12
Ovary	2								1					3
Breast	3		9		4	1	1		6		3			27
Prostate		2												2
Esophagus						2	1	2		5				10
Stomach	6	7	2	2	2	2	3	4	1	5	5	9		48
Intestine (non-spec.)											1			1
Colon		1							1	1	1			4
Rectum, anus	2	3			1			1		3		2		12
Abdomen						1	2		2			2		7
Liver	2	3		1	1	1		1	2	1				12
Pancreas									1					1
Skin							1							1
Lip						1								1
Upper resp. tract				1					1					2
Upper alim. tract												1		1
Lung				1						1				2
Kidney												1		1
Bladder		1												1
Hodgkin's disease														0
Leukemia	1								1		1			3
Nervous system														0
Sarcomata				1					1					2
Thyroid gland		1												1
Cervical lymph nodes				1										1
Spinal column				1										1
Total	22	18	17	8	9	8	8	8	22	16	12	15	0	163

A final review of the two materials shows that the incidence of cancer is practically the same among relatives of patients and control persons for cervical cancer, whereas there are 50 per cent. more cancers among the relatives of patients with cancer of the corpus than among the control relatives.

A comparison of the percentual distribution by site of the cancer total for relatives of patients, for relatives of control persons, and for a material from the Cancer Registry shows that in the case of cervical cancer, uterine cancer is more frequent, and mammary cancer less frequent among relatives of the patients than in the control materials. As to cancer of the

Table 23.
Site of 108 cases of cancer found among relatives of 60 control persons with cancer in their family.

Site of cancer	M	F	S	B	MGM	MGF	FGM	PGF	MA	MB	PA	PU	C	Total
Uterus	3		1		4				4					12
Cervix														0
Corpus														0
Non-specified	3		1		4				4					12
Vulva											1			1
Ovary														0
Breast	1		5		3		2		2		3			16
Prostate		1												1
Testis						1								1
Esophagus						1		2			1	1	1	6
Stomach	4	7		2	1	1			2	3	2	6		28
Intestine (non-spec.)					1									1
Colon			1							1		1		3
Rectum, anus	1		1	1						1		1		5
Abdomen		1	1		1		2		1		1	1		8
Liver	2					1			1		1			5
Pancreas				1					1					2
Skin	1			1						1				3
Lip														0
Upper resp. tract ..		1												1
Upper alim. tract ..										2				2
Lung			1	1					1					3
Kidney	1													1
Bladder												1		1
Hodgkin's disease ..														0
Leukemia									1					1
Nervous system														0
Other organs						1								1
Sarcomata														0
Thyroid gland	2								1					3
Cervical lymph nodes								1						1
Hip			1											1
Cancer									1					1
Total ..	15	10	11	6	10	5	4	3	15	8	9	11	1	108

corpus the percentages of uterine and mammary cancers are slightly higher among relatives of patients than among control relatives, but here the number of cases is small, and the results require further consideration (Chapter V).

There is a strikingly large percentage of esophageal cancers among male relatives of patients with cervical cancer.

When allowance is made for the small numbers in the individual groups, cancers of other sites show roughly the same distributions for relatives of patients and control persons as well as for the population in general.

These findings show that hereditary conditions are likely to be different in the two forms of cancer, which, as already mentioned, differ also in other respects.

Cervical cancer seems essentially determined by exogenous factors. It is not possible among the relatives of patients to demonstrate any increased incidence of cancer in general, but we find a considerable increase in the incidence of uterine cancer, especially among sisters of patients where the ratio amounts to ten cases to one. If this is not explainable by exogenous influence alone, it might suggest the existence of inherited localization factors — a point which will be discussed in Chapter V.

For cancer of the corpus uteri inheritance seems to play a considerably greater part, but figures are relatively small. As shown later, however, — in analogy with *Jacobsen*'s findings for breast cancer — a distinctly increased familial taint is distributed on nearly all sites of cancer. The incidence of cancer is increased in the families of the patients, for female relatives mainly in the group of uterine cancer. If this site is excluded, the difference in cancer incidence between female relatives of patients and of control persons is still present, but no longer significant. This suggests that in cancer of the uterine corpus there is — in addition to a general hereditary disposition to cancer, which anyhow causes an increased incidence of cancer among male relatives — also a genetical localization factor.

Thus conditions for cancer of the corpus are similar to those found by *Jacobsen* for breast cancer, with the exception that the latter showed an increased incidence also from cancers of other sites, among female relatives of patients. *Jacobsen* concluded that a hereditary factor exists, common to all sites but skin and lip ("endogenous cancer as a whole"), but it must be equally justified to conclude that breast cancer — and in our case cancer of the uterine corpus — is genetically determined as such.

Chapter V.

STATISTICAL EVALUATION OF CANCER FREQUENCIES

The statistical evaluation of the figures may be divided into two sections:

1) Evaluation of the differences between the cancer frequencies.
2) Evaluation of the cancer risk.

The first evaluation can be carried out either as a direct comparison between the cancer frequencies found among relatives of patients and of control persons, or since the control groups are rather small and hence relatively incomplete as a material, through a comparison between the relatives of the patients and the corresponding expected cancer frequencies computed on the basis of the mortality statistics; that is to say a comparison with the entire Danish population. The latter method devised by *Busk* (1948) must be considered safer and has been employed here.

It is difficult to obtain sufficiently exact information as to cancer cases among more distant relatives in the investigations of propositi employed, and a direct comparison between the figures found in the investigations of propositi and those based on mortality statistics will only be possible with regard to near relatives, of whom the information is complete.

It is therefore necessary to reduce the computed frequencies for categories of more distant relatives by a fraction which is a numerical expression of the discrepancy between the observed frequencies in the control group and those computed on the basis of the mortality statistics.

If the control groups were complete, agreement between the observed and computed cancer frequencies should be expected. As will be shown later, this is, however, the case only for the categories of close relatives.

Adapted in this way, i. e. with a view to the incompleteness of information as to the cancer frequency in more distant relatives, the cancer frequencies calculated on the basis of the mortality statistics must be said to form the basis of a much safer comparison than a direct comparison between the relatives of patients and controls.

Computations of the Expected Number of Relatives with Cancer must first be carried out.

If we have a number of persons and are interested in ascertaining how many of them have probably had cancer, it is necessary to know:

1. The age distribution of these persons, and
2. The probability of these persons developing cancer at a certain age.

As the formulae used are influenced only by the age, and as the cancer probability used is an average for the entire Danish population, certain demands must be fulfilled.

a) *The relatives must not have been selected on account of cancer.* As far as possible all relatives must be known, both those who have had cancer and those who have not. If only information of relatives with cancer is available, this will, of course, have an adverse influence on the result. (On the other hand, it does not matter if the relatives have a greater cancer risk than assumed, since we take it for granted that they have the ordinary cancer risk in order to examine if it should, nevertheless, be greater).

b) *The selection must be representative with regard to other factors, which affect the cancer probability,* e. g. the occupation.

c) Finally, in the choice of cancer probability a third assumption is made. The probabilities which have been used are based on the cancer mortality 1935—39, i. e., on figures notified to the National Health Service by means of death certificates. This means that we take it for granted that the information received from the families as to cancer frequency among their relatives comprises only (or approximately only) cases in which the relatives have died from cancer. In the materials collected the information obtained concerns almost exclusively deaths due to cancer. It must therefore be justifiable to use mortality statistics. Here the mortality figures from 1935—39 have been used, even though the cancer deaths of which information was obtained were distributed over a larger number of years, thus assuming that the cancer mortality has not changed essentially within the period in question.

In mammary cancer where exact information as to similar disease in relatives may be expected to be more frequent than in uterine cancer (because the former is easier to localize and thus apt to come to the knowledge of other relatives), it will be justified to use the morbidity statistics for similar computations, as done by *Busk* (1948) in a publication commenting on *Jacobsen*'s and *Videbæk*'s monographs and forming the basis of the following calculations.

These are the most essential assumptions. The calculations give the expected number of cancer deaths in the various categories of relatives. Since the calculations are based on approximation formulae, it must for purely mathematical reasons be required that in a comparison between the observed number a and the calculated number c that $c \geqq 5$. If $c < 5$, the groups must be added until this value has been reached.

Table 24 shows the mortality from cancer of all sites, uterine cancer, and esophageal cancer at the various ages for men and women respectively. The figures cover the period 1935—39 and have been worked out by the National Health Service on the basis of death certificates.

Table 24.

Values of μ_x. Mortality for the whole country 1935—39.

Age	Men		Women		
	Cancer of all sites	Esophageal cancer	Cancer of all sites	Uterine cancer	Esophageal cancer
—24 ...	0.000031	0.000000	0.000028	0.000001	0.000000
25—29 ...	74	1	123	52	0
30—34 ...	150	0	276	125	1
35—39 ...	251	3	589	195	3
40—44 ...	529	20	1039	317	5
45—49 ...	904	28	1760	422	12
50—54 ...	1688	90	2442	412	23
55—59 ...	2869	179	3715	594	50
60—64 ...	4803	302	4949	605	92
65—69 ...	7481	418	7106	687	189
70—74 ...	11174	763	10330	770	309
75—79 ...	15483	1027	13657	796	619
80—84 ...	15964	1248	15960	712	811
85— ...	15432	1228	15983	503	549

Table 6 a shows the age distribution of relatives of patients with cervical cancer and Table 6 b the corresponding age distribution of relatives of patients with cancer of the corpus. Each of the two tables also shows the age distribution of relatives of control persons. In the following it should be remembered that the two control materials are in part identical. The control group for cancer of the corpus is in all essentials a section of the control group for cervical cancer.

By the method used here it is *per se* unnecessary to ensure that the patient and control groups are of the same size. On the other hand, in the subsequent calculations it proves practical to have the same age distribution in the two materials, because it entails the same age distribution of relatives.

Table 25 shows the observed and computed numbers of cancer cases in relatives of patients with cancers of the cervix and the corpus. Comparisons of esophageal cancer have only been made for relatives of patients with cervical cancer.

Table 25.

Observed and computed numbers of cancer cases in the patient groups.

Category of relatives	Relatives of patients with cervical cancer Number of cases of						Relatives of patients with cancer of the corpus Number of cases of			
	cancer of all sites		uterine cancer		esophageal cancer		cancer of all sites		uterine cancer	
	obs. a	comp. c	obs. a	comp. c	obs. a	comp. c	obs. a	comp. c	obs. a	comp. c
F	26	19.7			8	1.2	18	13.0		
B	9	8.2			0	0.4	8	6.5		
MGF	17	23.0			3	1.6	8	10.6		
PGF	11	23.4			3	1.5	8	10.0		
MU	16	23.8			4	1.5	16	15.5		
PU	21	27.5			2	1.7	15	14.3		
Sn	1	0.3			0	0.0	0	0.1		
Males	101	125.9			20	7.9	73	70.0		
M	28	23.3	6	3.0	0	0.6	22	15.0	6	1.7
S	22	9.9	10	2.2	1	0.1	17	9.5	6	1.8
MGM	20	29.7	3	3.3	1	0.8	9	12.7	1	1.4
PGM	10	28.9	1	3.3	2	0.8	8	13.7	0	1.5
MA	21	31.0	3	4.3	0	0.7	22	23.5	4	2.8
PA	20	32.2	6	4.2	1	0.8	12	17.2	1	2.2
D	0	0.4	0	0.1	0	0.0	0	0.2	0	0.1
Females ...	121	155.4	29	20.4	5	3.8	90	91.8	18	11.5

(The computed number c has been found by application of the formula:

$$c = \sum_{V=0}^{\infty} \left[G(5v) \cdot 5 \left[\tfrac{1}{2} \mu_{5v+2.5} + \sum_{S=0}^{V-1} \left[\mu_{5s+2.5} \right] \right] \right]$$

(cf. *Busk*).

G(5v) denotes the number of relatives who either at the time of observation or, if they had died before, at death, were between the ages of 5v and 5(v +1) years. These age distributions are stated in Tables 6 a and 6 b. $\mu_{5v+2.5}$ denotes the mortality rate for persons between the ages of 5v and 5 (v + 1) years. These values for various forms of cancer are stated in Table 24.

G(5v) multiplied by 5 $\left[\tfrac{1}{2} \mu_{5v+2.5} + \sum_{S=0}^{V-1} \left[\mu_{5s+2.5} \right] \right]$ gives the number of deaths expected among these relatives before they reach the age in question. The results for the various age groups are finally added).

It is characteristic for Table 25 that the observed number for close relatives is larger than the computed number, while the reverse holds good of more distant relatives; esophageal cancer, however, forms an exception.

Corresponding to Table 25, Table 26 shows the observed and computed numbers of cancer cases among the relatives of the controls and in the last column the ratio between the observed and computed numbers of cases in the control group for patients with cervical cancer and cancer of all sites.

Table 26.

Observed and computed numbers of cancer cases in the control groups and their ratio.

Category of relatives	Relatives of controls (cervical cancer) Number of cases of				Relatives of controls (cancer of the corpus) Number of cases of				ratio
	cancer of all sites		uterine cancer		cancer of all sites		uterine cancer		cancer of all sites
	obs. a	comp. c	obs. a	comp. c	obs. a	comp. c	obs. a	comp. c	$\frac{a}{c}$
F	22	19.5			10	11.9			1.13
B	4	6.6			6	6.0			0.61
MGF	23	22.3			5	10.9			1.03
PGF	11	25.9			3	11.7			0.42
MU	16	25.7			8	16.5			0.62
PU	22	30.1			11	15.4			0.73
Sn	2	0.3			1	0.2			—
Males	100	130.4			44	72.6			0.77
M	25	24.2	6	3.1	15	15.7	3	1.7	1.03
S	9	9.7	1	2.1	11	9.8	1	1.8	0.93
MGM	24	30.7	3	3.6	10	13.4	4	1.5	0.78
PGM	12	26.1	0	3.0	4	10.5	0	1.3	0.46
MA	26	33.7	5	4.6	15	23.1	4	2.7	0.77
PA	26	31.4	1	4.3	9	15.8	0	1.9	0.83
D	1	0.2	1	0.1	0	0.2	0	0.1	—
Females ...	123	156.0	17	20.8	64	88.5	12	11.0	0.79

From the computations performed it should be expected that the observed and computed numbers of cancer cases in the control groups should be practically equal. This is also the case for the categories of close relatives, fathers, brothers, mothers, and sisters (and, of course, children). But the sets of numbers differ to some extent for remote relatives. The agreement is best for maternal grandfathers of patients with cervical cancer, where the observed number of cancer of all sites is 23, while the expected number is 22.3; but this is exceptional.

Since the control groups are partly identical, the ratio $\frac{a}{c}$ has only been computed for the largest group, i. e. cervical cancer, and from this the most numerous material has been used, i. e. cancer of all sites. Largely the ratio is the same for male and female relatives, who have the same relationship to the propositae. This fact supports the theory that the difference between observed and computed numbers of cancers is due to lacking knowledge about relatives on the part of the proposita, and that this proportion increases with the distance of relationship. As far as the closer relatives are concerned, the information obtained seems to be satisfactory, and this supported by the figures in Table 6 a where all fathers and mothers of the 200 propositae and the 200 controls are included. Such a control cannot be obtained for brothers and sisters, but the figures in Table 26 seem to indicate that sufficient information has also been obtained in this case. Nothing can be said about sons and daughters because of their small number.

On the other hand, if we regard the category of grandparents, conditions are quite different. The ratio for maternal grandfathers is certainly 1.03, but for maternal grandmothers only 0.78. For paternal grandfathers and grandmothers the agreement is very poor, ratios being 0.42 and 0.46. This might also be expected from the figures in Table 6 a, since it is seen that the 200 propositae have only 181 maternal grandfathers, 184 maternal grandmothers, 175 paternal grandfathers, and 170 paternal grandmothers. The corresponding figures for the grandparents of the control persons are: 173 maternal grandfathers, 189 maternal grandmothers, 176 paternal grandfathers, and 174 paternal grandmothers. The ratios for uncles and aunts vary from 0.62 to 0.83.

To avoid this difficulty in relatives of patients with uterine cancer it is assumed that the information obtained about them is equally insufficient as in the corresponding group of relatives of the controls, i. e., the computed number is to be multiplied by the ratio found. The ratios used are given in Table 27.

Table 27.

The ratios between observed and computed numbers of cases.

Maternal grandfathers and grandmothers	0.89
Paternal grandfathers and grandmothers	0.44
Maternal uncles and aunts	0.74
Paternal uncles and aunts	

It is a common experience, reflected in *Jacobsen*'s and *Videbæk*'s monographs, that information obtained about paternal grandparents is most insufficient. Presumably, the reason is that very often fathers are older than mothers. Very often the proposita does not know her paternal grandparents to the same extent as her maternal grandparents, because

the former have often died earlier than the latter, and finally it must be considered that most propositae will know more about the mother's than the father's family.

The ratios stated in Table 27 are also used for relatives with uterine cancer and relatives with esophageal cancer on the assumption that the lack of knowledge is the same for all forms of cancer. This last assumption is disputable, but we cannot work out corresponding ratios for the individual sites of cancer, since the groups here are too small to form a basis of an estimate of the ratio in the same way as for cancer of all sites taken as a whole.

Tables 28a and 28b show the observed number of cancer cases among relatives of the patients with cervical cancer and cancer of the corpus, as previously stated in Table 25. The computed numbers here are the computed numbers from Table 25 with corrections for the remote relatives. The following computation are based upon these figures.

Table 28 a.

Cervical cancer. Observed and computed numbers of cancer cases among relatives of patients after correction for lack of knowledge of remote relatives.

Category of relatives	Relatives of patients with cervical cancer: Number of cases of cancer of all sites		uterine cancer		esophageal cancer		cancer of all sites except uterus	
	obs. a	comp. c^1	obs. a	comp. c^1	obs. a	comp. c^1	obs. a	comp. c^1
F	26	19.7			8	1.2		
B	9	8.2			0	0.4		
MGF	17	20.4			3	1.4		
PGF	11	10.3			3	0.7		
MU	16	17.6			4	1.1		
PU	21	20.3			2	1.3		
Sn	1	0.3			0	0.0		
Males	101	96.8			20	6.1		
M	28	23.3	6	3.0	0	0.6	22	20.3
S	22	9.9	10	2.2	1	0.1	12	7.7
MGM	20	26.5	3	2.9	1	0.7	17	23.6
PGM	10	12.7	1	1.4	2	0.3	9	11.3
MA	21	22.9	3	3.2	0	0.5	18	19.7
PA	20	23.8	6	3.1	1	0.6	14	20.7
D	0	0.4	0	0.1	0	0.0	0	0.3
Females ...	121	119.5	29	15.9	5	2.8	92	103.6

Table 28 b.

Cancer of the corpus. Observed and computed numbers of cancer cases among relatives of patients after correction for lack of knowledge of remote relatives.

Category of relatives	Relatives of patients with cancer of the corpus Number of cases of					
	cancer of all sites		uterine cancer		cancer of all sites except uterus	
	obs. a	comp. c^1	obs. a	comp. c^1	obs. a	comp. c^1
F	18	13.0				
B	8	6.5				
MGF	8	9.5				
PGF	8	4.4				
MU	16	11.5				
PU	15	10.6				
Sn	0	0.1				
Males	73	55.6				
M	22	15.0	6	1.7	16	13.3
S	17	9.5	6	1.8	11	7.7
MGM	9	11.3	1	1.3	8	10.0
PGM	8	6.0	0	0.7	8	5.3
MA	22	17.4	4	2.1	18	15.3
PA	12	12.7	1	1.6	11	11.1
D	0	0.2	0	0.1	0	0.1
Females ...	90	72.1	18	9.3	72	62.8

A glance at the figures shows that where the difference between the corresponding sets of numbers is considerable, the observed number is larger than the computed; these differences appear almost exclusively among near relatives. From the totals for all relatives taken as a whole it appears that there is practically no difference for relatives of patients with cervical cancer when cancers of all sites are taken together.

But if the relatives are divided according to a certain diagnosis, a pronounced difference appears as far as uterine and esophageal cancers are concerned. On the other hand, for relatives of patients with cancer of the corpus great differences appear already when cancers of all sites are taken as a whole.

In the statistical test of the significance of the difference between the observed and computed numbers it is assumed that the mean value of $a\text{-}c\text{-}\frac{1}{2}$ is zero with the variance equal to the square root of the expected number. The formula (cf. *Busk*) is:

$$u_1 = \frac{a - c^1 - \frac{1}{2} \quad \text{sign.}\,(a - c^1)}{\sqrt{c^1}}$$

The values of this expression are found in Table 30. Against each value 0, 1, 2, or 3 asterisks will be found. No asterisk means that provided the assumptions are correct, the probability of obtaining such a value is greater than 5 per cent. (the value numerically less than 1.96). One asterisk means that the probability lies between 1 and 5 per cent. (the value numerically between 1.96 and 2.56); two asterisks mean that the probability lies between 0.1 and 1 per cent. (the value numerically between 2.56 and 3.29), and three asterisks indicate that the probability is less than 0.1 per cent. (the value greater than 3.29). A dash (—) indicates that the figures are too small to be used in approximation formulae. Asterisks in parentheses have the same meaning, but indicate that the exact test gives probabilities corresponding to the number of asterisks. The signs show whether the difference between the observed and computed numbers is negative or positive.

Table 29 shows the relation between the number of asterisks, probabilities, and u_1 values.

Table 29.

Key to the asterisks in Table 30.

Number of asterisks	Probability	Numerical value of u_1
0	Greater than 5 per cent.	Less than 1.96
1*	From 5 to 1 per cent.	From 1.96 to 2.55
2**	From 1 to 0.1 per cent.	From 2.56 to 3.28
3***	Less than 0.1 per cent.	Greater than or equal to 3.29

Conclusion: Among relatives of patients with cervical cancer only sisters show a significant deviation when cancers of all sites are taken together ($u_1 = 3.70$, three asterisks). This marked difference causes a significant difference also for close relatives taken as a whole, but not for all relatives.

If the diagnosis of uterine cancer is excluded, there is no longer a significant difference for sisters or other categories of relatives, nor in the totals.

The whole difference is due to uterine cancer (sisters show two asterisks) and manifests itself distinctly in the totals for this form of cancer.

Also for esophageal cancer fathers, and fathers only, show a significant difference with three asterisks, which influences all the totals, which also become significant with three asterisks. However, it must be noted that also in several of the categories of relatives there is some preponderance in the observed cases, but not by far so marked as in the event of fathers.

Table 30.

Test for significance of difference between the observed number a and the computed number of cancer cases c_1.

Category of relatives	Relatives with cervical cancer				Relatives with cancer of the corpus		
	Cancer of all sites	Uterine cancer	Esophageal cancer	Cancer of all except uterus	Cancer of all sites	Uterine cancer	Cancer of all sites except uterus
F	1.31		(+***)		1.25		
B	0.09		—		0.39		
MGF	−0.65		—		−0.32		
PGF	0.07		—		—		
MU	−0.27		—		1.19		
PU	0.04		—		1.19		
Sn	—		—		—		
Males	0.37		5.42***		2.27*		
F + B	1.24		(+***)		1.36		
M	0.88	—	—	0.28	1.67	(+*)	0.61
S	3.70***	(+**)	—	1.36	2.27*	(+*)	0.98
MGM	−1.16	—	—	−1.24	−0.53	—	−0.48
PGM	−0.62	—	—	−0.53	0.61	—	0.94
MA	−0.29	—	—	−0.28	0.48	—	0.55
PA	−0.68	—	—	−1.36	−0.07	—	0
D	—	—	—	—	—	—	—
Females ...	0.10	3.12**	—	−0.98	2.04*	2.76**	1.07
M + S	2.84**	4.51***	—	1.05	2.82**	(+***)	1.19
Total	0.35		5.20***		3.07**		
F+B+M+S	3.00**		(+***)		3.09**		

Accordingly it appears that there is no increased incidence of cancer among relatives of patients with cervical cancer such as was found by *Jacobsen* for near relatives of breast cancer patients and as shown later by the author for the families of cases of cancer of the corpus.

Thus it seems reasonable to exclude cervical as exogenous cancer from the group of "endogenous cancers". This exclusion harmonizes with the fact that the vast majority of cervical cancers are squamous-cell carcinomata, while *Jacobsen*'s "endogenous cancers" are chiefly adenocarcinomata. In animal experiments it has almost invariably been adenocarcinomata which have proved hereditarily determined. It is beyond doubt that several squamous-cell carcinomata are chiefly dependent on exogenous factors; confer, e. g., the relation of cancer of the skin to sunlight and that of cancer of the esophagus to the consequences of alcohol consumption.

As mentioned in Chapter III, a number of exogenous factors (in the widest sense of the word) play a rôle in the genesis of cervical cancer.

It will therefore be natural to assume the existence of a group of "exogenous cancers", including cervical cancer and probably cancers of the skin and the esophagus, in which the hereditary disposition to cancer is not greater than among the population in general, but if cancer develops, it seems to be apt to localize to the cervix uteri in the female and to the esophagus in the male; in other words, there may possibly be a tissue disposition localized to squamous epithelium. The high incidence of uterine cancer in sisters — far higher than the corresponding incidence among the control relatives — and an increased incidence of uterine cancer among relatives of patients with cervical cancer suggest that a hereditary localization factor may play a part, and the figures are compatible with the possibility that such a localization factor — dependent on one or several genes — is inherited recessively.

Here it is, however, very difficult to determine if we are facing a genuine hereditary disposition to cancer or an inheritance of other qualitites important to the development of cancer.

This obstacle to genetical investigation on cervical cancer is also found with regard to cancer of the esophagus where it is impossible to determine if the increased tendency to esophagal cancer among close relatives of patients (*Mogensen*) is due to inheritance of a tumour tendency or of the abnormal mind, which conditions alcoholism. That the cases of uterine cancer concentrate among sisters of patients may well be due to the same environmental conditions, including sexual habits and lack of personal hygiene, since such factors may be supposed to be important to the development of cervical cancer.

In order to elucidate this problem it would, of course, be of importance if it was possible to demonstrate an increased incidence of other squamous-cell carcinomata among relatives, and here it is striking that the frequency of esophageal cancer is higher among male relatives of the patients than of the controls. A statistically significant difference of this kind can, however, only be demonstrated for fathers; brothers cannot be expected to show an increased incidence since most of them have not yet reached the age, at which esophageal cancer is likely to develop. That a definitely increased incidence of esophageal cancer can be demonstrated for fathers and also for male relatives as a whole may to some extent support the supposition of a genetically determined tissue disposition.

Even though it is not possible to produce conclusive evidence of the presence of a heditary tissue disposition, the investigations made may suggest such a possibility.

Also for *cancer of the corpus* sisters of patients show a significant difference from controls when cancers of all sites are taken as a whole

($u_1 = 2.27$, one asterisk); the other groups — especially mothers — contribute, however, so largely that the difference for mothers and sisters together becomes significant with two asterisks ($u_1 = 2.82$). For all female relatives as a whole u_1 is equal to 2.04, one asterisk. For all male relatives as a whole the difference is also significant ($u_1 = 2.27$, one asterisk), but not for fathers and brothers taken together. For all relatives, males and females, together, and for all close relatives the difference is significant with two asterisks, u_1 being 3.07 and 3.09 respectively.

The significance for female relatives disappears when uterine cancers are excluded, i. e., the difference is concentrated on uterine cancer where the difference for mothers and sisters separately is significant with one asterisk, and for these two groups together with three asterisks and for all female relatives taken as a whole with two asterisks ($u_1 = 2.76$). The figures show that there is an increased incidence of cancer (chiefly "endogenous") in male relatives. In female relatives the cancer incidence is increased, also when uterine cancers are excluded; yet the difference is not statistically significant.

This suggests that genetically cancer of the corpus approaches the conditions found in cancer of the breast and leukemia. Cancer of the corpus seems to belong to the group of "endogenous cancers", the genesis of which depends on a hereditary character common to this group, and the investigations seem to indicate that yet another hereditary factor is responsible for the site of the cancer in this organ. However, once more I want to emphasize the difficulty, and hence the limitation of the material, involved in the fact that is has not been possible to distinguish between the two groups, cancer of the cervix and cancer of the corpus among relatives.

Evaluation of the Cancer Risk.

As there are reasons to believe that at any rate the development of cancer of the corpus depends on hereditary factors, the next step will be to search for the mode of inheritance expressed in Mendelian terms. Before this can be done, it is necessary to know the carriers of the genes. It is therefore not sufficient to operate with the frequencies of cancer observed among propositae and their relatives. Since the disease manifests itself at different ages, an age correction must be made for relatives who have not yet reached the cancer age. *The cancer risk*, i. e., the risk involved for a person to die of cancer if he passes through all the age groups in which it is possible to develop cancer (i. e. practically all age groups), must be determined for each individual category of relatives.

The cancer risk R_x up to a certain age, x years, is (cf. *Busk*):

$$R_x = 1 - e^{-\int_0^x \mu_t \, dt}$$

By means of the values of μ_x in Table 24, R_{90} is computed as the mortality risk (the cancer risk) for the Danish population in general up to 90 years of age from cancer of all sites, uterine, and esophageal cancers. The age of 90 years has been chosen because the knowledge of the mortality from cancer in the highest age groups is very limited.

It is seen from Table 31 that the cancer risk (the risk of dying from cancer) for the Danish population, calculated for cancer in general, is upwards of 30 per cent. This figure will also apply to close relatives in the control groups, where Table 26 shows a good agreement between the frequencies of cancer observed in these groups and those calculated on the basis of the mortality statistics. The cancer-risk figure for the Danish population — approximately 30 per cent. — is considerably higher than the total cancer-risk figure computed by *Jacobsen* on the basis of his control material, namely 10.8 per cent. for males and 8.5 per cent. for females, in both cases the morbidity risk for cancer of all sites. *Busk* emphasizes that these figures are at variance with the experience that almost 15 per cent. of all deaths in Denmark are due to cancer, and the definition of R shows that it cannot be less than 15 per cent. Thus *Jacobsen*'s figures for the cancer risk of the population are too small.

By corresponding calculations *Videbæk* finds that the cancer risk is at least 22 per cent. This figure is also calculated on the basis of his control material, but according to a procedure different from the one used here (no correction for lack of knowledge of the categories of remote relatives).

In order to estimate the cancer risk for relatives of patients with uterine cancer we must, since we do not know the mortality rate for relatives, assume that the cancer risk is increased by the same percentage in all age groups, i. e., if μ_x^{II} denotes the mortality for relatives, we have:

$$\mu^{II} = \frac{a}{c^1} \cdot \mu_x.$$

Here a denotes the observed number of deaths from Tables 28 a and 28 b, and c^1 the computed number from the same tables. Hence:

$$R_{90} = 1 - e^{-\frac{a}{c^1}\int_0^{90} \mu_t \, dt}$$

The values shown in Table 31 have been computed by means of this formula. It will be seen that these computations are only based on the knowledge of

1) the age distribution of the patients with the disease in question — in this case cancer of all sites, uterine cancer, and esophageal cancer,
2) the age distribution of the population corresponding to 1), and
3) the age distribution in the categories of relatives.

Table 31.

Estimate of the cancer risk R_{99} among relatives of patients with uterine cancer (in per cent.).

Material	Relatives	Cancer of all sites		Esophageal cancer		Relatives	Cancer of all sites		Uterine cancer		Esophageal cancer	
Danish population		29.2		3.0			29.5		2.9		1.2	
Cancer of the cervix	F	36.6	30.3	18.4	9.6	M	34.3	29.8	5.7	5.2		
	B	31.6		0.0		S	54.0		12.6			
	MGF	25.0		6.3		MGM	23.2		3.0			
	PGF	30.9		12.3		PGM	24.1		2.1			
	MU	27.0		10.5		MA	27.4		2.7			
	PU	30.1		4.6		PA	25.5		5.6			
Cancer of the corpus	F	38.0	36.6			M	40.1	36.4	9.9	5.6		
	B	34.6				S	46.5		9.4			
	MGF	25.2				MGM	24.3		2.2			
	PGF	46.7				PGM	37.3		0.0			
	MU	38.2				MA	35.7		5.5			
	PU	38.7				PA	28.1		1.8			

It is seen that in *cancer of the cervix* the average cancer risk computed for cancer of all sites is approximately 30 per cent. corresponding to the population (see also Table 30). If the groups parents and sisters and brothers are taken alone, it is seen that they are somewhat higher than 30 per cent. (36 per cent. and 43 per cent. respectively). Here again the large number of uterine cancers in sisters plays a part.

If a division according to different diagnoses of cancer is made — here uterine and esophageal cancers have been separated — the material shows a higher cancer risk for both these sites. Table 30 shows that this difference is significant. As the diagnosis of cancer of the esophagus — at least for remote relatives — is not absolutely reliable, and as a distinction between cancer of the cervix and cancer of the corpus could not be made, the figures must be taken with some reservation. However, they seem to afford suggestive evidence of a tissue disposition localized to squamous epithelium. It cannot be determined according to which principles such a tissue disposition must be presumed to be inherited.

In *cancer of the corpus* the total cancer risk both for males and females is seen to be higher than the average for the entire population (see also Table 30). This must be interpreted as favouring the view that hereditary factors play a part. If an attempt is made to disentangle the question as to recessivity or dominance, three categories of relatives are of interest, namely 1) parents, 2) sisters and brothers, and 3) grand-

parents and parents' sisters and brothers. The cancer-risk figures for these three categories are 39, 41, and 34 per cent.

While the cancer-risk figures in *Jacobsen*'s monograph on breast cancer for the corresponding groups are 63, 60, and 28 per cent., which with a frequency of disease of 10 per cent shows a distinct dominant behaviour of a cancer gene for "endogenous cancer as a whole", the corresponding figures for cancer in general in Videbæk's monograph are 41, 40, and 26 per cent. With a supposed general cancer risk of at least 22 per cent., the conditions here are not quite as clear as in mammary cancer, but the figures point to a dominant rather than a recessive inheritance.

If it is assumed that the cancer risk for the population in general is approximately 30 per cent., it is difficult to group the risk figures for relatives found in cancer of the corpus under one of the two headings, dominance or recessivity. From *Hultkrantz & Dahlberg*'s tables (1927), in which the expected taint figures for the said groups of relatives (sisters and brothers, parents, grandparents and parents' sisters and brothers) are stated for different frequencies of disease in the population, it is seen that the characteristic distribution figures for taint in the groups of relatives in recessive and dominant inheritance appear most distinctly when the disease gene occurs relatively rarely in the population (less than 10 per cent.); for increasing frequency of disease in the population the difference in the taint figures in recessive and dominant inheritance becomes more and more indistinct, and at a general disease risk (i. e. frequency of carries of the taint) of 30 per cent. the difference in the distribution figures is slight. On the basis of the risk figures found in cancer of the corpus it is therefore impossible to say with any certainty how the hereditary behaviour is. However, the figures seem to be in favour of a dominant rather than a recessive inheritance.

It is seen that the risk figures for uterine cancer are larger than in the population in general, and almost of the same order of magnitude as in cancer of the cervix (the difference statistically significant — see Table 30). Also here the figures suggest the presence of a — genetically conditioned — localization factor.

In order to be able to draw conclusions with regard to hereditary behaviour from the risk figures found it must — as also emphasized by *Videbæk* — be an assumption that cancer constitutes a genetic entity. Whether this is the case is unknown. At any rate cervical cancer (and possibly also esophageal and cutaneous cancers) seem to show a hereditary behaviour which differs from that of cancers belonging to the group of "endogenous cancers", the development of which is due partly to a cancer gene common to the whole group and apparently inherited dominantly, and partly to one or several genes responsible for the localization of the cancer.

Absolutely certain figures for the cancer risk in the various groups of relatives can scarcely be obtained by investigating a larger number of propositae, but only on the basis of an automatic registration of all cancer cases occurring in Denmark — as has now been done for several years by the Cancer Registry — extending over a number of years sufficient for obtaining indisputable information of all cancer cases during three generations.

Conclusive Remarks.

In summarizing the results of the investigations on heredity in mammary cancer, leukemia, and uterine cancer in humans so far undertaken at the University Institute for Human Genetics and the Cancer Registry, it may be said that a hereditary disposition seems to be a not inessential factor in the genesis of these malignant tumours. It was shown that hereditary disposition is a main factor in the development of mammary cancer, and other tumours (leukemia and uterine cancer) were found to be more or less dependent on hereditary factors.

The tendency to cancer in general, which occurs in the population with a frequency of approximately 30 per cent., is possibly a quality inherited with (incomplete) dominance. Multiple-factor inheritance cannot be excluded (*Kemp*, 1948).

The propositus method is, of course, rather complicated and beset with several possibilities of error, as already mentioned. One of the main shortcomings is the lack in sufficient registration of cancer cases in the groups of remote relatives. The diagnostic technique in cancer has been considerably improved during recent years; it might therefore with some justification be maintained that studies of heredity ought to be postponed until sufficient possibility of verification of all supposed cancer cases would be available.

However, the investigations have given a preliminary answer; the analyses of three forms of cancer of the group of "endogenous cancers" (mammary cancer, leukemia, and cancer of the corpus uteri) have all shown partly that there is a preponderance of cancer of all sites in the various groups of relatives, and partly (in mammary cancer and leukemia) that there is an increased incidence of the same form of tumour, and this is possibly also the case in cancer of the corpus uteri. That the results of the investigations are almost identical in this respect, may lend some support to the opinions expressed in them.

SUMMARY

The object of the study presented here is to examine the causative factors in uterine cancers by means of a genetical-clinical analysis of propositae.

CHAPTER I.

Earlier publications on heredity in human cancer are surveyed with a special view to previous reports on heredity in uterine cancer. It is shown that the results of earlier investigations suggest that hereditary factors are concerned in the development of uterine cancer. As uterine cancer has not been specified in several of the more comprehensive investigations, e. g. *Wassink* (1935), it is impossible to determine which of the two components is responsible for the familial preponderance of cancer. However, several investigations seem to indicate that inheritance is of greater importance in cancer of the corpus uteri than in cancer of the cervix uteri, but no conclusive evidence is available.

The "proband method" is discussed, and two previous Danish monographs on heredity in cancer of the breast (*Jacobsen*, 1946) and leukemia (*Videbæk*, 1947) are reviewed.

CHAPTER II.

The statistical-genealogical method analyzing the families of propositi is used in analogy with principles followed in the corresponding studies on heredity in cancer of the breast and leukemia. The practical application of this method is discussed. The material consisted of 200 patients with cervical cancer and 90 patients with cancer of the corpus, and in all cases the cancer of the propositae was histologically verified.

The cases of cancer stated to have occurred among relatives of the patients have been verified as far as possible, and in both groups of patients the author succeeded in verifying all accessible information of cancer as a cause of death among relatives, except in a very small number (3.5 per cent.).

In the control series comprising a corresponding number of healthy persons it was also possible to verify the majority of cancer cases among their relatives. It is shown that there is good agreement between the age

distributions of the propositae and control persons. In the two groups of propositae (and in the partly identical control groups) information of all relatives, except 4—5 per cent., was obtained. Also in this respect there was good agreement between the groups of propositae and control persons.

Since nowadays practically all cases of uterine cancer are hospitalized, the hospital material (collected chiefly from the Radium Centre in Copenhagen) must be said to form a representative, unselected material suitable for analysis. It is shown that there is no real difference in the age distribution between the author's material and that of a very comprehensive material of uterine cancer collected by the Cancer Registry.

CHAPTER III.

A. *Cancer of the Human Uterus.*

Sections 1, 2, and 3.

Following a brief review of some of the more important publications on uterine cancer, the frequency of the disease in Denmark where uterine cancers form 17 per cent. of all cancers in women is discussed. The ratio between cancer of the cervix and cancer of the corpus is at present 3 : 1.

While cancers of the corpus, being most frequently localized to the fundus uteri, in the vast majority of cases are adenocarcinomata, cancers of the cervix, being lozalized to the portio vaginalis, are most frequently squamous-cell carcinomata.

The object of the following sections is on the basis of a review of the literature and my own material to outline the difference existing on various points between cancers of the uterine cervix and corpus.

Section 4. Etiological Factors.

a. Age at Onset of Disease.

Cancer of the corpus has its highest incidence between the ages of 55 and 60 years, cancer of the cervix between 45 and 50 years.

b. Marital State.

There is a larger number of unmarried women among the patients with cancer of the corpus than in the corresponding age groups in the population in general; in cancer of the cervix it is seen that there are more married women than should be expected.

c. Fertility.

The fertility is lower among married women of the group of cancer of the corpus than in the population in general, higher among married women of the group of cancer of the cervix.

d. Influence of Hormonal and Inflammatory Changes in Cancer of the Cervix.

While the previously prevailing opinion that poorly healed cervical tears and cervicitis were concerned in the development of cancer of the cervix, an increasing number of investigators have claimed that also hormonal changes are of importance in the development. The latter view is supported partly be *Hofbauer*'s investigations in which he demonstrated an abnormal proliferation of the epithelium of the cervix uteri, and partly by animal experiments.

e. Influence of Hormonal Changes in Cancer of the Corpus.

It is shown that abnormal hormonal production from the ovaries must be supposed to play a rôle in the development of cancer of the corpus in which hormone-producing (theca-cell and granulosa-cell) tumours are not infrequently encountered. This view is also supported by the fact that patients with cancer of the corpus often have a delayed menopause.

A possible relationship of cancer of the corpus to hormonal therapy is mentioned, and it is pointed out — supported by experience gained in animal experiments — that only long-continued treatment with large doses of estrogenic hormones can be said to involve a risk, but information of the occurrence of cancer cases in the family — especially mammary cancer — should call for caution.

f. Social Conditions of the Patients.

The well-known fact that patients with cancer of the corpus are chiefly found among the higher social classes and cancer of the cervix among the lower social classes is confirmed.

g. Nationality.

The strikingly small number of cervical cancers among Jewesses and the exceptionally large number of cases among Japanese women are mentioned, and also that strange enough the sum of all cases of uterine and mammary cancers seem to be constant in all countries in which sufficient information of cancer cases in the population is available,

B. *Uterine Cancer in Experimental Animals.*

A brief account is given of animal experiments, chiefly on mice, in which it has been possible to induce a large number of cancers of the cervix uteri of a pronounced malignant character by means of estrogenic treatment. The development of these tumours seems to be independent of inheritance and of the milk factor.

By direct application of carcinogenic substances to the endometrium of mice, rats, and rabbits it has been possible to induce carcinoma of the endometrium.

CHAPTER IV.

A survey of the number of cancer cases among relatives of propositae and of control persons shows that the total cancer taint is uniform in the two materials for *cancer of the cervix;* for *cancer of the corpus* the number of cancers is 50 per cent. higher among relatives of patients, and here combined with a higher number of families with heavy taint, than among the control persons.

There is no increased familial taint for cancer of the cervix, apart from an essential increase of the incidence of cancer among sisters, while cancer of the corpus shows an increased number of cancer cases for nearly all categories of relatives.

Among the cancer cases found in relatives of patients all sites are represented, and mostly in quantitative conformity with the distribution by site among control relatives and in a material from the Cancer Registry. For *cancer of the cervix* there is, however, a strikingly large number of esophageal cancers among male relatives, and the incidence of mammary cancer is here lower than among the control relatives; the incidence of uterine cancer as a whole is, on the other hand, higher. For *cancer of the corpus* the percentages of uterine and mammary cancers are higher among relatives of patients than among the control relatives, but the actual numbers are small.

CHAPTER V.

On the basis of the figures collected a statistical evaluation is made 1) of the difference between the cancer frequencies found and 2) of the cancer risk.

In the evaluation of the difference between the cancer frequencies found a new method has been employed — devised by *Busk* — by which the incidence of cancer among patients' relatives is compared with a control material, computed on the basis of mortality statistics, and corrected for the imperfect knowledge of cancer cases among remote relatives of control persons. The advantage of this method over a direct comparison between relatives of patients and of control persons is due to the more comprehensive and thus more reliable control material.

A comparison made in this way shows for cervical cancer that only sisters display a significantly higher incidence of cancers of all sites taken as a whole; on the other hand, there is no significant difference when all relatives are taken together.

This difference for sisters is shown to be due to a preponderance of uterine cancer; when this diagnosis is excluded, the difference disappears.

For fathers it is possible to demonstrate a significant increase of the incidence of esophageal cancer.

Cancer of the cervix seems mainly conditioned by exogenous factors. It may possibly be the question of a — genetically determined — localization factor, but it is impossible to say anything definite about this. Nor is it possible on the basis of the increased incidence of esophageal cancer in male relatives to say anything definite about the presence of a hereditary tissue disposition, even though such a possibility may exist.

For *cancer of the corpus* a significant difference in the materials can only be demonstrated for sisters when cancers of all sites are taken as a whole. However, taken as a whole, both female and male relatives — in whom no significant difference can be demonstrated for brothers or fathers — show a significant increase of the incidence of cancer of all sites.

This is in favour of the supposition that cancer of the corpus — like mammary cancer and leukemia — for its development is dependent on a general cancer gene common to cancers of all sites but lip and skin (*Jacobsen*'s "endogenous cancers").

The significant preponderance in female relatives disappears when the group of uterine cancer is excluded. This is suggestive of the presence of a genetically conditioned localization factor.

The *cancer risk* is then computed. First the cancer risk for the Danish population is computed on the basis of the mortality statistics. It is calculated to be approximately 30 per cent.; this figure is higher than those found by *Jacobsen* and *Videbæk* (10 and at least 20 per cent. respectively).

For *cancer of the cervix* the cancer risk among relatives of patients is approximately 30 per cent. when all female and male cases are taken as a whole, i. e., corresponding to that of the population in general — only for sisters there is an essential diviation from this figure (54 per cent.).

For *cancer of the corpus* the total cancer risk for male and female relatives as a whole is higher than the average for the population in general. At a disease risk of this magnitude it is difficult on the basis of the risk figures to decide whether the supposed cancer gene for cancers of all sites but lip and skin is inherited dominantly or recessively. It may be a question of (failing) dominance or possibly multiple-factor inheritance. The cancer-risk figures are practically the same as those found by *Videbæk* in leukemia, but smaller than those found by *Jacobsen* in mammary cancer.

Both for breast cancer (*Jacobsen*), for leukemia (*Videbæk*) and now for cancer of the corpus uteri an increased incidence of cancer belonging to the group "all cancers but lip and skin" and an increase of the tumour form investigated (certain in mammary cancer and leukemia; probable in cancer of the corpus) have been ascertained among relatives of pa-

tients. All three investigations suggest that the development of "cancer of endogenous origin" is dependent on a common cancer gene, presumably transmitted with (failing) dominance, but probably also on a localization factor in which on one or several genes may be concerned.

CONCLUSIVE REMARKS

On the basis of the existing Danish works on heredity in human cancer it is concluded as a preliminary result that a hereditary disposition seems to be a not inessential factor in the genesis of tumours of "endogenous" origin.

Insufficient knowledge on the part of the propositi about cancer cases among remote relatives constitute one of the most serious shortcomings of the propositus method, and it cannot be eliminated by studying larger numbers of patients, but only if it is made possible to obtain reliable information of all cancer cases occurring in the families, preferably through three generations. When such a registration has been continued by the Cancer Registry for a large number of years, the results presented might be subjected to a renewed analysis.

RESUMÉ

INDLEDNING

Hensigten med det foreliggende arbejde er at undersøge årsagsforholdene til cancer uteri gennem en genetisk-klinisk probandundersøgelse.

KAPITEL 1

Der foretages en gennemgang af tidligere undersøgelser over arvelighedsforholdene ved human cancer med særligt henblik på tidligere meddelelser om arvelighedsforholdene ved cancer uteri. Det påpeges, at tidligere foretagne undersøgelser peger i retning af, at arvelige faktorer er medvirkende ved udviklingen af cancer uteri. Da gruppen cancer uteri ved flere større undersøgelser, således f. eks. hos *Wassink* (1935), ikke er udspecificeret, lader det sig ikke afgøre, hvilken af de to komponenter, der er ansvarlig for den familiære overvægt af cancer. Flere undersøgelser tyder dog i retning af, at arven er af større betydning ved cancer corporis uteri end ved cancer colli uteri, men noget afgørende herom foreligger ikke.

En særlig omtale vies probandundersøgelserne, og to tidligere danske arbejder over arvelighedsforholdene ved cancer mammae (*Jacobsen* 1946) og leucæmi (*Videbæk* 1947) tages op til drøftelse.

KAPITEL 2

Der anvendes den statistisk-genealogiske probandmetode efter samme retningslinier som tidligere fulgt ved tilsvarende arbejder over arvelighedsforholdene ved cancer mammae og leucæmi. Fremgangsmåden ved probandmetodens anvendelse i praksis omtales. 200 probander med cancer colli uteri og 90 probander med cancer corporis uteri er anvendt, i alle tilfælde er probandernes cancer histologisk verificeret.

De hos slægtningene angivne cancertilfælde søgtes såvidt muligt verificeret, og i begge probandmaterialer lykkedes det at verificere alle tilgængelige oplysninger om cancer som dødsårsag hos slægtninge på nær et ringe antal (3,5 %).

I kontrolmaterialet, som omfatter et til probanderne svarende antal raske personer, lykkedes det også at verificere de fleste af cancertilfæl-

dene hos slægtninge. Det vises, at der er god overensstemmelse mellem aldersfordelingerne i proband- og kontrolmaterialer. I begge materialer (samt i de delvis sammenfaldende kontrolmaterialer) lykkes det at skaffe oplysninger om alle slægtninge på nær 4—5 %, også her er der god overensstemmelse mellem proband- og kontrolmaterialet.

Da praktisk talt alle tilfælde af cancer uteri nu til dags hospitaliseres, må hospitalsmaterialet (overvejende hidrørende fra Radiumstationen i København) siges at give et repræsentativt, ikke særlig udvalgt, udgangsmateriale. Det vises, at der ikke er nogen reel forskel i aldersfordelingen mellem mit materiale og aldersfordelingen i et meget stort materiale af cancer uteri, indsamlet af Cancerregistret.

KAPITEL 3

A. *Cancer uteri hos mennesket.*

Afsnit 1, 2 og 3.

Efter en kort indledning, hvori nævnes nogle vigtige arbejder over cancer uteri, omtales sygdommens forekomst i Danmark, hvor cancer uteri udgør 17 % af al cancer hos kvinder. Forholdet mellem cancer colli og corporis uteri er 3/1.

Hensigten med de følgende afsnit er, udfra litteraturen og eget materiale, at trække den forskel op, der på en række punkter er mellem cancer colli og corporis uteri.

Medens cancer corporis uteri, der oftest er lokaliseret til fundus uteri, i langt det største antal tilfælde er adenocarcinom, er cancer colli uteri, der har sit sæde i portio, hyppigst plade-epithelcarcinom.

Afsnit 4. Ætiologiske faktorer.

a. Alder, hvori sygdommen optræder.

Corpuscancerens aldersmaksimum ligger mellem 55 og 60 år, collumcancerens mellem 45 og 50 år.

b. Ægteskabelig stilling.

Der er et større antal ugifte blandt patienter med cancer corporis uteri end i tilsvarende aldersgrupper i befolkningen; ved cancer colli uteri ses, at der er flere gifte kvinder end forventet.

c. Fertilitet.

Fertiliteten er mindre for gifte kvinder af gruppen cancer corporis uteri end i befolkningen, større for gifte kvinder af gruppen cancer colli uteri.

d. Betydningen af hormonale forandringer og betændelsesforandringer ved cancer colli uteri.

Medens det tidligere enerådende synspunkt, at cancer colli uteri udvikledes i dårligt helede cervixrifter eller i cerviciter, stadig har mange tilhængere, har der i de senere år — støttet af *Hofbauers* undersøgelser, hvor det lykkedes forfatteren at påvise abnorm epithelproliferation i collum uteri under graviditet — meldt sig tilhængere af, at også hormonale forandringer skulle have betydning. Eksperimentelle dyreforsøg støtter denne antagelse.

e. Betydningen af hormonale forandringer ved cancer corporis uteri.

Det påpeges, at abnorm hormonproduktion fra ovarierne — ofte påviselig ved tilstedeværelse af hormonproducerende tumorer — må antages at spille en rolle ved udviklingen af cancer corporis uteri. I samme retning tyder, at patienter med cancer corporis uteri ofte har en sen menopause.

Mulig sammenhæng mellem cancer corporis uteri og hormonbehandling omtales, og det påpeges — støttet af erfaringer fra dyreforsøg — at kun en langvarig kontinuerlig behandling med store doser oestrogen kan siges at indebære en risiko, men oplysning om tilfælde af cancer i familien — navnlig af cancer mammae — maner dog til forsigtighed.

f. Patienternes sociale stilling.

Det kendte faktum, at patienter med cancer corporis uteri fortrinsvis er at finde hos socialt bedre stillede, cancer colli uteri hos dårligere stillede medborgere, bekræftes.

g. Nationalitet.

Det påfaldende ringe antal tilfælde af cancer colli uteri hos jødiske kvinder og det enestående høje antal tilfælde hos japanske kvinder omtales, og der peges på den ejendommelige kendsgerning, at summen af tilfælde af cancer uteri og cancer mammae synes at være konstant i alle lande, hvor man har adgang til sufficient oplysning om cancertilfælde i befolkningen.

B. *Cancer uteri hos forsøgsdyr.*

Der gives en kort omtale af de eksperimentelle dyreforsøg, hvor det væsentligst hos mus med oestrogen behandling lykkedes at fremkalde cancer colli uteri med udpræget malign karakter i stort antal. Udviklingen af disse tumorer synes uafhængig af arv og mælkefaktor.

Ved direkte applikation af carcinogene substanser på uterinslimhinden hos mus, rotter og kaniner er det lykkedes at producere carcinom i endometriet.

KAPITEL 4

En opgørelse af antallet af cancertilfælde hos slægtninge i prôband- og kontrolmaterialet viser, at den samlede cancerbelastning er ens i de to materialer ved *cancer colli uteri;* ved cancer corporis uteri er antallet af cancertilfælde hos slægtninge til probander 50 % højere, og der er flere patienter med svær familiær belastning end i kontrolmaterialet.

Bortset fra en væsentlig forøgelse af antallet af cancertilfælde hos søstre er der ingen øget familiær belastning ved cancer colli uteri, medens antallet af cancertilfælde for næsten alle slægtningegrupper er forøget ved cancer corporis uteri.

De fundne cancertilfælde hos slægtninge til probander omfatter alle former af cancer, for de fleste gruppers vedkommende kvantitativt overensstemmende med fordelingen i kontrolmaterialet (og et materiale fra Cancerregistret). Ved cancer colli uteri er der dog et påfaldende stort antal tilfælde af cancer oesofagi hos mandlige slægtninge, og hyppigheden af cancer mammae er lavere end i kontrolmaterialet, hyppigheden af cancer uteri højere. Ved cancer corporis uteri er hyppigheden af cancer uteri og cancer mammae større i proband- end i kontrolmaterialet.

KAPITEL 5

Der foretages derefter på basis af de fundne tal en statistisk undersøgelse, dels 1) af forskellen mellem de fundne cancerhyppigheder, dels 2) af cancerrisikoen.

Ved vurdering af forskellen mellem de fundne cancerhyppigheder er anvendt en ny metode — angivet af *Busk* — hvorefter cancerhyppigheden hos slægtninge i probandmaterialerne sammenlignes med et kontrolmateriale, beregnet udfra mortalitetsstatistiken, for de fjernede slægtningegrupper omregnet i overensstemmelse med det mangelfulde kendskab til cancertilfælde i disse grupper i kontrolmaterialet. Fordelen ved denne metode — fremfor en direkte sammenligning mellem slægtninge i proband- og kontrolmaterialer — er, at man anvender et mere omfattende og derfor mere pålideligt kontrolmateriale.

En sammenligning foretaget på denne måde viser, at det ved cancer colli uteri kun er for søstrene, der er significant forskel, når alle arter af cancer tages under eet; der er derimod ingen significant forskel, når alle slægtninge tages under eet.

Forskellen hos søstrene ses at bero på en overvægt af cancer uteri; tages denne diagnose ud, er der ingen forskel længere.

Hos fædrene kan der påvises en significant forøgelse af incidensen af cancer oesofagi.

Cancer colli uteri synes væsentligt exogent betinget; der kan muligvis være tale om en — genetisk betinget — lokalisationsfaktor, men der kan intet sikkert siges derom, lige så lidt som der ud fra den øgede incidens af cancer oesofagi hos mandlige slægtninge kan siges noget sikkert i retning af arvelig vævsdisposition, selvom muligheden herfor foreligger.

Ved *cancer corporis uteri* kan der kun for søstrene konstateres en significant forskel mellem materialerne, når alle arter af cancer tages under eet. Taget samlet viser dog både de kvindelige og mandlige pårørende — hos hvem der ikke kan påvises significant forskel hverken hos brødre eller fædre — significant incidensforøgelse af cancer af alle slags i probandmaterialet.

Dette tages til indtægt for den formodning, at udviklingen af cancer corporis uteri — i lighed med forholdene ved cancer mammae og leucæmi — er afhængig af et alment cancergen fælles for gruppen "endogen totalcancer" (her som hos *Jacobsen* anvendt i betydningen cancer af alle slags med undtagelse af læbe- og hudcancer).

Den significante overvægt hos kvindelige slægtninge forsvinder, når gruppen cancer uteri tages fra. Dette kunne tyde på, at en arveligt betinget lokalisationsfaktor er til stede.

Der foretages derefter en beregning af *cancerrisikoen*. Cancerrisikoen for den danske befolkning beregnes udfra mortalitetsstatistiken at være ca. 30 %; der gøres rede for, at dette tal ligger over de tidligere af *Jacobsen* og *Videbæk* fundne (henholdsvis 10 % og mindst 20 %).

Ved *cancer colli uteri* ses cancerrisikoen hos probandernes slægtninge, når alle kvindelige og mandlige tilfælde slås sammen, at ligge omkring 30 % — kun for søstre er der væsentlig afvigelse herfra (54 %) — svarende til befolkningen i almindelighed.

Ved *cancer corporis uteri* ses cancerrisikoen både for mænd og kvinder at ligge over gennemsnittet for befolkningen. Ved så høj en sygdomsrisiko hos den almindelige befolkning er det vanskeligt på grundlag af risikotallene at afgøre, om det formodede cancergen for "endogen totalcancer" arves dominant eller recessivt. Der kan være tale om (svigtende) dominans eller muligvis multipelfaktor arvelighed. Cancerrisikotallene er praktisk talt de samme som de af *Videbæk* fundne ved leucæmi, mindre end de af *Jacobsen* fundne ved cancer mammae.

I begge de tidligere arbejder over arvelighedsforholdene ved cancer mammae og leucæmi og nu påvist ved cancer corporis uteri, er der i slægtningegrupperne — både på mødrene og fædrene side — konstateret forøget incidens af cancer tilhørende gruppen "endogen totalcancer" foruden en forøgelse af den undersøgte tumorform (sikkert ved cancer mammae og leucæmi, mulig ved cancer corporis uteri). De foretagne undersøgelser går alle i retning af den antagelse, at cancer af endogen type

udvikles som følge af et alment cancergen, der formentlig overføres ved (svigtende) dominans, men at der desuden muligvis gør sig en lokalisationsfaktor — afhængig af eet eller flere gener — gældende.

AFSLUTTENDE BEMÆRKNINGER

Det konkluderes på grundlag af de foreliggende danske arbejder over arvelighed ved human cancer som et foreløbigt resultat, at arvelig overført disposition synes at være en ikke uvæsentlig faktor i genesen af tumores af endogen type.

En af de væsentligste anker, som kan rettes mod probandmetoden — det manglende kendskab til cancertilfælde hos fjernere slægtninge — vil ikke kunne bortelimineres ved at undersøge et større antal probander, men kun ved at der åbnes mulighed for at få pålidelige oplysninger om alle cancertilfælde i slægterne helst gennem 3 generationer. Når en sådan årelang registrering af alle cancertilfælde er foretaget gennem Cancerregistret, vil der være grund til at tage de nu fundne resultater op til revision.

BIBLIOGRAPHY

The abbreviations used are those adopted by The Quarterly Index Medicus, Chicago, American Medical Association.

Figures in parentheses ( ) refer to the pages of the present volume where the particular author is quoted.

Figures in brackets [ ] following a quotation refer to the item in the bibliography, from which the quotation has been made.

1. *Ackerman, L. V. & J. del Regato:* Cancer. Sct. Louis 1947. Pp. 1115, pag. 825 (44, 48, 53, 54).
2. *Allen, E.:* Cancer of the cervix uteri after oestrogen treatment. Cancer Research, *1:* 723, 1942. (59).
3. — *& W. U. Gardner:* Cancer of the cervix om the uterus in hybrid mice following long-continued administration of oestrogens. Cancer Research, *1:* 359, 1941. (59).
4. *Andersen, F. & F. Truelsen:* Om morbiditeten af cancer uteri. Ugeskr. f. læger, *17:* 462, 1942. (22).
5. *Auvray, A.:* A propos de l'hérédité du cancer. Bull. Acad. de méd. Paris, *97:* 420. 1927. (11).
6. *Baily, K. V.:* Inquiry into the basic cause and nature of cervical cancer. Pathology of cervicitis and relation between cervicitis and cervical cancer. Surg., Gynec. & Obst., *50:* 513 og 688, 1930. (51).
7. *Bashford, E.:* Heredity in cancer. Lancet, *2:* 1508, 1908. (16).
8. *Blank, F.:* Genetic aspects of the cancer problem. Arch. Surg., *49:* 301, 1944. (53).
9. *Boehmert, W.:* Bull. internat. de'institut internat. de statistique, *29:* 1, 1937. Cit. Stocks. [116]. (58).
10. *Bowing, H. H. & J. Mc. Collough:* Carcinoma of the cervix uteri in childhood and adolescence. Am. J. Roentgenol., *45:* 819, 1941. (44, 48).
11. *Bullock, F. D. & M. R. Curtis:* Spontaneus tumors in rat. J. Cancer Res., *14:* 1, 1930. (58).
12. *Busk, T.:* Some observations on heredity in breast cancer and leukemia. Ann. Eugenics, *14:* 213, 1948. (73, 74, 76, 80, 84, 85, 92, 98).
13. — *J. Clemmesen & A. Nielsen:* Twin studies and other genetical investigations in the Danish Cancer Registry. Brit. J. Cancer, *2:* 156, 1948. (18, 20, 21).
14. *Butenant, A.:* Ueber »Progynon«, ein krystallisiertes weibliches Sexualhormon. Naturwissenschaft, *17:* 879, 1929. (50).
15. *Cholewa, J.:* Krebserkrankung und Vererbung. Ztschr. f. Krebsfosch., *37:* 214, 1932. (13).

16. *Clausager-Madsen, L. & H. Ytting:* Age of menarch and menopause in urban and rural population. Nord. med. *16:* 3677, 1942. (53).
17. *Clemmesen, J.:* Sygeligheden af livmoderkræft. Ugeskr. f. læger, *29:* 698, 1946. (43).
18. — Carcinoma of the breast. Results from Statistical Research. Brit. J. Radiol., *21:* 583, 1948. (32, 47).
19. — Endometrial changes resembling adenocarcinoma coinciding with oestrin treatment and granulosacelltumor of the ovary. Acta obstr. et gynec. Scandinav., *27:* 384, 1948. (53, 54).
20. — *& Th. Busk:* The incidence of malignant diseases in Denmark 1942—1944. Acta radiol., *29:* 321, 1948. (30, 43).
21. — — The age distribution of malignant diseases in Denmark 1942—1944. Acta radiol., *30:* 9, 1948. (32). (See allso Acta radiol., *31:* 51, 1949.)
22. *Crabtree, J. H.:* Observations of familial incidence of cancer. Am. J. Pub. Health, *31:* 49, 1941. (16).
23. *Craig, F. B.:* Carcinoma of the cervix from point of view of general practitioner. M. J. Australia, *1:* 886, 1938. Cit. Crossen [27]. (51).
24. *Cramer, W.:* Etiology of cancer of the mamma. Am. J. Cancer, *30:* 330, 1937. (54, 58).
25. *Craver, L. T.:* Etiology of cancer. J. A. M. A., *105:* 1820, 1935. (49).
26. *Croom, J. H.:* Adenocarcinoma of uterus in twins. J. obstr. and gynec. British Emp., *21:* 330, 1912. (21).
27. *Crossen, H. S. & R. J. Crossen:* Diseases of Women. London 1941. Ninth edition. Pp. 948, p. 520. (52).
28. *Cruveilhier, J.:* Anat. pathol. du corps humain T II, Livre 23. Cit. Wolff [139]. Bd. 2, pag. 945. (42).
29. *Deelman, H. T.:* Cancer et mariage. Gynéc. et obst., *1:* 493, 1920. (16).
30. — Heredity and cancer. Ann. Surg., *93:* 30, 1931. (49).
31. *Dietel, H.:* Zwillingforschung bei Utersurcarcinom. Arch. f. Gynaek., *173:* 130 og 140, 1942. (21).
32. *Doisy, E. A., S. Thayers & C. D. Veler:* The preparation of crystalline ovarian hormone from the urine of pregnant women. J. Biol. Chem., *86:* 499, 1930. (50).
33. *Emmet, T. H.:* Risse des Cervix uteri. Berlin 1878. Cit. Wolff [139]. Bd. 2, pag. 945. (49).
34. *Engelbreth-Holm, J.:* Om hyppigheden af dobbeltsidig brystkræft og om brystkræftens sammentræf med andre kræftformer. Ugeskr. f. læger, *17:* 456, 1942. (22).
35. *Engle, E. T., C. Krakower & C. O. Hågensen:* Oestrogen administration to aged female monkeys with no resultant tumors. J. Cancer Research, *3:* 858, 1943. (59).
36. *Fabre J.:* De la contagion du cancer. Paris 1892. (16).
37. *Faure, J.-L.:* Cancer de l'uterus. Paris 1925. Pp. 228. (43).
38. *Feilberg, O.:* Unpublished work. (23).
39. *Fibiger, J. & S. Trier:* Bericht ueber die am 1. April 1908 in Daenemark in aertzlicher Behandlung gewesene Krebskranke. Zeitschr. f. Krebsforsch., *9:* 275, 1910. (12, 16).
40. *Fremont-Smith, M., V. Meigs, R. M. Graham & H. Gilbert:* Cancer of the endometrium and prolonged estrogen therapy. J. A. M. A., *131:* 805, 1946. (54).

41. *Gardner, W. U., E. Allen, G. M. Smith & L. C. Strong:* Carcinoma of the cervix of mice receiving oestrogens. J. A. M. A., *110:* 1182, 1938. (54, 59).
42. *Geist, S. H. & U. J. Salmon:* Are oestrogens carcinogenetic in the human female? Am. J. Obst. & Gynec., *41:* 29, 1941. (54).
43. *Gemmel, A. A. & T. N. A. Jeffcoate:* Oestrogens and carcinoma of the uterus. J. Obst. & Gynaec. Brit. Emp., *46:* 985, 1939. (54).
44. *Gilbert, J. B.:* Carcinoma of body of uterus. Am. J. Obst. & Gynec., *24:* 402, 1932. (45).
45. *Hanharte, E.:* Auffaldend geringe Bedeutung der Belastung mit Krebs. Schweitz. med. Wohnschr., *15:* 446, 1943. (16).
46. *Hartmann, J. P.:* Gynækologi. København 1935. Pp. 358, p. 166. (55).
47. *Hauser, I. J. & C. V. Weller:* A further report on the cancer family of Warthin. Am. J. Cancer, *27:* 434, 1936. (13).
48. *Healy, W. P.:* Cit. Ackerman & Regato [1], pag. 828. (51).
49. *Henriksen, E.:* Carcinoma of the cervix. Clinical study of nine hundred and forty cases. Arch. Surg., *31:* 461, 1935. (16).
50. *Herrel, W. E.:* Studies of the endometrium in association with the normal menstrual cycle. Am. J. Obstr. & Gynec., *37:* 559, 1939. (53, 54).
51. *Hintze, O.:* Plattenepithelknoetchen der Korpussleimhaut. Zentralbl. f. Gynaek., *52:* 2209, 1928. (44).
52. — Klinische Nachuntersuchung 24 Faelle schwerer Hyperplasie der Korpussleimhaut. Zentralbl. f. Gynaek., *53:* 2396, 1929. (53).
53. *Hirst, B. C.:* Malignant growths of uterus in young girls. Am. J. Obstr. & Gynec., *18:* 104, 1929. (45).
54. *Hofbauer, R. J.:* Graviditaetsaenderungen des Cervixepithels in der Aetiologie des Uteruscarcinoms. Zentralbl. f. Gynaek., *55:* 428, 1931. (50, 91, 97).
55. *Hofbauer, R. J.:* Hormonal gynecological pathology and its clinical aspects. Am. J. Obst. & Gynec., *46:* 232, 1939. (50, 91, 97).
56. *Howitz, F.:* Observation sur la diagnose du cancer uterin et de la syphilis tardive de l'uterus. Nord. med. Arkiv, Afd. II, Hæfte 4, Nr. 14, pag. 1, 1907. (57).
57. *Hultkrantz, J. & G. Dahlberg:* Die Verbreitung eines monohybriden Erbmerkmals in einer Population und in der Verwandtschaft von Merkmalstraegern. Arch. f. Rassen- und Gesellschafts-Biologie, *19:* 160, 1927. (87).
58. *Hurdon, E.:* Cancer of the uterus. London 1942. Pp. 188. (17, 43, 44, 45, 46, 48, 49, 50, 56, 57).
59. *Ilfeldt, F. W.:* The experimental production of visceral tumors with hydrocarbons. Am. J. Cancer, *26:* 743, 1936. (59).
60. *Ingraham, C. B., W. C. Black & E. K. Rutlege:* Relationship of granulosa cell tumors of ovary to endometrial carcinoma. Am. J. Obst. & Gynec., *48:* 760, 1944. (53).
61. *Jacobsen, O.:* Heredity in breast cancer. Kbhvn: Nyt Nordisk Forlag, London: Lewis & Co. 1946. Disp. Pp. 306. (9, 11, 16, 17, 18, 19, 20, 21, 23, 25, 30, 33, 48, 49, 64, 72, 74, 78, 82, 85, 87, 89, 93, 95, 99).
62. *Johnstone, R. W.:* Cancer in the genital tract of women. Edinburgh 1935. Pp. 130, pag. 18—19. (55).
63. *Kemp, T.:* Heredity in human cancer. Brit. J. Cancer, *2:* 144, 1948. (23, 24, 88).

64. *Klotz, A. G.:* Krebs und Vererbung (mit besonderer Berüchsichtigung der Vererbung des Uteruskrebses). Diss., Hamburg 1940. Pp. 24. (21).
65. *Knack, A. V.:* Geburt und Gebaermutterkrebs. Z. f. Krebsforsch., *11:* 463, 1912. (48).
66. *Lacassagne, A.:* Apparition de cancers de la mamelle chez la souris mâle, soumise à des injections de folliculine. Compt. rend. Acad. de Scien., *195:* 630, 1932. (59).
67. — The carcinogenic action of certain oestrogenic hormones. Am. J. Cancer, *28:* 735, 1936. (59).
68. *Laine-Claypon, J. E.:* Reports on public health and medical subjects, 32, 1926. (17).
69. — Cancer of the uterus. Reports on public health and medical subjects, 40, 1927. (46).
70. *Mc Lead, D.:* Hormonal therapy in gynecological conditions. J. obst. and gynec., *46:* 15, 1939. (54).
71. *Lefevre, H.:* Multiple primary carcinomas; review of literature. Ugeskr. f. læger, *103:* 822, 1941. (21).
72. *Levin, J.:* The influence of heredity on cancer. Zeitschr. f. Krebsforsch., *11:* 547, 1912. (16).
73. *Levin, M. L., L. C. Kress & H. Goldstein:* Syphilis and cancer. New York State J. Med., *42:* 1137, 1942. (57).
74. *Little, C.:* The inheritance of a predisposition to cancer in man. Eugenics, genetics and the family, *1:* 186, 1923. (16).
75. *Lockhart, H. A.:* Cancer of the uterus in childhood. Am. J. Obstr., *30:* 76, 1935. (45).
76. *Martynowa, R.:* Studies in genetics in human neoplasms. Am. J. Cancer, *29:* 530, 1937. (17).
77. *Masson, J. C. & R. O. Gregg:* Carcinoma of the body of uterus. Surg., Gynec. & Obst., *70:* 1083, 1940. (46, 48, 52).
78. *Mogensen, E.:* Unpublished work. (83).
79. *Morse, A.:* Carcinoma of the female genital tract in childhood. Am. J. Obst., *19:* 520, 1930. (45).
80. *Moss, W. T.:* Common peculiarities with adenocarcinoma of the endometrium. With special reference to obesity, body build, diabetes, and hypertension. (54). »in press«, cit. Ackerman & del Regato. [1].
81. *Norris, C. & M. Vogt:* Carcinoma of the body of the uterus. Am. J. Obst. & Gynec., *7:* 550, 1924. (46).
82. *Novak, E.:* Postmenopausal bleeding as a hazard in dietylstilboestrol therapy. J. A. M. A., *125:* 98, 1944. (54).
83. *Olch, J. Y.:* The menopausal age in women with cancer of the breast. Am. J. Cancer, *30:* 563, 1937. (53).
84. *Orndoff, B. H.:* The pathologic cervix, a precancerous lesion. Radiology, *17:* 280, 1931. (51).
85. *Otto, C.:* Uteruscarcinomet. Kbhvn. 1900. Disp. Pp. 329. (12).
86. *Pack, T. G. & R. G. Lefevre:* Age and sex distribution and incidence of neoplastic diseases at the Memorial Hospital, New York City. J. Canc. Research, *14:* 167, 1930. (44, 46).
87. *Paget, J.:* Med. Times and Gaz., *15:* 191, 1851. Cit. J. Ewing: Neoplastic diseases. Fourth edition. Philadelphia and London, 1942. Pp. 1160, p. 94. (11, 16).

88. *Parabučev, A.:* Carcinoma of the uterus in young subjects. Med. mysl., *5:* 22, 1929. (Abstr. in Cancer Rev., *5:* 647, 1930.) (45).
89. *Parent-Duchâtelet:* De la prostitution dans la ville Paris. Paris 1857, T. I., p. 236. Cit. Wolff [139]. Bd. 2, pag. 963. (57).
90. *Pean, J.:* Diagnostic et Traitment des Tumeurs de l'abdomen. T. III, Paris 1895,p. 653. (43).
91. *Peller, S.:* Die Ergebnisse der von Oesterr. Gesellsch. für Erforschung und Bekämpfnung der Krebskrankheit veranstalteten Sammelforschung. Wien. klin. Wchschr., p. 154, 1922. (48).
92. *Penrose, L. S., H. J. Mackenzie & M. N. Karn:* A genetical study of human mammary cancer. Brit. J. Cancer, *2:* 168, 1948. (19).
93. *Perry, I. H. & L. L. Ginzton:* The dovelopment of tumors in female mice treated with 1:2:5:6-dibenzanthracene and theelin. Am. J. Cancer, *29:* 680, 1937. (59) .
94. *Pfleiderer, A.:* Statical contributions to carcinoma of the uterus and its treatment. Strahlentherapie, *40:* 13, 1931. (48).
95. *Pierson, H.:* Experimentelle Erzeugung von Uterusgeschwulsten bei Kaninchen durch Ovarialhormonen. Zeitschr. f. Krebsforsch., *41:* 103, 1934. (59).
96. *Poulsen, K.:* Om svulster i mamma. Kbhvn. 1890. Pp. 179. (16).
97. *Purdie, A. W.:* Cancer corp. uteri in two sisters aged 34 and 32 years. Proc. Roy. Soc. Med., *37:* 426, 1944. (11).
98. *Randall, C. L.:* Recognition and management of the woman predisposed to uterine adenocarcinom. J. A. M. A., *127:* 20, 1945. (53, 54).
99. *Récamier, J. C.:* Recherches sur le traitment du cancer. T. Ed. 2, Paris 1829, p. 217. (16).
100. *Regaud:* Cit. H. Schinz: Krebs und Vererbung beim Menschen [103]. (22, 23).
101. *Ruge & Veit:* Der Krebs der Gebaermutter. Leipzig, 1881. Cit. Deelmann: Cancer et mariage [29]. (43).
102. *Schiller, W.:* Ueber Fruehstadien des Portiocarcinoms und ihre Diagnose. Arch. f. Gynaek., *133:* 211, 1928. (50).
103. *Schinz, H.:* Krebs und Vererbung beim Menschen. Ergebnisse der Stammbauforschung, der Zwillingbeobachtung und der massenstatistischen Untersuchungen im Vergleich zum Tierversuch. Deutsche Ztschr. f. Chir., *247:* 728, 1936. (22).
104. — *& F. Buschke:* Krebs und Vererbung. Georg Thieme, Leipzig 1935. Pp. 280, p. 112. (11).
105. —, *Cocchi U. & J. Neuhaus:* Die Vererbung des Krebses beim Menschen. Archiv der Julius Klaus-Stiftung, Zürich, Band XXIII, Hefte 1/2, pag. 1—232, 1948. (14).
106. *Schottlaender, J. & F. Kermaner:* Zur Kenntnis des Uteruscarcinoms. Berlin 1912. Pp. 761. (43).
107. *Schreiner, B. F. & W. H. Wehr:* Malignant disease of female generation organs in the first three decades of life. Surg., Gynec. & Obet., *59:* 616, 1934. (51).
108. *Schroeder, C.:* Handbuch der Krankheiten der weiblichen Geschlechtsorgane. V. Ziemssens Handbuch, Leipzig 1886, p. 284. (55).
109. *Sibley, S. W.:* Contributions to the statistics of cancer. Med. chir. Transact. *42:* 111, 1859. (43, 46, 48).

110. *von Siebold, A. E.:* Ueber den Gebaermutterkrebs. Berlin 1824, Pp. 128. (42).
111. *Slye, M.:* The relation of heredity to cancer. J. Cancer Research, *12:* 83, 1928. (58).
112. —, *H. F. Holmes & H. G. Wells:* Primary spontaneous tumors in mice. J. Cancer Research, *8:* 96, 1924. (58).
113. *Smit, F. R.:* Nationality and carcinoma of the cervix. Am. J. Obst., *41:* 424, 1941. (57, 58).
114. *Smith, G. V.:* Carcinoma of the endometrium; review with results of treatment through 1935. New Engl. J. med., *225:* 605, 1941. (53).
115. *Smithers, D. W.:* Family histories of 459 patients with cancer of the breast. Brit J. Cancer *2:* 163, 1948. (19).
116. *Stocks, P.:* Distribution in England and Wales of cancer in various organs. Brit. Emp. Cancer Campaign. Sixteenth annual Report, London 1939, pag. 308. (57, 58).
117. *Suntzseff, V., E. L. Burns, A. Moskop & Leo Loeb:* Proliferative changes in vagina and cervix of mice. Am. J. Cancer, *32:* 256, 1938. (59).
118. *Taylor, H. C.:* Endometrial hyperplasia and carcinoma of the body of the uterus. Am. J. Obst. & Gynec., *23:* 309, 1932. (53).
119. — Endocrine factors in the origin of tumors of the uterus. Surgery, *16:* 91, 1944. (50, 52).
120. — *& R. Millen:* The causes of vaginal bleeding and the histology of the endometrium after the menopause. Am. J. Obst. and Gynec. *36:* 22, 1938. (53).
121. *Twombley, G. H. & G. T. Pack:* Symposium on endocrinology of neoplastic diseases. Surgery, *16:* 1, 1944. (54).
122. *Velpau, A.:* Traité des maladies du sein. Paris 1854, p. 695. (16).
123. *Verneuil:* Diathese néoplasique. Rev. scient. Paris 1884. (16).
124. *Videbæk, A.:* Heredity in human leukemia. Kbhv. Nyt Nordisk Forlag, London, Lewis & Co. 1947. Disp. Pp. 279. (9, 19, 20, 21, 25, 28, 29, 30, 37, 38, 64, 74, 78, 85, 87, 89, 93, 95, 99).
125. *Waaler, G.:* Ueber die Erblichkeit des Krebses. Oslo 1931, Pp. 75. (16, 17).
126. *Wagner, E.:* Der Gebaermutterkrebs, eine pathologische-anatomische Monografie. Leipzig 1858. Pp. 167. (42).
127. *Wainwright, I. M.:* A comparison of conditions associated with breast cancer in Great Britain and America. Am. J. Cancer, *15:* 2610, 1931. (17).
128. *Warren, S. & T. Ehrenreich:* Multiple primary malignant tumors and susceptibility to cancer. Cancer Research, *4:* 554, 1944. (22).
129. *Warthin, A. S.:* Heredity with reference to carcinoma. Arch. Int. Med., *12:* 546, 1913. (12, 13).
130. *Warthin, A. S.:* The further study of a cancer family. J. Cancer Research, *9:* 279, 1925. (12, 13).
131. *Wassink, W. F.:* Cancer et hérédité. Genetica, *17:* 103, 1935. (10, 17, 89, 95).
132. *Weinberg. W.:* Zur Probandemethode. Arch. Rassenbiol., *23:* 281, 1931. (25).
133. *Weinberg & Gastpar:* Die boesartigen Neubildungen in Stuttgart 1873—1902. Zeitschr. f. Krebsforsch., *2:* 195, 1904. (55).
134. *Weitz, W.:* Studien an eineiigen Zwillingen. Zeitschr. f. klin. Med., *101:* 115, 1924. (21).

135. *Wells, G.:* The influence of heredity on the occurrence of cancer. J. A. M. A., *81:* 1017 og 1103, 1923. (15).
136. *Wespi, H. J. & H. Sauter:* Die Einfluss von Alter und Geburtenzahl auf die Entstehung des Genitalcarcinoms. Z. Krebsforsch., *53:* 347, 1943. (45, 46, 48).
137. *Williams, Roger:* Note on multiple family cancer. Brit. med. J., *2:* 1612, 1898. (11).
138: — The natural history of cancer. Heinemann, London, 1908, Pp. 519, pag. 275, 360, 366. (11, 46, 48).
139. *Wolff, J.:* Die Lehre von der Krebskrankheit. Bd. I og II, Jena 1907 og 1911. (16, 43).
140. *Zondek, B.:* Oestrogens and tumour genesis. Acta radiol., *38:* 433, 1947. (54).