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The Etiology of cancer with particular reference to adeno-carcino corpus uteri

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The Etiology of Cancer
with Particular Reference to Adeno-
Carcinoma Corpus Uteri

by

Roy Johnson Allen

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Nebraska, Omaha, 1937

FOREWORD

The etiology of cancer has long been a puzzling problem to the scientific world and probably has stimulated more investigators with their resulting experimentation, research, and voluminous writings than any other medical problem. Especially has this been true of the past twenty years, largely because many of the other diseases have been controlled through less than a century of applied bacteriological theories, with a resulting swing toward the unanswered question of the cause of malignant tumors. Also during more recent years, education has made it possible for physicians to closely observe many more people than ever before and prescribe effective curative treatment for other disorders. It appears natural for all men to ask "why" concerning any problem which is not understood, so is the investigator of the present day carrying on the work of answering this question. However, the intelligent scientific man does not expect to solve the problem instantly, but is satisfied to contribute his share so that eventually time will give the answer.

In this work I have considered the etiology of all malignant tumors, in so far as I believe it necessary to give the reader an idea of the present knowledge concern-

ing the problem of etiology as a whole. I shall present the problem of etiology of primary adeno-carcinoma arising in the body of the uterus. Some reference will also be made to primary sarcoma of the uterus. Thus cervical tumors, tumor metastases from the ovary, etc. are not directly considered, except as is necessary to outline the question as it pertains to the general etiology of cancer. In constructing the first part of this paper, I have referred frequently to the noted work of Dr. H. E. Eggers and do not hope to approach any such degree of proficiency as he did in four years' work and with the abstraction of about 2000 articles, but only attempt to give in brief some of the more important ideas relating to the general question of neoplastic etiology especially from the experimental view. Thus, detail in the first part of this thesis is not my aim.

Thesis

The histogenic theories are now almost entirely being replaced by experimental work and so as the occasion arises brief comments will be included.

The Malignant Cell.

The normal mouse cell contains 40 chromosomes and numerous writers have given the number occurring in malignant cells from 24 to 80, (2). I have found that all of the other cellular characteristics vary in a similar way, so almost any thing one wishes to describe with reference to the number of the malignant cells can be contradicted; one only adds to the confusion by such a discussion. Volumes have been written on the malignant cell, but Ludford's conclusion that, "there exists for the malignant cell no precise morphological diagnostic character of any kind" (2) (19) is quite widely accepted. Warburg believes that the malignant cell has an abnormal ability to split sugars either under aerobic or anaerobic condition (76), mainly because of his work in which he discovered that cancer tissue contained a higher percentage of lactic acid than normal tissue. However, it is accepted that if marked disproportions exist among the relative sizes of cell body, nucleus, and nucleolus, the growth is most apt to be malignant;

of course being considered along with other evidences of tumor growth.

Experimental Study: Parasitism.

The early investigators spent their efforts trying to prove cancer the result of some parasitic infestation. "Even (19) the earlier experiments on the transferability of cancer had in the background the idea of causation by transfer of a parasite rather than of the cancer itself." Early (52) in the 19th century workers began to report cancer in animals following injections of fluids from human tumors. Eggers, Langenbeck, Wyss, Goujon, and others reported cancer transmission to the dog and white rat but their experiments on rabbits and guinea pigs failed. Quinquand reported similar experiments on the fowl and later Thiroloix included the transfer of rabbit tumor fluids to the mouse; Francotte and de Rechter added a report in which they believed that they had transferred human cancerous material by injection successfully to mice. In this same year Mayet included a report on transference of cancer to the rat. Of this early work it can be strongly questioned as some authors suggest that often tumors arise in animals spontaneously and (19) some of the descriptions concerning the pathological picture portray inflammatory

changes. Many of these experiments have not withstood reinvestigation.

Erdmann (20) claimed to have transferred the Flexner-Jobling rat carcinoma by a cell free filtrate but this work has not been confirmed so far as I know. In this case 32% of takes were claimed in 30 inoculations which is a much higher percentage than is usually found given by earlier workers, as many found 3 to 20 % or even less. Rous (26) (19) reported a type of fowl sarcoma which he transferred by both a solution of dead cells and a berkefeldt-filter filtrate to other fowls. This tumor was a freely metastasizing spindle cell osteo-sarcoma, killing the host in about twenty-eight days. The tumor was rather specific in the beginning for blood relatives of Plymouth Rock chickens and the tumors' malignancy was increased by continued passage. The Rous sarcoma is referred to in almost all extensive works on cancer and has caused a great deal of controversy as to the character of the etiological agent. The Rous agent was and still is considered to be a filterable virus as well as a chemical agent. Gye (11) reports that acraflavine kills the Rous virus. Fraenkel (26) in a recent study concerning the carcinogenic factor concluded it to be of a chemical nature

and not a virus. Russel (68) believes the Rous agent to be a virus, as Amies separated the etiological factors by centrifugal force 30,000 times that of gravity. Some of the agents are free of protein and contained within certain observable bodies which the adult fowl has antibodies against. This is not true of the young chicken as agglutination does not result. The various discussions on the agent's character are most numerous and as far as I know the question is yet in dispute, but many reliable workers still hold the Rous agent to be a strong point in favor of the parasitic theory with regards to the etiology of animal cancer.

Histological reports began to describe unusual inclusion bodies and degenerative morphological changes as early as 1839 (19) which were suspected of being numerous forms of lower animal life. Thus protozans were given by Pfeiffer as being a possible cause of cancer. Following this, numerous investigators attempted to demonstrate a conjectured parasite in cancerous tissue and as a result the literature was filled with such reports. These writers described almost every possible type of protozoan along with its transference to animals. Adamkiewics (19) and others even referred to the cancer cell itself as being a foreign protozoan parasite.

As the word might

Along (42) with the work of this time came various reports concerning bacteria and one can readily understand this as bacteria can be isolated from almost any source. Doyen (19) and others named organisms following their names as micrococcus neoformans, etc.; because they believed they had discovered the etiological agent, as the term "neoformans" suggests. Even past 1920, work was still being done on Busse's blastomycetes. Russell's "fuchsin bodies" were proved to be degenerative changes, but still many new things were coming into the literature, as the pathogenic yeasts and molds. In this report one can easily see why workers were led astray as (19) the pathogenic yeasts will cause considerable cellular hyperplasia and the epithelial piling up of cells can most closely simulate cancer. I mentioned the filterable virus as a cause mainly referring to the Rous sarcoma, as this work was the earliest and remains as an unexplained phenomena, while suffice it to say, most of the other reports are now known to be unfounded.

There is a vast collection of literature dealing with the evidences of the infectivity of cancer which may as well be referred to here, with respect to at least "cancer houses" and "cancer a deux", as one often is confronted with these terms. Haviland (19) and

others (80) have referred to cancer houses as a local community in which cancer was found in certain houses and families. Often this type of community was located along a river or in a swamp, the authors thus trying to show that a common etiological agent was being spread similar to diseases over certain geographical areas. Now one can be certain that these happenings were coincidental, as these early reports were a part of the many misinterpretations. With reference to cancer a deux, one can not be certain this is true as I will include here one rather convincing case: a (19) medical student while aspirating fluid from a cancerous breast accidentally stuck his own finger and developed a fatal sarcoma at the injection site. Levin reported 18 cases out of 4000 cancer patients. Therefore, I hardly see how one can doubt the possibilities of cancer a deux altogether; but it is certain that an etiological factor it is not of much importance when considered in the light of present day knowledge which will be alluded to later.

As (52) against the theory of the infectivity of cancer Jensen observed that when cancer tissue was transferred to another animal, infection rarely resulted and if infection did result the animal was not affected in

the same manner as one which received a known bacterial inoculation. The reasoning here, however is not at all convincing and is not equally based.

Fibiger (83) in 1913 brought out the helminths in association with experimental studies of cancer. It had long been suspected clinically that worms of various types might give rise to malignant growths. Babler (19) reported carcinoma of the lip; Babes reported cancer of the bronchus and Fibiger reported carcinoma of the tongue, all associated with trichinosis. Almost all types of this group have been discussed too much to even be mentioned here but in general it has been concluded that the helminths evidently can not be dismissed lightly with respect to certain kinds of tumors; however, their exact methods of influence are not known. With respect to parasites, Woglam (83) states that even Fibiger reports the production of cancer in rats by feeding cockroaches (*Periplaneta Americanus*); thus one can see that almost no possibility has been overlooked with respect to the cause of cancer due to parasites.

Heterologous Transfer of Cancer.

Following along with this early work, the transference of tumor tissue from one animal to another was begun, the workers hoping to gain more knowledge of the

early malignant process. The (19) transference of cancer from one species to the other has not revealed a great deal of knowledge. Probably because a larger share of the early work has now been shown to be faulty, as some of the injection transfers of cancer which I have mentioned heretofore, and due to the fact that most evidence shows that animal tissues can not be transferred from one species to another except in rare instances. I think that one should easily deduct this from a knowledge of serology as even skin grafting from one human to the other is best accomplished when the blood groups coincide, let alone the transfer of tissue from one animal to another. Ewing (20) mentions one of the many questionable exceptions where a type of dog sarcoma was transferred to foxes, but here I believe the two animals have a cousin-like relationship although it must be admitted they are of different species. Numerous reports appear in the literature and many can not be regarded as of any great value with respect to the problems of tumor etiology.

Homologous Transfer.

Rather early (17) (52) different investigators succeeded in transferring cancer within the species. Virchow (19) as early as 1863, Kaufmann in 1879 and numer-

ous other writers gave favorable reports but a failure in humans was noted by Senn in 1888 who used himself as the subject. Since (52) early work, enumerable tumor transfers have been carried out repeatedly, but I have found no authentic evidences on the transmission between humans except as to cancer a deux as previously mentioned. I suspect it can and has occurred at some time. However, I believe it only natural for an investigator to be slow in admitting the death of a fellow human. So far with insufficient proof, the idea cannot be wholly accepted as true. The homologous transfer of cancer, while very successful, has not yielded the great amount expected toward the etiology of cancer, because in a sense only the artificial metastasises are studied. Also with reference to man, one must always hesitate to accept proved animal experiments until the same has occurred in man with sufficient frequency to make the evidence overwhelming. Hilario (34) mentions that experimentally direct innoculations of carcinoma in man have been failures.

Known Etiological Factors.

Heredity has long been considered as an important etiological factor in the causation of cancer as well as age, acquired susceptibility, and other factors like trauma which has of late been severely questioned, especially in relation to chronic irritation. In (19) 1866 Paget reported among the offspring of cancerous parents about a 25 percent occurrence. Numerous writers continued to report similar findings, while some found families with a much higher percentage and still other authors pointed out families with a very low incidence. One (19) case of great incidence was reported by Broca in which a cancerous mother's six daughters all died of carcinoma; however, I believe that clinical data shows such happenings to be most rare. Warthin (77) concluded from family studies that when cancer is found clinically to be common in a certain generation, one is most apt to find an ancestral history. With reference to the same idea, Hutchinson (19) stated that if cancer be found in a young person, an ancestral history will often be found associated, and this has been found by most clinicians usually to be true. In (19) animals, Tyzzer concluded that animal tumors might be hereditary but not in accordance with the rule of Mendelian charac-

teristics. Sly (71) reported after experimenting with mice that:

- A. The inbreeding of tumor animals (double cancerous parents) definitely increases the incidence of cancer in the succeeding generations, even to 100 per cent in some types inless the young die before the cancer age.
- B. The hereditary etiological factor behaves as a Mendelian recessive characteristic.
- C. The first generation of mixed parents (one cancerous parent) may have a majority of cancer free offspring but they will be part carriers and transmit the tendency.
- D. The tendency of tumor specificity for certain organs is also transmitted.

With regard to work of this type although it is questioned by many and somewhat indefinite, I do not feel that it can be taken too lightly. Tumor heredity has often been brought out in my clinical teachings as most significant part of history taking, especially by the surgical staff when one is confronted with obstructive jaundice and biliary disease in an undiagnosed case whose grandfather and mother, for example, both died because of cancer of the liver or biliary system. This thought further brings up

the afore mentioned question of an inherited tendency for certain organs. Ballance (5) reports that the acquired tendency fraction may be increased experimentally in mice by the injection of arsenic and indol before the application of certain carcinogenic agents to the organ or area, as tar, etc.

As yet however, I think this matter is very much in question as to its being of major importance. Although it must be accepted in certain animals as proven fact. Eggers (19) mentions that Sly's work proved tumor inheritance to exist to the extent of 44 per cent in mice, beyond the possibilities of spontaneous tumor origin. Lusch, after working with spontaneous tumors in mice, decided that the tumors showed a definite hereditary tendency which even might be said to be of a dominant character. Here, I believe, as he was also working with tar and other substances, that one must be careful in evaluating the data as chronic irritation may add to the results amazingly, especially in mice as they are the most susceptible animal yet studied with the production of tar cancer.

One might wonder then about the inheritance of congenital anomalies in relation to cancer as Cohnheim's hypothesis which will be given later has caused much

work to be done on misplaced embryonic tissue, tissue rests, etc. Many investigating embryonic cells can be found in the literature but their inability to cause cancer regularly makes its mention her_ brief, as no light has been thrown upon the problem of cancer, unless other factors were added, which will be discussed later.

Some writers have said that a hereditary predisposition must exist or else be acquired before malignancy will develop. Of course the word acquired, as I see it, can be used to cover almost everything that inheritance does not, but proof of the acquired tendency is not complete. However, Geschicter (28) states that experimental evidence has been shown and malignancy will not develop unless the site is prepared, so at least in animals some form of an acquired susceptibility may be possible. I think from the standpoint of an endocrine unbalance an acquired susceptibility in humans is probable as Roberts (64) during the past year concluded that by studying cellular reactions one can estimate the inherited susceptibility to cancer along with endocrine dysfunction. This may be true but in general as yet hereditary factors in man are not as convincing as in animal studies where many generations can be observed;

because in America families can not be traced and questioning often leads one to believe that the Mayflower must have been a bridge rather than a boat. Heredity in man is said by some of the most recent writers as Craver (14), Simpson (70), and Hoffmann (37) to play a minor role in the production of cancer, except for malignant tumor formations in the central nervous system, bone, and cartilage. Craver (14) states that, "Sly's work is now looked upon as having little importance in regards to human cancer." He and Verslugs (14) both favor the idea that heredity is not a general etiological factor.

Along with the experimental work arose the question of immunity. Here again the animal and human reactions differ. Foulds (25) working with fowl carcinoma, which is difficult to transmit because chickens possess a high natural immunity to cancer, states that fowl immunity can be decreased by successive tumor passage but will recur later rendering the family cancer free. Even in the Rous tumor some fowls were especially immune and Amie (68) states that young chickens especially possess the highest degree of immunity to the Rous sarcoma.

Sly in her experiments on mice took cognizance of an immunity factor. Likewise, much work has been done on numerous species, especially from the standpoint of

the reticulo-epithelial system. Bruda (8) reported that malignant tumors grew much more rapidly in mice which had been previously injected with India ink. It is well known that India ink will saturate the reticulo-endothelial system and decrease its functions of antibody formation as related to bacteria. He also found the immunity factor was decreased by splenectomy in mice but not to such an extent. Against this work a great deal of evidence can be found. In this respect Russel (68) mentions that in a review of this work he found that all the investigators agreed the immunity factor to vary greatly in the different tumor bearing animals and also that the immunity differed greatly from that found present against various bacterial diseases. He and others have added that some species have a strong natural immunity to malignant disease. One might conclude from all this work that probably the reticulo-endothelial system has little to do with cancer immunity. In experimental work it has been found (19) that the mouse has the least resistance to cancer while the rat (20) has a very high resistance as well as the afore mentioned fowl. It is known, however, that an immunity of short duration may be produced in an animal by the injection of cells from another member of the same species. This im-

munity is rather passive as it only lasts for two or three months and will not prevent the spontaneous origin of a new growth during its existence.

Racial immunity is known to be rather highly resistant to cancer, according to Lee among the primitive races. This (40) is also said to be true of Indians. Lynch (42) states that Negroes are evidently less resistant to cancer of the uterus, but here as in the preceding factors with relation to the uterus I prefer to mention more later. Mayo (49) believes the local tissue response, according to experimental evidence, depends on general systemic factors, which are both not well known and may either delay or hasten the development of a malignang tumor. However, in the human at least, Bullock (8) and others have concluded that, "It is impossible to produce a lasting immunity against malignant tumors." However, Russel (68), Lynch (42), and others have showed the factor of lower animal immunity to cancer to be variable but definite.

Age (14) is not generally considered as important in the etiology of all types of malignancy. German (78) writers early stated that the functional age of the tissue had much to do with the age factor; thus when cancer of the uterus occurs during middle life, one would expect

to find carcinoma of the skin arising ten or fifteen years later in the same individual or about age 65. While in these particular examples this may be true, I do not believe the rule holds in general. Pack's study, so Craver(14) states, does not find sarcoma occurring any oftener at 80 than at 20, nor any of the years in between when one considers the relative number of people living at the various ages. Weller (78) believes that carcinoma and sarcoma both decrease with age until 50, at which time sarcoma rapidly falls while carcinoma continues its advance until 65 years of age. He adds that cancer is ten times as frequent at 80 years of age as it is at age 30, which I am sure most present writers *at this time* strongly disagree with. Cancer in young people exists much more commonly than is known by most people according to both Warthin (77) and Williams (80). Their view indicates that these tumors are apt to be much more highly malignant than those in adults. It is now evident that the general trend of modern thought tends to minimize the relations of age and general cancer. In general (14) we may expect an increase in cancer because science has increased the average length of life. Cancer of the uterus will be considered separate.

Environment, Diet, etc.

With regards to the general etiology of cancer, one naturally rules out such factors as diet, soil, climate, etc. after reading the various reports on all forms of life down to the reptilis. However, (83) in man and certain animals, the environmental factors are well ruled out except for those of chronic irritation and certain other special causes like radiation.

Irritation.

Even (19) before Virchow's work in 1863, the origin of malignang tumors had been associated with chronic irritation as a causative factor. Since that time only a few are mentioned as skin cancer in chimney sweeps, intra oral cancer from rough teeth, cancer of the tongue associated with both trichina and lues, cancer of the bladder in aniline workers, arsenic and epithelioma formation, scar formation with malignancy, sunlight among sailors with skin cancer, epithelioma of the lip in pipe smokers, and cancer following radiodermatitis. These came along with many other instances from the records of early clinical men. Experimental work on many of these products began early but with no apparent success. It was not until 1910 that Curie and others (19) produced sarcoma in rats by the use of radium. In (14) 1915 Yamagiwa and Itchikawa reported that the use of tar would produce can-

cer in rabbits. Due (19) to the world war their work was not generally known until about 1920, when Fibinger and Bang also described similar results.

I would like to insert trauma here as a type of physical irritation. Acker (1) gives Kolodny's etiological explanation which connects trauma with malignant cellular changes as follows. The animal cell has certain growth qualities which are transferred to it by way of the ovum. This growth proceeds until growth is attained, but then changes occur which call a halt to the physiological processes and a stage is reached that might be termed "growth restraint". If this did not occur, no one can answer the question as to where the organism would stop. This potential growth ability of the tissue cell is probably retained throughout adult life, then if this be true, trauma temporarily removes the growth restraint so repair can be accomplished. Thus under certain conditions trauma might lead to a loss of growth restraint in a certain tissue, especially bone, and the cells repair or overgrow themselves to death, as one with hemophilia might hemorrhage to death.

One must admit that the reasoning given here is rather brilliant but as mentioned "under certain conditions" leaves a large opening. Craver (14) mentions that bone

tumors are in a large part now considered to be hereditary and many recent writers believe that trauma, without heredity or some other more definite factors is incapable of producing cancer in man. Eggers (19) mentions that trauma is very hard to control with respect to animal experimentation and its results per se are not convincing.

With regards to infective trauma, it can not be doubted that clinical findings often show cancer arising in syphilitic lesions of the tongue, lupus of the skin, and etc. However, in these cases as in animal experiments, infective trauma may not be a lone agent, and certainly these instances are not impressive in the whole cancer problem, but may in certain instances actually give rise to cancer in man.

Mayo (49) says that malignant cells contain more salts than normal cells. This apparently has been known for some time as Rodenburg (65) and others have written on the subject. Rodenburg believes that the killing of cells by repeated trauma causes them to become alkaline and to undergo autolysis, breaking up their materials with the liberation of their salts, all of which is continually progressing in a localized area tends to produce a hypertonic condition by which more fluids, blood

vessels, and nourishment is attracted. Thus cells become overfed and cancerous by way of their overactivity. This material, like that of lactic acid content, is part of cell metabolism and will be summarized later.

A vast amount of experimental has followed the early work concerned with chemical irritation in which harmones, benzine derivatives, and various chemicals were all shown to be related to a group of substances now termed as the carcinogenic group. Most of these compounds are classified as hydrocarbons. Here again a great deal of work can be mentioned but some of the irritative phenomena are of considerable interest, especially those being directed toward an explanation of how these carcinogenic substances cause malignancy to develop. Orr (58) while working with tar, benzpyrene, and dibenzanthracene, used staining intra vitam with phenal red in mice. This indicator dye was used to follow the carcinogenesis. The earliest change appearing in the treated area was an increased color intensity. Next, numerous small foci began to appear simultaneously with small tumors and the minute areas were yellow in color. This yellow reaction was believed to be the result of a local ischemia as it disappeared on rapid growth. Work of this type leads one to consider such factors as cell metabolism, neurotrophic disturbances,

endocrine control, and other factors like systemic intoxication. While the carcinogenic substances were effective in producing cancer, the mechanism of cellular shift to the malignant cell is not pointed out, so the more detailed work has followed. About 1930 (49) most of the carcinogenic substances known produced a purplish fluorescent spectrum when intense ultra violet light was used. I mention this because it may help in certain instances to easily determine whether or not various compounds are dangerous to health.

Metabolism and Endocrine Control.

That (19) cancer might result from impaired oxidation or local acidosis was mentioned by Van den Corput in 1883. He also mentioned acidosis and an increase in salt and mineral content as being related to oxidation. Necroharmones is a term used to include the dead cell materials which many have claimed do stimulate tissues to become cancerous. This work was followed by Marchand (19) as he expressed the idea in 1902. I have previously mentioned Rodenburg's work. As opposed to this work, a great deal of work has been done following someone's origination of the theory that because lactic acid was always found in malignant tumors and a very high percentage in some types, perhaps cancer might be linked with carbohydrate metabo-

lism. Not only carbohydrate metabolism but nitrogen, lipid, and others have been investigated by numerous workers. Eggers, as well as other less detailed writers, who have summarised the literature, have concluded that, although metabolism has not been shown to be an etiological factor, it has eliminated many possibilities and theories.

The work concerning endocrine products appears more hopeful, especially in female cancer, as will be considered later. A large share of the more important work concerning general cancer and hormones, I believe, is now being done and is yet to be evaluated. Foster (24) concludes that as everyone accepts malignancy to be a problem of disorderly growth, certain endocrine secretions definitely accelerate growth to the point of cancer formation. He refers especially to the anterior pituitary secretions of growth, but adds that pancreatic, thyroid, and certain liver evidently can also be offenders. A great deal of writing like this has followed the numerous works which showed how certain sex hormones were related to the carcinogenic hydrocarbons compounds and that some of these compounds might produce estrus in animals. Now many chemists are busy analyzing and showing the chemical relationships between endocrine products and

various carcinogenic substances. Where all this may lead is of course strongly doubted by many and time is bound to reveal more than is known at present concerning the general etiological factor of cancer, if there be one related to endocrine imbalance.

The Nervous System.

Investigation (57) concerning the relationship between the nervous system and endocrine system has not added to the etiology of cancer in general. A disturbed relationship may be important in malignancies of the female genitalia, but here the offender is probably in the endocrine system.

Trophic nervous changes were brought forth by Lang (19). Many workers who were using tar gave this theory as a possible explanation for the origin of malignancy in response to nerve atrophy and destruction. Masani in 1911 suggested that the disorderly growth of cancer might be due to a lack of control usually distributed through nerves. Numerous claims might be sighted but none have contributed a great deal as experimental work has shown that nerves, especially the sympathetic fibers, (19) tend to inhibit the growth of cancerous tissue.

Radiation.

Wyss (19) in 1906 first described cancer following

x-ray dermatitis but did not attribute the radiation to be the etiological factor. A resulting series of experiments followed until, as is known today, cancer may be caused by high x-ray dosage to most animals and man. Craver (14) gives the following statement concerning radiation, "Any wave length of the electro-magnetic spectra between heat and the gamma ray may cause cancer." He is referring to man in this respect. Even heat and sunlight are now not doubted in their ability to produce skin cancer. The ultra violet light band varies from 1900 to 2400 angstrom units. Some (19) question is held toward its carcinogenic properties with regards for animals but (14) it probably has no such effect in man. However, I noted that a case was reported arising in a scar. Of course, here one wonders concerning the scar as these areas are of course many times predisposed to the origin of a malignancy.

Radium has likewise been proved to be an etiological agent of rather wide distribution. It was generally known a short time ago that in the watch factories where radium salts were painted by hand upon the faces of instruments and where the workers moistened the brushes in their mouths, that many became afflicted with, at that time, an unexplainable illness. Many of these workers

died from the effects of radium. Recently some of the writers were able to study some of the less severe cases which lived to develop osteogenic sarcoma. They (14)(37) found the radium to be deposited similarly to lead in the ends of bones. Hoffman (37) gives another good report of radium in industry as it is related to carcinoma of the lung in arsenic miners. The studies were carried on in two mines, Schneeberg and Joachimstal. The former group's lungs showed marked anthracosis while the bodies examined at Joachimstal did not, nor did they show on chemical analysis any arsenic bismuth, nickel, or uranium. He states that the Joachimstal miners wore respirators and this explains the findings. He calculated that each miner during fifteen years inhaled and retained at least an equivalent of 55 milligrams of radium as radium emanation. There is a chance that arsenic might have played a part in these cases as it was present in the air of both mines as dust. The fact that the body eliminates arsenic very rapidly might explain its not being found at autopsy in sufficient amounts to be demonstrated. The fact remains that such an amount of radium would cause cancer to develop. The question will be solved in some 10 or 15 years beyond doubt as these mines now require their workers to wear respirators in which

animal charcoal is put to catch the radium emanation.

Theories.

The theories concerning the etiology of cancer are nearly as numerous as are writers in the related literature. For this reason only a few of the more generally known theories will be mentioned.

Virchow's irritation theory was one of the earliest. This of course covers physical, chemical, and infectious irritants, which possess carcinogenic powers of great invariance in animals of certain types as previously discussed. In man the question is proved to be a small factor except in certain tissues and as mentioned before without some of the other, it is strongly questioned. Cohnheim originated the theory concerned with embryonal rests. Numerous workers have since added to this theory as Meikle (51) by saying that probably cancer arises from cell rests when an unbalanced endocrine system adds the carcinogenic impulse. It is well known that, while many tumors may arise in a congenital anomaly or misplaced embryonal tissue; it has not withstood investigation. With regards to the modification of this theory, it may in certain types of cancer be etiologically bound; however, some mention of this will be included under uterine cancer as it is not as yet proven.

Rodenburg's theory has been mentioned.

Warburg's theory related the origin of cancer to the cell's abnormal glycolysis. Proof here has been like that concerned with the metabolic hypothesis.

Lang's suggested that cancer might arise from neurotrophic disturbances as mentioned heretofore. *gram*

The parasitic theory was of course, both the earliest to be suggested and disproved, at least almost wholly in man. In a certain few animal tumors it must be admitted as a fact. In man without irritation, etc. the question is very doubtful as to whether a parasite can produce malignancy alone. *sep*

With respect to these theories, it is evident that some are based on clinical observations, others on experimental work, and many are purely philosophical conjecture. Of this latter group, I would like to mention Karg's theory (19), because it shows that many of these early workers were deep thinkers. Many of these theories stood for some time against the careful experimental workers' efforts. Karg's theory was based on nuclear fusion, there being a leucocyte involved so that the offspring gained the ability to rapid infiltrative growth and metastasize. Eggers mentions that the fact that as bizzare nuclear pictures are the rule in cancer tissue, *gram*

one can easily see why such lines of thought arose in conjunction with histological study.

Simpson (70) is one of the more recent clinical observers interested in cancer, and he advocates the following viewpoint, which I will refer to hereafter as his, but which is what might be called the modern conception of cancer. He states that from the etiological standpoint malignancy should be considered as a group of diseases just as are the bacterial disorders of the animal kingdom, as the various types of cancer differ markedly as to their causative factors. However, he admits that the process by which a benign cell becomes malignant is nearly as obscure as ever. In (14) (70) (37) recent writings the etiology of certain tissue malignancies is claimed to be known; as for example, certain central nervous system tumors are largely hereditary as well as osteo-sarcoma on the basis of multiple echondromata and exostoses, etc; carcinoma of the lung being due to the inhalation of radium emanations, combustion products from gasoline, and particles from tarred roads, etc; cancer of the bladder from aniline; cancer of the penis is largely due to chemical irritation of the retention of smegma under the prepuce; and etc. Numerous special types of cancer are thus listed in recent literature

with their etiological factor or factors. Among them heredity is often considered to include (14) "a combination of factors such as age, occupation, habits, and anatomical or physiological peculiarities, rather than a true inheritance of susceptibility or resistance to cancer."

Adeno-Carcinoma Corpus Uteri

I like to think of the etiology of carcinoma of the uterus as one of the special types of cancer in accordance with Simpson's viewpoint. I fully agree, however, that this concept may be found faulty; but whether his conception is right or wrong, it does make the problem a new part of preventive medicine with regards to each type of tissue malignancy. For example, it appears rather useless for an investigator to try to prove tar products the cause of skin cancer in an animal which is highly resistant; so in this manner, I believe many unnecessary things can be excluded by careful reasoning. A few references will be made to other types of uterine tumors; and in regards to endometrial hyperplasia, the change from benign to the malignant mechanism is considered as an etiological process.

Classification

Lynch (43) gives a good classification to which I have added fibroid tumors as they may contain epithelium and are termed endo-myomata.

Adeno-carcinoma arising from the uterine body

A. in surface epithelium

1. everting

2. inverting

B. in endometrial glands

1. everting

2. inverting

C. in benign uterine tumors, especially endo-myomata where misplaced glandular tissue is present.

Squamous cell carcinoma of the uterine body is very rare as a primary growth and there is considerable controversy in regard to it, so it will not be discussed.

It is supposed that the reader is familiar with the anatomy and physiology of the uterus.

Incidence

Ewing (20) claims that about 10 per cent of pelvic tumors start in the uterine body. In 1924, Mahle (47) gave 30 per cent concerning the frequency of corporeal cancer (34); Cullen gave 25 per cent; Peterson, 16 per

cent; and Baldy, 8 per cent as to the early clinical findings in 1910 of all uterine cancers. Many more writers agreed with Baldy and claimed numbers below 10 per cent. Findley in 1921 stated that "although many feel that cancer of the uterine body is rare, it is true that out of every 24 women past 40 years of age, one dies of cervical cancer and corporeal cancer afflicts one-tenth as many." Thus his work shows one cancer of the body of the uterus in 240 women over 40 years of age and that uterine malignancy made up about one-third of all female cancer. Most of the statistics since 1900 have showed an increase. Wilson (81) mentions that the great variations probably occur because many cases are seen late and errors in classification are made. Meikle (51) states that corporeal tumors are more common than those of the cervix, which is probably true, as every clinical man commonly sees many benign uterine tumors.

Novak and Yui (56) recently reported on 12,813 women in which they found 104 cases of adeno-carcinoma corpus uteri. Among the 12,800 cases they found 1.6 per cent of the cases showing endometrial overgrowth. This will be considered later as well as Craver's statement that, "carcinoma of the body of the uterus is found in single women four times as frequently as carcinoma of

the cervix and it occurs mainly beyond the menopause." McGlinn (50) believes that statistical data has fooled many writers and admits that even he himself was not a critical observer until 1934. At this time he collected data on 4,767,304 women who were over 35 years of age, and of these he found 156,465 died from all causes, among which were 16,879 cases of cancer. He then concluded that one cancer death occurred in 283 and all uterine cancer was only responsible for one in a thousand. Cancer of the uterine body is much rarer, as a complication of pregnancy than is cervical cancer. I only found one case reported in the literature (50).

Now if we combined the various views on the frequency of corporeal uterine cancer and keep in mind that about one in 10 of all uterine cancers involve the corpus, then one case in every ten thousand women is a most conservative estimate as I believe it is somewhat more common. Hoffman and Hilario (37) (35) claim cancer of the uterus is second to gastric cancer, but it must be kept in mind that these men consider all types of cancer of the uterus.

Predisposing Causes

Age

Cancer (30) (80) (77) is generally considered to be rare in young people but actually it is relatively common.

Gilbert (29) reports five cases of corporeal uterine cancer in young girls under 15 years of age, one being at age 11. Mahle (47) mentions a case in a woman 21 years of age. However, it must be admitted that the disease is uncommon in young women just as the later tables will show it to be rare past 70 years of age. Gilbert (29) (60) and others have studied data collected from the United States and five other countries. This work has showed the highest average of corporeal uterine cancer to occur at 53 years of age. Under 35 years of age only one and two-tenths per cent was found. Norris and Dunne (54) present a rather complete table from ages 20 to 80.

Age in Years	Patients	Per Cent
20-29	4	1.5
30-39	18	6.7
40-49	49	18.3
50-59	124	46.3
60-69	57	21.3
70-79	16	5.9
Total	268	100.0

Their work shows that 46 per cent of the cases between fifty and sixty years of age. Also two-thirds of them were post-menopausal.

In the relationships of age where the menopause and fundal carcinoma appear, as against the menopausal age of normal women, I wish to include the following table.

Age at Menopause	Fundus Cancer	Normal
36-40	2 %	12 %
40-45	4 %	26 %
45-50	30 %	41 %
50-55	60 %	15 %

In this work Crossen (15) has accepted Krieger's normals as given in the right hand column. Here, we notice that 67 % of the normal women have their menopause between the ages of 40 and 50 years. However, the most interesting fact is that 60 % of the fundal carcinomata appear in women past 50 years of age or post-menopausal. Although (45) women are past fifty, one must grant that they still may be menstruating in a small percentage of cases. In these cases of late menstruation Crossen (15) found as Novak, Yui (56), and others (55) have reported, a marked tendency toward endometrial hyperplasia. This finding is commonly found in post menopausal cases according to Novak (56). It is mentioned that an artificial menopause should be induced in women past fifty by radiation of both ovaries as a prophylactic measure (15).

That (15) a late menopause is found four times as often in cases of corporeal carcinoma of the uterus is now known to be true. Macfarlane and Howe (45) found 50 per cent of their cases to be forty or under. Meikle (51) gave the majority of his cases between 50 and 55 years of age and Peterson included most of his cases in the fifth decade except for sarcoma which usually were found before 50 years of age. Beattie's (6) cases of adenocarcinoma averaged 57 years of age with three-fourths of all cases being in the fifth and sixth decades. Mahle (46-47) gives the average age as 55 and Stacy (73) found in reviewing Mayo's data that only 11 per cent were under 45 years of age. I believe one must conclude, after reading the literature, that the majority of cases of adenocarcinoma corpus uteri do occur past 50 years of age and in most cases the menopause is well established. However, it appears as though a late menopause does predispose to endometrial overgrowth which will be considered in some detail.

Regarding heredity and immunity with corporeal cancer, little can be said except as has been mentioned. However, it can be said that some immunity probably results from numerous pregnancies.

The disease occurs in all races but according to

Lynch is more frequent in the Negro as are fibroid tumors. That carcinoma of the uterine body is rare in Jewish women is showed by Horwitz' report (38) from the Mayo clinic. He restudied some 1200 cases of uterine cancer which covered a five year period and found only ten of these cases occurred in Jewish women.

Copied

Childless Women

Beattie (6) presents a rather interesting table, before which he states 25 per cent of his cases were never pregnant.

Number of Pregnancies	Number of Cases
1	9
2	7
3	1
4	1
5	3
7	1
8	2
11	1

This work seems to hint that in adenocarcinoma of the body of the uterus we must include also women who have had only one or two children as being predisposed. He mentions however, that 50 per cent were multipara and half of the other 50 per cent who were childless as

mentioned while the other remaining 25 per cent had had an abortion.

Quigley (62-63) says corporeal carcinoma is a disease of single women. Norris (53) gives 26 per cent of his cases as spinsters, while Buben (7) states that cancer of the body of the uterus is much more common in childless women than is cancer of the cervix. This latter idea, I think, is rather widely accepted as true. In Macfarlane and Howe's report (45) 52 per cent are given as those having had no pregnancies which agrees with Findley's statement that over one-half of the cases of corporeal carcinoma occurs in childless women. In this respect Whitherspoon (82) states that childbearing does not predispose to fundal cancer. Dr. L.S. MacGoogan's statement that cancer of the uterine body is found commonly to be a disease of wealthy women rather than cancer of the cervix which is a disease of the poorer class in general; one does not doubt after studying in the dispensary.

As regarding the childless women and those who have had only one child or an abortion, McGlinn (50) says the infective irritation because of insufficient uterine drainage must be considered as an etiological factor. I think Quigley's description is rather complete. His idea is that in multipara the uterine drainage is good but in the

spinster this is not the case as she suffers from a low grade endometritis which disturbs the normal alkaline state. The acid change is gradual, often covering years, but results in exciting cell growth or even the cancer cell. One cannot say that such a series of events could not be a major factor in the spinster. Lynch (43) and others claim that no definite knowledge concerning infection as a cause of uterine cancer exists. He cites Cullin's report in which no evidences occurred with respect to an antedated infection. Findley is of the opinion that infection may excite hyperplasia within a gland and thus cause it to pass into the malignant stage.

Precancerous Lesions

Many writers have described certain histological patterns which are similar to cancerous tissue and frequently become malignant but which lack heterotopia, *no carcinoma* (the power of invasion). Clinically leucoplakia is one of the more common precancerous lesions seen frequently in the mouth of the cervix and external genitalia as well as in other areas. Histologically (48) Martzloff and other writers claim that the areas of endometrial hyperplasia are identical with leucoplakia spots. That endometrial hyperplasia, areas of localized necrosis, hyperemic areas, and benign tumors are precancerous lesions

is not definitely accepted but many authors are enthusiastic about their early recognition and removal. Findley (22) states that cancer develops in tissue where long standing changes are gradually occurring, never in normal tissue. This concept throws most of the abnormal endometrial cellular derangements into the precancerous group. Ewing (20) attaches great significance to local areas of hyperemia, ulceration, and toher cellular upsets which are frequently found in the endometrium. He considers chronic endometritis and irritation due to the presence of other tumors as being causative of these precancerous conditions. Many clinical books refer to the hyperplastic changes in the endometrium as being chronic endometritis, which is known to be a misnomer and the reader should keep the idea pertaining to overgrowth constantly in mind. Findley gives a rather widely mentioned cause of precancerous changes as a minor possibility, respectively that these conditions result with sterility in certain women because of an inherited congenital anomaly.

That (9) often endometrial disturbances result in some women because of anemia, malposition of the uterus, ovarian disease, circulatory interference, and sometimes unknown causes, is accepted by all gynecologists.

Polypo of the endometrium are looked upon by Hellwig (33) and others (10) (74) as being precancerous just as are those of the rectal mucosa. However, cases of this type are rare in the uterus while rectal polypi usually do undergo malignant changes is well known.

Stacy (27), as well as many other clinical observers, believe myomata may lead to malignancy. Ewing (20) believes myomata and other mixed tumors are the primary causative factor of cancer in the uterus. Various men report the coexistence of myoma and cancer as follows: Stacy 37 per cent; Osterlin (59) 25 per cent; Howe (45) 26 per cent; Dunne (54) 35 per cent; and Cohen (12) 35 per cent. Cohen also states that about 35 per cent of women between the ages of 30 and 40 have myomata. Some authors give slightly lower figures but the average seems to be about 25 per cent. Mayo's report (27) 25 per cent of myomas in their cases of carcinoma of the body of the uterus according to Stacy.

What do you mean

Many ideas are given concerning the malignant process which results from myomas in the uterus. Findley remarks that many precancerous changes occur in the endometrium commonly associated with myomas and he concludes that myomata predisposes to cancer, even stating, "The hyperplastic changes in the endometrium in conjunction

Findley

with fibroids of the body of the uterus form the connecting link between the normal mucosa and cancer." Whitherspoon (82) relates that fibroids may possibly be caused and cause cancer by way of certain estrogenic substances, primarily by way of an over activated ovarian system due to hyperpituitrinism. Meikle's (51) idea is similar as well as is De Snoo's (39). However, De Snoo thinks that fibroids arise first from "genitoblasts" which are considered to be quiescent undifferentiated cells and go into action normally when pregnancy requires the organ to enlarge. These cells probably do not exist as will be mentioned later. Numerous other theories exist explaining both the origin of benign uterine tumors and a resulting cancer of the uterine body but they like those mentioned are far from proved. Meikle and others suggest mixed tumors arise in the uterus during menstrual life. This probably is true and especially in the Negro, as I have gotten this impression from clinical lectures.

Precancerous changes have been said to occur in the human uterus following certain allergical reactions by Gilbert (29). It has also been mentioned by him and others that uterine symptoms, such as edema, muscle spasm, etc., can be relieved by removal of the cause or desensitization as is the case asthma. This problem is indeed

somewhat logical; but as yet, I fell it can not be given much consideration as too little is known concerning its existence. sp

The endocrine relationships have been noted by surgeons for some time with respect to endometrial changes and disturbed ovarian function. These men (55) also found that often coexisting tumors of the ovary and uterus were present in the same case and that the ovarian function would persist longer if some of the endometrium could be left intact and vice versa. Endometrial hyperplasia with ovarian tumors has been brought out by many writers. Experimentally Loeb (41) and others (70) have produced mammary carcinoma in mice by excessive hormonal injections, mainly theelin. These substances have their greatest carcinogenic effects on tissues normally linked in the sexual cycle. Some mention was made earlier of the anterior pituitary and other endocrine secretions in their relations to cancer in general. Finola (27) and others have concluded that the anterior pituitary if excessively stimulated will produce pseudocancerous proliferation or hyperplasia of the endometrium and may even lead to cancer.

The nervous system has been investigated in connection with the endocrine system as well as will its distri-

bution to tumor cell. What part the nervous system plays in controlling many of the glandular secretions is not well known; however, one might expect rather reactions to result where trauma is concerned with nerve endings. Certel (57) and his coworkers say that nerve filaments end in cell nuclei, intercellular tissue, and the blood vessels of tumors just as in normal tissue human tissue. Histologists have reported similar findings in immature tissues. The parenchyma of certain organs is known to be well supplied with nervous elements as well as most types of tumors. However, the part played by these structures is as mentioned most obscure.

Endometrial Hyperplasia

The ovarian hormones are probably the most direct governors of the uterine endometrium. The cyclic changes which normally take place in th endometrium are not well known by most pathologists according to Sevringhaus (10) and his associates. He mentions that even the clinical man does nto understand the endometrial physiology.

Time and space do not permit its discussion her, but mention of the early work concerning endometrial physiology is worth while. The modern concepts regarding the normal histological changes which take place in the endometrium with each menstrual cycle date from Alder and

Hitchmann's work in 1908 (10). Bartelmez (10) since has added to the earlier works and made the histological changes understandable with an explainable knowledge of the endocrine functions involved. This later work clearly revealed that often a hyposecretion might result in just as definitely an endometrial overgrowth as would a hypersecretion of especially theelin.

Novak (56), Campbell (10), Hobbs (15), and many other clinical workers of late have been reporting cases of uterine cancer and endometrial hyperplasia. The general conclusions of all this work have led to the belief that carcinoma of the uterine mucosa may result by a process of cellular hyperplasia because of various reasons.

First, as to how the uterus enlarges during pregnancy, Stieve's idea that the uterus contained embryonic immature cells, as fibroblasts, cell rests, and blood cells which became active in adding to the uterine structure, has been more or less discarded. Fisherwasels (23) and his aids studied uterine sections from mice, which were injected with harmones, collected from the urine of pregnant women and found the hypertrophy which normally takes 21 daus was completed in 100 hours. By this method they were able to add vital stains and exclude the possibility of blood elements, cell rests, fibroblasts, and

every type of cell foreign to the uterine muscle or mucosa as playing an active part. They concluded that the uterus hypertrophies only by a very rapid and mitotic cellular division of the structures present in a normal uterus. This work of course does not exclude the possibilities of embryonic accidents as misplaced cells and the like.

Novak and Yui histologically examined the endometrium of over 12,800 cases and put special study on 804 cases showing endometrial hyperplasia among which were found 104 fundal carcinomata. Numerous other men interested in uterine cancer have carried on studies with reference to endometrial hyperplasia and reported similar findings. I have mentioned heretofore that certain endocrine changes, tumors, infections, and circulatory retardations, etc. will cause hyperplasia.

The histological studies are most detailed so I wish only to include some of the more important analyses that have been commonly accepted, especially as they are believed to be related to malignancy. Pathologically endometrial hyperplasia is a benign process, but it does present many proliferative features which often cause the observer much mental conflict in deciding whether or not the area in question is malignant. In mild degrees of

departure from the normal "Swiss cheese pattern", one may find only an unusual amount of epithelial proliferation as evidenced by psuedostratification most frequently in the small glands. In the more advanced stages, actual stratification is plainly noted in all the glands and surrounding mucosa with numerous bizzare cellular mitotic figures present as well as pearl formation and other evidences of malignancy. The intermediate stages are graduated accordingly and a small area of adenocarcinoma may be present without doubt in almost any stage; however, a small adenocarcinoma may exist in a normal endometrium. Novak mentions the fact that he found 1.3 per cent of women in the childbearing age to have an adenocarcinoma with only a mild degree of endometrial hyperplasia; also that metaplasia is common in women past the menopause. In many sections of endometrium it is possible to demonstrate graduating changes from benign to malignant tissue, while in most cancers this can not be done as the malignant tissue is sharply defined by a well marked line from the normal tissue. This degradation may be rather sharp, however, in some few cases. Taylor's conclusion in regard to hyperplasia of the endometrium is that it is as definitely a cancerous process as occurs in the epithelial hyperplasia of the breast tissue and that they both should

be regarded in the same. From this standpoint, as I referred to Crossen's report previously, many clinical men now feel that when aberrant endometrial activity is found present, such measures as an artificial menopause should be induced in young women as a prophylactic measure against cancer. In such cases as Novak's where 10 per cent of the cases were post-menopausal, some men suggest that an early hysterectomy be done as the condition should be regarded as cancerous when repeated curettage shows marked hyperplasia of the endometrium to be present. The condition is usually called marked when histologically, stratification is evident, as well as adenomatous proliferation, marked atypicalness of the glands with a syncytial like proliferation, and squamous metaplasia of the glandular elements and surface mucosa. Findley states that, "no one who has observed the structural alterations in the uterine mucosa can fail to be impressed with the conviction the glands of the endometrium can pass from a normal to the so called inflammatory stage and then to the malignant." So perhaps, Novak may be right when he believes that with the finding of hyperplasia during repeated examination, there may be justification for the dictum, "Nicht Karzinom aber besser heraus." sp

Opposing endometrial hyperplasia as a cause or mechanism of cancerous development in the uterus, many writers can be sighted. Shaw wrote according to Taylor (75) that he could in no way see how the two might be connected, while Meyers relates they may be only different in degree. Even some of the theories' supporters as Campbell (10) and Hellwig (33) make statements to the effect that tumor biopsys are often misinterpreted and so far a good clinical history is concerned, if well interpreted, is more accurate than a biopsy report. Such a statement as this, I do not believe true as the pathologist certainly is more accurate than a patient's story; however, I know they are open to question in that they often disagree. Part of the disagreement must be based on the variety of diverse endometrial processes seen in different stages of the menstrual cycle. The fact that many agree on endocrine influences, to me, strongly suggests that the malignant process may arise during endometrial hyperplasia in the uterine cavity, but at present one can only surmise the process as actually being the intrinsic cellular shift from benign to malignant.

Although the hydrocarbon compounds are chemically related to human endocrine products and will produce estrus with epithelial hyperplasia and cancer in the

experimental animal, and clinically uterine hyperplasia of the mucosa is found with precancerous lesions and a late menopause certainly it does not follow that human adenocarcinoma corpus uteri is the result of such a process. But is the result of an unproved factor. *What is subject*

In commenting on the etiology of cancer in the various species of the animal world, much might be said, but it is inevitably true that no causative factor is known and proved. It must be admitted that phenomena, like the Rous sarcoma, are exceptions. I feel it is not justifiable to agree that the cause of any human cancer is fully known, although it be claimed. In this respect, to the problem as a whole it must always be kept in mind that animal experimentation is not sufficient proof in man; however, much of the work has not been done in vain.

Conclusions

1. Cancer is not infectious in man.
2. Malignancy may result in certain tissues because of local or general hereditary factors, irritation, radiation, or the actions of carcinogenic substances, and other discussed factors, but probably because of secondary or combined actions or other unknown causes. *These alone or in combination*
3. Cancer may be a group of diseases, each having a somewhat different etiology.

4. Advancing age seems to be a factor complex, predisposing the individual to the development of cancer.
5. The etiology of cancer in general is not known.
6. The majority of women who have carcinoma of the uterine body are in the fifth decade of life, apt to be childless, past the menopause, or having a late menopause and present histological evidences of endometrial hyperplasia or some other precancerous lesion.
7. Hyperplasia of the endometrium may be the process by which malignancy develops in the uterine body.
8. The etiology of adeno-carcinoma corpus uteri is not definitely known.

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