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Precancerous dermatoses

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THE PRECANCEROUS DERMATOSES

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CONTENTS

ILLUSTRATIONS

INTRODUCTION

The purpose of this paper is to present a simple and correlated report on the much discussed and disputed subject of precancerous dermatoses or precancerosis.

After reviewing the literature from the year 1916 to 1942 these results and theories, gained after many years of the study of case findings and research by reliable authorities, seemed to be of value in studying the condition known as precancerous dermatoses which is day by day becoming a more important and widely recognized entity.

In this thesis the author makes no attempt to inject into the writing any of his personal ideas or criticism. The ultimate purpose is to present the facts as found in the literature.

MORBIDITY AND MORTALITY OF CUTANEOUS CANCER AND ITS GEOGRAPHIC DISTRIBUTION

Cancer is probably the most dreaded disease known to man. To fully appreciate the scope of this malady, and to study it in the light of learning more about the different phases in its attack with the hope of more absolute diagnoses and cures thus decreasing the death rate and brightening the prognosis of its victims, it will be profitable to study its past record in the form of statistics collected from different areas of the United States.

This will not be an easy task as cancer, in its multitude of forms and syndromes, is not a reportable disease. There is not to be found in the literature an accurate statistical record of malignancy, either treated or untreated, which have been controlled and cured and did not in some hidden way, shape, or form predispose its victim to his exodus. Nor is there any complete record of the number of precancerous conditions which have been permanently cured. With this inadequacy of records on which to base the morbidity and mortality statistics Hoffmann (1) and Wood (2) suggested a more careful analysis of cancer cases in the form of a questionnaire method to gain accurate statistics. With such an arrangement as suggested above cancer cases

would become a matter of record. With such data as the degree of disease development, time of onset and duration, treatment and results, and autopsy findings in fatal cases there would be a solid foundation for accurate morbidity and mortality figures. This method has never been adequately applied in the United States, although it was being applied in Germany up to the outbreak of the present war. The results have not been reported from Germany up to this present date. With these facts in view it is very difficult to ascertain the morbidity of the disease.

As was pointed out by MacKee and Cipollaro (3) in their monograph; it has been estimated that the number of cancer cases is about three times the number of cancer deaths reported in any given area for a given period.

The mortality statistics quoted are taken from the MacKee and Cipollaro Monograph (3) and were originally published by the American Society for the Control of Cancer, by the Metropolitan Life Insurance Company, by the United States Bureau of the Census, by the Department of Health of New York City, and by other agencies:

1. During 1934 over 134,000 persons died of cancer and other malignant tumors in the Registration Area in the United States, the cancer mortality rate being

106.3 per 100,000 as compared to 97.2 in 1930, an increase of about two percent per year.

2. In 1900 cancer was tenth in the list of fatal diseases in the United States Registration Area with a rate of 64 per 100,000. By 1932 it held second place, being exceeded only by heart disease. Thus in the period of thirty two years the mortality rate of all forms of cancer was nearly doubled.

3. This increased mortality may be explained in part by more accurate diagnosis and better statistics, but the most important factor is undoubtedly the rising average age of the population. In 1930 about twice as many persons reached the age of greatest susceptibility to cancer (fourth, fifth, and sixth decades) as in 1850. It has been estimated that by 1950 this number will be one and a half times greater than in 1930. Thus in spite of increasing success in preventing, controlling, and curing the disease, a continued increase may occur in cancer incidence and mortality during the next two decades. However Hoffmann (4) in 1932 in his statistical reports was certain that the cancer death rate in this country and other countries had reached its maximum, his assumption being based on the facilities of early diagnosis and treatment. We see that his prophecy was incorrect when compared with these more

recent figures presented some five years later.

4. The following tabulation is of great value in realizing the importance of early diagnosis and treatment of skin cancer when faced with the fact that the mortality rate is continually rising.

Total Deaths Due to Cancer in the U.S. Reg. Area	Deaths Due to Cancer of the Skin (No.)
1921	
76,274	2,433
1934	
134,428	3,315

Thus in this period of thirteen years death from cancer of the skin showed an increase of 882. According to the statistics above and in the foregoing paragraphs it proves that approximately 6 percent of deaths due to cancer in the United States are attributable to cancer of the skin (this figure includes death rate due to cancer of the oral mucous membranes), in other words, cancer of accessible parts.

In comparison with these figures of MacKee and Cipollaro (3) it is interesting to see what Dublin's (5) deductions were after studying the subject of morbidity and mortality of cancer in the United States. His statistics were very inclusive and included cancer in ages from 1 - 74 years during the years 1911 - 1935.

Organ	Total No. of Deaths	% of Total Deaths All Causes	% of Total Cancer Deaths
Skin	4,315	0.1	1.6

Death rate per 100,000

1.6

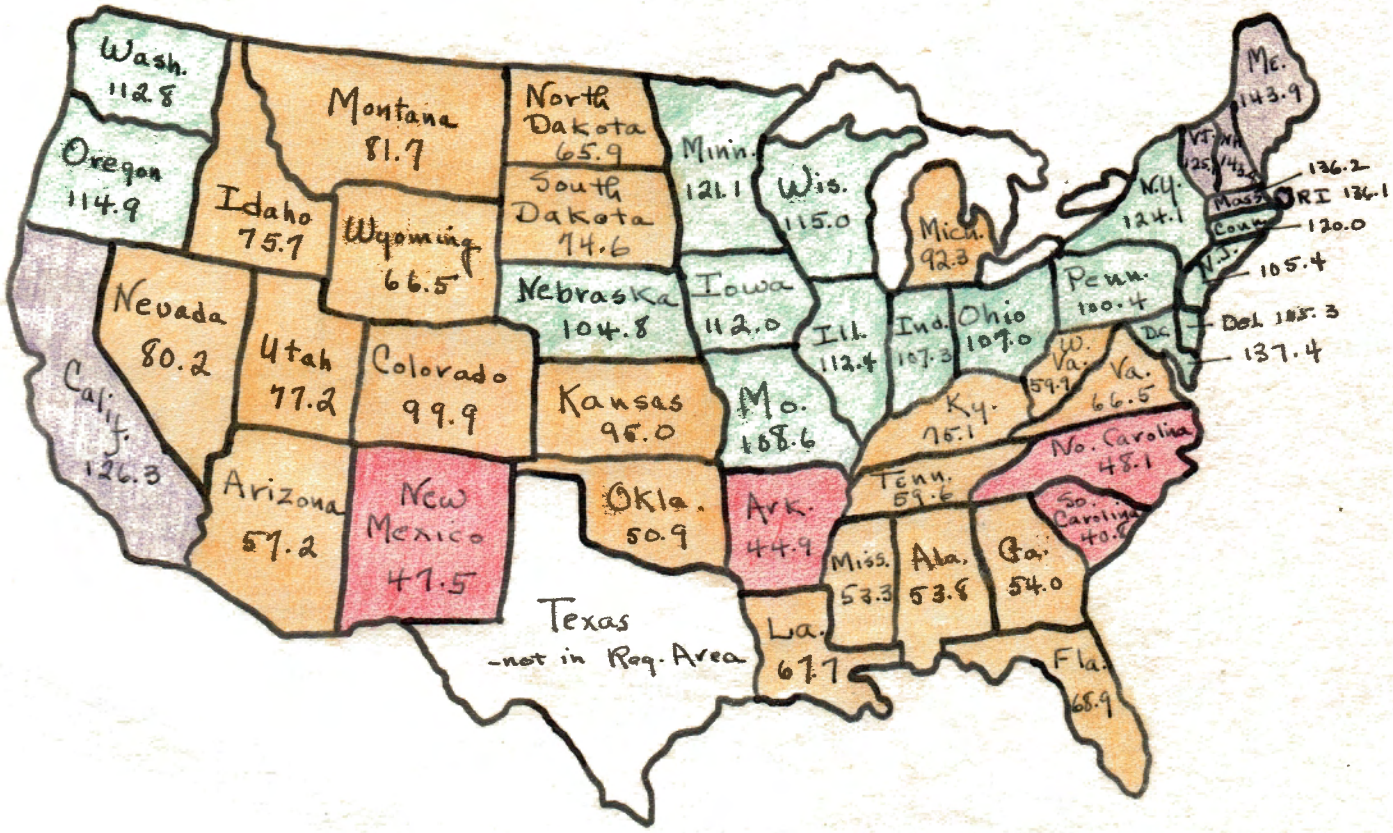
In 1934 Rector (6) published a map of the United States showing the geographic distribution of death rates due to cancer and other malignant tumors (see Chart I). This chart is only a crude representation of the number of deaths due to cancer but it serves the purpose to orientate one with the states and areas of highest cancer mortality. However this cannot be assumed to indicate the areas with the highest incidence of malignancies, because the area a given person lived when he discovered the cancer and the area to which he may have gone to receive treatment but finally died are not always one and the same. But the chart is an attempt to show those areas in which cancer is more likely to be found. The map shows that the areas with the highest incidence of cancer fatalities are the Western States, California having the highest rate, and the New England States. It is interesting to compare this geographic distribution for cancer fatalities as a whole to those areas with the highest mortality of skin cancer. There is a marked similarity in the areas, but it is probably on a coincidental basis since skin cancer mortality is such a small percentage

Chart I

CANCER AND OTHER MALIGNANT TUMORS

crude death rates per 100,000 population 1930

U.S. Reg. Area



Death rates per 100,000

- 0-50
- 50-100
- 100-125
- 125-150

of cancer mortality as a whole.

Petersen (7) made a very interesting survey of the geographic incidence and mortality rate of cutaneous cancer in the United States. The geographic distribution of the mortality of cutaneous cancer is shown on Chart II. It shows the mortality to be the highest in general in the New England States; this being ascribed to the preponderance of an older age group on the one hand and to better diagnoses on the other. Petersen doubted the authenticity of these statements and presented a very ingenius but plausible theory to explain the apparent predilection of cutaneous cancer for certain fairly well outlined areas. Since this is the only attempted explanation, presented in recent literature, for the geographic distribution of cutaneous cancer, the major points will be presented.

He stated that for the white race, cancer of the skin occurs in three focal regions:

1. New England, including Nova Scotia

2. The Southern States (it should be kept in mind that Texas and S. Dakota are not included in the area of registration)

3. The West Coast, which shows increasing susceptibility as one proceeds southward.

Petersen's (7) deductions were as follows, quote:

"Presumably the irritation from light plays a dominant role as an etiological factor for skin cancer; a supposition that receives support from the fact that the Negro, whose skin is protected against ultraviolet irradiation, has less cancer of the skin in the south. But I should call attention to the fact that for the Negro Kentucky and Louisana present the highest rates. How is one to explain these curious differences? As a working hypothesis, let us postulate five components as making up the factors in an uncertain constellation, the sum total of which might bring about a transition from normalcy to malignancy. These might be classified:

1. Age
2. Genophasic factors
   a. Hereditary resistance
   b. Hereditary susceptibility
3. Chronic irritation
4. Proper ion balance
5. Proper endocrine balance.

Given the first three as conditionally propitious for the change of the cell from normalcy to malignancy at some particular time, it might seem that the additional factors of humoral environment must still be considered. Experimental evidence seems to be accumu-

lating that the Ph plays some role (relative alkalin-ity), and probably the same holds true for the glands of internal secretion.

If the tissue fluid remains unchanged, or the fluctuation in the ionic and endocrine concentration swing within a small range, the probability is that the attainment of a proper constellation of ions and endocrines of just the right proportion to change the course of some cell at just the right time of its reproductive cycle will occur less frequently than if the tissue fluid is constantly swinging in a wide range between the two extreme poles of normalcy.

The Ph may be considered for a moment. If a relatively high Ph is desirable to enhance the transition from normalcy to malignancy: (1) the pyknic person will be more liable to cancer, because he is in general more alkaline; (2) one might expect more malignancy in the south, provided meteorological quiescence, sunshine and diet raise the Ph to a sufficiently high degree; and (3) if unusual degrees of Ph are obtained, even if for only short periods of time, one might expect a proper constellation to occur more often in the cyclonic tracks, for with the passage of each cyclone or the summation of several, one notes transient alkalotic peaks occurring as overcorrection after periods of acidity.

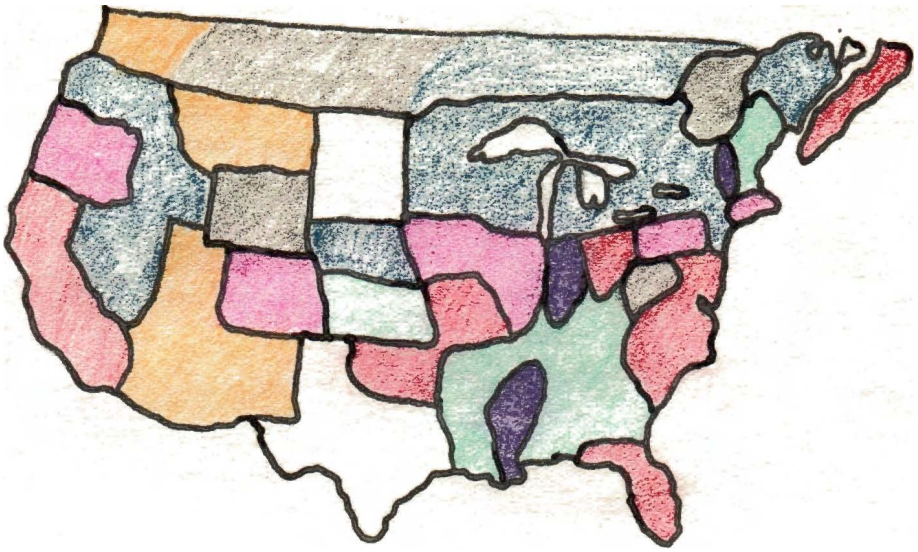
The same reasoning holds for the endocrine tide that is so largely involved in the mechanism of meo-teorological adjustment (the thyroid and suprarenal glands). With tides that have a fixed rhythm one might anticipate less influence. If it requires possibly the factors 1, 2, and 3 and just the right constellation occurring with the combination of 4 and 5, the more frequently the endocrine glands are stimulated and depressed, the greater is the possibility that some time an optimal point is reached for the change from normalcy to malignancy.

Perhaps this can be best illustrated by a diagram. In Chart III there is indicated a theoretical Ph curve (merely typical biologic rhythm) with a low value of 7.34 on the sixteenth day of the chart and a high value of 7.53 on the thirty-seventh day. One may assume that the high Ph affords an environment favorable for the beginning of malignancy, curve 4 chart III. Of the innumerable other factors that might be considered, three have been indicated at the top of the graph: (1) gradually increasing age (2) the gentypic factor, possibly a balance of inherited resistance or inherited susceptibility (3) chronic inflammation, varying from day to day both in the number of newly formed cells and in the degree of stimulation and degen-

Chart II

MORTALITY RATE OF CANCER OF THE SKIN

White



Death rate per 100,000

4.4-4.2
3.5-4.0
3.0-3.5
2.5-3.0
2.0-2.5
1.5-2.0
1.0-1.5

MORTALITY RATE OF CANCER OF THE SKIN

Colored

Death rate per 100,000

Kentucky
0.9
0.7
0.6
0.5

eration. Indicated in the diagram at X, a constellation would obtain when, because of the peculiar relation of age, susceptibility, irritation and proper humoral environment (in this case indicated by the Ph level), some cell might reach just the proper state for the change in its character from benignancy to malignancy.

In studying a Van Cleef storm track we see that the pathways along which cyclones are constantly passing is from the west to the east coast, more marked in the northern section. Each alternation of the atmos-phere brings about a distinct alternation of the blood chemistry; a synchronous and definite rhythm takes place with alternating periods of vascular spasm followed by vascular dilatation, increased Ph followed by a decline toward acidity and an increase in cholesterol followed by a diminution. This will in general result in far greater instability of the blood chemistry in the region of the storm tracks than in the relatively stable southern sections. In a general way, too the seasonal effects will be greater, and thenorthern population will be relatively more acid; the southern, more alkaline.

The regions of greatest autonomic demand are probably those indicated in the stippled portion of the

Chart III

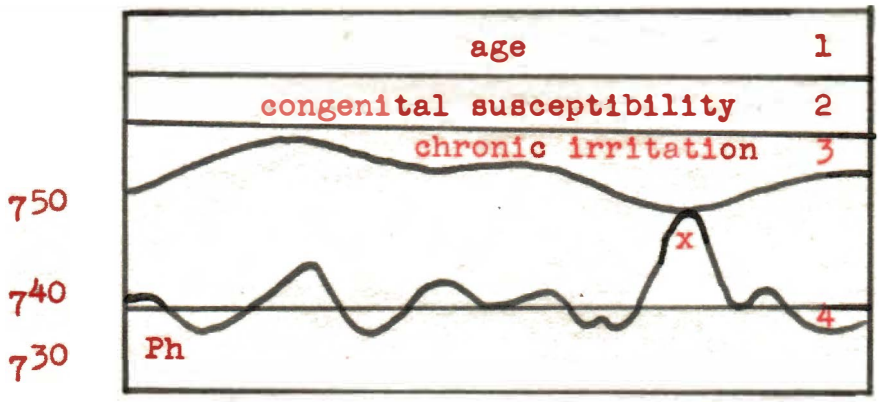


Diagram illustrating the role of meteorological factors in the constellation of factors favoring malignancy:

1. Gradual increase in age
2. A certain degree of congenital susceptibility (resistance : susceptibility)
3. Varying degree of chronic irritation
4. Fluctuating tide of the tissue fluids; illustrating the changes in the Ph curve, the changes being incidental to the meteorological adjustment.

map shown in Chart IV, and reach maximal proportions in the areas 1, 2, and 3.

If one now surveys such a map as Chart II (cancer of the skin), one observes that, apart from California, the distribution actually followsthe map of autonomic demand rather closely. The western coast forms a region of high mortality; the second transition from a low to a high rate occurs west of the Great Lakes, and finally the New England region under the north-eastern terminus of the storm tracks presents the high-est rates. The south has a very high mortality rate, due to the added insults of direct irritation of the skin by the sun in addition to the above mentioned condition.

The explanation of why California has such a high mortality rate lies in the fact that there is migration of a large number of persons of an advanced age group who have sought to escape from the tracks of the storm region.

The rate at the northeastern end of the storm tracks is still high; that on the northwestern coast is high, and beginning in Colorado, one finds the same basic spread northeastward through Nebraska and Minnesota and again reaching a focus in New England. One finds increasing rates for cancer of the skin as

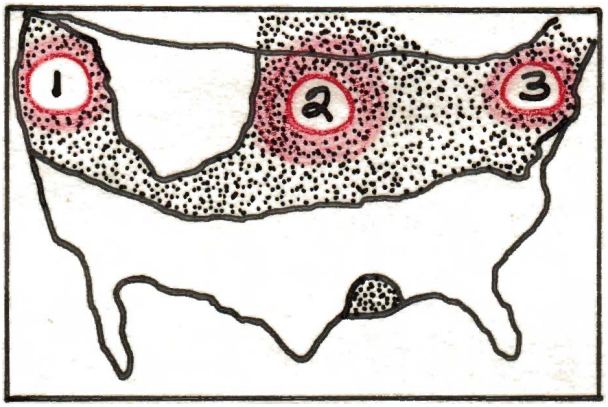
one passes through Oklahoma, Arkansas, and Louisana. But again the Negro shows the expected reversal. While he is, in general, immune to the effect of undue light, he is not immune to the effect of autonomic instabil-ity; as this increases, his cancer rate increases.

One finds that Kentucky has the highest mortality rate for the Negro. "

Petersen (7) sumed up this hypothesis by saying: "As long as one has reason to believe that the transition of cell growth from normalcy to malignancy depends on an entire series of conditioning factors, any one of which may be of paramount importance in the constellation of events, the chemical and endocrine instability that results from the severe environmental demands incident to life in the region of the storm tracks must be considered. In this note attention is called to certain peculiar features of the regional distribution of superficial cancer in America which may possibly be related to meteorological instability."

It must be borne in mind that Petersen's theory is more properly designated as an hypothesis, and that the role of ionic disturbance in the genesis of cancer has not been proven according to the literature. Do the facts of geographical distribution in the United States admit some other explanation? Dismissing the

Chart IV



Regions of Maximum Meteorological Demand

high occurrence in the New England states as being a matter largely of age distribution, and the high mort-ality rate of California as the result of migration of the older age group, there remains an excessive occur-rence of skin cancers in the western states, and parti-cularly in the southwestern states, to be accounted for. With the unquestionable effect of exposure to sunlight as a recognized etiological factor, an effect which has been confirmed experimentally, it is possible to account for the geographical distribution of skin cancers on a simpler basis.

Rector (6) in his Cancer Survey of Nebraska in 1934 reported that the general death rate of the state was declining in keeping with other sections of the United States, but the cancer death rate was rising. From 1920-1930 cancer deaths increased 32 percent, and the death rate 38.3 percent, while the increase in population of the State of Nebraska during this period was but 6.3 percent.

As was previously reported for the United States as a whole, so it was with Nebraska, and in 1932 cancer was the second cause of death in the statistics of twenty principle causes of death in the state. There were 1,424 deaths due to cancer during the period 1928-1932, only surpassed by heart disease causing

1,926 deaths. During this period cancer caused 50-80 percent of reported deaths, and cancer deaths were 65.4 percent of all deaths in this group. Of this group of malignant death dealing cancer the frequency of occurrance of skin cancer was 1.2 percent.

Even though the mortality rate for skin cancer is low compared to that for cancer of other areas of the body, it would be an important contribution to cancer control to be able to effectively diagnose early precancerous skin conditions and eradicate them completely and permanently. As will be pointed out in the body of this paper; precancerous dermatoses, as a whole, can be cured if diagnosed early enough. When that time comes there will be a substantial reduction in both the morbidity and mortality of skin cancer. (8)(9)(10)

As stated by MacKee and Cipollaro (3): "The value of early diagnosis and prompt and adequate treatment cannot be over emphasized. Continued efforts to educate the public, the popularization of periodic health examinations, and adequate undergraduate, and graduate instruction in the diagnosis and management of early cutaneous cancer and the conditions that lead to it are necessary for complete success."

DISCUSSION OF THE TERM PRECANCEROSIS

Precancerosis, or the conditions of the skin coming under the heading precancerous dermatoses, have been an everlasting source of controversy for all these preceding two decades and six years. The term precancerous dermatosis, or just the term precancerous, was first used by Debreuilh in his thesis at the Third International Dermatological Congress in London, 1896, to designate a certain group of skin conditions. (11) The term was quickly accepted because in its depths there was a great potential value, and gave a basis however vague for the early treatment of early cancerous conditions since the etiology of cancer was unknown. However the term has been used very loosely and in some cases, much to the dismay of the patient, used incorrectly in diagnosing some questionable skin condition. Thus it has been questioned by many medical men in the past years who feel it served as a waste basket for undiagnosed skin conditions, or better idio-pathic dermatoses. (11)(12)(13)(14)(15)(16)(17)(18)(19)(20)(21)(22)(23)(24)

Heimann (12) said the term "precancerous dermatoses" have that alluring quality which captivates the imagination and courts acceptance until analysis reveals that it is inappropriate and that its significance is scarcely clear. Does precancerous imply a

state preceding an inevitable cancer, or one in which the possibility of cancer is latent and need not perforce gain expression? If so, what are the criteria by which we become cognizant of this potentiality? If the criteria clearly indicate early cancer, why precancerous; why is it not indeed cancer? At what point does precancerous lose its prefix? Is the problem one of medicine or etymology?

In the same article Heimann (12) pointed out that in 1913 Bowen (13) described and reported a definite cutaneous picture as the precancerous dermatosis, but he was more prophetic than accurate because no malignancy appeared in either of these original two cases he reported.

Darier in 1914 (12) substantiated Bowen in a paper called "La dermatose pre'cancereuse de Bowen". Whether his cases were truly forerunners of malignancy, or whether he met with the same unsuccessful results as Bowen, was not reported.

Heimann (12) decided that one criterion was wanting which would at once set us aright; the lack of a control, and standard of comparison. He stated that the most serious argument against the theory of precancerous lesions was the fact that many carcinomas are not proven to be preceded by such changes. He maintained

that the precancerous stage is unrecognizable, both clinically and microscopically, even if individual experience may justify the impression that such lesions are capable of leading to cancer, that is vastly different from assuming that they will.

Bloch (11) stated that great difficulty arises with the term precancerous. The term is vague and unsatisfactory, the definition is a clinical statistical one, and is an absolutely arbitrary condition. He pointed out that the morphological criteria of precancerosis is no nearer classification than before. The criteria which are employed in general pathology as signs that cancerization has taken place are often useless in dermatology. It is apparent that the difficulties in the way of a sure and simple definition of the precancerous conditions are fundamentally due to our inability to define exactly and biologically the cancer cell or cancer. As Schurch has already said, "As long as we do not know the biological changes which characterize the cancer cell and differentiate it from the normal mother cell, we shall be unable to know wherein lies the essential characteristics of a precancerous change, or in other words, the problem of an unequivocal definition of precancerosis is at present insoluble".

Bloodgood (14) stated that too many cancers of the skin develope from some small abnormality of the skin to be coincidental. He felt that such skin can--cers do not come from normal skin, but that there must be some intermediary skin condition, what it was he wasn't sure. He did not however endorse the term pre-cancerous dermatoses.

Fukamachi (15) presented a rather progressive account through the years of reported cases of precancerous conditions. Evidentally those who reported these cases of precancerous skin conditions either accepted the term as an entity, or presented these cases with some reservation as to the true condition.

1. Hartzell in 1903 called attention to some precancerous conditions affecting the skin.

2. Engman in 1915 in an article on "Precancerous Conditions of the Skin", noticed that the clinical factors which predispose the skin to cancer are senility, actinism, chemical trauma, mechanical trauma, and chronic inflammatory disease.

3. Marrow and Lee in 1918 reported two cases of the Bowen type of epithelioma in which three types of visible manifestations of the malady were noted, name-the nodule, the plaque, and the fungus growth, and concluded, "It is to the plaque form of the dis-

ease that the term precancerous is applicable, but since the plaque is only one variety of the affection, and inasmuch as the other types are characteristically epitheliomatous, it seems best, for the present at least, to class the malady under the name Bowen's type of epithelioma rather than a precancerous dermatitis".

4. In 1921 Chagrin, Highman, and Sequerira reported cases of precancerous dermatoses.

Szodoray (16) stated that precancerous conditions are not a state but a process which cannot be determined morphologically. He pointed out in his article that Korenyi found that the changes thought to be associa-ted with precancerous degeneration may be seen in malignant or entirely benign tissue and thus could not be regarded as a link between benign and malignant lesions. He agreed with Young (17) who suggested such a term as "potential skin cancer".

Highman (18) remarked that language instead of remaining a vehicle for thought becomes perverted into a slogan, and although he doesn't endorse the term pre-cancerous dermatoses admitted it had a catch penny quality. Whether a lesion is or isn't precancerous can only be determined at the time it becomes cancer-ous, and since 50 percent of cases of so called pre-cancerous dermatoses showed frank cancer the term is

a misnomer, and might as well be called "postcancerous dermatoses".

Highman in 1933 (19) pointed out that the term precancerous has insinuated itself into the vocabulary as a clinical designation, an intellectual disadvantage even though it stated a fact. That it stated a fact he questioned its authenticity. He said Eller suggest-ed the phrase "cancer supervention on skin disease" but pointed out that this merely inverts the term pre-cancerous dermatoses. He suggested we use the term precancerous to describe the skin of the older age group and not use it in association with skin lesions, rather say that epitheliomata supervenes on precancer--ous skin.

Singer (20) sumed up his opinion concerning pre-cancerous conditions by using the doctrine set forth by the following statement: "If from facts no law emerges, the facts themselves become an obstacle, not an aid, to scientific advance".

Sutton (21) emphatically stated that malignancy is not potential, either it is there from the start, or it is not there at all. Cancer does not occur as a degenerative phenomena from some preexisting skin lesion. Warts are not warts, they are cancer from the start. They do not degenerate they grow. They do not

become malignant they are malignant. Thus there is no such intermediate condition as suggested by the term precancerous dermatoses.

The most recent discussion of the term precancerous dermatoses was written by Montgomery (22) of the Mayo "Clinic, Department of Dermatology. He stated: In the group of precancerous dermatoses are included true Bowen's disease, senile keratoses, keratoses resulting from arsenic, tar or radiation and leukoplakia or the mucous membranes. In 20 percent or more of the cases, epithelioma of varying degrees of malignancy eventual-ly will develope usually starting as squamous cell epithelioma in situ. The conditions are all inter-related by their common histologic picture and , hence, a possible common carcinogenic factor. They are not to be confused with the relatively rare epithelioma in lesions of lupus vulgaris or other benign dermatoses, such as psoriasis and lichen planus. Precancer-ous dermatoses also must be distinguished from various conditions which result in the histologic picture of pseudoepitheliomatous hyperplasia. The incidence of epithelioma associated with lupus erythematosus or with scars from burns or other causes will vary up to 10 percent in cases of such involvement, but senile cutaneous changes, the age of the patient, the situa-

tion of the lesions, including the factors of repeat-ed trauma and irritation, and the previous treatment employed must be considered. In many cases of precancerous dermatosis, histologic transitions between a benign and malignant process may be seen in the same section. The peculiar or distinctive and predominant histologic feature of epithelioma in situ with the phenomena of Bowen's disease, together with their relatively long duration as such, without clinical or histologic evidence of malignant invasion, I believe, justify the grouping of true Bowen's disease, senile keratosis, keratosis resulting from arsenic, tar, and radiation and in most cases leukoplakia of the mucous membranes under the term precancerous dermatoses. If the term precancerous dermatoses is used in the limited sense that I have defined, it has a definite value and meaning both clinically and pathologically and is of value from the standpoint of prognosis and treatment until more is known about the cause of cancer. The term precancerous dermatoses, however, should not be used loosely when the pathologist is in doubt regarding the clinical or histological picture, despite the fact that at present there is no general agreement regarding the distinction between cancer and precancerosis of the skin."

Thus since the year 1896 when Dubreuilh introduced the term precancerous dermatoses there has been a great deal of discussion, pro and con, over the merits of the term. We shall let the issue rest with the fact that during the year 1942 literature was still being presented under the title "Precancerous Dermatosis". And many authorities such as Montgomery, MacKee, and Cipollaro agree that the term has its merits when used with full knowledge of its significance, thoroughly understanding that it presents a rather vague line of demarcation between the benign and the malignant, and knowing the criteria both clinically and histologically for its use.

CLASSIFICATION OF PRECANCEROUS DERMATOSES

It is interesting to note the many different classifications for premalignant skin conditions presented in the literature during the forty six year interum since the term was introduced by Debreuilh in 1896. The outstanding point seems to be the fact that no two authorities agreed on one standard classification during all these years. Apparently each man presented his own classification according to his theories concerning this disputed subject. Another interesting fact is, that although many of these men did not endorse the term precancerous dermatoses, with some even condemning it, they all presented a make-shift classification of the condition to suit their own convictions and needs. However, as will be shown in the following pages, the most recent discussions of precancerous dermatoses by Eller, Montgomery, and MacKee and Cipollaro show that they make no definite attempt to classify the conditions they term precancerous, but rather merely list serially a number of conditions they think are forerunners to skin cancer. Only a few of the more interesting classifications will be presented here.

Fukamachi (15) reported that Debreuilh under the heading "Precancerous Dermatoses" described:

1. Corni cutaneum
2. Senile keratoma

3. Xeroderma pigmentosum

4. Arsenic cancer

5. Chimney sweep's cancer

6. Cancer in paraffin and tar workers

7. Leukokeratoses

In the same report Fukamachi (15) noted that Bowen in 1912 made the following concluding remark: "Precancerous dermatosis, while it cannot be advocated as an exact term, serves to call attention to the group of cutaneous affections which includes Paget's disease of the nipple, xeroderma pigmentosum, keratoses senilis, arsenical keratoses etc. in all of which carcinoma results much more frequently whan in other skin affections, and all of which have many points of histologic resemblance. The cases under consideration belong to this category, at least for purposes of study, until a more scientific and exact classification can be offered"

Fukamachi himself placed his ease in precancerous classification because of the fact that there was no exact line of demarcation between the benign and malignant neoplasm. On the histological examination of his specimans he found only a few signs of malignant change, epithelial pearls, while there was marked overgrowth of atypical epithelial elements. He classified them

as "papillomatous carcinoma", based on: 1. Advanced age of the patient 2. Course, recurrence, and characteristic border of the ulcer 3. Hard elevated infiltration and couliflower like features of the ulcer 4. The slow progress characteristic of the lesion.

Probably one of the first definite classifications for premalignant skin conditions was presented by Heimann (12) in 1916. He presented it as follows:

A. Congenital
   1. Malformations - naevi
   2. Dystrophies - xeroderma pigmentosum
B. Acquired
   1. Inflammations
      a. Hyperkeratoses
         (1) Seborrheal keratomas
         (2) Inveterate psoriasis
         (3) Leukoplakia
         (4) Horns
      b. Specific inflammations
         (1) Lupus vulgaris
         (2) Lupus erythematosus
      c. General inflammations
         (1) Ulcers and fistulae
   2. Physical agents
      a. Exposure - sailor's carcinoma

b. Actinic rays - roentgen carcinoma

3. Chemical agents - arsenic, paraffin, soot

4. Regressive changes - senile keratomas

5. Malformations - dermoid cysts

6. Scars from any cause - syphilis, lupus, burns

7. Unclassified - Paget's disease

Highman (18) presented the following classification in 1922. He stated the classification of precancerous dermatoses fell into five groups:

A. Congenital anomalies

1. Pigmented, hairy, vascular naevi

2. Cysts - dermoid, sebacious

B. Infectious

1. Lupus vulgaris causing scars which later degenerate into basal cell carcinomas

2. Syphilis - with the formation of scars and leukoplakia

C. Irritations

1. Mechanical

a. Habit - smoking

b. Functional - nursing of the infant

c. Heat - burns with resultant scars

2. Actinic and other rays - Xray, radium, sun

3. Chemical - arsenical keratoses, chimney sweep cancer

4. Pre-existing dermatoses - seborrhea, psoriasis, lupus erythematosus

D. Regressive changes - cutaneous horns, Darier's disease, Paget's disease, Bowen's disease

E. Unclassified - xeroderma pigmentosum

Savatard (24) divided the so-called precancerous conditions into two groups:

A. Dermatoses on which cancers do rarely arise but which in themselves cannot be considered as conducive to malignancy. Under this heading he would include active lesions of lupus vulgaris, lupus erythematosus, secondary syphilis, and psoriasis. He has seen squamous variety in only lupus vulgaris and lupus erythematosus, but in the latter two has seen both squamous and basal cell carcinoma.

B. Dermatoses which not infrequently become cancer:

1. Congenital conditions

a. Malformations - naevi

b. Dystrophies - xeroderma pigmentosum

2. Acquired conditions

a. Inflammatory - hyperkeratosis, and chronic ulcers

b. Physical agents - exposure to climate, and actinic rays

c. Chemical agents - tar, arsenic, paraffin

d. Atrophic lesions - biotripsis (Lenthal Cheatle) and senile keratoses

e. Scars of lupus vulgaris and erythematosus, burns, and syphilis

f. Trauma

g. Paget's disease

In this classification of Savatard's we see some resemblance to that presented by Heimann, but there is still some degree of individual variation. The new term "biotripsis", which Savatard classified under the heading of atrophic acquired lesions, was introduced by Cheatle. Crawford (25) pointed out this term of Cheatle's and called it an apt term that meant lifes wear, and which was characterized by transparent thining, atrophy, macular pigmentation, dilated capillaries, and keratosis which the skin often showed in old age when growth, resistance, and vitality of the skin was greatly reduced.

Knowles (26) pointed out a very simple but applicable classification presented by Volkman, who divided the precancerous dermatoses into three groups:

1. Those developing on chronically inflammed tissue
2. Those developing on warts or moles - congenital or acquired
3. Those developing in apparently normal skin

Von Brum a few years later, using Volkman's classification, in a series of 321 cases found:

227 cases conforming with the criteria of Group 1

46 cases conforming with the criteria of Group 2

48 cases conforming with the criteria of Group 3

Highman (19) said if he were to classify precancerous dermatoses he would throw out all lesions of the mucous membranes, and would not include Bowen's disease, Paget's disease, or xeroderma pigmentosum as they are malignant and thus not precancerous. He would consider as precancerous lesions of the skin: moles, keratoma senilis, lupus scars, cutaneous horns, and sebacious cysts. All the rest he would exclude because of rarity of the lesions (kraurosis vulvae and arsenical keratoses), or because the lesions are so common an occasional cancer arising from them would not be significant (lupus, burns, psoriasis, lichen planus, or eczema).

McFarland (27) divided precancerous lesions into five groups:

A. Hyperkeratotic changes involving mainly sebacious glands

1. Senile keratoses
2. Seborrheic keratoses
3. Cutaneous horns

4. Adenoma of the sebacious glands (multiple benign cystic epitheliomata)

B. Essentially lesions of a tumor type

1. Warts - seed warts (verrucae vulgaris), and juvenile warts
2. Moles
3. Molluscum bodies

C. Lesions which are characterized by a hypersensitiveness to, or are influenced by over treatment with some type of light rays

1. Xeroderma pigmentosum
2. Hydroa aestevole
3. Xray and radium burns

D. Malignant changes which are secondary to disease more or less of systemic origin.

1. Lupus erythematosus
2. Lupus vulgaris
3. Mycosis fungiodes
4. Leukaemia cutis

E. Miscellaneous lesions which may become malignant

1. Birthmark
2. Paget's disease of the nipple
3. Leukoplakia
4. Kraurosis vulvae

Conrad (28) thought that the only important etio-

logical factor in skin cancer was "trauma". He classified skin cancer as those due to different types of trauma: 1. Mechanical 2. Physical 3. Chemical 4. Actinic 5. Disease

Hand (29) classified precancerous dermatoses into three groups:

Group I: Bloch and others felt that all of these lesions would eventually lead to cancer if the patient lived long enough.

1. Senile keratoses
2. Dermatoses due to tar and other hydrocarbons with high boiling points
3. Arsenical keratoses
4. Xeroderma pigmentosum
5. Cutaneous horns
6. Naevi

Group II: are frequent sites for malignant degeneration, but are much less common than Group I (Bloch).

1. Xray and radium dermatoses
2. Leukoplakia
3. Erythroplasia
4. Kraurosis

Group III: malignant degeneration is extremely rare, and it is questionable whether some of these are precancerous.

1. Seborrheic keratoses
2. Lupus erythematosus
3. Lupus vulgaris
4. Scars
5. Papilloma of the mucous membranes

Montgomery (22) merely listed a number of cutaneous diseases in which the incidence of carcinoma is relatively high. He limited the term precancerous dermatoses to true but infrequent Bowen's precancerous dermatosis, senile keratosis, keratosis resulting from arsenic, tar, or radiation and various forms of leukoplakia of the mucous membranes of the mouth and genitalia, including the so-called erythroplasia of Queyrat.

MacKee and Cipollaro (3) and Eller (30) merely list a number of precancerous dermatoses which are discussed in a serial order with no attempt at a definite classification. Some of the more important and common precancerous dermatoses will be discussed later in this thesis.

IMPORTANCE OF EARLY RECOGNITION OF THE PRECANCEROUS DERMATOSES IN PRESENT DAY MEDICAL PRACTICE

In the treatment of apparently minor skin irritations and affections too many medical men use the old dictum "don't bother it if it is not bothering you". That is the main mistake in relation to precancerous dermatoses. This statement was made by Gaines (31), and probably sums up the main reason for the high morbidity and mortality of skin cancer in this country. Early recognition and adequate treatment is a must in relation to the reduction of mortality in skin cancer.

The cancer survey of Nebraska in 1933 by Rector (6) showed:

1. There were 41,213 admissions to 23 specified hospitals in the State of Nebraska.
2. 1,355 of the admissions, or 3.2%, were for cancer.
3. The total death rate was shown to be 5.3% of all the admissions, or approximately 2,191 deaths.
4. 13.5% of the cancer patients died in the hospital, thus there were 184 cancer deaths out of the 1,355 cancer admissions.

These comparative figures tend to show that cancer patients are being seen too often in the late stages

of the disease. This would lead one to believe that precancerous lesions are being overlooked, or that treatment has been inadequate. These figures, which apply to the cancer problem as a whole, show a tendency which can be applied to skin cancer alone as it is probably the only cancer state of the body which can be treated and cured early in the disease on the basis of precancerous lesions. Missildine and VanCleve (32) reported the same situation for the State of Kansas in 1932. Every state in the United States would probably show the same statistics if all cancer surveys were collected and correlated.

Bloch (11) stated that deaths from cancer would be greatly reduced if all precancerous conditions were as easy to diagnose as those of the skin. Also Farrell (33) remarked that no organ of the body offers as great an opportunity to eradicate cancer while still in the insipient stage as does the skin. Thus we see that many authorities agree that precancerous dermatoses can be easily diagnosed and that early and adequate treatment will assure complete recovery. This fact was brought out by Tucker (34) who maintained that you could assure the patient absolute positive cure with proper early treatment.

It is evident that we are dealing with a condition

which can and must be eradicated by early medical consultation, on the part of the patient; and conscientious medical service, on the part of the doctor. As MacKee and Lewis stated (35): "Every M.D. should be aware of the possibility of precancerous dermatoses, and guard against the same in the prevention of this dreadful disease." Many other authorities agree that it is as much the duty of the physician to know and understand the early diagnosis and basis of treatment for precancerous dermatoses, as it is the duty of the patient to seek early consultation and treatment. (36) (37)(38)

Wallenberg (39) stressed the point that it is the imperative duty of the physicain to recognize precancerous skin conditions early and apply adequate treatment. Every one should help educate people about such conditions instead of letting them wait until sudden discomfort, pain, growth, or bleeding send them to the doctor.

It must be accepted that in this twentieth century the medical profession is facing a challenge which is of utmost importance to the population of the United States. As pointed out before, the problem of the early treatment of precancerous dermatoses and the control of skin cancer is not impossible, and will not

be improbable if every doctor will attempt to study and know the subject of precancerous dermatoses in relation to early diagnosis and treatment. With only an average amount of knowledge on this subject 3,000 untimely deaths could be prevented each year in the United States. As Feldman (40) remarked: "Many benign lesions are such for long periods of time then suddenly become malignant. This consideration of early diagnosis is important because medicine in the future will be devoted as much to prevention as to cure. For both an early diagnosis is imperative. Some have a known etiology and thus are preventable. Usually the cause is unknown and there can be no question of prevention".

Thus in dealing with precancerous dermatoses we are dealing with a condition in which, usually, the etiology is known, and with early treatment is preventable. An honest attempt in this direction would greatly reduce the hazards of skin cancer, and the medical profession would be conscientiously applying the Golden Rule: "Do unto others as you would have them do unto you!"

DISCUSSION OF THE RARER PRECANCEROUS DERMATOSES

In this section, the purpose will be to present a short discussion of some of the uncommon precancerous skin conditions seen in medical practice. The material was very inadequate in regard to these rarer precancerous dermatoses, so there will be no attempt to give a complete discussion of symptoms, pathology, and treatment.

It is interesting to note that some precancerous skin conditions which are considered rare in this country, are a rather common occurrence in other countries. The explanation for these differences in the incidence of precancerous dermatoses from continent to continent is still a mystery to the author, even after reading current literature on the subject, so will not be discussed in this paper.

Kennedy (41) stated that occupational cancer was quite rare in the United States; but that when it did occur, prolonged irritation was an important factor. He pointed out that according to O'Donovan, tar cancer was the most frequent occupational cancer seen in England. White (42) substantiated this statement of O'Donovan's, and discussed the subject of occupational dermatose leading to cancer in the British Isles very extensively. He reported cases of occupational dermatoses with malignant changes from practically

every industry known in England and surrounding isles. Even after his extensive study of these occupational dermatoses he did not hazard an opinion to explain the marked difference in incidence of these skin conditions between England's industries and our own.

Kennedy (41) reported that occupational cancer may develop in tar distillers, gas workers, stokers, creosote workers, tar road sprayers, chimney sweeps, paraffin workers, benzine distillers, anthrocene laborers, coal oil workers, pitch handlers, lamp black workers, aniline dye workers, and those who sprinkle soot (ie gardeners).

Ormsby (43) said that keratoses occurring in tar and paraffin workers are often associated with acneform lesions and areas of dermatitis, together with scars, the previous site of epitheliomatous ulceration that healed spontaneously. He too said that cancer from tar was an industrial disease that has been often reported in England.

Kennedy (41) also pointed out that arsenic cancer may be seen in workers with Paris green, smelters of tin and lead ores, furriers, tanners, taxidermists, and those using arsenic spray. This condition however cannot be classified as a rare precancerous dermatitis, and will be discussed later under the heading of

Keratoses. It should be added that the precancerous condition is termed arsenical keratosis, which later often shows epitheliomatous changes. Thus there is really no true arsenic cancer.

Another interesting predisposing cause to skin cancer is seen in the people of Tibet. (41) In Tibet people have a habit of wearing "hot stoves" around the abdomen in cold weather. These stoves are called Kangri pots, and after wearing these for many years the chronic irritation on the abdomen causes a skin condition called "Kangri" cancer.

Another rare condition reported in the literature is "swimmer's trunk" nevus. It is a nevus which is localized to the lower trunk and pelvic girdle, and appears like a pair of swimming trunk were being worn. It most generally leads to sarcoma which is very fatal. (44)

Knowles (26) pointed out that Hazen listed some twenty-three skin conditions which he considered pre-malignant. Some of the rarer were: keratosis follicularis, sailor's skin, farmer's skin, Marjorlins ulcer, leg ulcers, blastomycosis, sinuses, fistulae, and wens. It might be said that farmer's skin, sailor's skin, shepard's skin are practically all of the same etiology and really are different names for the same

condition, senile keratosis. This subject will be discussed later. They are a rather common occurrence and should not be listed under the heading of rare precancerous skin conditions.

MacKee and Cipollaro (3) stated that the skin of the face and hands and even of the covered parts in elderly people may show atrophy, "permanent freckles", and keratoses. Another name for these permanent freckles is "lentigo". This condition, which may resemble farmer's skin, is known as senile skin. Occasionally it is seen between the ages of thirty-five and fifty. It may occur in those who have not been exposed excessively to actinic rays. Keratoses occurring in senile skin have the same potentialities as senile keratoses and are treated in the same manner. Permanent freckles sometimes change to a keratosis and the latter condition may give rise to cancer. Thus it is not necessary to treat lentigo unless a keratosis forms. They further stated that sebacious adenomas, umbilicated papules or nodules seen most frequently on the forehead of middle aged and elderly persons, may show epitheliomatous changes. Also paraffinoma may undergo malignant changes, epithelioma has been reported in cases of Darier's disease, and benign lesions such as fibromata may undergo malignant degeneration. They

made a special point of the fact that Von Recklinghausen's disease, or neuro-fibromatosis, showes malignant change in 13 percent of the cases.

Becker and Obermayer (45) pointed out that although radio dermatitis is not a rare disease of the skin, it is at present uncommon among workers with Xray and radium because of the protection offered by modern Xray equipment and knowledge of the correct usage on the part of the operator. These conditions are most commonly seen in general practitioners who try to operate Xray units without thorough knowledge of how to operate them. Small dermatoses should be treated early by electro-dessication, while more extensive third degree reactions should be treated by extensive surgery or cautery. Radium has been used successfully in the treatment of some minor Xray burns, which show some malignant changes.

This meager attempt to present some of the rarer precancerous dermatoses may aid in broadening our scope and aid our understanding of the extensiveness of the subject.

SOME THEORIES ON THE ETIOLOGY OF CANCER; WITH REFERENCE TO THE ETIOLOGY AND PROGNOSIS OF SKIN CANCER

Before discussing in detail some of the theories on the etiology of cancer, it is interesting to note some of the numerous theories propagated to explain the mysterious phenomena of cancer. Fukamachi (15) listed some of the more important theories presented by men doing research on the etiology of cancer. A few of these theories are:

1. Thiersch's destruction of tissue balance theory
2. Ribbert & Cohnheim's blast theory
3. Hanseman's anaplasia of epithelial cells
4. Hauser's new cell race theory
5. Beneke's cataplasia theory
6. Hertwig's return of cells from the organs typical to the zytotypical growth
7. Ehrlichs' specific nutritive or growth element

Eggers (46) presented a very extensive treatise on the etiology of cancer. After reviewing most of the literature on the subject he made the following comment: "It will be apparent that while a wide variety of irritants; chemical (tar, other pyrogenic agencies,, Scharlack R and the fat soluble dyes, tobacco, betel, aniline, arsenic, indol, occasional chemical irritants), physical (mechanical and thermal)(injury by radiant energy - Xray, radium, ultraviolet rays, sunlight,

and mitogenic radiation), and infectious (syphilis, tuberculosis, and other infections and noninfectious inflammatory processes) may be concerned in the causation of cancer, there is a marked diversity in the regularity with which their action is followed by neoplastic growth. In part this is unquestionably a matter of the agents themselves, in that they possess the power of cancerogenesis to varying degrees; in part it appears to be a matter of the individual, in that the likelihood of neoplastic response is an inconstant factor.

As to the mode of action of these irritants, there is little in the way of actual knowledge. The theories by which explanation has been attempted are numerous, and to the extent that they are matters of surmise, detailed discussion of them would be of questionable value.

An outstanding feature of the irritants in their induction of cancerous growth is their additive effect, to which allusion has several times been made in preceding discussions. Berenblum, as a result of experiments on the causation of cancer by combinations of tarring and freezing with carbon dioxide snow, found that if the two agencies operate simultaneously and together but at different times, the usual additive

effect is observed. Apparently the exact nature of the irritant is of little importance, provided it has a cancerogenic effect and acts at no time in too great intensity. It would seem that the effect of irritants in causing cancer is a gradual deviation from the normal, a deviation that occurs in response to forces at times of different character, and which, if Berenblum's results are correct, connot be accomplished by too violent application of these factors.

Although it is not intended to discuss at this point the matter of predisposition to cancer, one phase of that subject needs brief consideration. With practically all of the irritants mentioned in this section, age appears to play a role greatly subordinate to its usual importance in cancer incidence. Woglom would explain this by assuming that the effect of age on cancer incidence is merely that of allowing sufficient time for the development of cancer from some previous irritation. While it is possible that this explanation is correct, it is at best only a surmise, and until more definite knowledge is obtained of the factors that contribute to cancerous predisposition, it would be well to accept this as what it actually is - a hypothesis."

Both Eggers (46) and Jorstad (47) pointed out a

theory presented by Burrows on the etiology of cancer. This one theory will be reviewed to illustrate the ingenious mechanisms presented to explain the etiology of cancer cells. After the study of tissue cultures by Burrows he concluded definitely that an active stimulating substance is present in cancer. This substance he called "archusia". It is soluble in water, and is present in high concentrations in all actively growing tissue. It resembles Vitamin B of nature. He found another substance in ageing tissue. He called this substance "ergusia". It is soluble in fats and proteins but not in water. His theory is that normally we have a balance of these two tissue substances. If the blood supply of a part is reduced and ergusia is lost, archusia collects and malignant change is imminent. Ergusia is removed by any lipoid solvent, then there is a precipitation of the remaining protein as hyalin, this causes a decreased blood supply to the part and a malignant change ensues. Thus he explains precancerous dermatoses and cancer as a progressive process: hyalinization, atrophy, decreased vascularization with scattered nests of cells with pathological processes of these lesions.

In reference to precancerous conditions let us consider some conclusions reached by men in research

medicine. Kilgore (48) reported on the extension of skin cancer by transformation of normal cells, at the margin of a malignancy, to malignant cells. He stated: "It is not the purpose of my report to assert that cancer never extends by transformation at the periphery of normal epithelium into malignant cells, but an attempt has been made to show that, in a considerable number of cases in which conditions for the occurrence of this transformation were theoretically very favorable, it has not been observed. I conclude from these facts: 1. In 50 instances of exposure of epidermal epithelium to cancer approaching from below, seen in 475 cases of mammary cancer, no picture was observed which could be interpreted as transformation of normal into malignant cells, 2. In 7 cases there was a union of skin and underlying cancer, which may appear as a transition, but really wasn't. 3. It is against the transformation of normal epithelial cells into cancer at the advancing margin of a tumor.

Des Ligneris (49) attacked the following question in his research: Does the cancerization of normal tissue occur more or less suddenly or is it always preceded by an intermediary stage, the precancerous condition? He concluded after much research: "Industrial cancer is practically always preceded by a

well marked precancerous stage. In spontaneous cancer we more or less expect to find a pronounced precancerous stage, the more pronounced the less cancer susceptible is the particular tissue involved." He maintained that the whole problem revolves around the same old principle; "The resistance of the organism against the virulence of the attacking agent or factor".

As pointed out by many men, Sheridan (50) pointed out the hereditary factor in the causation of cancer, this theory being backed by the experimental evidence gained by Maude Slye after years of animal experiments.

With special reference to the etiology of skin cancer we must consider the Mutation Theory presented by Sutton (21). This theory has been accepted by some men as the most logical explanation for skin cancer. Sutton remarked: "The mutation theory for the origin of cancer is eminently satisfactory philosophically, biologically, and practically. No better explanation will come forward, until the chemistry and physiology of chromasomes and their component genes are better understood. The human body is a culture of proliferating cells, some of which undergo mitotic division frequently. Those of the basal layer of the epidermis reproduce throughout the lifetime at a rate of the order of once a day, implying some 60,000,000,000 individual cellular reproductive events daily. All the phenomena

of cancer of the skin can be fitted consistently with the theory that can begin with one single aberrant mitosis, a mutation. The colony of progeny of the one altered cell constitutes a cancer."

Kennedy (41) summed up the prognosis for skin cancer with the following statistics:

1. With early treatment 95-99% of skin cancer can be cured.
2. In clinics where precancerous dermatoses are seen in all stages, one man reported over 300 fairly early cases treated with the following results; 86.5% were well and alive after five years, and of 33 patients with far advanced cases of skin cancer 11% were well after five years.
3. In another report of 138 cases, which were all treated fairly early, 84% were well and healthy after three years.

DISCUSSION OF EIGHT COMMON PRECANCEROUS DERMATOSES

In this section we shall discuss eight of the precancerous skin conditions which occur with more or less regularity as compared to the many other precancerous dermatoses. Most of the authorities on this subject disagree as to which skin conditions should be classified as precancerous. To simplify this controversial matter the author selected out of the multitude of discussions on precancerous dermatoses those which were fairly well agreed upon as being truly precancerous. (52)(53)(54)(55)(56)(57)(58)(59)(60)(61)(62)(63) etc. Ormsby (51) discussed only Bowen's disease under the heading of precancerous dermatoses. MacKee & Cipollaro (3) considered Paget's disease and Bowen's disease as true cancer and not as precancerous states, however Montgomery (22) and Becker & Obermayer (45) both included Bowen's disease in their discussion of precancerous states. Most authorities agree that Xeroderma pigmentosum always leads to multiple epithiolomata, thus some believe it to be a true precancerous state while others think it to be cancer from the start. However Xeroderma pigmentosum is not a commonly encountered skin condition so will not be discussed in this paper. The authorities to which reference will be made in the following discussion are; MacKee & Cipollaro (3), Montgomery (22), and Becker & Obermayer (45).

The precancerous dermatoses which apparently occur quite regularly and thus are worthy of discussion are:

1. Leukoplakia
2. Cicatrix
3. Cutaneous horns
4. Farmer's or sailor's skin
5. Keratoses - senile, seborrheic, and arsenic
6. Kraurosis vulvae
7. Nevi
8. Bowen's disease

Before beginning the discussion of these precancerous dermatoses attention should be called to a very compact differential diagnosis on the precancerous lesions. This table (see Page 56) was presented by Van Cleve (52) and was the only short differential table found in the literature on precancerous skin conditions, and thus bears repetition and consideration. Of course such a short table is not complete in any sense of the word, but gives one a compact correlated basis for the early diagnosis of suspected precancerous dermatoses.

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LEUKOPLAKIA

Discussion: The mucocutaneous junctions and the mucous membranes covered with squamous epithelium often react in a different manner to chronic irritation than

PRECANCEROUS

NAME	PREDISPOSING CAUSES	LOCALIZATION (COMMON)	CLINICAL APPEARANCES
1. Senile Keratosis	Old age Sunlight Dry non-pigmented skin	Face Hands Forearms	Irregular, brown or gray scaley patches with ill defined borders. Firmly adherant scales. Usually multiple.
2. Seborrheic Keratosis	Old age Seborrheic skin	Back Chest Face & hands	Sharply circumscribed, round or oval, brown to brownish black, elevated patches. Greasy friable scales.
3. Leukoplakia	Smoking Dental caries Syphilis Poor dental hygiene	Tongue Oral & genital mucosa	Irregular milky white patches, and streaks. Slight elevation and induration.
4. Kraurosis Vulvae	Unknown Chronic inflammatory condition with trauma Trophic Endocrine	Vulvae	Atrophy of labia minora. Thin, dry, atrophic skin with leukoplakia. Pruritis.
5. Radiation Dermatitis	Overdose of Xray or radium	Any location	Dry, atrophy, pigmentation or depigmentation. Telangiectasia, sclerosis, keratosis, scar and late ulceration.
6. Xeroderma Pigmentosum	Congenital Lack of protective mechanism to sunlight	Face Hands Exposed surfaces	Pigmentation and atrophy, keratosis, freckling. Resembles chronic radio dermatoses.
7. Lupus Vulgaris	True Tbc of skin. Scar-long duration	Face Hands Any part of body	Deep seated, yellowish brown nodule. Crusting and ulceration, scarring and atrophy.
8. Moles (Naevi)	Embronic rests Irritation	Any part of body	Pigmented or nonpigmented tumors of skin(soft)
9. Cornu Cutaneum	Irritation	Face Hands Scalp	Peculiar horny outgrowth of the skin.

LESIONS

BIOPSY	PATHOLOGY	TREATMENT
Necessary when indurated or shows inflammatory borders or if it bleeds easily.	Hyperkeratosis Mild perivascular infiltration in the corium.	Electro-dessication Cautery, Radium, Xray or CO_2 snow.
Necessary when indurated or shows inflammatory border.	Hyperkeratosis Acanthosis Perivascular infiltration in the corium.	Electro-dessication Cautery, Radium, Xray or CO_2 snow.
Necessary when thick, warty, or fissures are present.	Hyperkeratosis Acanthosis Chronic inflam. of papillary & subpapillary layers of corium.	Improve dental hygiene Remove carious teeth Omit tobacco & alcohol Electro-dess., Cautery, Radium. & treat lues
Necessary when warty nodule is present. Fissured. Leukoplakia present.	Atrophy of both derma and epidermis. Chronic inflam. of corium. Areas of leukoplakia.	Local hygiene Xray Complete vulvectomy with plastic repair.
When ulceration or keratosis develop.	Atrophy of epidermis. Basophilic degeneration of cutis framework. Dil. of the capillaries.	Fulguration Surgery
Necessary if keratosis is present.	Can find changes of lentigo, atrophy, verrucous, papillomatous, carcinomatous.	Is incurable Protect against sun Remove keratosis and cancers with fulguration, Xray, or Radium.
Necessary if ulceration present. Pearly nodule or warty growths.	Tubercles in upper corium. Acanthosis, hyperkeratosis.	Rest & good hygiene Gerson diet Fulguration Finsen light
Necessary if lesion is growing & inflam.	Nevoid cells, vary with the type.	Surgery Fulguration
Always necessary	Tremendous hyperkeratosis, chronic inflammation of the corium.	Fulguration Surgery

does the skin. As early as 1818 whitish patches were reported in the mouth by Alibert and were considered to be identical with ichthyosis. The designation which is used today was given to the disorder by Schwimmer in 1877, who called the condition "leukoplakia."

Etiology: The causes of leukoplakia are systemic and local. There is undoubtedly some predisposing cause, since many persons whose mouths are constantly irritated do not develop leukoplakia. The one known systemic predisposing cause is syphilis, but here, too, it must be remembered that a majority of patients with syphilis do not develop leukoplakia, even though irritating factors are present. Leukoplakia occurring in syphilitic patients has certain characteristics by which it can be identified. Commissural leukoplakia, located just within the oral commissures and not farther back, is practically pathognomonic of syphilis. Atrophic glossitis with diffuse leukoplakia of the tongue is also usually associated with syphilis. McCarthy stated that lack of Vitamin A may result in atrophy of the lingual leukoplakia. Atrophic glossitis occurs in prolonged secondary and also primary anemia. Leukoplakia of the tongue in women usually follows glossitis of anemia.

Local precipitating causes are irritation from teeth,

produced either by faulty occlusion or by carious teeth; improperly fitting plates; irritation from dental appliances, such as crowns and bridges, lingual bars, and others; and electric currents set up between dissimilar metals used for fillings may perhaps occasionally be responsible for the development of the disorder.

In all countries, the lay term for leukoplakia is "smoker's patches". Smoking certainly tends to the production of leukoplakia, especially pipe smoking, where the pipe is often held in one side of the mouth, producing constant irritation of a portion of the tongue by the hot smoke. The heat from the pipe and the smoke, and chemical substances, tar which contains phenolic bodies and ammonia compounds, are responsible. Beverages high in alcoholic content, wine containing tannic acid, prolonged contact with tea and coffee as used by testers, hot fluids, and highly spiced dishes are incriminated also as the cause of leukoplakia.

Leukoplakia is a disease of middle life and past. It is seen more frequently in men than in women, and is rarely seen in the colored race.

Diagnosis: The initial reaction of the vermilion border or the mucous membrane to the causative factor results in a red, granular, sharply defined, slightly sensitive area, which remains in this stage only a

short time and becomes slightly opalescent and cloudy. Later, the epithelium thickens and the color turns to a whitish gray. The lesion is sharply outlined and level with the surrounding tissue so that it cannot be felt but appears pasted on the normal mucosa. It is adherent and cannot be curetted or rubbed off. Small plaques have the appearance of mucous membrane after painting with silver nitrate. The lesions become gradually more opaque and thicker until they represent milky-white, silvery, or pearly plaques. The surface tends to be covered with fine lines, representing wrinkles or furrows. The lesions may become still more thickened, especially on the tongue, where rindlike patches may develop, which may have tender fissures about their margins. On the buccal mucosa, the process tends to be less pronounced but to occupy more estensive areas; at times localized thickening in this location tends to the production of verrucous lesions. More rarely, other mucous membranes, such as those of the genitalia, and anus, have been involved.

The symptoms experienced by the patient are at first a feeling of roughness of the mucosa, which may be irritating to a sensitive individual. Many patches of the leukoplakia of which the patient has not been aware are discovered during routine examination. When the plaques become very thick, as frequently happens

on the tongue, the organ feels stiff. When fissures develop at the borders of the thick plaques, subsequent bacterial invasion produces discomfort, and the pain and tenderness associated with ulcerative malignant degeneration is likewise often the result of secondary infection. Not all fissures and ulcers are malignant, but it is advisable to perform biopsy to make certain. A small punch biopsy after novocaine anesthesia, and the hemorrhage can be controlled by the electric cautery. This condition must be differentiated from Fordyce's disease, lichen planus, lupus erythematodes, moniliasis, stomatitis aphthosa, and syphilitic mucous patches.

Pathology: The microscopic changes of leukoplakia consist of a mild round-cell infiltration of the superficial connective tissue in the early stages; later in the process there appears an infiltration of plasma and mast cells and some polymorphonuclear leukocytes. Even in lesions of leukoplakia definitely associated with syphilis, cellular reaction typical for syphilitic lesions is not found. This is the reason that the condition does not yield to antisyphilitic therapy. Changes in the epithelium appear later and are characterized by formation of a stratum granulosum, normally not present in the mucosal epithelium, and thickening of the stratum cornium. When malignant degeneration originates, there is first of all proliferation of the basal

layer with bluging of the rete processes, disarrangement of the palisade basal cells, and later penetration into the connective tissue.

Treatment: The treatment of leukoplakia consists first of all in removing the precipitating causes, if possible. If syphilis is present, it should be treated, not with the expectation of causing the leukoplakia to disappear, but for the purpose of removing a further source of irritation, and of course, for the patient's future health. Smoking must be abandoned. Various corrective measures may be employed to eliminate irritation from improperly fitting plates, brides, lingual bar, etc. Local treatment must be destructive. For smaller patches, the electric cautery or surgical diathermy are efficacious; the effect can be easily controlled, and there can be no serious sequelae. Treatment of large plaques on the tongue and hard palate is difficult. On the tongue, a technic similar to that used for obtaining Thiersch grafts may be employed in order to peel off extensive leukoplakic areas.

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CICATRIX

Discussion: A cicatrix (scar) is a lesion which results from healing after destruction of the epidermis and part of the dermis following an ulcer. If destruct-

has been limited to the epidermis and the superficial portion of the papillae (producing an erosion), a scar does not result, since the papillae govern the skin lines, and their restoration restores the normal lines of the skin. Deep papillary destruction finally leaves a scar with which we are all well acquainted. Scars are of two types, atrophic and hypertrophic. If the skin is allergic to certain organisms, atrophic, non-contractile scarring is produced at all times. Typical examples are: the tubercle bacillus (tuberculids), Spirochaeta pallida (late syphilids), pyogenic organisms (ecthyma) and, possibly, the agent or agents producing lupus erythematodes. Variola, varicella, and herpes zoster also produce atrophic scarring. Other forms of destruction, such as burns, may result in either atrophic or hypertrophic scars. Scars following deep burns about the joints are usually contractile. Lupus vulgaris about the eyelids is frequently followed by contractile scars, producing extropion. Some persons, especially Negroes, are apt to develop keloids in scarred areas. Burns are more apt to be followed by keloid than other types of destruction.

Etiology: While scars are premalignant in only a small percentage of instances, they are discussed to emphasize this possibility. Scars following burns, lupus vulgaris, lupus erythematodes and roentgen and

radium ulcers are especially prone to malignant degeneration. The resulting lesion is usually a carcinoma but sarcoma occasionally occurs.

Diagnosis: Scars usually present no diagnostic difficulty. History of trauma is always obtained except in the rare instances of primary macular atrophy. Hypertrophic scars are differentiated from keloid by the fact that keloid extends beyond the limits of the original injury, while hypertrophic scar does not.

Pathology: The epidermis is atrophic. The papillae are flattened or entirely absent and the dermis consists of irregularly arranged bundles of connective tissue fibers. The older the scar the greater the tendency for the vascular and cellular elements to disappear.

Treatment: That used for depressed scars is unsatisfactory. Superficial scars with depigmentation may be treated locally with measures advised for vitiligo; exposure to sunlight and ultraviolet rays. Small, slightly elevated scars that are frequently traumatized may be excised and primary union obtained. If there is a keloidal tendency, hyperplasia can often be prevented by judicious postoperative roentgen or radium therapy. At times, an elevated scar can be reduced to the level of the normal skin without resorting to surgery; the elevated portion may be removed with surgical dia-

thermy, especially with a loop electrode, radium or roentgen rays being used subsequently to prevent hyperplasia. These measures are applicable to small elevated scars such as occur in the bearded region of the male adult and which may be cut frequently with the razor. Such scars, when not subjected to frequent irritation or traumatism over a long period of time, are probably no more likely to undergo malignant change than is apparently normal skin. Large scars should be inspected at least once a year. Ulcers, either traumatic or spontaneous, which occur in scar tissue and which do not heal in a few months under the influence of treatment, should, from a clinical standpoint, be regarded as a possible early stage of cancer. In such instances it is well to make a microscopic examination. Even without proof of cancer, in the absence of a favorable response to the various medicinal and physical measures recommended for chronic ulcers, it seems preferable to perform a plastic operation and remove the danger.

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CUTANEOUS HORN

Discussion: Cutaneous horn (cornu cutaneum) is a premalignant lesion consisting chiefly of an overgrowth of cornified cells, producing a narrow, elongated, con-

ical or cylindrical, twisted or angular excrescence which varies in length from a few millimeters to several centimeters or longer. The lesions are usually single and of a yellowish, brownish or blackish color. Their base is often slightly erythematous and is sometimes elevated above the cutaneous surface. The sites of predilection are the scalp, the forehead, the nose, the eyelids, the glans penis and the scrotum but the condition may be encountered on any part of the body surface. Cornu cutaneum may persist or the cornified portion may be shed spontaneously wherupon the lesion usually recurs. In many instances malignant degeneration occurs eventually though the condition often remains unchanged for many years. The keratotic material is removed with considerable difficulty, although during fixation, dehydration and embedding, the corneous mass usually separates from the rest of the section.

Etiology: It is generally believed that the process has some similarities to that of senile keratosis. Cornu cutaneum is usually encountered in older people and, as in senile keratosis, persons with a sandy complexion and a fair, relatively poorly pigmented skin, often develop the disorder. However, cutaneous horns may occur at times in very young people and have been observed even in infancy.

Diagnosis: Cornu cutaneum must be differentiated from filiform verruca if the lesion is small. Microscopic examination is necessary for differentiation and for detection of early precancerous changes.

Pathology: The microscopic examination shows the tumor to be primarily epithelial. The horny material consists of thickened stratum corneum, with irregular parakeratotic change. The stratum mucosum is also thickened, and the rete processes tend to the same type of proliferation as seen in keratosis senilis, with eventual formation of carcinoma. The dermis shows elevation and elongation of the papillae and moderate perivascular infiltrate.

Treatment: This consists of extirpation followed by cauterization or electro-coagulation of the base.

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FARMER'S OR SAILOR'S SKIN

Discussion: The condition known as farmer's or sailor's skin occurs in exposed areas in adults, mostly middle-aged and elderly persons, who have been exposed to the sun for many years and who probably have a low actinic toleration. The present fad for sun-bathing and the use of ultraviolet radiation in the home may possibly cause a numerical increase of cases in the future. Epithelioma, often of the squamous cell

type, develops quite commonly in farmer's skin. As a rule, a keratosis or an ulcer precedes the neoplasm. The squamous cell growth often is of a comparatively low grade of malignancy.

Etiology: Fairly constant exposure to actinic rays over a long period of time, and a low actinic tolerance seems to be the two main etiological factors in the production of this condition.

Diagnosis: The skin becomes wrinkled and dry, and permanent lentigo (freckles), telangiectasia, and white sclerotic spots may appear. The lips are apt to be dry and may fissure easily. Keratoses of the senile type frequently develop on such skin. The condition bears some resemblance to chronic radiodermatitis, senile skin, and xeroderma pigmentosum. McCoy states that 37.7 percent of all cutaneous cancers have occurred on the face (exclusive of the lip margins), hands and neck. In other words, on parts that are exposed to sunlight. The majority of persons so affected are farmers, their wives, and those with outdoor vocations. Blondes are affected more frequently than brunettes.

Pathology: There appears on examination of a section of the skin varying degrees of degeneration and atrophy of the connective tissue in the upper layers of the true skin. The epidermis is somewhat atrophic

except in areas where a keratosis is developing. In such areas the histologic changes are similar to those that occur in senile keratosis.

Treatment: Treatment consists in avoiding direct and strongly reflected sunlight, or in adequate protection against such light. Such protection may be obtained by the use of walnut stain, or by rubbing into the skin a dark colored cream followed by the application of a dark powder. An ointment consisting of equal parts yellow vaseline and anhydrous lanolin with 10 percent zinc oxide, applied to the skin just before exposure to the sun, provides sufficient protection in many cases. After the ointment has been rubbed into the skin, powdered talc may be applied. Patients with well developed farmer's skin should have the involved areas inspected at least once a year. It is well to destroy the keratoses with electro-dessication. The main treatment is prophylaxis against excessive drying of the skin and mucous membrane of the lips. To prevent such drying an ointment or cream, such as almond emulsion (U.S.P.), should be applied several times daily.

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KERATOSES: SENILE & SEBORRHEIC

Discussion: Keratoses are lesions produced by a

peculiar hyperplastic change in the epidermis of the skin or of the epithelium of the muco-cutaneous junction. Their clinical appearance is characteristic and though the lesions are produced under the influence of widely different etiologic factors they are essentially all of the same clinical type.

SENILE KERATOSES

Discussion: The senile keratosis (keratoma senilis; hyperkeratosis senilis) is seen most commonly on the face and backs of the hands and forearms, in other words in the areas that are exposed most frequently to direct or indirect solar radiation. Occasionally it occurs on the trunk or other parts even when such areas have never been exposed to sunlight. It affects chiefly elderly people, although it is sometimes encountered, also, in the third and fourth decades. It is rarely observed in Negroes, American Indians, or Arabs. The surface of an early lesion is barely above the level of the skin. Older lesions may appear a little more elevated. Such elevation is a danger signal, since it usually indicates epithelial proliferation, inflammation, and other evidence of early malignant change. The senile keratosis is perhaps the most common, the most typical, and one of the most dangerous of the precanceroses. It gives rise to epithelioma of both the

basal cell and squamous cell type, the latter being the more common. A senile keratosis occurring on the mucous surfaces of the lips is especially dangerous. It it probable that most such lesions when neglected terminate in epithelioma of the prickle cell variety.

Etiology: The etiology of this type of keratosis is not definitely known, nor is the agent known that is responsible for the carcinogenic change in such lesions. Possibly senile degeneration of the skin is a causative factor. Excessive exposure to ultraviolet rays for many years and low actinic toleration may also play a role. Bruno Bloch (11) questions this, since the senile keratosis is no more common in high altitudes, where the ultraviolet rays are intense, than at sea level. On the other hand, Findlay is of the opinion that ultraviolet radiation plays and important part. Recent experiments on albino animals have shown that long continued exposure to sunlight or ultraviolet light may incite cancer, but animals with dark hair do not develop cancer from exposure. There is evidence to support the belief that some hyperkeratotic changes of the skin are caused, at least in part, by a deficiency of Vitamin A.

Diagnosis: The lesions range in size from a diameter of 1 or 2 mm. to a centimeter or more. They develop as a rule, in skin that shows either macroscopic

or microscopic evidence of senile degeneration. They are often multiple. They are irregular in contour and in the early stage consist clinically of a thickened horny layer or scale which is firmly adherent and usually of a gray color, although sometimes brown, yellowish or dull red. While the scale may exfoliate, recurrence is the rule. The lesion may or may not be sharply outlined. Occasionally, a lesion may be verrucous in appearance.

Pathology: In keratoses of the senile type there is a marked thickening of the horny layer consisting of hyperkeratosis with occasional areas of parakeratosis. The horny layer dips deeply into the follicles and ducts. In early lesions the underlying epidermis is thin. In older lesions there is an atypical proliferation of epithelium, often with finger-like processes penetrating into the derma (senile acanthoma). Tangential sections through these strands may show epithelial cell nests in the cutis. At times, especially in lesions from the mucosa of the lips, a number of these acanthomas may be seen in a single specimen (multiple foci of origin). In early lesions there may be slight or moderate inflammation in the cutis, but in a well developed acanthoma there is often considerable reaction in the true skin, consisting in edema, vascular dilatation, and an infiltration of lymphocytes

and plasma cells. When evolution is rapid, the lymphocyte usually predominates; when slow, the plasma cell is likely to predominate. Some of these cells may be found in the epidermis.

Frank epithelioma begins, as a rule, in the epithelial strands. Usually the cutis is invaded, from the margin of a strand, by a mass of cells which retain the characteristics of prickle cells. The new growth may be well marginated or it may occur in bands, the margins of which are defined with more or less exactness. Occasionally the invasion of the cutis is by finger-like processes composed of round epithelial cells without prickles and with poorly defined margins. There is no well defined lymph system. Pearl formation may or may not be present. Some regard these epitheliomas as basal cell growths, while others think they represent an atypical type of prickle cell epithelioma.

In most instances of senile keratosis there is more or less basophilic degeneration of connective tissue. This probably is due to senile changes in the skin and is not pathognomonic of keratosis.

Treatment: Whether or not a given senile keratosis of the skin should be destroyed is a question of judgment. Because of the potentialities it seems advisable, as a general rule, to eradicate all such lesions as soon as diagnosed, especially when the patient has a

reasonably long expectancy of life. When an old person presents numerous lesions, it may be best to keep him under observation and destroy only those that appear to be changing from keratosis to cancer. Since the evolution of a cancer developing in a senile keratosis is usually slow, the physician has ample time to detect the transition and to apply proper therapy. When a keratosis develops on the mucosa of the lips, it should be destroyed as soon as the diagnosis is established. Senile keratoses may be destroyed in various ways. A satisfactory treatment consists of electro-dessication. The area is sterilized and anesthetized. The lesion is then dehydrated with the electro-dessicating current. The memmified tissue is removed with a sharp skin curet and the base of the wound is again electro-dessicated. Such treatment is likely to cause more or less scarring. Some patients object to a scar or to an area of depigmentation, but in treating a senile keratosis, it is advisable to concentrate on a permanent cure rather than on an esthetic result. Roentgen ray and especially radium are efficacious for selected cases when properly applied. Beta rays may be employed for very thin superficial lesions, especially after the scale has been removed. Gamma rays are more efficacious for thicker lesions. It is customary to apply a quantity of radiation sufficient to cause an

erythema. When one form of treatment fails to effect the desired result, it is preferable to resort to another method. Usually there is no scar but occasionally a visible defect results, such as atrophy, depigmentation, or telangiectasia. Solid carbon dioxide or even trichloracetic acid may prove satisfactory for exceedingly superficial lesions but the cases must be carefully selected. The actual cautery is recommended by some dermatologists. Scalpel surgery is preferred by many dermatologists and by most surgeons, especially for well developed lesions. It has the advantage of permitting a microscopic study of the tissue.

Persons who have a tendency to develop senile keratoses on the mucous membrane of the lips and on the skin should avoid excessive exposure to strong actinic light and apply ointment and cream frequently. In fact, the preventive treatment is that recommended for farmer's skin. Encouraging results in cases of senile skin, farmer's skin, and senile keratoses, in respect to both prevention and cure, have been obtained by the ingestion of cod-liver oil.

SEBORRHEIC KERATOSIS

Discussion: The lesion of seborrheic keratosis evolves slowly and ranges in diameter from one or two millimeters to one or several centimeters. It is sharp-

ly circumscribed, round or oval. At first only slightly raised above the surrounding skin, it later becomes considerably elevated. In consistency it is firm rather than hard. The surface may be smooth, rough or even somewhat verrucous. The color ranges from yellowish brown to brownish black. There may be no perceptible thickening of the horny layer or there may be a thick scale. Keratoses of this type occur most frequently on the trunk. They often resemble certain clinical types of non-hairy pigmented nevi and have been called nevoid keratoses. They are most common in elderly persons but they are seen occasionally in younger subjects. There may be a single lesion, a few, or a great many.

There is a marked difference of opinion as to whether or not this acanthotic type of seborrheic keratosis ever gives rise to cancer. Hartzell, Debreuilh, McCarthy, Eller & Ryan, and others, including the writers (MacKee & Cipollaro), believe that they have seen epithelioma, usually of the basal cell type, develop in these lesions. On the other hand, such excellent dermatologists as J. Jadassohn, Bloch, Freudenthal, and Hookey have never seen anything suggestive of malignant change in this type of keratosis.

There is a type of keratosis which differs clinically from the one just described and from the senile keratoma. It is seen mostly in the so-called seborrheic

areas, the sites of predilection being the face, scalp, and upper portions of the trunk. It may appear in the third and fourth decades of life, but is far more common in middle-aged and elderly persons. The lesions correspond in size with the senile keratosis. Very often they are multiple. They are irregular in contour and vary in color between yellowish brown and brownish black. The margin is usually well defined. Clinically, the lesion may consist of nothing but a thick scale which is waxy and which can be easily removed. Often the scale is shed spontaneously but it usually recurs. At times the surface may be somewhat verrucous or there may be a definite thickness under the scale causing some elevation. The clinical differentiation between this hyperkeratotic seborrheic keratosis and the senile keratosis is often difficult. It has been our esperience (MacKee & Cipollaro (3)) to find, under the microscope, that most such lesions represent the hyperkeratotic type of seborrheic keratosis, some the acanthotic type of seborrheic keratosis, a few the senile type; some of the former show Bowenoid dyskeratosis. We believe that the hyperkeratotic type of seborrheic keratosis occasionally gives rise to epithelioma, usually of the basal cell variety.

Etiology: The etiology of verruca seborrheica is unknown, but because it is so often encountered in

seborrheic skin it is tempting to assume a common cause. Senile changes in the skin may be a factor.

Diagnosis: Under this heading a differential table will be presented which is of great value in differentiating between Senile keratosis and Seborrheic keratosis. This table was presented by Eller & Ryan (64).

Senile keratosis	Seborrheic keratosis
1. Lesions usually seen past 60 years of age	1. Most commonly seen in middle aged and elderly persons
2. Lesions seen on the temples, face, neck, and back of hands	2. Lesions occur on chest, interscapular region, waist, and face
3. Etiology - elements of weather and exposure, thus seen mostly in males	3. Etiology - not definitely known
4. Flat lesions, from size of a pea to a dime, yellowish or dark brown in color. Surface covered with scales and crusts which upon removal leave a moist red surface with slight hemorrhage.	4. Multiple lesions. Covered with greasy friable scales. They have a granular surface, which is freely movable on underlying skin.
5. No subjective symptoms in uncomplicated cases	5. No subjective symptoms, unless itching
Histo-pathology	
1. Marked hyperkeratoses	1. Nevoid grouping of epithelial cells
2. Acanthosis	2. Islands of connective tissue separates cell groups.
3. Maybe parakeratosis	3. Horny cyst formation
4. Inflammatory reaction	4. Parakeratosis maybe
5. Maybe basophilic degeneration in basal layer of the upper cutis	

6. Pigment granules in basal layer - maybe
7. More mitotic figures in epidermis than in siborrheic keratosis
8. No horny cysts as seen in seborrheic keratosis
9. Perivascular edema of basal cells (Freudenthal)

5. Pigment varies greatly in the basal cells
6. Mitotic figures rare
7. Non-specific inflammatory exudate at the cutis.

Summary

1. Senile keratosis and Seborrheic keratosis are different disease entities. They are difficult to differentiate if they occur simultaneously on the face.

2. Senile keratosis is distinctly a precancerous condition. If they become malignant after many years of benignity, they always develop into a prickle cell epithelioma.

3. Senile keratosis never occurs on other than exposed body surfaces.

4. Seborrheic keratosis, especially those on covered parts of the body, may undergo malignant change. If they are do they are rare, and Eller & Ryan (64) have never seen such a case.

5. Seborrheic keratosis of the face and exposed parts of the neck may become malignant.

6. Whenever Seborrheic keratosis become malignant they are always basal cell epitheliomas.

Pathology: The most striking histologic feature

of seborrheic keratosis is a rather marked acanthosis, throughout which there occur islands of connective tissue and horn cysts representing sections of papillae and hyperkeratotic follicles cut at various levels. A net-like appearance is thus produced. McCarthy calls attention to intraepidermic whorls and columns composed of prickle cells. Pigmentation may be greatly increased. Normally there are no important tinctorial changes, no epithelial downgrowths, and no dyskeratosis, but occasionally a lesion is seen in which some of these features are present.

The horny layer in seborrheic keratosis is slightly or moderately thickened, occasionally considerably so. It is rather loosely attached and extends into the follicles and ducts. As a rule, nuclei are absent. Inflammation in the derma is usually slight unless there is evidence of carcinomatous change in the epidermis. Senile changes are commonly found. These consist of basophilic degeneration of connective tissue and, beyond the margin of the lesion, more or less atrophy of the epidermis.

Treatment: Seborrheic keratoses need not be destroyed, but because of the possibility of subsequent epithelioma it is advisable to inspect the lesions periodically. Frequently, indeed, patients prefer to have the lesion destroyed either to avoid possible

future malignancy or for cosmetic reasons. On the exposed parts, particularly in women, it is preferable to avoid a scar if possible.

Electro-dessication, with or without curettage, is a popular method for the destruction of thick lesions. Scalpel excision is practised by many and has the advantage of permitting a microscopic study. X-rays and radium in safe dosage are not very efficacious.

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KRAUROSIS VULVAE

Discussion: Kraurosis vulvae is an eminently chronic, obstinate precancerous disorder of unknown origin. It is essentially a disease of the mucocutaneous junction at the vulva. The term "kraurosis" is derived from the Greek word meaning "dry", and scarcely suffices to describe the condition according to present standards of pathologic terminology. The disease first manifests signs of inflammation, followed by those of atrophy, so that the term "vulvitis atrophicans" or "atrophying vulvitis" has been suggested, and is considered the best pathologic term for the disease. The process may be divided into three stages.

The first stage is one of subacute inflammation. The vulva becomes edematous, erythematous, and tender. Due to burning and itching the patient scratches and

and superficial abrasions and petechiae may be present. Secondary pyogenic infection may result from scratching.

The second stage shows chronic inflammation producing thickening, and the mucocutaneous junction assumes a whitish or grayish color, with isolated erythematous areas due to petechial hemorrhage. The tissues become inelastic, the labial and preputial folds flatten out. The changes may also involve the skin of the perineum, extending even posterior to the anus.

The third stage is characterized by atrophy. The epithelium of the vulva becomes smooth, glistening, semitranslucent and parchment-like. It is pearly white or bluish white in color. The labia minora and the preputial folds have completely disappeared, and the vaginal orifice is greatly constricted and rigid. The chief symptom during this final stage is intractable pruritus which may be intolerable. Plaques of leukoplakia may develop in the involved region.

Beyond the discomfort of the patient due to the severe itching, the chief concern is that of carcinoma production. Adair & Davis state that malignant degeneration occurs in kraurosis vulvae in a higher percentage of cases (over 50 percent) than in any other premalignant disease. It may arise in either the hypertrophic or atrophic stages and is always squa-

mous cell in type.

Etiology: The disease occurs during the menopausal or postmenopausal years. Diminution or cessation of the ovarian function is an important factor. The average age of onset is around 50 years. Various secondary etiological factors have been suggested, but probably are not instrumental in causing the condition. The various stages through which the vulval tissues go during the progress of the disease are not unlike those in acrodermatitis chronica atrophicans, a disorder in which external etiological factors are likewise absent. Since many patients seek medical care only after the condition has fully regressed to the atrophic stage, the early signs and symptoms are not well understood as are those of the later stages.

Diagnosis: The disorder is not easily diagnosed during the early stages. Prolonged observation is necessary to rule out other chronic conditions of the vulva. The disease must be differentiated from ordinary pruritus vulvae, fungous and yeast infection of the vulva, leukoplakia, the uncommon psoriasis vulvae, and neurodermatitis.

Ordinary pruritus vulvae is characterized by pruritus alone, with only secondary changes due to scratching and secondary infection. There may be pronounced lichenification and thickening of the tissues, but

atrophy is never observed. If the condition is due to nervous exhaustion, the onset is predominantly during the third decade, two decades before the usual time of appearance of kraurosis vulvae.

Fungous and yeast infections of the vulva are characteristically subacute or chronic inflammatory changes and the development of plaques with sharply demarcated borders. Vesiculation or scaling are usually present. Fungus or yeast elements are readily demonstrated by maceration of the scales in 10 percent potassium hydroxide.

Leukoplakia consists of sharply circumscribed plaques of whitish, opaque, rough epithelium.

Pathology: The microscopic examination shows inflammatory changes, followed by atrophy. After the acute signs of erythema and edema have been replaced by those of chronic inflammation, the second, or so-called hypertrophic stage is present. The entire epithelial layer is hyperplastic and shows hyperkeratosis with acanthosis and a thickened stratum granulosum. In the superficial connective tissue, there can be seen abundant cellular infiltration, consisting chiefly of round cells, with some polymorphonuclear leukocytes and plasma cells. Vascular dilatation and edema predominate, with degeneration of elastic tissue. The atrophic stage is characterized by thinning of the

epithelium, chiefly of the stratum mucosum, with disappearance of the rete processes. The stratum corneum remains relatively thick. The cells of the basal portion show liquefaction necrosis. The connective tissue is edematous in its superficial layers and likewise shows liquefaction recrosis and also disintegration of elastic fibers. Beneath this edematous layer there is an infiltrate consisting of round cells, polymorphonuclear leukocytes and mast cells. If sebacious glands have been present within the involved area they become atrophic and eventually disappear completely.

Treatment: This depends on the stage of the disorder. Local calamine liniment and menthol-phenol paste may be tried. Roentgen therapy has been efficacious in the early stage, but usually gives only temporary relief. The newer hormones (estrogens) have been given by the parenteral route and have been applied locally as vaginal suppositories, with improvement in some cases. After the atrophic stage has been reached, surgical vulvectomy is the treatment of choice. Such a step should only be taken after the physician is absolutely certain of the correctness of his diagnosis. There have been patients in whom the operation was followed by recurrence because the disorder from which they suffered had not been kraurosis vulvae but chronic pruritus vulvae with secondary lichenification.

NEVI

Discussion: Birth marks or nevi occur in great variety, and most of them appear to be harmless or almost so. We have been unable to locate statistics of the incidence of cancer in birth marks, but since almost every one has at least one mole of some variety on some part of the body, the percentage incidence must be low in spite of the fact that cancer arising from such sources is fairly often seen.

While the type of lesion and the degree of danger can be determined with greater certainty with the microscope, experienced dermatologists can supply the same information with a satisfactory degree of accuracy by inspection.

Nevi give rise to neoplasma of various types and various degrees of malignancy. Almost every physician is familiar with the highly malignant melanocarcinoma that develops in a small pigmented mole either spontaneously or as a result of irritation, traumatism, or injudicious treatment. At the other extreme is the relatively benign basal cell epithelioma which may originate in a pigmented mole. Occasionally the neoplasm is a sarcoma.

It seems to be the prevailing opinion among clinicians that only the deeply pigmented very black mole

is dangerous but as cancer originates in both pigmented and non-pigmented nevi, it is obvious that pigment alone is not a satisfactory indicator of the degree of danger. Also, many physicians who are not dermatologists fail to recognize a lesion as a nevus or birth mark unless it is present at birth or develops shortly after birth. Possibly every nevus is microscopically present at birth but many of them do not become visible to the unaided eye for many months or even years.

Etiology: Probably a congenital anomaly, either microscopic or macroscopic at the time of birth.

Diagnosis: The very common mole, a few millimeters to a centimeter in size, elevated, skin colored or with various amounts of brown pigment, with or without hairs, is not considered potentially dangerous unless subjected to repeated irritation or injury over a period of years. Large brown or brownish-black nevi, flat or elevated, with or without hair, seldom give rise to cancer, but they have been known to do so especially when traumatized or repeatedly irritated. The same is true of the verrucous nevus. Cerebriform nevi may undergo malignant change. There are records of a number of such lesions changing to cancer following incomplete destruction or an injury. Cancer rarely if ever develops in vascular nevi or lymphangiomas. Non-pigmented moles are frequently multiple. Both non-pigmented and

pigmented lesions which appear clinically to be nevi may show the histological structure of fibroma.

Of the many forms of birth marks possibly the most dangerous is the so-called blue-black mole. This may occur on any part of the body, even in places where it is likely to be overlooked as, for instance, between the toes, under a nail, in the ear, and so on. It is occasionally very small, 1 or 2 mm. in diameter. It may be flat (macule) or slightly or even considerably elevated. The surface is smooth and perhaps somewhat shiny. The color may be blue-black, gun-metal, or slate gray. Many melanomas have their origin in lesions of this type. While malignant change may be spontaneous, it is much more likely to follow traumatism, frequent irritation, or injudicious treatment. In some instances the cancer may develop slowly and metastasis may be late, but metastasis may occur while the lesion is very small and before the cancer is suspected. Clinically, it is often difficult to know whether an apparently inactive blue-black lesion is a nevus or a malignant neoplasm. If present since birth, it is undoubtedly a nevus. If of a few years duration, it may be a so-called nevus tardus. Occasionally a small sebaceous cyst or steatoma that happens to contain pigment of dirt may suggest a blue-black mole or a melanoma, and a hemorrhagic epidermic vesicle has been known

to simulate a melanoma.

Pathology: To give a detailed histological description of all the nevi or even of those which are considered to be dangerous, and to discuss the production and function of pigment and the origin of the nevus cell, would require much space. All that can be attempted here is an outline.

The small pigmented macule, called by many a blue-black mole (Dubreuilh's lentige malin des viellards; Hutchinson's infective melanotic freckle, etc.) shows, in the early stage, hardly more than an abnormal amount of pigment in the basal cells. Some of these cells may be larger than normal and show swollen, pale-staining nuclei. They may proliferate and invade the upper layer of the corium and eventually may give rise to melanocarcinoma. The chromatophores are increased numerically and are heavily pigmented. In the non-pigmented type of melanocarcinoma the process is the same except for lack of pigment and fewer chromatophores. Moles give rise to a malignant neoplasm known as nevocarcinoma, but in advanced cases the histological picture of nevocarcinoma and melanocarcinoma or melanoma is similar or identical.

There are several varieties of the so-called acanthotic nevus. These are identified by hyperplasia of either the basal cell layer or the prickle cell layer

of the epidermis. The form assumed by this proliferation varies with the clinical type. It may be verrucous. It may form a thick epithelial plate. There may be a marked hyperkeratosis. Keratinization of the prickle cells is not uncommon. There may or may not be an increase of intracellular and extracellular pigment. The abnormality as a whole is in the nature of a developmental defect rather than a tumor. The nevoid hyperplasia, when it invades the corium, may form nests, columns, a network, or a dense tumor like mass. The nevus cell, which is thought to be derived from the epithelium, is large, round or oval and has a somewhat nebulous nucleus which, however, usually stains well. While it may be regarded as a melanoblast, as is the basal cell, it may or may not contain pigment. In uncomplicated cases the derma is practically normal.

The sebaceous nevi, which occur on the face, chest, and elsewhere on the body, are generally discrete but may be grouped. They do not exceed a few millimeters in diameter, are of firm consistence and yellowish color. The surface is uneven. These tumors are hypertrophic sebaceous glands. There is a great increase in the number and size of these glands; occasionally the glands disappear leaving a dense fibroma.

Nevus hidradenoides is a sweat gland tumor manifested clinically as a discrete, elevated, white, trans-

parent lesion. Histologically the sweat gland structures are readily recognized.

Clinically three types of nevus vasculosus are described. The superficial type or port wine mark, the raised type or angioma cavernosum, and the so-called senile angioma. Histologically, they show dilated blood vessels, a proliferation of new blood vessels, or both.

In the blue nevus microscopic examination shows pigmented melanin cells in the lower two-thirds of the cutis. These cells are spindle shaped with the nucleus in the center and the abundance of the pigment at the extremities. The upper third of the cutis is normal.

The neurofibromata are made up of loose fibrous tissue, fine fibers of young normal connective tissue, and unaltered nerve fibers. Sometimes, in young tumors, there is excessive production of nerve tissue. Elastic tissue fibers are absent. The fibrous bundles encompass sweat and sebaceous glands.

Treatment: In the past, attempts at removal or destruction of an apparently quiescent blue-black mole have been so often followed by recurrence and metastasis that many physicians prefer to leave them alone. Undoubtedly in many of these cases the lesion has been a melanoma instead of a nevus. While potentially dangerous, the majority of blue-black moles that have

been present since childhood do not eventuate in cancer. When in a location reasonably safe from injury they may be neglected therapeutically and inspected occasionally. When, however, they are likely to be traumatized or irritated, or when they exhibit any evidence of activity, such as increase in size, scab formation, or ulceration, it is advisable to remove or destroy them. While radium, Xrays, and the electric cautery have given excellent results in some instances, the outcome is uncertain, and, in many men's opinion, they should be used only for an occasional well selected case. Every cell must be destroyed or removed. Obviously the best way to be certain of this is to excise the lesion either with a scalpel or with the curring current and make a microscopic examination of serial sections. When the lesion is small and suitably situated, scalpel excision is preferable because the cutting current may so modify the tissue as to make a microscopic study useless. The incision should be well beyond the visible and palpable margin of the lesion and should extend outward and downward to the underlying muscle, since nevus cells or malignant cells may take such a course, following the nerves and vessels. The bottom of the excised mass should thus be wider than its surface. It is well to examine frozen sections at once and to make the usualy study of the

tissue later. Subsequent action depends upon the result of the microscopic findings. When the lesion is proved to be a nevus and it has been completely removed, nothing further need be done. In some instances a more radical excision, plastic surgery, Xray or radium treatment for regional lymph nodes, or a combination of such methods may be advisable.

All other moles, so far as concerns danger, may be let alone unless they are likely to be repeatedly injured. They should, of course, be inspected at each periodic health examination. The common mole may be handled satisfactorily with electrolysis with little if any permanent defect. Dermatologists have been employing this method for thirty or more years and there has not been a single instance of cancer. One must be certain of the diagnosis, however. It is unwise to treat a cerebriform nevus by any method that fails to remove every abnormal cell. For many years it has been customary to destroy ordinary pigmented and verrucous nevi with solid carbon dioxide or with electro-dessication, especially the former. The results have been satisfactory but whenever possible surgical excision is to be preferred.

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BOWEN'S DISEASE

Discussion: Bowen's disease is a precancerous

dermatosis which eventually assumes a typical clinical picture. Since the study of dermatology is one of processes rather than static pictures, it is more logical to identify the process as seen under the microscope than to insist on a definite clinical entity. Just as there are many clinical forms of basal cell carcinoma, there are many clinical pictures with the microscopic changes first described by Bowen. Frequently, the disorder appears first as a plaque of chronic scaling dermatitis which is slightly elevated and may attain several centimeters in diameter. The border of the plaque often presents as annular or serpiginous outline. Papular, lenticular and nodular lesions have also been described which may be discrete, grouped or confluent. The failure of the disorder to heal under conservative treatment and its persistence in the same location with gradual extension directs attention to the possibility of Bowen's disease. Squamous cell carcinoma eventually develops.

Etiology: Not definitely known. Chronic irritation may be a factor.

Diagnosis: This can be established with certainty only by biopsy.

Pathology: The microscopic examination reveals hyperplasia of the epithelium, with parakeratosis. The stratum mucosum is thickened, and many of the cells

are vacuolated. There are three changes characteristic for the process. Some of the cells undergo individual keratinization, some of them are multinucleated, and others are definitely anaplastic. The cells in the basal region have lost their palisade arrangement. The dermis contains a heavy cellular infiltrate, characteristic for precancerous conditions. On the basis of the presence of all the characteristics of carcinoma except actual invasion, some workers have designated Bowen's disease as "carcinoma in sity".

Treatment: This consists of thorough destruction by means of high frequency electricity. The patient should be carefully watched for recurrence.

COMMENTS AND CONCLUSION

In this paper the author has attempted to present a condition which has great potential value in present day and future medical practice. The important facts which should be stressed over and over again are:

1. Precancerous dermatoses are increasing in incidence every year over the United States as a whole.

2. Precancerous dermatoses cause approximately 3,000 deaths annually, of which 90 percent could have been prevented with early diagnosis and adequate treatment.

3. Precancerous dermatoses, in its multitude of forms, is common to every geographic location in the country, be it city, town, village of farm.

4. Precancerous dermatoses <u>can</u> be prevented by proper treatment following an early diagnosis.

5. It is a challenge to the medical profession, as a whole, to combat and conquer the condition and thus lower the morbidity and mortality.

Thus by only a minimum of effort on the part of the medical profession, knowing and understanding the conditions, a great service could be rendered to humanity. It is a simple problem, when understood, with a simple treatment when started early, and as Andrews & Kelly (65) stated: "Perserverance is more prevailing than violence; and many things which cannot be over-

come when they are together, yield themselves up when taken little by little."

In conclusion the author quotes a paragraph from an article by Bruno Bloch (11) which fairly well sums up the question of precancerous dermatoses, and which is as applicable today as it was in 1934. He stated: "The conception of precancerosis is partly clinical-statistical, partly morphological and histological in nature. We cannot, as yet, define it exactly in theory. Practically, it is sufficient if we call precancerous all those pathological changes in skin and mucous membrane, and particularly those of the epidermis, which potentially form cancer, that is to say, those which, if left alone, will in a large but not yet exactly fixed percentage sooner or later (sometimes after a long time) turn into actual cancer. To a certain degree precanceroses are histologically characterized by: irregular epithelial proliferation, irregularities and unrest in the cell structure, atypical and polymorphous cells and nuclei; furthermore, by pathological mitoses and amitotic figures, dyskeratotic manifestations and by reactive inflammation in the adjacent parts of the cutis. None of these features alone is typical; the combination of all or the majority is required."

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