SYMPOSIUM ON SKIN CANCER

EPIDEMIOLOGY OF SKIN CANCER*

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Epidemiology is that branch of medical science which deals with quantitative differences in the incidence, morbidity and mortality caused by diseases and by natural agents in various groups of people; utilizes these differences for the detection and demonstration of causative relationships in order to gain insight into the pathogenesis of diseases; and tries also to throw open new approaches to the combat against disease.

The more a population group deviates from the usual regarding a disease, the smaller is the number of observations required for the disclosure of the peculiarity and the less are elaborate statistical technics necessary. Thus, simple clinical observation of "climbing boys" led Percival Pott to the discovery of the neoplastic nature of the scrotal lesion and of soot being a carcinogenic agent responsible for it (1). Pott saw scrotum cancer in chimney sweeps who were 13 to 15 years old. This cancer is rare. At present, in the United States of America 1.2% of all fatal skin cancers originate on the scrotum; in England the ratio is higher, 7–8%. This indicates a difference in the distribution of the carcino-relevant agents acting upon the two populations. Below the age of 30 years, scrotum cancer is very rare, as it was in Pott's time. Yet in chimney sweeps he observed several cases at the age of puberty. Thus it became clear that this type of cancer became manifest within ten years after repeated and frequent exposure to soot.

In his short communication Pott established, first, the principle that exogenic factors play a role in the pathogenesis of cancer (in its frequency and in the age of appearance) and, second, the existence of a latent period of cancer due to the local action of soot. Following restriction of child labor, and with increasing personal cleanliness, the appearance of scrotum cancer in chimney sweeps was observed to rise in age.

During the 19th century, Paris, Volkmann, Bell, Unna and others, following Pott's method, enriched the knowledge of dermotropic carcinogenic agents. They showed the role of arsenic (in copper-smelters), of tar and paraffin, of shale oil (in spinners), of sun rays (in farmers and sailors). It also became known that epithelioma tends to develop in scars after burns, in lupus vulgaris and syphilis, in psoriasis, in various lichen eruptions, etc., the common denominator to all these observations being Virchow's theory of chronic irritation.

These discoveries were made before vital statistics and experimentation had become useful tools in cancer research. At first, the experimental side rather retarded progress. Hanau's failure to induce tar cancer in dogs (1888) outweighed clinical experience. Thus, in 1911, Wolff (2) in his standard work still maintained that chemicals cannot induce cancer. This opinion was revised after Yamagiwa, Itschikawa and Tsutsui succeeded in inducing tar cancer in the

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skin of rabbits and mice. But still early in the 1920's the great majority of skin cancers were believed to be "spontaneous" and not of exogenic origin. At present, a substantial number of all skin cancers is related to known agents, most prominent of which is ultra-violet light. This reversal of opinion resulted from epidemiologic studies and from experimentation on animals (Findlay, Huldschinsky, Putschar and Holtz, Roffo, Blum and others).

There are questions in epidemiology which cannot be answered either by clinical observation or by animal experimentation. They require research on man, that is statistical research relating to incidence, morbidity, mortality, race, age, geography, occupation, wealth, nutrition, habits and so forth.

Until a few decades ago, very little information existed about mortality from skin cancer, and nothing was known about its incidence. Skin cancer seemed to play an inconspicuous role. It is now clear that the ratio of fatal skin cancer to all fatal cancers is between 2% and 3%; for women it is less, that is 1.6%. Even in the age group of 70 and older, in which almost $\frac{2}{3}$ of all deaths from skin cancer occur, only one cancer death in twenty is due to skin cancer.

According to the data from the last census year, 1940, in this country 3.6 men and 2.1 women per 100,000 died from skin cancer. In England the corresponding figures for the last three years prior to the second world war were 3.0 and 1.3 respectively. These rates are lower than those of the United States, the difference probably being due to greater amount of sunshine in the southern states.

Only England's statistics in skin cancer reach back to almost the middle of the 19th century. They indicate that between the 1860's and the end of the 1920's mortality from skin cancer varied but little[1] and only recently started to decline.[2] In the last 30 to 40 years skin cancer therapy has made great progress; but there was progress also prior to the introduction of radium and X-ray therapy. Thus, the stability of the death rates indicates an increasing frequency of skin cancer in England within that period of time. This increase was more pronounced in other countries, especially in Central Europe, but owing to the lack of reliable data on the case fatality ratios, the changes cannot be translated into figures.

In the early years of this century, in southern plantations the observation was made that white workers suffered more frequently from skin epithelioma than Negroes. This difference has always been reflected in United States vital statistics; per 100,000 colored men there are annually 0.7 deaths from skin cancer, and in women 0.6 deaths,[3] the ratio between whites and colored being 5.1 in men and 2.7:1 in women.

Vital statistics disclosed relatively large differences in skin and lip cancer mortality between social strata in disfavor of the lowest group, the unskilled

[1] In 1868, 1888 and 1909 deaths from skin cancer per 100,000 men 35 and more years of age occurred in 4.6, 4.3 and 4.3, and per women in 2.0, 2.2 and 2.5 persons.

[2] In 1911–20, 1921–30, 1931–35 and 1936–38 standardized mortality per 100,000 of all age groups was for men 3.3, 3.5, 3.2 and 3.0, and for women 1.5, 1.5, 1.35 and 1.3 respectively.

[3] The corresponding death rates per 100,000 from lip cancer are for whites 1.0 and 0.1 and for colored men as well as women 0.1.

workers.[4] How much of this difference is due to unequal incidence and how much to unequal therapeutic facilities and results is a matter of conjecture. As to the differences of incidence between men and women, we do not know how much they reflect degrees of exposure, of susceptibility and resistance, nor do we understand why these differences are limited to whites.

Women are hardly less exposed to sun rays than men. I do not believe that the cosmetic make-up successfully counteracts exposure. If this were so, then in countries in which considerably less cosmetic make-up is used, the difference between male and female death rates from skin and lip cancer would be much smaller than here. This is not the case. While it is true that women are less exposed to the more common chemical dermotropic agents, it is nevertheless no proof that such exposure is the complete explanation. A striking example serving to illustrate the effect of equal exposure and unequal reaction, is the difference in the statistics of cancer of male and female cotton-spinners. In England both groups are exposed to the same carcinogenic agent, namely, lubricating oil. Only the men show an increased skin cancer mortality, their scrotum cancer rate being 54 times the "normal" while their rate from cancer of all other parts of the skin is increased only 3 times. Do female spinners escape the action of the hydrocarbon upon the skin because the latter is less sensitive or because of better personal hygiene which prevents absorption of the oil? The carcinogen in the oil has affinity also to some of the internal organs. If personal hygiene were the decisive factor and if the difference in the skin cancer increase were indicative of degrees of cleanliness, then the female spinners should have either no reaction in the internal organs or at least a weaker response than male spinners show. However, the opposite is true; the female spinners show the stronger reaction in the internal organs and, therefore, show a total cancer mortality elevation of 56% above "normal" while their male working partners' mortality is increased by only 14%.

Perhaps female spinners escape the action of the oil upon the skin because their internal organs are apt to react after a shorter latent period than those in men. This would coincide with the fact that in the middle age groups of the general population female cancer death rates are higher than those in men. Such an explanation is logical only if cancerous reaction in one organ protects to some degree other organs, in this instance, the skin, against the action of the carcinogen, or if the skin has a much longer latent period.

Little is known today about the anatomic and physiologic factors which influence the skin's susceptibility to and resistance against the development of a primary tumor. Heredity, which in xeroderma pigmentosum, for example, is a dominant factor, seems to play a role in the reaction of the normal skin only to the extent that the pigment itself is a matter of heredity. The different response of white and colored, of blond and brunet to ultraviolet rays is related to the presence of the screening pigment. But is the melanin also responsible for the

[4] Per 100,000 men over 16 yrs in 1920–22, there died from skin and lip cancer 2.5 in the two highest social classes, 7 in the skilled class, and 12 in the unskilled class of labor. In the 1930's the difference between the extremes diminished.

asserted low incidence of skin cancer in Negroes exposed to tar or lubricating oil? (Incidentally, we do not know anything about the incidence of internal cancers in these Negro workers, and I would not be surprised to find the incidence considerably increased).

The necessity of incidence data is apparent in a discussion of problems of skin cancer on the basis of mortality statistics. In cancer of the stomach or lungs where the case fatality ratio is practically 100% and the duration of the disease relatively short, we are inclined to accept mortality statistics, provided they are reliable. Also in malignant melanoma, reliable mortality statistics should be satisfactory. Melanoma behaves differently from all other skin cancers, whether we study the relation between histology and clinical findings, the case fatality or epidemiology; fortunately, it occurs in only 5.3% of all skin cancers, the percentage being smaller in populations less exposed to mechanical traumas. With regard to the other skin cancers, direct studies on incidence are needed since the knowledge of the case fatality ratio—both past and present—is meager indeed.

The lack of satisfactory therapeutic statistics is attributable to three reasons: 1) the low case fatality makes large series of cases imperative; 2) the long duration of the disease demands long observation, invalidating 3 or 5 year follow-ups; and 3) the high incidence of multiple cancers and of multicentric cancers—14.5% in skin cases instead of 2% in cases of internal cancer—brings a factor of uncertainty into the whole calculation.

Statistics on the frequency or incidence of skin (and lip) cancer cover only short periods of time. In this country, several surveys have been carried out: 1) in the Navy and Army of the United States; 2) in the St. Elizabeth Hospital for the mentally ill in Washington, D. C.; 3) in several oil refineries and 4) in several city areas (series of the United States Public Health Service). In these surveys all types of cancer (including also those of the skin and lip) were observed.[5]

In the United States Navy, I found the incidence of skin and lip cancer to be between 7 and 8 times as high as the mortality in this body of men and over 22 times as high as the standardized mortality of the American male population (3). In the active personnel, in 1929 to 1936, not less than 42% of all cancer cases were those of the skin or lip. Thus, while in mortality statistics skin plus lip cancer occupy an inconspicuous place—3 to 4% in the male general population and 6% in the Navy—in incidence statistics they constitute a large segment. In the United States Army (1927–1937), I found skin and lip cancer in 35% of the white and in only 6.5% of the Negro cancer patients. Thus in the Negro 93.5% of all cancers originated in an internal organ, as compared with 65 and 58% respectively in the white personnel.

Within the surveyed period, among the active white personnel of the Armed

[5] I mention this as in England surveys on cancer, e.g. in male spinners, are limited to the skin. There, in 1923–40, out of 32,000 spinners, 1,116 persons developed skin cancer and 360 died of it. Thus the annual incidence of skin cancer in spinners is about 194 per 100,000 and the case fatality ratio is 32%.

Forces there occurred 764 cases of cancer, of which 333 patients were born south of the 40° latitude, and 431 north of it. Among the former, 166 (49.9%) had skin or lip cancer, and among the 431 northerners the corresponding values were 118 (27.4%) (4, 5). While in service, southerners are not separated from northerners; both live under equal conditions and under the same medical supervision. Diagnostic inequalities are out of the question, and therefore the difference between these two groups of men regarding skin and lip cancer must have its origin in the living conditions of the pre-service time (childhood and adolescence). This conclusion is supported by the fact that during the time of service the difference in the frequency of surface cancer between south and north diminishes and the visceral distribution of cancer undergoes changes in both the southerner and the northerner.

Percentage of surface cancers in white persons of each group

AGE	SOUTHERN-BORN	NORTHERN-BORN	ALL
	per cent	*per cent*	*per cent*
16–34 years	53	23	39
35–64 years	47	29	36
All	50	27	37

According to these figures, exposure to dermotropic agents in childhood is more effective in changing the distribution of cancer in a population than is exposure in later life.

Our figure of 50% skin and lip cancers among the white southern-born cancer patients in the Army and Navy is almost identical with the percentage found by Mountin and Dorn of the Public Health Service in Atlanta, Georgia (6, 7) and slightly higher than found by Dorn (7) for men in all surveyed southern areas. The percentage of surface cancer for the northern-born soldiers and sailors, 27%, is almost twice as high as that of the northern city areas surveyed by the Public Health Service. According to this series of studies, in the white civilian population of the southern city areas, the annual incidence of skin and lip cancer is 144 per 100,000 men and 75 per 100,000 women, while for the northern cities the corresponding figures are 31 and 19, or about $\frac{1}{5}$ to $\frac{1}{4}$ of the southern figures. On the other hand, according to the same series of studies, in the southern cities cancer of some digestive and of the respiratory organs is about 33% below the level of the northern areas. This is in agreement—at least in principle[6]—with my findings in the Armed Forces as well as in the St. Elizabeth Hospital. (8)

In comparing cancer in the South with that in the North (of the United States) I correlated the differences in skin and lip cancer with the action of the sun, e.g., with the action of a dermotropic carcino-relevant agent which has no affinity for

[6] The figures of the Public Health Survey must be taken *cum grano salis*, because of the many handicaps in this work. This series of surveys is more of a pioneer work than a basis for definite conclusion (8).

internal organs. Nevertheless, in the Armed Forces just as in the civilian population in the South, there is an association between the increased incidence of surface cancers with a lowered incidence of cancer in some internal organs, e.g., in the digestive tract and lungs. This inverse association is not accidental; it exemplifies a general law, whether actinic rays, chemicals, hormones or thermal traumas are brought into play. The inverse association is of great epidemiologic significance and of both practical and theoretical importance. *If in a population the number of cancer cases having a low fatality ratio increases while the number of highly fatal cancer cases correspondingly—case for case—diminishes, the total cancer mortality must decline.* It declines even if the highly fatal (internal) cancers diminish numerically less than the number of surface cancer cases increases. If, however, the primary tumors of the organs involved in the process of inverse association have about an equal fatality ratio, the effect will not be visible in the mortality of the population but may come to the fore in the changed age and organ distribution of cancer incidence. An example is seen in the effect of pregnancies, of their number and spacing. The effect of the inverse association may also result in an increased mortality, e.g., if the agent produces cirrhosis of the liver and through it an increase in the incidence of hepatoma malignum which replaces cancer in other organs where the fatality ratio may be smaller.

Due to the hypothetic compensatory process and in spite of the highly increased mortality from surface cancer, the personnel of the armed forces has very low age specific and standardized cancer death rates. Compared with New York City, with London or Vienna, the Navy's active and retired personnel has a cancer mortality lower by 46%. For the same reason the civilian white population in the South has a low total cancer mortality. However the difference between southern and northern states is smaller than the official statistics indicate because of the greater lack of completeness of the statistics in the South as compared with the North.

Let me demonstrate the inverse association and the compensatory process with two other examples. In the first, the dermotropic factor is repeated thermal trauma. Glass-workers exposed to heat and burns at the glass smelting furnace have 4.25 times as high a mortality from skin and lip cancer as glass-workers who are not exposed to these injuries. This was to be expected. But this excess is more than compensated by diminished mortality from internal cancer (9). The second example regards ultraviolet rays and the race factor. Among the white inmates of the St. Elizabeth Hospital for the mentally sick, the ratio of skin and lip cancer to all other cancers is ten times as high as in Negro inmates. On the basis of New York City statistics, I expected to find a total of 210 cancer deaths but found only 157; for the white inmates the corresponding pair of figures was 150 ± 12 and 101, and for the Negroes 59.8 ± 7.7 expected and 56 actual (10). Under equal conditions of life, of sun exposure and medical supervision, in the South, Negroes have a cancer mortality higher than whites, because the law of inverse association acts in favor of the latter.

With the knowledge of the law of inverse association we are able to search for

the explanations of phenomena which otherwise remain either unexplained or are subject to wrong interpretation. A few examples may be presented. Some time ago the question whether American lubricating oils are carcinogenic was under discussion. Heller (11) thought they were, while Gafafer (12) who surveyed 11,000 refinery workers for six years denied it, saying that the actual annual mortality from cancer was 78 per 100,000 versus 96 expected. For unrevealed reasons skin cancer was lumped together with other cancers, but I have been assured that no case was omitted and that medical and recording services were beyond criticism. Altogether 70 cases occurred and 46 died of cancer during this period. In shortened form, Gafafer's table is as follows:

Cancer among 11,000 refinery workers, 1933–38

	CASES	DEATHS
Oesophagus, stomach, other abdominal organs, lungs and general	50	40
Oral region, trunk and extremities	20	6
All	70	46

The difference in the percentage of fatalities between the "oral region, etc.," and the others is so striking that the bulk or almost all of the 20 cases were most probably skin cancer. I assume that the refinery workers had a considerably increased incidence of, and mortality from, skin cancer and a compensatory decline in the internal organs which led to a deficit of the total cancer mortality amounting to 19%. The compensatory decline tends to prove the oils to be carcinogenic.

Any statistical analysis which ignores the compensatory process is bound to lead nowhere, as the development of cancer in an internal organ depends also on the carcino-relevant happenings in other organs. In a recent report, Stocks (13), chief medical statistician of the Registrar General, found that in England in areas with less than 1,150 hours of sunshine per year, lung cancer mortality was 2.5 times as high and also the death rate from stomach cancer was increased as compared with areas of more than 1,400 hours of sunshine. Stocks did not discover the reason and could not find it because he lumped skin cancer deaths together with all other cancers and, second, because he did not have any incidence statistics. Sun rays act upon the skin and not upon the lungs but reach them, figuratively speaking, via the inverse association in populations with a changed skin cancer incidence.

It is not always the lung where, following increased exposure to sun, the compensatory mechanism becomes most apparent. In the Alpine regions of Central Europe, sun exposure has become increasingly popular since the end of the last century, and the total cancer mortality gradually declined, but the lung cancer mortality was and has remained high (14). The organs in which the compensatory mechanism demonstrates itself depends on an interplay of many cancer-relevant factors.

The inverse association is a group phenomenon. Its meaning for the individual is: 1) that we are able to influence and to choose the organ of cancer origin, 2) that a person whose skin cancer had been cured is less likely to develop an internal primary tumor than a comparable average person who had no skin cancer (15), and 3) that because of the low frequency of metachronous primary tumors in the combination skin-internal organ, the life expectancy of cured skin cancer cases is longer than that calculated from Life Tables. This point I proved for skin and lip cancer cases past the age of 60 years (16).

Organ distribution of cancer in a human population is changeable almost to the point known only in purely bred strains of mice (17). Two conclusions can be drawn from these observations: a) we do not have to leave the organ distribution of cancer to chance; b) cancer disposition of the disposed individual is not limited to one organ. In spite of this and although throughout our life we are exposed to a variety of carcino-relevant agents acting upon various organs, as a rule, in the disposed individual only one organ develops a primary tumor and, after the latter's cure, the other organs only seldom are sites of another primary tumor. Evidently, powers are active to keep silent a great number of potential tumor foci, dispersed widely in the human body.

REFERENCES

1. Pott, Percival: The Chirurgical Works, vol. V, Chap. III: Observations on the Cancer of the Scrotum: p. 63–68, London, 1775.
2. Wolff, J.: Die Lehre von der Krebskrankheit von der altesten Zeit bis zur Gegenwart; second volume, p. 37.
3. Peller, S. and Stephenson, C. S.: a) Am. Jour. of Med. Sci. 1937, **194:** 326. b) Am. Jour. of Hyg. 1939, **29:** 34.
4. Peller, S.: International Cancer Congress, Atlantic City, September 1939.
5. Peller, S., Stephenson, C. S. and Souder, C. G.: Am. Jour. of Hyg. 1940, **32:** 39.
6. Mountin, J. W. and Dorn, F. H.: J. A. M. A. 1939, December 30.
7. Dorn, F. H.: Public Health Rep. 1944, vol. 59, Nos. 2, 3 and 4.
8. Peller, S.: J. of Heredity, 1944, **35:** 175.
9. Peller, S.: Human Biology, 1937, **9:** 57.
10. Peller, S. and Stephenson, C. S.: Pub. Health Rep. 1941, **56:** 132.
11. Heller, I.: Jour. Indus. Hyg. 1930, **12:** 169.
12. Gafafer, W. M. and Sitgreaves, R.: Pub. Health Rep. 1940, **55:** 517.
13. Stocks, P.: Regional and Local Differences in Cancer Death Rates; H. M. Stationery Office, 1947.
14. Peller, S.: Zeitschr. f. Krebsforschung 1925, **22:** 317; Wien. klin. Wochschr. 1936, No. 45.
15. Peller, S.: Am. J. of Hyg. 1940, **31:** 109.
16. Peller, S.: Am. J. of Med. Sci. 1940, **19:** 449.
17. Peller, S.: Human Biology, 1939, **11:** 139.