

1961

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SEMEN AS A MALE FACTOR IN SQUAMOUS CELL
CARCINOMA OF THE CERVIX

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Submitted in Partial Fulfillment for the Degree of
Doctor of Medicine

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March 24, 1961

Omaha, Nebraska

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INTRODUCTION*

Nearly every substance which at one time or another has had contact with or alters the condition of the uterine cervix has been implicated as an exciting agent in squamous cell carcinoma of the cervix. In the evolution of present day concepts, many of these factors have been found to be insignificant and disregarded, while certain conditions having a less direct relationship with the cervix have been found to be significantly increased in incidence in women with this disease. Before it can be assumed that these seemingly unrelated agents and conditions are separate causes of cancer, it must be proved that a specific common denominator does not exist among them. Therefore, the purpose of this paper is twofold:

1. To review and evaluate the literature dealing with the etiology of squamous cell carcinoma of the cervix.
2. To present the results of an experiment dealing with female hypersensitivity to human semen as a possible etiological factor in this disease state.

* Unless otherwise stated, when reference is made to cervical carcinoma, it is not meant to include adenocarcinoma of the cervix.

RELATED CONDITIONS

Jewish Women: Treusch, Jones, Gusberg, Ober, Smith, and Rothman have all expressed the low incidence of squamous cell carcinoma of the cervix in Jewish women as compared to Gentiles.^{1,2,3,4,5,6,7} Jones found the disease to be eight times as common in non-Jewish women,² Rothman and Ober nine times as common,^{4,7} and Gusberg 333 times³ as common, as in Jews.

A lower incidence of circumcision in the husbands of non-Jewish women with the resultant exposure to smegma has been implicated by many as being the cause of this disproportion of cervical cancer in the two groups.^{5,8,10} Pratt-Thomas produced squamous cell carcinoma of the cervix and vagina in one strain of mice by repeated application of horse smegma over a period of 14 months.⁹ According to Fisher, the carcinogenic action of smegma may be due to a substance, possibly squalene, having the reactive unsaturated double bond $-CH=CH-$ in its dimer molecule.⁸ However, Fishman was unable to produce cervical or vaginal epidermoid carcinoma in mice by repeated direct application of human smegma to these organs.¹⁴

Several authors have questioned the effect of circumcision and smegma in cervical disease. First, if circumcision is a factor, non-Jewish women married to circumcised males should have a lower incidence of cervical cancer than those married to noncircumcised males. Wynder, in 1954, studied 589 cases of cervical cancer and 1311 controls by a method of blind interview.¹⁰ He considered non-Jewish white, Jewish, and Negro patients separately in an effort to statistically correlate some of the previously suggested factors. He found that non-Jewish women with the disease had been more frequently exposed to noncircumcised males than the controls. However, Jones, also using a thorough method of interviewing patients and controls, found that when Jewish women were excluded, the frequency of circumcision of the first husband or partner of longest duration was the same for cases and controls.² Dunn and Buell also report an equal frequency of circumcision of husband among cases and controls, 34.1% for the former and 33.7% for the latter.¹¹ They also emphasize pitfalls in this particular type of interviewing. Twelve percent of their patients and 8.1% of their controls did not know the circumcision status of their husband. Even

if these "unknowns" worked completely in favor of circumcision being a factor, the relative risk of being married to an uncircumcised male was only 1.5 to 1 in their series. A more important result of these "unknowns" was their prompting Dunn and Buell to make an analysis of the circumcisional status of men. On questioning non-Jewish men, they found that of those reporting circumcision, only 48% were found on examination to be completely circumcised while some 7% of those reporting "not circumcised" were found on examination to be completely circumcised. Lillienfield and Graham found one third of the men claiming circumcision were uncircumcised on examination and one third of those who stated that they were not circumcised were found to be so.¹² The difference in the percentages presented by the two author groups lies in their use of different criteria for circumcision and non circumcision. For example, Dunn and Buell found that only about one half of non-Jewish men thought to be circumcised by examination had actually lost all of their foreskin as a result of the surgery.¹¹ If complete circumcision is thought to prevent cancer and these partially circumcised men are included in the completely circumcised group by interview, the

relative risk of noncircumcision is minimized. Furthermore, some men have a naturally shortened foreskin, resembling that of an incompletely circumcised male. If these men, by interview, are included in the noncircumcised group and in reality their partial "natural" circumcision does offer some protection, then the relative risk on noncircumcision is further diluted.

Wynder, in a later report, emphasized that information concerning circumcisional status would be even less accurate when the women were used as information sources.¹³ Assuming, however, that wives would have been as accurate as the men in Lillienfield and Grahams experiment, the lack of knowledge concerning circumcision could dilute an assumed risk of 10 times as great in couples with noncircumcised males to 1.69.

The above statistics are presented neither to support nor contradict circumcision as a factor in cervical carcinoma, but to point out that further study will be necessary to settle the issue. It has been suggested that interview techniques be coupled with physical examination of the male partners of both cancer cases and controls.^{10,11}

Factors other than circumcision have also been accused of accounting for the incidence variation of cervical carcinoma between Jewish and non-Jewish women. Inbreeding in the Jewish race may be important, but cancer of other organs is as common in these people as in other population groups.⁶ Abstinence from intercourse during and seven days after menstruation, as is supposedly practiced by orthodox Jews, is thought by Kenneway and Smith to lessen exposure to some factor to the extent that it may lower the incidence of cervical carcinoma in this group.^{6,15} The ritualistic dietary laws followed by orthodox Jews has also been suggested as a factor.^{2,16} Clemmesen believes that a "racial" or hereditary hormonal status in Jewish women is as important, if not more so, than the above mentioned racial rituals.¹⁷ None of the theories concerning abstinence from intercourse, dietary rituals, or hormonal differences in Jews are supported by adequate statistics at the present time. That the lower incidence of cervical cancer in Jews may be attributed to some inborn racial factor, as suggested by Maliphant,¹⁹ is doubted by Hochman who found that while the Jewish population of Israel is composed of communities of different ethnic typology, the

incidence of carcinoma of the cervix in all these groups is the same.⁵

Other Racial Groups: The natives of the Fiji Islands, a group in which the males practice circumcision, have a much lower incidence of cervical cancer than do the Indians coming to the Islands from other locations, a group which does not practice circumcision.¹⁸ On the other hand, Moslems, a group universally practicing circumcision have the second highest incidence of all of the ethnic groups in Israel.⁷ Also, carcinoma of the cervix has a low incidence in Parsies, Indian Christians, and possibly some Dutch in whom the factor is absent.¹⁵ To properly evaluate these findings, the material presented earlier concerning circumcision must be applied.

Infection: Erosion and inflammation of the cervix caused by exogenous organisms such as bacteria, spirochetes, Trichomonas vaginalis, whether by primary invasion or involvement secondary to birth trauma and lacerations of the cervix, are probably not as important in this disease as was previously thought. While prompt postpartum repair of cervical lacerations and complete cauterization or conization of all cervical

erosion, as advocated by many,^{20,21,22} may be beneficial in reducing chronic leukorrhea or may conceivably result in a diminished susceptibility of the tissue to a specific carcinogen,²³ there is no proof that chronic cervical infection and cervical lacerations are etiological agents in cervical cancer.^{24,25,26} For example, Gagnon's failure to find a single case of cervical carcinoma among 13,000 nuns who demonstrated 14 cases of endometrial carcinoma is significant,²⁷ but it cannot be assumed that this is the result of less cervicitis in nuns. Similarly, a higher incidence of carcinoma in parous than in nonparous patients,^{19,20} if such were the case, does not justify the conclusion that unrepaired lacerations is the factor that caused the increased incidence.

Syphilis is more common in patients with cervical cancer than in other female groups. Raphael found that 5.5% of the cervical cancer patients in the Rhode Island Hospital had positive serology while only 0.74% of all female adult patients admitted to the hospital had positive tests.²⁸ Similar findings have been published by Levine.²⁹ They have been used as further evidence that inflammation is a direct agent in carcinogenesis. As will be pointed

out later, certain socioeconomic factors in women with cervical carcinoma help to explain these statistics and they are not as significant as they may first appear.

Hormones: Hormones, especially estrogen, and their effect on cervical epithelium have added a certain element of cloudiness to gynecological pathology, especially in relation to cervical carcinoma. Disagreement has stemmed partially from lack of knowledge about hormonal effects on normal cervical epithelium, but more so from contradictory opinions on the effect of conditions characterized by hormonal imbalance.

The normal architecture of cervical epithelium, both squamous and glandular, depends on the cyclic variations of estrogen and progesterone as is seen in a normally menstruating woman. It has been proposed that conditions which result in prolonged absolute or relative increased estrogen levels and therefore unopposed stimulation of cervical epithelium may be responsible for epidermoid carcinoma of the cervix.³⁰

Chronic infection, mentioned earlier as a direct etiological agent, is thought by Ayre to serve in a

different capacity. It was postulated that dietary deficiency in the vitamin B complex, especially thiamine, resulted in inadequate detoxification of estrogens by the liver with accumulation of these substances in the blood stream.³¹ It was Ayre's contention that these estrogens were trapped and concentrated in chronically inflamed cervical epithelium and in 50 patients with cervical carcinoma, he found evidence of excessive tissue estrogen, as judged by cervical cornification smears, in 92% of these cases and thiamine deficiency in 38.8%.^{32,33} It should be mentioned that his opinion is partially based on the work of Brunelli, who found high concentrations of estrogens in artificially produced edematous skin inflammations in rabbits. Such an edematous reaction is not characteristic of chronic cervicitis.³⁴

The theory of long standing estrogen stimulation with or without chronic cervicitis has met opposition along three different lines. First, many patients with cervical carcinoma have symptoms of diminished estrogen activity. Nieburgs found that 71% of premenopausal cervical cancer cases had a diminished estrogen level as determined by exfoliative cytology.³⁰

He believes that a pituitary factor, increased in low estrogen states, by long term stimulation of cervical epithelium unopposed by estrogen, is an important factor in cervical carcinoma. Factual evidence in favor of this viewpoint is limited. Sommer, on the contrary, in studying the endocrine glands from patients who had died from cervical carcinoma, found the disease more often in endocrinologically normal women.³⁵ While he did find some acidophilic cell hyperplasia of the pituitary, he considers this a reaction to invasive cancer of diverse sites.

If estrogens are the causative agent of squamous cell carcinoma of the cervix, one would expect a high incidence of endometrial hyperplasia accompanying the disease. A failure to observe such a high incidence is the second factor opposing the hormonal stimulation theory. Marzloff found five cases of endometrial hyperplasia in 208 cases of cervical carcinoma or an incidence of only 2.4%.³⁶ Green and Suckow found one case of hyperplasia in 11 cases of cervical cancer.³⁷ Bainborough and others found this incidence to be 50%, but they used unusual criteria for the diagnosis of hyperplasia and found the incidence of endometrial hyperplasia to be 69% in their controls.³⁶

Bayly and Greene found the incidence of hyperplasia in association with this disease to be 5.2% while their unmatched control series had an incidence of 9.7%.³⁹ Therefore, if endometrial hyperplasia is used as an index to excessive estrogen activity, the latter does not seem to be as an important factor in carcinogenesis as was once supposed.

The third factor opposing this theory is the fact that even though squamous cell carcinoma has been produced by application of estrogens directly to mice cervixes,⁴⁰ this is the only species in which this has been accomplished and relatively tremendous doses applied over long periods of time have failed to produce the lesion in rats, rabbits, guinea pigs, monkeys, or dogs.³⁷ While estrogens administered therapeutically to women for various reasons cause increased desquamation of the superficial squamous cells, they do not produce any signs of excessive or abnormal epithelial proliferation, as determined by vaginal biopsy.⁴¹

Pregnancy: If pregnancy is related to cervical cancer in an etiological sense, this relationship is probably on an hormonal basis. However, since it is considered to be so important by so many, has caused

so much controversy, and has added so much confusion to cervical pathology, the subject will be considered separately. In so doing, the assumption will be made that carcinoma in situ is a malignant lesion and is the precursor of invasive carcinoma of the cervix. The problem of pregnancy and cancer can be approached from two angles. One, the incidence of carcinoma in the pregnant and nonpregnant state can be compared, and two, the cervix can be studied histiologically in the pregnant state and compared to the nonpregnant organ.

MacFarlene was one of the first to statistically emphasize an increased incidence of cervical carcinoma in the parous female.²⁰ She found an incidence of 0.6% in single, nulliparous women, 1.4% in white, married nulliparous women and 3.7% in married parous women. Maliphant also found a higher risk among childless married women and a still higher risk for parous women.¹⁹ Lawson agrees that family size may be a factor but that it must be analyzed in the light of age, social status, and family size.⁴² The studies of Nieburgs do not concur with these findings. Sixty two percent of his cases were nulliparous or uniparous.³⁰ He found that the shortest time between

the last pregnancy and the diagnosis of preinvasive cancer is an average of 10 years in the premenopausal group while in the postmenopausal group both the preinvasive and the invasive are diagnosed on an average of 25 years after the last pregnancy. Similarly, Pund reported that 46 of 69 preinvasive carcinomas were diagnosed 10 years after the last pregnancy, making the pregnancy an unlikely cause.⁴³ This time interval would be even greater for invasive carcinomas as there is a latent period of 11.1 years between the preinvasive and the invasive disease.³⁰ As a matter of fact, if preinvasive carcinomas were not included in a series studying the effect of pregnancy, the average age would be considerably higher than had the preinvasive cases been included due to this latent period. In this older age group, one would expect to find more women of higher parity. Probably more significant, however, are the findings of Wynder, who could discover no statistical association between the number of pregnancies and cancer cases after eliminating the effects of age at first marriage, considering only married women, and comparing groups of similar economic status.¹⁰ Stocks also thinks that environmental factors lead to the association

of cervical cancer and family size.⁴⁴ When considering types and numbers of pregnancies, Jones and others found no difference between cases and controls.² If these authors' findings are correct, it should be evident that if women of higher parity have more cancer, it is due to factors other than the parity per se.

The difficulty of evaluating pregnancy as having a relationship to cervical carcinoma is further demonstrated by considering the microscopic appearance of the cervical epithelium during gestation. If hormones are effectual in this state, one would expect to see in the pregnant cervix a higher incidence of specific changes which appear as precursors of or more actual carcinoma in situ than in the nonpregnant cervix. Danforth studied 22 pregnant and 46 nonpregnant hysterectomized cervixes and found a significantly higher incidence of differences in the size, shape and staining reaction of the nuclei in the basal and "metaplastic" zones, mitotic activity, the presence of active nuclei in the midzone and infection among the pregnant cervixes.⁴⁵ He considered these reactions reversible. Epperson found 5 cases and Hirst one case of cervical lesions indistinguishable

from carcinoma in situ which regressed after pregnancy.^{46,47} TeLinde is convinced that the microscopic picture of carcinoma in situ in pregnancy does not have the same significance as it does in the nonpregnant state.⁴⁵ The above authors feel that pregnancy causes specific changes in the cervix which may be confused with preinvasive carcinoma and that the diagnosis of preinvasive carcinoma should be made with reservation in the gravid female.

Peckham and others, to the contrary, could find no specific changes in the cervical epithelium during pregnancy and believe that if the criteria for the diagnosis of preinvasive carcinoma are present, the diagnosis should be made regardless of the physiological status of the female. Of 37 cases of preinvasive carcinoma found during pregnancy, the largest series to date, 78.4% persisted in the postpartum state. They emphasize repeatedly that pregnancy does not have the power to mimic preinvasive carcinoma and that in all probability, the disease develops despite the pregnancy status.^{48,49,50,51,52} According to them, the diagnosis can definitely be made during pregnancy.

The object here is not to decide which of these

viewpoints is seemingly more valid, but to make note of a common factor in all of these authors' observations; i.e. pregnancy is probably not related to cervical carcinoma in situ in an etiological sense. On one side of the argument are those who believe that a large percentage of changes in the pregnant cervix only mimic, but are actually not, preinvasive carcinoma and on the other side are those who believe that carcinoma in situ is carcinoma in situ no matter when it is found and that pregnancy causes no specific changes whatever in cervical epithelium.

Socioeconomic Factors: Within the last decade, attention has been paid to the total environment of the patient with cervical cancer, with the hope of finding particular trends of life in these patients. These investigations have been carried out largely by thorough interviewing of patients as well as carefully picked controls. Several conditions were found more frequently in cases than in controls.

Cervical carcinoma comprises 4.3% of all cancers among private patients and 17.6% of all cancers among state hospital patients. Therefore, low economic status seems to be a factor.⁵³ Marriage prior to the age of 20 and multiple marriages were also more

common among the patient groups.^{10,44,53,54} Cervical cancer patients have an earlier age of first coitus. Therefore, those groups who had a "late age of first coitus and first marriage, and a low remarriage rate, had a lower rate of carcinoma of the cervix".¹⁰ Jones also emphasizes "the socioeconomic complex of relative poverty with rapid maturation sexually and a lust to begin early, and early to terminate, the reproductive phase of biological destiny--marriage, intercourse, first and last pregnancies, separation, divorce--all of these events occur significantly earlier in the life of women destined to develop uterine cervical cancer than women without the disease, in similar age groups".² The authors presenting these socioeconomic relationships all agree that at present the reason for them is unclear.

THE PRESENT STUDY

Male Factor: In evaluating the material thus far presented, it is evident that if a specific etiological agent is responsible for carcinoma of the cervix, it remains to be discovered. One of the factors which those conditions listed earlier in the socioeconomic section; i.e. those few conditions which occur significantly more frequent in cervical cancer patients

than in controls, have in common is early and frequent intercourse with exposure to a larger number of sexual partners. This view is supported by Pereyra, who found cancer of the cervix six times more common in women admitted to the California Institute for Women than in a similar civilian population. "The one mass social characteristic found in common to these women was the diversity of their sexual activity. The multiple marriage, common-law husbands, general promiscuity, prostitution and incidental high venereal disease rate attest this fact."⁵⁵

Intercourse per se is of course not the cause of cervical carcinoma. However, more frequent exposure to a male factor concomitant with this intercourse may be significant. One such male factor may be an infectious agent, as previously mentioned. Another may be smegma, also discussed earlier. A third factor and one which has been immune to suspicion thus far is semen. It is the purpose of this experiment to investigate semen as an etiological agent in cervical carcinoma. It and experiments to be carried on later are based on the presumption that cervical carcinoma represents an abnormal reaction at a cellular level between some constituent of cervical secretion and

something in the semen. At present, a hypersensitive reaction is being investigated by skin testing cervical cancer patients with their husbands' semen.

Human semen is composed of spermatozoa and seminal plasma, the latter being composed largely of secretions from the prostate gland and the seminal vesicles. Ross, Higgins, Grey, and others have studied seminal plasma composition and found it to be rich in protein.^{56,57,58} This protein fraction has been found to consist of components with electrophoretic mobilities similar to those of serum albumin and alpha, beta, and gamma globulins. The exact composition of these proteins is unknown, but it is conceivable that they or the proteins of the spermatozoa may function as antigens on coming in contact with the female cervix.

That semen does possess antigenic properties is a well known fact. Baskins was able to produce immunity against spermatozoa by injecting freshly collected semen into the buttocks of women.⁵⁹ Serum from these women agglutinated spermatozoa when brought into contact with them. The spermatozoa to be agglutinated did not have to come from the original donor.

Another example of semen and cervical antigen-antibody reaction has been found in studying antagglutins

of the male and female genital tract. In the reduced form these antagglutins become attached to the surface of the spermatozoa and prevent agglutination of the latter. It has been postulated that antibodies formed against the antagglutins may be significant in certain cases of infertility.^{60,61,62} Furthermore, Rümke found the sera of 2 out of 80 patients with oligozoospermia to contain sperm agglutinins to a high dilution (1:1000). One of these 2 sera also had an obvious immobilization effect on the spermatozoa.⁶³ Thus it seems obvious that semen does contain antigenic properties.

Experimental Results: The files of the University of Nebraska College of Medicine and those of a private gynecologist were reviewed and of the patients who had been successfully treated for squamous cell carcinoma of the cervix in the last 5 years and who had been married more than 10 years to the same man, 10 were found who would cooperate in this experiment. Six of the patients were private and four were from the University. The ages varied from 28 to 53, the number of children from 0 to 10, and the stages of the disease from I to III according to the International League of Nations classification. None of the women

had allergic histories. As a control series, 5 University clinical and 5 private gynecological patients were used. These women were being seen for gynecological and medical diseases other than carcinoma of the cervix. They were free from cervical cancer as determined by a recent Papanicolaou smear, were between the ages of 25 and 51, and had been married to their respective husbands more than 10 years, although one of the University patients had been remarried 13 years previously. The number of children varied from 2 to 8 per patient.

Semen was collected from the husbands of these women in nonspermicidal seminal pouches. One specimen obtained from a case husband was mixed with 5% formalin in saline and the other 19 with 5% phenol in saline, the latter being a standard diluent for material used in skin testing. These materials were used for bacteriocidal purposes. The concentration used was one part semen to one part diluent. After mixing, the resulting suspension was allowed to stand for 48 hours at a temperature of 40° F. It was then inoculated in tryptocase soy broth and Brewers thioglycollate broth, incubated for 24 hours, and subcultured on tryptocase agar, chocolate agar and blood agar.

On two occasions, a Staphylococcus, nonhemolytic and coagulase negative, grew out. These were not considered harmful and the specimens were used regardless.

For the skin test, 0.1 c.c. of the semen suspension was injected intracutaneously in the forearm of the wife of the husband from whom the semen was obtained. As a control, 0.1 c.c. of the diluent was injected into the same area on the opposite forearm.

With two exceptions which will be discussed later, the reactions were the same in every case and every control. Within five minutes, the area around the injection site of the semen suspension developed a rather intense erythema which varied from 4 to 7 cm. in diameter and which was preceded by a mild burning sensation. The burning subsided within 15 minutes while the erythema persisted from 4 to 18 hours. In no case did the site of injection of the diluent develop burning or erythema.

The exceptions mentioned above were both in the cancer group. The first case was a 28 year old white female, para 2, gravida 2. She was a private patient and had been married to the same man for ten years with no previous marriages. She had been treated in 1959 for a Stage I squamous cell carcinoma

of the cervix with radioactive gold and radium implants followed by a radical hysterectomy and pelvic lymph node dissection. Papanicolaou smears since that time have been negative. After injection of the semen, a 4 cm.-in-diameter area of erythema developed immediately and within two hours the whole forearm was moderately swollen. By 24 hours, the erythema had become 7 cm. in diameter and this persisted for another 24 hours after which it slowly subsided, as did the swelling, until at 92 hours after the injection, no evidence of a reaction could be found. At no time did a wheal or an area of induration develop. The phenol injection in the other arm caused no reaction.

The second case was a 53 year old white female, para 1, gravida 1. She was a University patient and had been married to the same man for 13 years. Her only child was one born out of wedlock 19 years prior to the test. Her husband had been married twice previously, one of the former wives having died from carcinoma of the face and one from heart disease. The patient was treated for a Stage III squamous cell carcinoma of the cervix in 1955 with radium and deep x-ray therapy. Papanicolaou smears since that time have been negative. She was the one case in which

5% formalin had been used as a diluent rather than phenol. Neither the formalin-semen injection site nor the formalin injection site developed a reaction.

The assumption was made that the reactions obtained in both case and control groups were irritative rather than allergenic, as if some substance in the semen had resulted in the release of a histamine-like substance, had acted as a direct vasodilator or simply as a foreign protein. If this assumption is correct, it is interesting to note that the only case in which 5% formalin was used did not develop a reaction. Two explanations for this were considered. One, the formalin may have altered the chemical structure of the irritant, or two, the phenol used in the other cases may have combined with something in the semen to form an irritant which was not previously present. Therefore, five more controls were selected using the previously mentioned criteria and formalin rather than phenol was used to dilute the semen in these cases. Each of the five developed the same erythematous reaction with complete disappearance within 24 hours. These results seem to render the above explanations invalid. Furthermore, the present author injected 0.1 c.c. of his own semen, untreated, into his skin and

developed the same slight burning and a 4 cm.-in-diameter area of erythema, both of which disappeared completely within 5 hours. The substance causing this particular reaction was undoubtedly a primary constituent of the semen since nothing was added to the latter prior to the injection.

DISCUSSION AND CONCLUSIONS

It was originally intended to expand this series to a significant volume if this preliminary study revealed any variation in reaction between the cases and controls. However, the monotonous appearance of the same reaction in the majority of cases and all of the controls precludes the possibility of investigating hypersensitivity in cervical cancer by a means of skin testing. For example, if the reactions obtained were manifestations of an immediate type of allergic reaction as is found in atopic allergies, it would have to be assumed that the majority of women are hypersensitive to their husbands semen. This is unlikely, especially since the wheal which is characteristic of atopic allergenic reactions was absent in all of the reactions except one in which it was questionably present and since antibodies in a women's serum against her husbands semen would

alter either the spermatozoa or their vehicle, the seminal plasma if they were present in cervical secretions. However, assume that these reactions were possibly hypersensitivities. The point is that an irritative type of reaction, as mentioned earlier, cannot be ruled out and it is this fact that precludes further study by skin testing.

The reaction which lasted for 2 days before beginning to subside is interesting. First, it may have been a similar, but more intense, reaction than the others, the only variation being the length of persistence and the slight swelling of the forearm. Second, the persistence after 24 hours may have represented a delayed type of reaction as is seen with positive tuberculin tests. However, the characteristic induration which is present in delayed allergic reactions was absent in this one.⁶⁴

The case which did not react at all is also interesting, since formalin did not alter the reaction in 5 other women. It is unexplained at present.

If an irritant in semen was responsible for the reactions, it is conceivable that it may effect cervical epithelium in a similar manner and more intensely in those cases in which the semen has the

substance in higher concentration. Of course, this is speculation and one cannot assume that the reaction of cutaneous and cervical epithelium to such an irritant would be the same.

From this experiment, two conclusions are evident:

1. It is probable that the erythematous reactions obtained were the result of the introduction of an irritant which acted either as a foreign protein or as a direct vasodilator.
2. If hypersensitivity is a factor in cervical cancer, it will have to be studied in some manner other than skin testing. The most logical method would be the study of antigen-antibody reactions between the serum of patients with cervical cancer and their husbands' semen. The presence of a precipitin or an agglutinin titer in the patients' serum could be investigated by tube precipitation tests and by slide agglutination tests, respectively.

If the patients' serum were found to possess antibodies at titers significantly higher than the controls', the

matter could be further investigated by separation of the semen into seminal plasma and spermatozoa by centrifugation and testing each of the fractions against the patients' serum.

SUMMARY

1. Squamous cell carcinoma of the cervix is discussed in relation to the Jewish race, other racial groups, infection of the cervix, hormones, pregnancy, and socioeconomic factors. The significance of each of these factors is discussed. It has been pointed out that carcinoma of the cervix is more common in those groups having an earlier age of first coitus, an earlier age of first marriage, and a higher remarriage rate.

2. The possibility of a male factor in carcinoma of the cervix is considered. Hypersensitivity to semen is discussed as one such male factor.

3. The results of an experiment in which women were skin tested against their husbands' semen are presented. Ten cases and fifteen controls were used. All but two of the women developed the same reaction, a mild burning sensation and a 4 to 7 cm.-in-diameter area of erythema which disappeared within 24 hours.

One woman, a cancer case, developed a more severe reaction which persisted longer, while another, also a case, developed no reaction. Possible explanations are presented.

3. There were no reactions characteristic of either immediate or delayed hypersensitive skin reactions. It is thought that these reactions were due to the presence of a primary irritant in the semen and that they preclude the study of cervical carcinoma and hypersensitivity by the means of skin testing.

4. Possible methods of studying antibodies against semen in cancer patients' serum are presented.

ACKNOWLEDGEMENTS

I would like to thank Dr. Colin B. Schack,
Dr. Donald C. Nilsson, Dr. Harry W. McFadden, and
Pauline Socha for their suggestions, time and effort
given to me in preparation of this thesis.

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