

SYPHILIS AND MALIGNANT DISEASE.

A SEROLOGICAL STUDY.

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(With 3 Diagrams.)

THERE exists some doubt as to the precise importance to be attributed to syphilis in the etiology of malignant disease. Esmarch (1889) believed that malignant disease was referable to a predisposition inherited from syphilitic forbears, and syphilis has been regarded as of great importance in the production of cancer by some French writers, who have termed it "le lit du cancer." By others, however, the relationship has been considered much less definite. The evidence provided by previous writers is somewhat doubtful, as the examinations have been either partial and confined to certain regions of the body, or if general, the number of cases used has been small. Foerster (1911) examined 35 cases of cancer at the Cancer Hospital and found that 4 gave positive Wassermann reactions. Caan (1911) performed the Wassermann reaction in 85 cases of carcinoma with positive results in 41 per cent., a result which must be attributed to an early technical error from the use of a heterophile antigen, alcoholic extract of guinea-pig's heart, since so high a percentage has never been obtained by subsequent observers. Fox (1913), in 207 cases, obtained 5 positive Wassermans. MacCormac and Morson (1914) examined 137 cases with 10.2 per cent. positive Wassermans.

Having been engaged for some time in serological investigations of malignant disease, in which Wassermann reactions have been carried out in almost every instance, I thought it would be of interest to ascertain, in a series sufficiently large for statistical analysis, the relation of syphilis to malignant disease as determined by the Wassermann reaction. For this purpose I have taken 1000 unselected cases of malignant disease receiving treatment in the In-Patient and Out-Patient Departments of the Cancer Hospital, and compared the figures of the Wassermann reactions obtained with a control series of patients similarly attending the hospital, but found to be suffering from diseases other than malignant. I have excluded sera from normal persons or those not coming within the above categories.

METHODS.

With regard to the Wassermann reactions the results have the advantage that the tests were carried out by myself or my assistant, using the same method throughout, and what is more important the same alcoholic extract.

The Wassermann method employed may be described as Harrison's technique (Medical Research Council, Method I) (1918). 0.1 c.c. of serum is diluted 1 in 5 with 0.85 per cent. saline, and the serum, complement and antigen are put up in equal volumes of 0.5 c.c. The sheep red cells are sensitised with 10 M.H.D. of amboceptor, the final suspension being a 1.5 per cent. dilution of the red cells. Both the antigen and the haemolytic serum employed are those prepared at the Wellcome Physiological Research Laboratories, the former being an alcoholic extract of sheep's heart, with cholesterol. 2 M.H.D. have been used for the serum controls and 3 and 5 M.H.D. for the tests. Parallel tests put up in many cases with falling dilutions of serum and a fixed dose of complement have not shown any variations in the results and in general the fixed amount of serum with varying dose of complement has been used. The usual positive and negative serum controls, and antigen and complement controls have been put up simultaneously with the tests.

No serum has been regarded as giving a weak positive unless there was complete (+) or at least partial (±) inhibition of haemolysis in the tube containing 3 M.H.D. of complement. In the latter case, the sera were re-examined on a subsequent occasion or a fresh sample taken.

RESULTS.

The total figures obtained show that a smaller percentage of positive Wassermanns is obtained in cancer cases than in controls; and if buccal cancers be excluded, which form, as will be seen later, a special section, this difference in the figures becomes even greater (Table I), the percentage of positive Wassermann reactions in cancer cases being exactly half that obtained with controls.

Table I.

| | Sex | | Wassermann positive | | | | Total | | |
|--|-----|-----|---------------------|------|----|------|-------|--------|------|
| | M. | F. | M. | % | F. | % | Cases | W.R. + | % |
| Malignant disease | 470 | 530 | 64 | 13.6 | 33 | 6.2 | 1000 | 97 | 9.7 |
| Controls | 377 | 491 | 63 | 16.7 | 52 | 10.5 | 868 | 115 | 13.2 |
| Malignant disease excluding buccal cancers | 310 | 525 | 22 | 7 | 33 | 6.2 | 835 | 55 | 6.6 |
| Controls | 377 | 491 | 63 | 16.7 | 52 | 10.5 | 868 | 115 | 13.2 |

This unexpected result seems to suggest that syphilis does not have much influence upon the incidence of malignant disease as a whole. It may be noted that in the gross figures for cancer cases the percentage of positive Wassermann reactions in females is about half that in males, but that when the buccal cancers are excluded the percentage becomes more closely comparable.

DISTRIBUTION.

Alimentary system. If the cases are analysed with regard to the site of the cancers in the different systems, we find a very marked difference in the distribution in male and female cases in the upper part of the alimentary canal.

Cancers of the buccal cavity, including tongue, lip, etc., are almost entirely confined to men, and in these a fairly high percentage of positive Wassermanns is obtained. The relative disproportion of this form of cancer between the sexes is remarkable, the condition being almost a sex limited one (see Diagram I). Out of the 165 cancers in my series, only 5 were in women (3 per cent.), and in a series of 1093 cases compiled from the literature only 38 cases were found amongst females, 3.5 per cent., a figure which shows a close agreement with

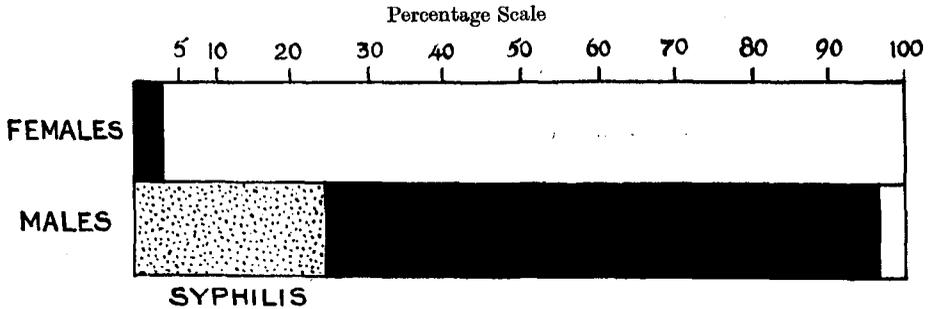


Diagram I. Bar diagram showing the relative proportion of cancer of the buccal region in males and females, the stippled portion showing the percentage of positive Wassermanns in males.

my own. In my own series of 80 cases of carcinoma of the tongue (Table II) we have 35 per cent. of positive Wassermanns, and taking both bucco-labio-pharyngeal cases together there are 165 cases with 25.4 per cent. of positive results. In a recent series of bucco-pharyngo-laryngeal cancers, Roussy and Bertillon (1927) obtained 35 per cent. of positive Wassermanns. Simmons

Table II. *Digestive system.*

| Organ | Sex | | Wassermann positive | | | | Total | | |
|----------------------------|-----|----|---------------------|------|----|------|-------|--------|------|
| | M. | F. | M. | % | F. | % | Cases | W.R. + | % |
| Tongue | 76 | 4 | 28 | 36.8 | — | — | 80 | 28 | 35.0 |
| Buccal: | | | | | | | | | |
| Tonsil | 16 | — | 2 | 12.5 | — | — | 16 | 2 | 12.5 |
| Pharynx and floor of mouth | 43 | — | 7 | 16.3 | — | — | 43 | 7 | 16.3 |
| Palate | 9 | — | — | — | — | — | 9 | — | — |
| Jaw | 17 | 7 | 4 | 23.5 | 1 | 14.3 | 24 | 5 | 20.8 |
| Oesophagus | 26 | 4 | 2 | 7.7 | — | — | 30 | 2 | 6.6 |
| Stomach | 37 | 22 | 5 | 13.5 | 2 | 9 | 59 | 7 | 11.8 |
| Intestine | 11 | 14 | 1 | 9.0 | 1 | 7.1 | 25 | 2 | 8.0 |
| Rectum | 96 | 62 | 5 | 5.2 | 2 | 3.2 | 158 | 7 | 4.4 |
| Pancreas | 2 | 3 | — | — | — | — | 5 | — | — |
| Liver and gall bladder | — | 2 | — | — | — | — | 2 | — | — |

(1926) found only 30 positive (16 per cent.) in 184 cases of cancer of the mouth. MacCormac and Morson (1914) had 15.2 per cent. of positive Wassermanns out of 46 cases. Cary (1920) gives figures for cancer of the tongue, lips and buccal mucosa from the records of the laboratory of the Johns Hopkins

Hospital. From a total of 771 cases he found positive Wassermanns or a history of syphilis in only 48 (6.2 per cent.). It must be stated however that these figures include cases from a period before the Wassermann reaction was introduced. He also notes the sex limitation, since only 3 cases of this form of cancer occurred in white females, in none of whom was there evidence of syphilis, and no case occurred in black females and only 2 in black males, in spite of the alleged prevalence of syphilis in the negro.

This disproportion between the sexes does not seem to hold good for non-cancerous affections of the tongue, since in 20 cases of chronic superficial

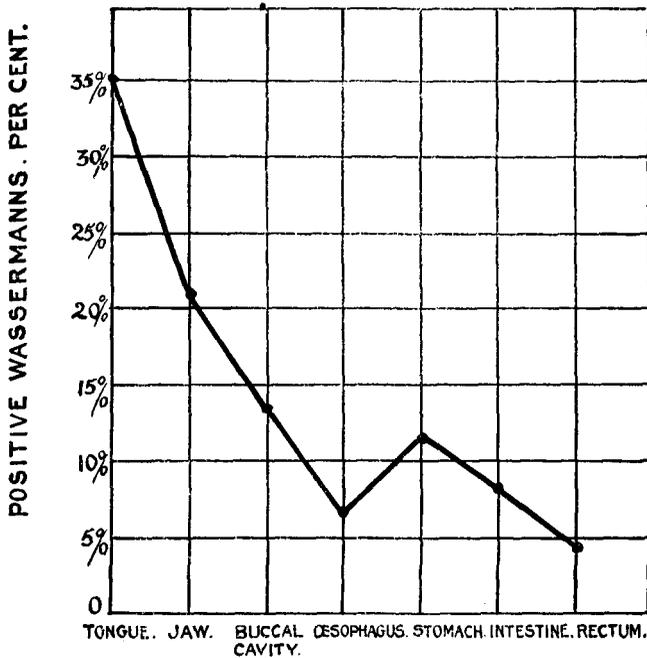


Diagram II. Graph showing percentage incidence of positive Wassermanns in cancer of the digestive tract.

glossitis, fissured tongue and allied conditions I found 7 in women, and of the 8 cases of these conditions which gave positive Wassermanns 4 were women. It is evident therefore that women contract syphilitic affections of the tongue and buccal cavity, but that, for some reason, cancer does not subsequently develop often at this site. This suggests that there is some factor other than syphilis which is chiefly responsible for the incidence of cancer of the tongue in men, possibly smoking, to which Fournier attributed great importance¹. In this series of 80 cases of cancer of the tongue, the average age of those giving positive Wassermann reactions was 58.6 years as against 60.8 years

¹ It will be interesting to note in the future whether women, on account of increased cigarette smoking, will show a larger proportion of tongue cancer.

for those with a negative Wassermann reaction, so that a difference in age cannot be regarded as a factor in this problem.

It may be noted that in a site so closely related as the jaw there is not so great a difference in the incidence of cancer in men and women nor in the percentage of positive Wassermans obtained, though in both cases it is relatively higher in men than women, and the actual percentage is fairly high.

With the exception of the stomach there is a steady fall in the incidence of positive Wassermans in cancers of the digestive tract from its upper to its lower orifice (see Diagram II). In cancer of the rectum a very small percentage of positive Wassermans is obtained. Although this is also an area which may be exposed to a considerable degree of chronic irritation, the syphilitic factor in cancer of this region stands in marked contrast to that in the mouth.

Attention is drawn to the fairly high percentage of positive Wassermans in cancer of the stomach (11·8 per cent.). Warthin (1928) has recently alluded to syphilitic infection and its relation to various diseases of the stomach, and it seems possible that carcinoma in some cases may be grafted upon a syphilitic ulcer or some other syphilitic condition of the stomach. On the other hand in 149 cases of non-malignant disease of the stomach diagnosed clinically as gastric ulcer and allied conditions I have obtained a positive Wassermann in only 8·7 per cent., 84 males with 7 positive Wassermann reactions, and 65 females with 6 positive Wassermans. In this connection it may be observed that in Switzerland, where syphilis has diminished very greatly, especially in recent years, cancer, particularly cancer of the stomach and digestive tract, shows no sign of diminution and its incidence still remains very high.

Genital system. With regard to the genital system (Table III), in which, if syphilis was a factor in malignant disease, the number of positive Wasser-

Table III. *Genital system.*

| Organ | Total | | Female Wassermann positive | | Total % |
|----------|-------|-----|----------------------------|----|---------|
| | M. | F. | M. | F. | |
| Uterus: | | | | | |
| Cervix | — | 157 | — | 21 | 13·3 |
| Body | — | 4 | — | 1 | 25·0 |
| Ovaries | — | 15 | — | — | — |
| Vagina | — | 5 | — | — | — |
| | | | Male | | |
| Penis | 3 | — | 1 | — | 33·3 |
| Testicle | 4 | — | 1 | — | 25·0 |
| Prostate | 11 | — | — | — | — |

mans might be expected *a priori* to be high, in cancer of the cervix the percentage (13·3 per cent.) of positive Wassermans is not very large. In Martzloff's (1923) series of 116 cases in which Wassermann reactions were done 8 (6·8 per cent.) were positive. In the case of carcinoma of the body of the uterus and of the male genital system the numbers at my disposal are too small to be of any statistical value.

Urinary system. Cancers of the urinary tract (Table IV), although in close anatomical relation to the genital tract, gave no positive Wassermanns.

Cutaneous system. In the cutaneous system (Table V) cancers of the lip, which might be considered as part of the buccal system, show a high percentage of positive Wassermanns, 29·4 per cent., and here again the disease

Table IV. *Urinary system.*

| Organ | Sex | | Total | Wassermann positive | | Total % |
|---------|-----|----|-------|---------------------|----|---------|
| | M. | F. | | M. | F. | |
| Bladder | 15 | 6 | 21 | — | — | — |
| Urethra | — | 3 | 3 | — | — | — |
| Kidney | — | 1 | 1 | — | — | — |
| Adrenal | 1 | 1 | 2 | — | — | — |

Table V. *Cutaneous system.*

| Organ | Sex | | Wassermann positive | | | | Total | |
|------------------|-----|----|---------------------|------|----|---|-------|----------|
| | M. | F. | M. | % | F. | % | Cases | W.R. + % |
| Lip | 16 | 1 | 5 | 31·2 | — | — | 17 | 5 29·4 |
| Vulva | — | 14 | — | — | 1 | — | 14 | 1 7·1 |
| Scrotum | 1 | — | 1 | — | — | — | 1 | 1 100·0 |
| Face and neck | 17 | 13 | 1 | 5·9 | — | — | 30 | 1 3·3 |
| Anus | 4 | 2 | — | — | — | — | 6 | — — |
| Hand and fingers | 4 | — | — | — | — | — | 4 | — — |
| Leg | — | 1 | — | — | — | — | 1 | — — |

is confined to males. Simmons and Daland (1922) in a series of 172 cases of cancer of the lip, of which only 2 were females, record the Wassermann reaction in 56, with 12 positive results (21·4 per cent.). On the other hand Brofeldt (1927), who examined 26 cases of carcinoma of the lips and 25 cases of leukoplakia, of which 16 were women, an unusually high proportion, found that none of these had a positive Wassermann reaction or other evidence of syphilis. The vulva, although the commonest site of a primary sore in women, shows in contrast to the mouth a comparatively low incidence of positive Wassermanns in cancers of this region, being only a little more than half the percentage found in the case of carcinoma of the cervix. The rest of the cutaneous system also shows a low percentage.

Respiratory and Glandular systems. Cancers of the respiratory system exhibit a small syphilitic incidence. In a fairly large series of 170 cases of carcinoma of the breast (Table VI) only 2·3 per cent. of positive Wassermanns was obtained.

Table VI. *Respiratory and Glandular systems.*

| Organ | Sex | | Wassermann positive | | | | Total | |
|--------------|-----|-----|---------------------|---|----|-----|-------|----------|
| | M. | F. | M. | % | F. | % | Cases | W.R. + % |
| Larynx | 17 | — | 1 | — | — | — | 17 | 1 6·2 |
| Lung | 2 | 2 | — | — | — | — | 4 | — — |
| Breast | 2 | 168 | — | — | 4 | 2·4 | 170 | 4 2·3 |
| Thyroid | 3 | 3 | — | — | — | — | 6 | — — |
| Parotid | 4 | — | — | — | — | — | 4 | — — |
| Submaxillary | 1 | — | — | — | — | — | 1 | — — |

Sarcomata. In 48 sarcomata, 32 in males and 16 in females, no positive Wassermann reaction was obtained.

AGE DISTRIBUTION IN CANCER AND CONTROL CASES.

I have worked out the average age in unselected samples of the cancer and control cases in this series, and I find that the average age of the cancer patients is 53 as against 48 for the controls. In order to examine more closely the question of age distribution between cancer and control cases in relation to the presence of a positive Wassermann reaction the controls were set out in decades, commencing 11-20 years up to 71-80 years, and the percentage of positive Wassermann reactions in each age group was determined. This is shown in the accompanying Table VII.

Table VII. *Control cases in age groups.*

| Age group | Male | Female | Total | W.R. + | % |
|-----------|------|--------|-------|--------|------|
| 11-20 | 8 | 6 | 14 | 1 | 7.1 |
| 21-30 | 21 | 43 | 64 | 4 | 6.2 |
| 31-40 | 66 | 84 | 150 | 17 | 11.3 |
| 41-50 | 80 | 158 | 238 | 31 | 13.0 |
| 51-60 | 106 | 111 | 217 | 38 | 17.5 |
| 61-70 | 62 | 58 | 120 | 17 | 14.1 |
| 71-80 | 16 | 14 | 30 | 4 | 13.3 |

The following four large series of cancer cases, tongue, buccal cavity including lip, cancer of alimentary tract and genital cancer, were then grouped in a similar manner. These groups were chosen because they were representative of common malignant conditions and comprised a sufficiently large number of cases. The control rate of positive Wassermann reactions in each age group was then compared with the rate observed in the same age group of each of these types of malignant disease. This is set out in Table VIII, from which it will be observed that in the case of cancer of the

Table VIII.

| Age group | Total cases of cancer of | | | | | | | | Control cases | |
|-----------|--------------------------|--------------|---------------|--------------|-----------------|--------------|----------------|--------------|---------------|--------------|
| | Tongue | | Buccal cavity | | Digestive tract | | Genital system | | W.R. + | No. of cases |
| | W.R. + | No. of cases | W.R. + | No. of cases | W.R. + | No. of cases | W.R. + | No. of cases | | |
| 11-20 | — | — | — | 7 | — | 1 | — | — | 7.1 | 14 |
| 21-30 | — | 1 | — | — | — | 9 | — | 1 | 6.2 | 64 |
| 31-40 | — | — | 50 | 4 | 4.5 | 22 | 8.3 | 24 | 11.3 | 150 |
| 41-50 | 41.6 | 12 | 15.8 | 19 | 6 | 67 | 12.2 | 57 | 13.0 | 238 |
| 51-60 | 37.5 | 24 | 22 | 41 | 10.3 | 97 | 13.8 | 58 | 17.5 | 217 |
| 61-70 | 35.5 | 31 | 13 | 31 | 7.4 | 67 | 9.0 | 33 | 14.1 | 120 |
| 71-80 | 25.0 | 12 | 12.5 | 16 | — | 14 | — | 4 | 13.3 | 30 |

tongue and buccal cavity the percentage incidence of positive Wassermanns is generally higher than in the controls in almost all the age groups. On the other hand in cancer of the digestive and genital systems, it is uniformly lower than in the controls in all the age groups. It is evident therefore that a difference in age between the cases of cancer and the controls does not account for the difference in the total incidence of positive Wassermann reactions in the malignant conditions and the controls.

ANALYSIS OF CONTROLS.

An objection that might be raised is that the control group does not fairly represent a general non-malignant population. This is to some extent true, since all the control cases were patients who attended the hospital for "tumours or allied diseases." This formula however covers such various conditions among the controls, as for example enlarged cervical glands and pregnancy, that the control group may be regarded as representing a non-cancerous

Table IX.

| Condition | No. of cases | W.R. + | % |
|------------------------|--------------|--------|------|
| Cutaneous | 94 | 29 | 30 |
| Buccal (including lip) | 35 | 11 | 31.4 |
| Lingual | 39 | 14 | 36 |
| Oesophageal | 15 | 5 | 33 |
| Gastric and duodenal | 178 | 11 | 6 |
| Intestinal | 28 | — | — |
| Rectal | 32 | 5 | 15.6 |
| Liver and gall bladder | 30 | 3 | 10 |
| Abdominal | 17 | 4 | 23.5 |
| Blood diseases | 17 | — | — |
| Cardio-vascular | 12 | 4 | 33 |
| Ductless glands | 12 | 1 | 8 |
| Breast | 44 | — | — |
| Genital | 69 | 5 | 7 |
| Larynx and trachea | 4 | 1 | 25 |
| Respiratory | 15 | 1 | 6 |
| Urinary | 130 | 5 | 3.8 |
| Central nervous system | 34 | 12 | 32 |
| Skeletal | 28 | 3 | 10.7 |

hospital population. It is possibly true that in the case of cancer of the tongue and buccal cavity, in which syphilis has been regarded as an important factor, patients with a history of syphilis and suspicious conditions of the tongue would have a greater chance of being sent to hospital, so that cancers of the tongue in hospital patients may present a higher percentage of positive Wassermanns than cancers of the tongue among the general population. The great diversity of conditions and their more indefinite nature have made an exact analysis of the control cases rather difficult. They have been grouped on a clinical basis for comparison with the cancer cases (Table IX). It should be explained that various conditions are included under the same headings. Thus, under tongue are grouped such conditions, for example, as leukoplakia, innocent papilloma, and among the cutaneous diseases are included syphilis, warts, ulcers, chronic inflammations, granulomas, etc.

DISCUSSION.

It may be objected that the Wassermann reaction is not a satisfactory indication of syphilis in these cases. This however would apply equally to the non-malignant cases and to the malignant cases, so that the relative proportions of the figures remain unaffected. I have made no inquiry as to the history in these cases, since its unreliability in most instances makes it almost worthless. Nor have I taken into account anti-syphilitic treatment, the

efficiency of which is so variable. Against the possible criticism that the average age in the cancer cases might be much higher than that in the control cases, allowing either greater opportunities for treatment or for gradual diminution in the strength of the Wassermann reaction, the average age of the cancer patients has been found to be 53 as against 48 for the controls, so that the difference in age is not very great. If the difference in the percentage figures for positive Wassermans between the malignant cases and the con-

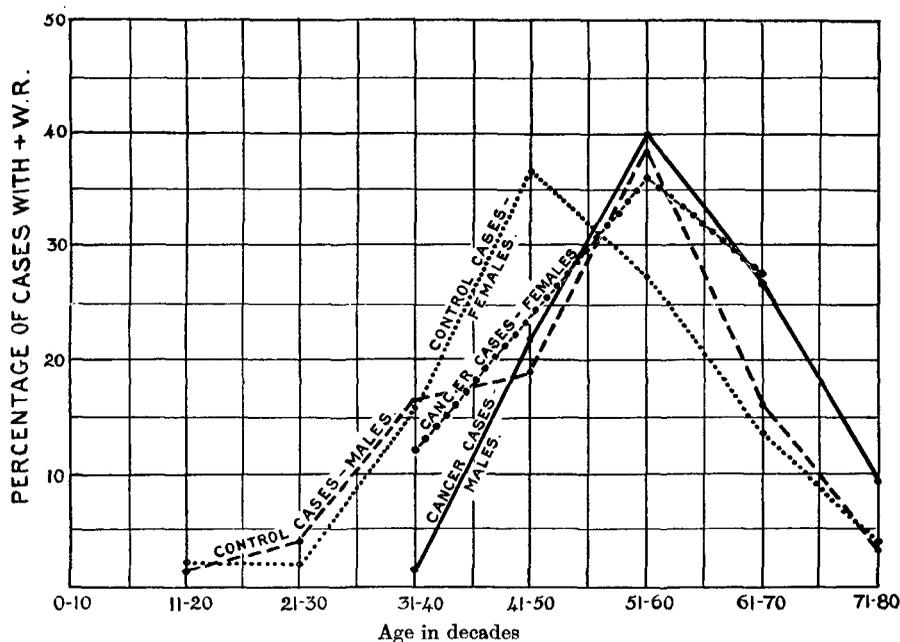


Diagram III.

trols were due to treatment, half the malignant cases would have had to have received efficient treatment between the ages of 48 and 53 to make the figures comparable. Obviously this could hardly be the case¹. The average age of cancer patients with positive Wassermann reactions is 57.5 years in males and 52.8 years in females. In non-malignant cases the corresponding ages of patients with positive Wassermann reactions are 50.5 for males and 50 for females. If the cases showing positive Wassermans, both in the malignant and control series, are grouped in decades of age, then it is found that in the malignant cases, both male and female, and in the control group for males, the highest percentage of positive Wassermans occurs in the period 51-60 years. In the female control group the highest percentage occurs in the previous decade 41-50 years. This seems to indicate that there can be no definite correlation between the incidence of syphilis and malignant disease,

¹ It is evident also from the age distribution that a difference in age does not account for the difference in the incidence of positive Wassermans between the cancer and control groups.

since in the non-malignant cases the age incidence of syphilis is fairly closely comparable to that of malignant cases, apart from the period prior to the cancer age (see Diagram III).

SUMMARY.

1. There is a lower percentage of positive Wassermans in cases of malignant disease than in a similar population of non-malignant cases. If buccal cancers are excluded, the percentage is half that in non-malignant cases.

2. Cancer of the tongue and buccal cavity, in which a high percentage of positive Wassermans is found, is almost confined to males and is probably due less to syphilitic infection than to some factor such as smoking.

3. There is a low percentage of syphilis in cancer of the digestive tract, except in cases of cancer of the stomach, and the incidence diminishes from mouth to anus.

4. Syphilis does not appear to be a factor of importance in cancer of the glandular organs, nor, apart from the lip, in the production of cutaneous cancer.

5. In general, from the above figures there is no evidence that syphilis plays any direct or very important part in the production of cancer.

REFERENCES.

- BRUFELDT (1927). *Arbeit. a. d. Pathol. Inst. d. Univ. Helsingfors*, 5, 34, quoted 1928, *Cancer Review*, 3, 270, Abstract 459.
- CAAN (1911). *München. med. Wochenschr.* 58, 731.
- CARY, N. A. (1920). *J. Amer. Med. Assoc.* 75, 858.
- ESMARCH, A. von (1889). *Arch. f. klin. Chir.* 39, 327.
- FOERSTER, A. (1911). *Lancet*, i, 1695.
- FOX, F. J. (1913). *Med. Record*, 84, 283.
- MACCORMAC, H. and MORSON, A. C. (1914). *Arch. Middlesex Hosp.* 33, 126.
- MARTZLOFF, K. H. (1923). *Bull. Johns Hopkins Hosp.* 34, 141.
- Medical Research Committee (1918). *Special Report*, No. 14. The Wassermann Test.
- ROUSSY, G. and BERTILLON, M. (1927). *Bull. Assoc. franç. pour l'étude du Cancer*, 16, 885.
- SIMMONS (1926). *Surg. Gynecol. and Obstetrics*, 43, 377.
- SIMMONS and DALAND (1922). *Ibid.* 35, 766.
- WARTHIN, A. S. (1928). *J. Cancer Res.* 12, 266.

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