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FREDERICK J. FOX, M.D.,
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(From the Research Laboratories, New York Skin and Cancer Hospital.)

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During the past few years numerous articles have appeared in the medical literature announcing positive Wassermann reactions in affections other than syphilis. Certain investigators have reported high percentages of positive findings in leprosy, in scarlet fever, in trypanosomiasis, and in scleroderma, while occasionally the reaction has been obtained in such diseases as diabetes mellitus, malaria, idiopathic epilepsy, leucemia, puerpural eclampsia, lupus erythematosis, pellagra, and others. These findings have led investigators to test the reaction in a large number of diseases, and it was therefore quite natural that the blood of patients suffering from malignant disease should be put to the test. It is sometimes difficult, sometimes impossible, to differentiate clinically between certain forms of malignancy and specific disease, and observations which seem to diminish the value of the Wassermann reaction as a means of differential diagnosis should be carefully examined. As a matter of fact, investigators along this line have reported widely different findings, and the purpose of this paper is to briefly review the literature on the subject, and to give our results at the New York Skin and Cancer Hospital.

The highest percentage of positive reactions has been given by A. Caan, who reports that he applied

the test in 85 cases of carcinoma with positive reactions in 41 per cent. The test was positive in 6 out of 7 cases of carcinoma of the lip, in 67 per cent. of epitheliomas of the lip and chancroids, in 9 per cent. of carcinoma of the breast, and in 17 per cent. of his gastrointestinal cases. Caan says that he applied the test in all its various modifications in each case, and obtained parallel findings. Leo Newmark reports two unusually interesting cases of tumors, both of which gave positive reactions. His first case was that of a woman suffering from word-deafness and paraphasia. On the strength of a positive Wassermann reaction, treatment with potassium iodide and mercury was commenced and for several weeks her progress was considered satisfactory. Then the original trouble returned, and about the same time a tumor in the left breast was discovered. One month later the patient died. A complete autopsy was not allowed but the tumor in the breast was found to be a carcinoma, and that in the brain a gliosarcoma. Furthermore, there was no trace of syphilis in the brain although the cerebrospinal fluid from the cranial cavity was examined and was found to give a strong positive Wassermann reaction. His second case proved to be an intradural psammoma, although both the blood serum and the spinal fluid had given positive reactions shortly before the operation. The reaction in the cerebrospinal fluid obtained during the operation was negative, and 18 days later the reaction in the blood serum was also negative. Positive reactions have also been obtained by Oppenheim and Marburg, each of whom reported a case of fibroma of the pons cerebelli in patients whose blood serum showed inhibition of hemolysis when subjected to the Wassermann test.

While these findings are interesting and sugges-

tive they are not conclusive, for we find other investigators reporting results directly opposed to those given above. In an article in the *Lancet,* Foerster publishes his results on a series of cases which he had tested to find out how often syphilis could be traced in patients suffering from cancer. His tables show further, however, that cases of cancer giving no evidence of clinical history of syphilis almost invariably give a negative Wassermann reaction. In 36 cases, only one gave a positive test. In this case, as he points out, there is reasonable room for doubt, in the fact that both the patient and his wife were in ill-health, and the wife gave a history of miscarriages. Nonne, who has published the results of a very large series of Wassermann reactions on brain and spinal cord conditions, comes to the conclusion that all cases of non-syphilitic conditions of the nervous system with positive Wassermann reactions in the blood have to do with patients, who, at some earlier date, have been infected with specific disease and that even a negative section of the tissues is no proof that the reaction in the blood was incorrect, for an individual infected with syphilis can, at the same time, have non-syphilitic condition in any other organ. Further negative results have been reported by Noguchi, who found 38 negative reactions in 39 cancer cases from the wards—his one cancer case having also had a history of chancre some years previously—and 50 negative results in 51 cases in which syphilis could be excluded with a fair degree of certainty, and working with the Noguchi modification, Orleman-Robinson reports 30 negative reactions in 30 cases of epithelioma. Lastly, Boas, of the State Serum Institute at Copenhagen, has published the results of 1,064 investigations with non-syphilitic sera. These included cases of tuberculosis, lobar pneumonia, malaria, leprosy, carci-

TABLE I.

| *Epithelioma of:* | | | *Sarcoma of:* | | | *Carcinoma of:* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Lip | 16 | Cases | Face | 3 | Cases | Breast | 59 | Cases | Glioma of brain | 1 | Cases |
| Cheek | 7 | " | Breast | 1 | " | Uterus | 12 | " | Malignant papilloma of tongue | 1 | " |
| Chin | 1 | " | Scalp | 1 | " | Abdominal viscera | 12 | " | Papilloma of chest | 1 | " |
| Scalp | 2 | " | Neck | 2 | " | Stomach | 1 | " | | 3 | " |
| Ear | 5 | " | Back | 1 | " | Glands of neck | 31 | " | | | |
| Nose | 6 | " | Thigh | 3 | " | Tongue | 21 | " | | | |
| Back | 1 | " | Testes | 2 | " | Rectum | 5 | " | | | |
| Penis | 2 | " | Mastoid and brain | 1 | " | | 141 | " | | | |
| Eye | 5 | " | Eye | 1 | " | | | | | | |
| Head | 1 | " | Sarcomatosis | 2 | " | | | | | | |
| Vagina | 3 | " | | 17 | " | | | | | | |
| | 49 | " | | | | | | | | | |

noma, and other diseases in which the occurrence of the Wassermann reaction has been alleged from time to time. In the entire series, only one result was positive and that was a case of scarlet fever.

In our series, the following technique has been used: Patients' serum, inactivated at 56° C. for half an hour, has been used in doses of 0.1 and 0.2 c.c. Guinea-pig's serum and anti-sheep amboceptor have been used in quantities found necessary by preliminary titration. In 190 of the tests 1 c.c. of a 1:10 dilution of complement was titrated against varying amounts of amboceptor, and 2 units of the latter used in the test. In 25 cases the amount of amboceptor was kept constant at 1 c.c. and the amount of complement varied from 0.4 to 1.2 c.c. of a 1:10 dilution, according to titration. Three antigens have been used: an alcoholic extract of a syphilitic fetal liver, the acetone-insoluble fraction of guinea-pig's heart, and the acetone-insoluble fraction of normal liver. From 0.1 to 0.3 c.c. of a 1:10 dilution in salt solution was required in the test.

The required amounts of serum, complement and antigen were put into respective test tubes and the amount brought up to 3 c.c. by the addition of salt solution. The contents of the tubes were then mixed, and incubated for one hour at 37° C. Then the necessary quantity of amboceptor and 1 c.c. of a 5 per cent. suspension of sheep's corpuscles were added and the tubes again incubated for one hour. The following controls were used with each series tested: (1) Antigen control (antigen, complement, amboceptor and sheep's corpuscles). (2) Serum control (patient's serum, complement, amboceptor and sheep's cells). (3) Hemolytic system (complement, amboceptor and sheep's cells). (4) Known specific serum, with and without antigen. (5) Known negative serum. The series was further

controlled, in a measure, by 1,300 reactions which were done in the same series as those on cancer cases.

Table No. I shows that 210 cases of various kinds of tumors gave negative results.

The diagnosis in practically all these cases was confirmed by section or autopsy.

In Table No. II are placed five cases which gave positive reactions.

TABLE No. II.

1. Carcinoma of jaw and neck.
2. Carcinoma of jaw and neck.
3. Carcinoma of rectum.
4. Sarcoma of heel.
5. Carcinoma of tongue and jaw.

In this series cases 1, 2 and 3 can be discarded, as they gave a history of earlier luetic infection. Case No. 4 was that of an unmarried girl, 21 years of age and a domestic. At 12 years of age a "corn" appeared on her right heel. She cut it off several times but it always returned. At 18 years of age she took *x*-ray treatments but this seemed to make the condition worse. During the next two years she underwent two operations, and a section following one of the operations was diagnosed keloid. Two months before coming to the Skin and Cancer Hospital a second tumor appeared on the inner side of the right leg and shortly afterwards a third appeared in the right groin. On admission to the hospital, the Wassermann reaction was positive in the blood serum. One month later it was still found to be positive, and an intravenous injection of salvarsan was given, with apparently no result. A section was then removed from the original tumor and a diagnosis of sarcoma was made. A third Wassermann was done six weeks after the administration of salvarsan and was negative. Case No. 5 was that of a man 58 years of age, a sailor. In July, 1910, a part of his tongue was removed on account of a growth, and a pathological

diagnosis of epithelioma made. Thirteen months later he returned with enlarged cervical glands which, on examination, were found to be malignant. The Wassermann reaction, ten weeks after his operation, was weakly positive. The patient at this time was anemic, was running a subnormal temperature and was very weak. He had given a history of gonorrhea, but denied the knowledge of luetic infection. An autopsy could not be performed, and there was no means therefore of proving or disproving the reaction given by the blood.

It is quite possible that more than one element has been responsible for the variation in the findings of different investigators. Apart from the various methods of performing the test, and the possibility of an error in technique, it has seemed to the writer that the different kinds of antigen used may have been responsible for many of the results. In view of the more recent work reported by Dungern and others on complement fixation in cancer, using as antigen preparations of cancer material, this seems more than probable. There are, moreover, other factors which may be responsible. The majority of antigens used to-day are not prepared from syphilitic organs, but from normal tissues, human or animal. The reaction is therefore not a specific one. These same preparations may contain bacterial as well as syphilitic antigens, and, in the presence of the corresponding antibody in the serum, may cause inhibition of hemolysis.

It seems fair to conclude, from the above series, that cancer rarely, if ever, gives a positive Wassermann reaction under the technique outlined above, and that, in the presence of a positive finding, a coexisting luetic infection should be suspected.

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146 East Nineteenth Street.