HISTOLOGIC EXAMINATION OF OTHER TISSUES

Just prior to our departure from Lima, and after our investigations there had been completed, we obtained from the Hygienic Laboratory and from the Dos de Mayo Hospital blocks of tissue from necropsies not performed by ourselves. In these cases a diagnosis of Oroya fever or of verruga peruviana had been made during life. We were unable to obtain complete histories of these cases. In some it was stated there had been verrugas on the skin during life, or in the viscera at necropsy. However, our experience in Peru has led us to believe that lesions may be sometimes referred to as having been due to verruga peruviana, which more careful investigation showed to be of an entirely different nature. These tissues were sectioned and studied, and the results of this study are interesting.

From the description which we have already given of the pathology of Oroya fever, it is evident that the histology of this disease is pathognomonic. In the study of the tissues just referred to, the finding of the characteristic lesions, and particularly the presence of the swollen endothelial cells containing the parasites, in at least one of the cases, enabled a definite diagnosis of Oroya fever to be made. As has been stated, the diagnosis of some of these cases given to us was verruga peruviana with Oroya or Carrion's fever.

It is evident that cases of verruga peruviana have been mistaken for cases of tuberculosis, and the tissues from two of the cases referred to above evidently came from patients suffering with tuberculosis, since tubercles and tubercle bacilli were found in the sections. It seems evident that the tubercles present in the liver in these cases were considered as verrugas of the miliary type. That other such mistakes have been made we are confident from the fact that miliary tubercles in the spleen and liver due to *Bacillus tuberculosis* have been shown us by physicians as internal verrugas. It is clear, therefore, that in Peru, miliary tuberculosis has sometimes been diagnosed incorrectly not only as verruga peruviana, but also as Oroya fever. Obviously also, miliary tuberculosis may occur as a complication of either disease.

ETIOLOGY OF CANCER IN THE LIGHT OF RECENT CANCER RESEARCH*

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I had in mind calling attention to certain recent developments in cancer research. As it would be impossible, however, in the limits of this paper, to outline the advances made in so extensive a field, I shall attempt to appraise the value of certain new discoveries, without attempting sweeping generalizations, in the belief that this will prove more profitable than a more general survey of the subject.

Perhaps the more important problems in cancer research center in the so-called parasitic theory. In the past there has been intense and at some times almost bitter controversy over the tenability of this theory. To-day, however, through the discoveries of filterable viruses causing different types of sarcoma in chickens, we may assume that the parasitic hypothesis is at last justified. When it has been determined that one genuine neoplasm is caused by a viable agent or organism, those who have contended for the parasitic theory as a working hypothesis will feel that the period of controversy on the merits of the hypothesis has passed. The question which will mostly concern us in the future is whether only a few neoplasms are caused by living organisms or whether living organisms are responsible for a large part of that group of tissue growths which we call malignant.

There are striking indications that the views of investigators of cancer in general are gradually coinciding. The views of those who have been opposed to a parasitic theory have been modified by the results of research to such a degree that there has been a steady drawing together of opinion as to the cause or causes of neoplasms. Thus we find Versé, in Marchand's Institute in Leipzig, reviewing the more recent discoveries of cancer research in an inaugural address in which he concludes that the agent which endows a normal cell with malignant characteristics is, in many cases, a biochemical agent acting from without the cell. We also hear of activators, and we find that some workers still contend that the filterable agents of Rous are not viruses, but hypothetic bodies of the nature of ferments or other biochemical products. We do not need to concern ourselves with the question whether or not there exists life in unorganized form, and whether there may exist agents so closely allied to ferments as to be able to fulfil the requirements of filterable viruses. The significant thing is that the agent which Rous has separated from the cells fulfils the requirements of, and belongs in, the group of filterable viruses. Most of these are the cause of well-known infectious diseases.

It is now generally recognized that there are well-defined agencies which work at least locally in a predisposing manner. These bring about what may be properly termed precancerous conditions of the tissue. They are mechanical, physical (thermic and actinic), chemical, infectious-inflammatory and other agents. They are of such varied nature that we find generalizations being made that the cause of cancer is really the multiplex complications and activities of modern life. So far as they may be determined locally, they are well summed up as chronic irritation, but it has been shown in exceptional cases that the predisposing changes in the tissue are not of a chronic nature, that even a single trauma may suffice; but such cases are exceptionally rare. The time between the establishment of the so-called precancerous condition and the advent of cancer may frequently be very long, many years, but by careful study of individual cases, the local predisposing features may be definitely determined in a high percentage of cases. Thus von Brun, who confined his study to the superficial skin cancers which are most easily studied, was able in 368 cases to determine a predisposing irritant in all but forty-eight. The relation of remote trauma and chronic irritation to malignant tumors is so well known to clinicians that it is not necessary to dilate on this phase of the question. The evidence of chronic irritation as a predisposing feature in the advent of cancer has been recently revived by the demonstration of nematodes, mites and acarines in the well-known cancer of the breast in mice, and the interesting cases of both carcinoma and sarcoma in rats starting from the walls of echinococcus cysts and cysticerci. Febiger has determined the cause of the irritation to be a minute nematode in cancer of the

* Read before the Chicago Medical Society, Nov. 11, 1914.

esophagus and stomach in rats. The significance of worms and their embryos in bilharzia disease has long been known. In such cases these larger parasites set up chronic irritation, which, however, is not always followed by cancer. This indicates clearly that they are not an efficient cause of the disease, but act as some would believe through toxic biochemical products, which they elaborate, or as carriers of a specific virus.

Besides the local predisposing or precancerous conditions, it is now known that there are predisposing factors of a more constitutional nature. Thus, since 1904, through experimental work with mice and other animals, it has been known that there is a definite constitutional susceptibility to the disease. This is both of the so-called natural and the acquired type.

As a result of the important studies in heredity of Dr. Maud Slye, many believe that there is at least a transmissible predisposition to the development of cancer in mice. This knowledge is certainly of the greatest importance to clinicians, and many of the vagaries of the development and course of cancer in human beings can now be more or less satisfactorily explained. The principal advance is found in the knowledge that factors which determine the advent of cancer in the human being have to do not alone with the direct action of a biochemical agent or living organism on the cell, but also with equally important, and probably equally varied, causes which diminish the resistance of the individual to the disease.

It has been well said by several writers that the time has come when we should study cancers and not cancer. It has been shown that the local predisposing factors included under the head of chronic irritation are of the most varied sort. With the positive knowledge which we have acquired of certain neoplasms in animals in which the existence of a neoplastic virus has been definitely established, it is no longer possible to believe that there is such a thing as a single cancer parasite. We are face to face with the probability that if the various types of cancer are to any great degree caused by such viruses, there are many of them and probably each has marked specificity for one type of tissue. The discovery by Peyton Rous of a filterable agent which causes a spindle-cell sarcoma in chickens, and his more recent demonstration of two other types of sarcoma, one a clefted sarcoma with sinuses, and the other an osteochondrosarcoma, each caused by a specific virus capable only of producing that type of tumor and no other, show for these three viruses a degree of specificity which no one had ever anticipated. Rous' work is of epoch-making character in that he has demonstrated the existence of what was previously a hypothetic cancer virus.

Besides the tumors which he has studied there are several other neoplasms in the lower animals in which there is more or less definite evidence of infectivity. They are a round-cell sarcoma in the dog, spindle-cell sarcoma in German hares and the so-called adenocarcinoma of the thyroid in the salmonoid fishes. It may be stated for this entire group that we have either positively determined the infectious cause, as in the chicken sarcomas, or that we have arrayed an amount of evidence in favor of the parasitic nature of the others which places it almost beyond a reasonable doubt. It is, therefore, interesting to note that writers who are antagonistic to the parasitic hypothesis have classed these neoplasms as growths of undetermined status, whereas in reality they are neoplasms of determined or nearly determined status: the great bulk of neoplasms from which these authors would attempt to separate them are really the neoplasms of undetermined status. From this group we learn that although they have in common a positive or probable parasitic origin, yet the mode of operation of these known or nearly demonstrated viable causes indicates great points of difference. From them we learn that it is difficult to make sweeping generalizations on the probable causes of the great group of neoplasms of undetermined status. There is no longer any impropriety in speaking of a cancer virus because such a virus has arrived in the chicken sarcomas, yet the positive knowledge regarding cancer has been so meager in the past that the temptation is great to search the facts relating to cancers in general in the light of these specifically determined ones.

We have always defined neoplasm as a growth of cells deviating from the normal, which possesses the power of limitless growth, which infiltrates the surrounding structures, thus living at the expense of the organism, and which, when transplanted through the circulation or lymph, is capable in most cases of setting up secondary growths or metastases. Experiment has shown that a malignant neoplasm may not present at one time all the characteristics enumerated above. Thus the power to form metastases may be wanting, and in the course of transplanting the neoplasm this characteristic may appear. We have included in this group tissue growths of the most diverse character, even those resulting from proliferation of embryonic structures such as dermoids. These have but the slightest resemblance to genuine neoplasms. Theories regarding the nature of cancer, based on the similarity of embryonic development to the growth of tissues in pathologic conditions, are responsible for their inclusion. When finally the causative agents have been determined for each type within this group, we shall have a rational basis for the classification of neoplasms.

The existence of an immunity to transplanted cancer was established by the observation at the Gratwick Laboratory, by Clowes, Baeslack and myself, that mice which were inoculated with cancer of the breast sometimes recovered after the tumor had made appreciable growth, and that for a long period after such recovery they could not be successfully reinoculated with the same tumor. This observation was followed with the further observation by Clowes that in the particular cancer at that time under observation, the Jensen mouse carcinoma, if the blood of the recovered mouse was mixed with a suitable portion of the cancer to be transplanted, incubated for a period and then injected into an animal, it usually failed to grow. If the interpretation of this observation was correct, it proved the existence of a slight but definite passive immunity. The experiments of Crile and Beebe with the round-cell sarcoma in dogs strengthened these observations, these authors showing that if the blood of a dog, recovered from implants of the round-cell sarcoma in question, was transfused into an animal with growing tumors, in many cases a prompt regression with recovery occurred. Levin, working with a spindle-cell sarcoma in rats, reported experiments confirming the existence of an immune factor in the blood of recovered rats capable of inhibiting the growth of implanted sarcomas in these animals. Von Dungern, working with a spindle-cell sarcoma in rabbits, also obtained marked evidence of passive immunity. The conditions

which surround observations of this kind in a given transplanted carcinoma or sarcoma in the mouse or rat are so variable that many observers have failed to confirm these observations. It is interesting to find that an investigator like Bashford, who has previously opposed the idea that the blood carries anything approaching antibodies, states in his last report that cancer cells in the mouse injected into the circulation of recovered or resistant animals are robbed of their power of proliferation.

The existence of a specific immunity in cancer was obscured by the observations of Schöne and others that a certain amount of resistance to the implantation of mouse cancer could be obtained by using normal tissues, either adult or embryonic. It was pointed out at once that it was possible that this form of resistance was of a different quality from the resistance in the animal which had recovered from cancer. It was possible that normal tissues produced a resistance in the animal to the transplantation of foreign cells, but that there was still a specific immunity to the disease directed against the cause and not against foreign cells implanted in the animal.

Attempts to inoculate tumors of an alien species into animals were first undertaken by Ehrlich, who succeeded in inoculating mouse cancer into rats or vice versa. They were found to grow for short periods. Later it was shown that in embryos, such as an incubated egg of the chicken, with proper technic, rat sarcoma or mouse cancer or other tumors of alien species could be grown indefinitely, thus indicating that the immune mechanism to tumors had not yet developed. As this applies also to alien normal tissues and bacteria, it may be assumed that in the chick embryo the entire immune mechanism is not yet established. These experiments, made by Murphy on the chick, have recently been extended by Bashford to very young mammals, and it would appear that here also the immune mechanism has not yet come into activity.

In this connection it is interesting to note that one of the most effective normal tissues available for setting up a resistance in animals to implanted cancer is the spleen. The first attempts to immunize with splenic tissue were made by Bridré and later by Woglom, and an extremely interesting contribution on this subject was made in 1911 by Braunstein of Moscow, who showed that removing the spleen in mice made them susceptible to the implantation of mouse cancer when they were otherwise resistant. Braunstein argued that the site of the resistance to cancer as well as to infectious diseases, and probably also to implanted foreign tissues, was in the lymphatic apparatus. He proposed that the splenic tissue of immunized animals should be used in the treatment of established cancer. His evidence, while not conclusive, is extremely suggestive of the correctness of his theory. He also observed that mice which had been splenectomized died in a few days after the injection of alien cancer without developing tumors, and viewed this as evidence of the destruction of the immune apparatus. In support of his theory he has made the following interesting points: First, the extremely rare occurrence of metastases in the spleen; second, the prompt destruction of transplanted embryonic tissue of the same species when implanted in the spleen; third, the demonstrated immunizing power of splenic tissue against malignant tumors; fourth, the rapid death of splenectomized animals when injected with cancer of other species, and fifth, the evidence pointing to the spleen as the principal source of all antibody formation of both bacterial and nonbacterial nature.

Murphy has recently been able to accomplish transplantation of heterotypic neoplasms, such as the Ehrlich mouse sarcoma, in the adult rat, by injuring the lymphatic apparatus of the hosts by repeated treatments with the Roentgen ray. At the time of his first publication on the subject he had succeeded in carrying the mouse sarcoma through three successive transplantations in rats thus injured, the growth varying from twelve or fourteen days to over thirty.

The difficulty of determining whether the immunity against cancer is a tissue immunity or a specific immunity against an agent was originally complicated by the observation that the best results were obtained with living cells, either normal or cancer cells. In 1910 we were able to report an interesting case of spindle-cell sarcoma of the jaw in a human being, which was influenced by injections of fresh rat sarcoma and later by injections of dried rat sarcoma material. We were led to attempt this experiment by an observation made in 1907, when it was found that in a slowly growing transplanted spindle-cell sarcoma of the rat, secondary and tertiary inoculations could be made to grow. By inoculating on each successive sixth day, twenty-five out of forty rats developed more than one tumor. These multiple inoculations proceeded side by side for a period equal to that usually required to kill, and then all of them retrograded, leaving the animals immune. This indicated that in some tumors there was a concomitant immunity set up by a first inoculation which could be stimulated by subsequent inoculations to a point at which it overcame the disease and brought about the regression of the tumors with cure. Since 1909, attempts have been made to influence human cancer by vaccinating with the patient's own cancer cells or with cancer cells from other human cases, and with some sporadic successes such as the cured case of cancer of the breast treated in this way and demonstrated at the Second International Cancer Congress by Bertrand of Antwerp, and several cases of sarcoma.

If a living cell were always required to produce the immunity to cancer, it would be impossible to demonstrate the existence of a specific immunity. Our own experiments with two cases of human sarcoma, favorably influenced three years ago and apparently now cured by the use then of dried, powdered rat sarcoma, strongly indicate that there is an immune mechanism opposed to the cause of cancer and not alone to the growth of cells. Extensive and important experiments to determine this question were again made in 1914 by Koenigsfeld, working in Pfeiffer's Laboratory in Breslau. This observer finds that a definite immunity against the growth of mouse cancer can be induced in susceptible mice by an intraperitoneal injection of small but increasing amounts of dried, sterile mouse cancer. This resistance can be produced against the most virulent tumors, and lasts for many weeks. In experiments to determine whether the dried powder of normal cells would induce a comparable immunity, he found that this was not the case. Whereas the living cells of the spleen, kidney or liver of the mouse produced the well-known resistance of previous investigators, the dried powder was devoid of such action. This author concludes that the protection thus obtained with dried tumor material is specific and probably due to the development of genuine antibodies.

When we realize that the dry tumor powder of Peyton Rous' chicken sarcomas contains the living virus which causes these neoplasms, we have at least a basis for extending the possibilities of these results. Rous has recently published an article on the immunity of transplantable chicken tumors and arrives at the following conclusions:

> The phenomena of natural and acquired resistance to transplanted chicken tumors strikingly resemble those observed in the case of transplanted mammalian growths; and no more than those do they suggest that the tumors have an extrinsic cause. That there may exist in fowls implanted with a chicken tumor a resistance directed against the tumor-causing agent distinct from the resistance manifested against the alien tumor cells has been shown in a previous article, both sorts of resistance in such an instance being acquired. That directed against the agent is largely specific, giving little if any protection against the agents causing other tumors. There is some evidence that the conditions on which a fowl's natural resistance depends are the same for the agents causing different chicken tumors.

The case, therefore, for the existence of a specific cancer immunity directed against the cause of cancer and not against a cell, which we strongly advocated before the International Cancer Congress in Paris, 1910, so far as Rous' group of tumors is concerned, is now demonstrated, and the striking similarity of the results obtained with his tumors, so long as transplanted tumors are used as the basis of his observations, shows how closely these tumors agree in behavior with the transplanted mammalian tumors in the smaller animals. In the light of our present knowledge of the immunity to cancer, we may review certain clinical facts which have impressed every observer of this disease. It has been shown in mice that when an animal is inoculated with a tumor, it promptly develops a certain amount of resistance to the growth of the tumor. If an attempt to inoculate it in the early stage with a second tumor is made, the second tumor will frequently not grow. If, therefore, it is known that the power of growth can be taken from cancer cells by treating them with the blood of recovered animals or by injecting them into the circulation of resistant animals, we have an explanation of the mechanism of metastasis formation.

Goldmann, many years ago, showed by careful histologic studies of cancer of the breast that individual cancer cells, in the early stages of the disease, penetrated into the blood vessels and were thus transported, but that in many cases they did not produce metastases. He reasoned from these observations that there was an immunity exerting itself through the blood. Experiment has now shown this to be the case, and we may assume that the resistance which is concomitant with the development of cancer even in man is the force which protects the organism from secondary growths; but when this immunity finally fails, this occurrence is marked by the advent of metastases. This type of immunity may be a tissue immunity directed against the cancer cell. This phase of the immunity may explain those cases in which early operation has not been successful in removing all of the cancer tissue, yet the growth has not recurred. These observations are also in accord with the theory that there is developed in the human being as well as in animals both a tissue immunity and a specific immunity.

That the blood in cancer cases contains antibodies or antiferments opposed to the cancer cell is clearly shown by the presence in such cases of reactions such as the deviation of complement reaction and the more recent Abderhalden reaction. All of these reactions are, however, non-specific. All of them are found in pregnancy, which is characterized by the growth of foreign tissues in the organism, and they are also found in certain other pathologic conditions associated with the destruction of tissue. It must be remembered that all these reactions are based on the use of antigens made from cancer tissue. As we have as yet no means of isolating even the known viruses from the protein constituent of the cells, it is impossible to determine whether or not a specific reaction can be perfected for a given cancer. That such reactions as the Abderhalden are non-specific is shown by an interesting clinical observation. The antibodies in the blood in pregnancy are opposed to the growth of the embryonic epithelium of the chorion in the placenta, and it is believed that they serve to protect the mother from the invasion of her tissues by these cells. Now there is an especially interesting type of carcinoma which develops in the chorion epithelium and is known as chorion carcinoma, and chorion carcinoma has been known to develop during the course of pregnancy in the face of the Abderhalden reaction, which thus shows that the antiforces demonstrated by this reaction are opposed strictly to the normal chorionic epithelium and not to the agent which brings about the change in its structure in producing a cancer. The non-specific nature of the Abderhalden reaction is further illustrated by an interesting case, reported by Versé, of a woman in the fifties who was found to have a marked Abderhalden reaction, and examination showed that she had a developing chorion carcinoma from a previous pregnancy.

Experiments made many years ago in our institute showed that the growth of implanted cancer in a mouse could be expedited by repeated and prolonged anesthesia with ether and chloroform. It was not determined whether the anesthetics produced their apparent injury to the immunity directly in the blood or by an injury to the spleen and lymphatic apparatus, but these experiments suggested that prolonged anesthesia at operation in the case of cancer in human beings might be a very prejudicial factor in the subsequent history of such cases. Every surgeon has had the disheartening experience of finding cancer cases promptly made worse by surgical interference.

Something similar has been noted in the treatment of tumors by radiation. Thus we find Lazarus, in 1914, warning radiologists to protect the spleen and lymphatic apparatus, and by experiment showing that there is a degree of radiation which greatly stimulates the growth of tumors. He says that by the photographic method he has been able to demonstrate in a case of cancer of the uterus treated for twelve hours with 86 mg. of mesothorium in the cervix, that the entire organism was affected by radiations. Plates which he laid over the lungs, the heart, the liver, the spleen, the kidney, the ovaries and the tibia during the period showed pronounced blackening. It is possible that the explanation of these remarkable results of Lazarus is to be found in recent observations indicating that the serum and red blood cells of the blood can take on photo-activity as the result of exposure to the Roentgen ray. Eden, at a recent meeting of the Natural Science and Medical Society of Jena, reported experiments which indicate that the red blood cells and serum after exposure to the Roentgen ray have a

slight but distinct power of reducing photo silver on plates. These experiments were made by exposing the blood in vitro in petri dishes, and producing the blackening of photographic plates through the usual layers of black paper. If the blood serum and red blood corpuscles are capable of carrying radio-activity, then the remote injury to the lymphatic apparatus and the results obtained by Lazarus might be explained.

Tyzzer and Duvane have recently shown that injection of small amounts of radium emanation in the circulation of mice causes a prompt and extensive destruction of the lymphatic apparatus, and other observers, working with the Roentgen ray and radium, have shown the same phenomenon. The frequency with which cases treated with radium or the Roentgen ray show marked stimulation of growth with rapid fatal termination may well be explained as an injury to the lymphatic apparatus with a loss of immunity. The whole picture of cancer from a clinical point of view must now be viewed in the light of the facts pertaining to immunity, and we may also begin to consider the existence of viruses or infectious agents as the cause of the disease. The existence of specific cancer viruses in chickens entitles us to this point of view. The general similarity of the immune phenomena in experimental animals, correlated with many facts which occur in the clinical course of human cancer, strongly suggests that such agents will be found to play a more or less extensive rôle in the cancers of undetermined etiology.

In closing, it may be asked what has become of the inclusions in cancer. It may be stated that specific inclusions are more or less characteristic of a considerable group of infectious diseases caused by filterable viruses. These inclusions have been gathered together by Prowazek into a group of protozoan organisms to which he has given the name of clamydozoa. The diseases are variola, vaccinia, trachoma, hydrophobia, molluscum contagiosum, epitheliosis desquamativa conjunctivae, inclusion blennorrhea, verruga peruviana, contagious epithelioma of birds, yellow blight of silkworms, alastrim, sheep pox, and probably hog cholera, scarlet fever, varicella, Samoa-pox and lesions with Kurloff bodies. In all of these diseases there are quite distinct and characteristic inclusions in the cells. At the meeting in 1913 of the German Pathological Society, Rocha of Hamburg presented a paper on this group of inclusions as organisms. In the discussion we find authorities like Marchand frankly agreeing that the questionable bodies in several of these diseases, but particularly molluscum contagiosum, are parasites. There are thirty-odd known filterable viruses. From the list already given it is to be seen that they cover a very wide range of diseases, and among them must now be included the three specific viruses causing neoplasms discovered by Rous. It is interesting also to remember that but recently Noguchi has cultivated the virus of hydrophobia. The scope of cancer research is thus tremendously broadened. It is possible that at a later date we shall know the true significance of inclusions in these diseases and in cancer, and the question of their significance may well be left to future investigation.

As stated early in the paper, one of the most fruitful advances in cancer research must be a realization of the fact that cancer no doubt represents a great group of pathologic changes having many points of similarity which have led us to classify them under one head, cancer. Within this group there must be a great range of agents, probably a number of specific viruses which we have yet to discover and to study. The cancer problem will never be taken by assault as Ehrlich once stated, but it will be broken up into a great field which will require many years of patient and extensive work of many investigators.

PREVALENCE OF SYPHILIS AMONG THE INMATES OF THE GOVERNMENT HOSPITAL FOR THE INSANE

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The following investigation was undertaken for the purpose of obtaining further information with regard to the prevalence of syphilis among the insane in this country. There seems to be comparatively little accurate information bearing on this topic, probably because there are few insane asylums in which the Wassermann reaction is performed as a routine procedure.

Ivey[1] reported the results of a Wassermann test among the negro insane of Alabama. The test was performed in every case in the asylum, with the following results: 357 males were examined, of whom 90, or 25 per cent., were positive; 349 females were examined, of whom 102, or 29 per cent., were positive. Among the 90 males positive, 48 showed clinical signs of syphilis, and among the females positive, 49 showed clinical signs. It is an undoubted fact that syphilis is more common among the negro race than among the white race, and therefore these figures give little information as to the prevalence of syphilis among the white insane.

Matson,[2] who applied the Wassermann reaction in the study of the insane in 1910, says:

> The importance of syphilis in the psychic infirmities is indicated by our examination of 470 inmates of the Oregon State Insane Asylum. Nearly 20 per cent. gave positive reactions while only 5 per cent. gave specific histories, and none presented visible or clinical manifestations. . . . Nearly 15 per cent. of 51 cases of dementia praecox were positive, while none gave a syphilitic history. Sixteen per cent. of 151 cases of paranoia were positive. Twenty-five per cent. of 40 cases of chronic mania were positive, 20 per cent. of 26 cases of chronic melancholia were positive, and 20 per cent. of 62 cases of dementia were positive.

Mitchell[3] states that at the Warren State Hospital for over a year, the Wassermann test has been used in the examination of all new cases. He says:

> The percentage of syphilitic cases among our new admissions is of primary interest. During the last year 18.5 per cent. of female admissions showed positive serum on the first test, and 22.3 per cent. of the males gave the same result.

1. Ivey: The Wassermann Reaction in Negro Insane, Med. Rec., New York, 1913, lxxxv, 712.
2. Matson: On the Application of the Wassermann Reaction in General Medicine, Based upon 968 Examinations with Especial Reference to the Blood of the Insane, South California Practitioner, 1910, xxv, 49.
3. Mitchell: General Paralysis of the Insane, New York Med. Jour., 1914, c, 605.