the first time I heard Dr. Brill, over two years ago, I have believed this disease in New York to be nothing more than typhus fever. My paper, read before the Academy of Medicine in New York, in 1911, and published in the *Archives of Internal Medicine*, showed that typhus fever had lost much of its virulence; that it was constantly present in many communities; that it is not easily communicable under good hygienic and sanitary conditions; and that where sporadic cases are present, an epidemic may at any time break out; that in New York City and all over this country, cases of typhus must have been constantly present, but not recognized; and that the mortality among certain races may be a little over 5 per cent. I always thought that to admit that typhus fever is as dreadful now as it was considered by the masters of medicine in their time would be to reflect on the science of medicine; it is equivalent to admitting that our modern hygiene and sanitation have been of no use.

Drs. Anderson and Goldberger did not obtain a rash in their monkeys; but this is of no importance. When one has seen many cases of typhus one will note that the rash is frequently absent, especially in children. A few weeks ago, through the kindness of Dr. Bullowa, I saw three typhus patients in one family—a father and two children. The father had a pronounced maculopapular rash. The older child had a rash, but not so pronounced; and the younger child had no rash at all. Yet all had typhus fever.

It has been asked why Mt. Sinai Hospital sees cases mostly in summer. Epidemics of typhus are usually at an end before summer. In the winter, cases of typhus are taken for influenza, because accompanied by coryza and bronchitis, and to the layman this diagnosis seems very plausible. But in the summer, it is entirely different. When the physician makes such a diagnosis, the people do not agree with him, for they do not believe in influenza in summer, and are alarmed. Therefore, they send the patient to the hospital; and the physician himself probably wavers a little about his diagnosis of influenza.

DR. V. C. VAUGHAN, Ann Arbor, Mich.: I think that Dr. Goldberger stated that Cole had said that the temperature was in direct proportion to the amount of blood injected, but that he had proved otherwise. That is an interesting point. You can inject the whites of three eggs into a rabbit, and get no elevation of temperature. I have done that every two hours for six weeks, and failed to get a rise of temperature. If, however, you inject one-twentieth of a drop of a dilution of egg-white with an equal portion of salt-solution, you can get a fever. There is a relation between the amount of protein material going into the animal and the height of the fever. The explanation of this, I do not know. I have a theory, but it is not satisfactory; and that is, that the fever results from the cleavage of the protein. The rapidity of cleavage is due to the surface exposure of the protein that is injected. If you inject a large amount of any protein into an animal, you get no fever; but a small amount causes fever. When a large amount is injected, it disappears from the blood in a very short time. We can demonstrate this by taking some blood from the heart of an animal and injecting it into the guinea-pig, sensitizing it against that protein. It is a very interesting thing, but I do not understand it.

Another very interesting thing is the following: You can take an animal and give it a sudden lethal dose of the protein poison, and get all the symptoms characteristic of that poison; yet, while the animal is suffering from this dose, you can give it two or three times a fatal dose, and it will not kill him. There seems to be a point beyond which the effect will not go, unless it is given at one dose. One man at work on that subject says that this is an evidence that the protein poison is not a chemical poison, because no chemical poison would act in that way; but I find that Gebbert, working with hydrocyanic acid, forty years ago, found that if he gave a non-poisonous dose to an animal, he could give it, while suffering from the first dose, enough to kill it, and it would not prove fatal. These things I cannot explain altogether, but they are undoubtedly facts.

DR. J. GOLDBERGER, Washington, D. C.: The length of time that the virus will live in the louse has not been determined.

The epidemiologic points raised by Dr. Brill, pointing to differences between these diseases, are such points as arise in connection with other diseases as these are more thoroughly and carefully studied. We have learned, in recent times, that a disease of the classical type is not the only type of the disease that exists. Yellow fever, for example, is not, as we used to think and as many still believe, exactly synonymous with black vomit and a funeral. The classical conception of typhoid is certainly very different from many of the cases that clinicians now recognize, and the same thing may be said of almost every infectious disease with which we are acquainted. It is true of typhus; and the only reason that it has not been recognized is that the American profession labors under the delusion that the disease does not exist in the United States. There is no doubt that it does; and, sooner or later, we may be brought to a sharp realization of the fact by an epidemic outbreak.

IMMUNITY AND SPECIFIC THERAPY IN EXPERIMENTAL CANCER*

ISAAC LEVIN, M.D.

NEW YORK

An important biologic phenomenon is presented by the immunity or resistance of certain animals to the growth of transplantable tumors of white rats and mice. It may be helpful in establishing rational methods for treating human cancer if the assumption is correct that there undoubtedly exists as complete an analogy between human cancer and the tumors in these animals as the analogy between other human diseases and those that can be reproduced artificially in lower animals.

In a recent publication von Hanseemann¹ has again cast doubt on the analogy between human cancer and the inoculable tumors of white rats and mice, and declared that the latter are a great deal more benign in their course than human cancer. This assertion, while uttered by a man of great authority, does not coincide with the facts ascertained by a great deal of painstaking and careful experimental study. The spontaneous tumors which occur in these animals give rise to metastasis in 20 to 38 per cent. of the animals; they recur after an apparently radical operative removal and kill the animal in about six weeks after the tumor has come under observation. Consequently the spontaneous tumors of white rats and mice are truly malignant in their clinical behavior, and morphologically also they are similar in every respect to human malignant tumors.

The tumors which are reproduced artificially in these animals by the usual method of subcutaneous inoculation seem to be more benign in their character than the spontaneous tumors and consequently also the human cancer. The tumors inoculated subcutaneously are circumscribed, encapsulated growths; they do not recur on removal, do not invade the surrounding tissue and seldom form metastases. In a recent investigation² I have shown that these apparent differences between spontaneous and inoculated tumors of the animals are due to the technic employed in inoculation. Various tumors were inoculated into different organs, including the brain, kidney, liver, spleen and testicle. Tumors thus induced artificially showed all the characteristics of

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¹ From the Department of Pathology, College of Physicians and Surgeons, Columbia University. Work conducted at the expense of the George Crocker Special Research Fund.

1. Von Hanseemann: *Berl. klin. Wchnschr.*, 1912, xxix, 223.

2. Levin, I.: *Jour. Exper. Med.*, 1912, xvi, No. 2.

malignancy described in human cancer. The tumor cells infiltrate diffusely and replace the substance of the organ. Consequently symptoms of clinical malignancy must occur as soon as a sufficient amount of a vital organ has been replaced by the tumor. These animals do not live any longer than about ten weeks after the inoculation and frequently die with much smaller tumors than are obtained on a subcutaneous inoculation. Metastases form with much greater frequency than after a subcutaneous inoculation and the tumors recur after an apparently complete operative removal. Thus tumors of white rats and mice inoculated into organs, as well as spontaneous tumors, are identical in their biologic behavior with the malignant tumors of man; and in elucidating human cancer, results obtained in the experimental study on animal tumors may be used with the same caution that is required in all other subjects of experimental medicine.

IMMUNITY TO INOCULATED TUMORS

It was stated above that the most important phenomenon observed in the course of these studies is the immunity of certain animals to the growth of an inoculated tumor. The mechanism of this immunity differs in many respects from the immunity of an organism against bacterial diseases, though it resembles somewhat the active immunity induced by vaccination. No irrefutable evidence is brought forward to indicate that a passive immunity may be induced by treatment of a normal animal with the blood-serum of an immune. The further fact that unimpaired living tissue seemed to have been required to immunize an animal against tumor growth and that there is no specific relationship between the character of the tissues used for immunization and the tumors used for subsequent inoculation was the cause of the prevailing idea that immunity in experimental cancer is due to a purely cellular activity of the organism of the host.

The most popular theory of cancer immunity is the one advanced by Ehrlich³ under the name of "athrepsia," which is based on the following considerations: Growth of inoculated cancer is due to cellular activity and indicates that the tumor cells possess a great avidity for a certain specific foodstuff within the organism of the host and consequently obtain it from the normal tissue cells of the organism. When cancer fails to grow, then either the organism of the host does not possess the necessary specific foodstuff or else the avidity of the cancer for this food is not strong enough to deprive the normal tissue cells of it. When the organism of the host is immunized by treatment with a cell emulsion, these cells bind the specific food and consequently the cancer cells inoculated subsequently do not find the necessary nourishment, and die.

Bashford⁴ in his conception of immunity in experimental cancer, also considers it to be a kind of cellular activity and furthermore denies that there is any direct influence of the organism of the host on the inoculated cancer cells. According to his idea, an inoculated piece of cancer tissue causes in the new host the formation of a specific connective tissue and vascular scaffolding. This connective-tissue stroma surrounds the graft and furnishes it with the mechanical support and nutrition necessary for its development. Immunity, then, consists in the failure of the organism of the host to supply the specific stroma reaction. The immune organism does

not produce a direct deleterious effect on the cells of the inoculated cancer, but alters its own normal connective-tissue cells so as to render them insusceptible to the chemotactic properties of the inoculated cancer cells. Other investigators, including Borrel,⁵ incline to accept the view that the immunity in experimental cancer is analogous to the immunity in bacterial diseases and is caused by certain cytolytic antibodies circulating in the blood.

I have investigated the subject of immunity from various standpoints.⁶ In the first place, these investigations have shown that it is possible to immunize an animal against a subsequent tumor inoculation not only by a previous injection of an emulsion of living cells but also by one of autolyzed tissue; i. e., of tissue in which the cells have suffered dissolution but in which the endocellular ferments apparently remain active. This fact militates against the supposition that immunity in experimental cancer is due to a peculiar cellular activity. This immunity is probably due to action of ferments and hence is analogous to bacterial immunity. In the same investigation it was also indicated clearly that the result of tumor implantation is determined by two separate factors: first, by the implantability of the ingrafted tumor; and, second, by the rapidity and rate of its growth if ingrafted.

In collaboration with M. J. Sittenfeld,⁷ I have shown that athrepsia may serve to explain solely the condition of the resistance and susceptibility of an animal to the grafting of tumor tissue, and that the success of such grafting of the inoculated cells may depend on conditions of nutrition. On the other hand, the differences in nutrition cannot explain the reason why in one successful tumor graft there forms a small nodule which is subsequently absorbed, while in another the nodule grows into a large tumor and kills the animal. The latter phenomenon can be explained only by an active inhibitory influence exerted on the cancer cells by the organism of the host.

Further studies of mine⁸ have shown that Bashford's theory of a specific connective-tissue scaffolding has no general application in the explanation of cancer immunity. The condition appears to be quite different when the tumor is inoculated into an organ instead of subcutaneously. When a piece of tissue is inoculated into an organ, the first visible step is not the formation of a surrounding connective-tissue stroma. The inoculated cells immediately begin to proliferate and invade diffusely the normal tissue. On the other hand, in an immune animal⁹ the tumor inoculated into an organ does not grow but dies and is surrounded by an extensive connective-tissue stroma like any other dead foreign body. Consequently the immune organism does not lack the capacity to form connective-tissue scaffolding but actively inhibits the proliferation of the cells of the implanted piece of tumor.

In a recent investigation¹⁰ on the so-called "precancerous state" I have gained another striking proof that the condition of immunity in animal cancer is not due to exhaustion of nutrition but to an active inhibitory influence of the organ cells on the tumor cells. It appears that immunity in experimental cancer is not always a general condition of the whole organism but

5. Borrel: *Bull. de l'Inst. Pasteur*, 1907, v, 207.

6. Levin, I.: *Proc. Soc. Exp. Biol. and Med.*, 1910, vii, 64; *Jour. Exper. Med.*, 1910, xii, 504.

7. Levin, I. and Sittenfeld, M. J.: *Jour. Exper. Med.*, 1911, xiii, 511.

8. Levin, I.: *Jour. Exper. Med.*, 1911, xiii, 604.

9. Levin, I.: *Jour. Exper. Med.*, 1911, xiv, 139.

10. Levin, I.: *Jour. Exper. Med.*, 1912, xv, 163.

3. Ehrlich, P.: *Abh. a.d.k. Inst. f. exper. Therap. zu Frankfurt*, 1906, No. 1, p. 77.

4. Bashford, Murray and Cramer, T.: *Scientific Reports of the Imperial Cancer Research Fund*, 1908, No. 3, p. 315.

may also be localized in one organ. I found that Flexner-Jobling carcinoma of the white rat, which grows readily on a subcutaneous inoculation, does not grow when inoculated into a normal testicle. This resistant testicle may be rendered susceptible to the growth of the tumor by treatment with scarlet R oil or ether. These substances impair the normal functions and consequently the inhibitory action of the parenchymatous cells on the cancer cells. This purely local treatment of the organ cannot diminish the amount of the specific food which the inoculated cancer cells may find in the organism of the host.

Thus the mechanism of immunity in experimental cancer consists most probably in an active inhibitory influence of the normal organ tissue on the cancer cells and is analogous to immunity in bacterial disease. But the conditions are by no means identical and new methods will have to be devised in order to discover the presence of antibodies in the organism and to determine its nature.

The malignant tumors of white rats and mice are analogous, as stated above, to human cancer and it seems feasible to suppose *a priori* that similar conditions of resistance may exist in man. It is difficult to ascertain the matter in view of the chronic course of the disease, but rare cases of spontaneous cure in human cancer reported by Orth¹¹ and others, and my investigations¹² on the heredity in human cancer make it probable that a condition similar to an immunity may exist in human cancer.

SPECIFIC THERAPY

The great practical significance of the phenomenon of immunity in experimental cancer is due to the fact that there exists a direct relationship between immunity and specific therapy of a disease. Ehrlich was the first to indicate this relationship and to create a new science of experimental specific therapy. The action of antitoxin shows clearly this relationship. Blood-serum which is capable of passively immunizing a healthy organism will at the same time cure a diseased organism. Such specific serotherapy is as impossible to obtain in experimental cancer by present methods as to show the existence of antibodies in the blood-serum of a tumor-bearing animal.

Better success followed the treatment with substances containing free enzymes. I stated above that I have succeeded in immunizing animals against cancer growth by injection of autolyzed tissue. Blumenthal¹³ and Carl Lewin¹⁴ have reported successful treatment of cancer in rats with injection of autolyzed tissue. I have been quite as successful with the same method of treatment. The following is a short summary of the experiments:

Sarcoma tissue of a white rat was removed under aseptic precautions and autolyzed for three days. The fluid was then filtered and injected subcutaneously into rats with a large growth of the same sarcoma. Twenty-four hours after the injection the removed tumor showed a severe hyperemia with numerous hemorrhages in the parenchyma. Subsequently many of the tumors liquefied and either sloughed off or became absorbed. But at present the results of this specific ferment therapy, if this term may be used, are as yet unsatisfactory. The true nature of the therapeutic action of the substances is not known. The same autolyzed tissue may be active

in one series of experiments and not in another. All my attempts to obtain the same results with treatment of sarcoma of the white mouse with autolyzed mouse sarcoma failed.

CHEMOTHERAPY

The greatest discovery of Ehrlich in the whole field of specific therapy is the finding of a mechanism of the specific therapeutic action of certain chemicals. It was known empirically long before that certain drugs have a specific action against a disease, as for instance quinin in malaria or mercury in syphilis. Ehrlich noticed that in certain infectious diseases, mainly in those caused by such animal parasites as trypanosomes or spirilla, it was extremely difficult to produce an active immunity, and consequently the formation of a passively immunizing and curative serum. It occurred to him then to try to obtain a chemical which would have a specific action on the parasites and consequently be a true curative agent against the disease. Ehrlich¹⁵ was led to the idea by the results of his previous studies on vital staining.

These investigations have shown that certain dyes when introduced into a living organism may stain one group of cells or organ and leave the other organs unaffected, as for instance, methylene-blue, which stains only the central nervous system. Another dye closely related chemically to the first may lack the same specific effect on the same organ. Ehrlich arrived at the view that specific action of chemical substances depended on three factors: (1) the chemical constitution of the substance; (2) its pharmacodynamic action; and (3) its specific distribution in the different tissues of the organism. *A priori* it seemed further possible that chemicals might be found which might be toxic for parasites and not toxic for the body cells, and thus a specific therapeutic measure might be found against the disease caused by the parasites. The theoretic deductions of Ehrlich proved to be correct and the brilliant discovery of salvarsan and of a new science of chemotherapy followed.

Since both serotherapy and ferment therapy have been of comparatively little value in the treatment of cancer, it is natural to expect that chemotherapy will be tried. Indeed, recently von Hansemann¹⁶ reported on a series of experiments in which he succeeded in curing tumor in mice with intravenous injection of a chemical combination of selenium and eosin. Von Wassermann asserts that the action of both substances is needed for the success of the treatment. Selenium in accordance with his ideas is toxic for all animal cells, while eosin is not toxic but has a selective action on the tumor cells. It enters the tumor and acts as a carrier transporting with it the selenium to the tumor cells. He further states that the same chemical combination of the two substances may be active in one series of experiments and inactive in another due to the biologic differences of the combination. It is also apparently difficult to differentiate between the curative dose and the dose which is toxic to the animal, as many animals died immediately after the injection.

The main difficulty in the selection of a correct chemotherapeutic agent, as stated by Ehrlich, consists in the fact that no chemical is strictly specific as an antitoxin, for instance. It is always both organotropic and parasitotropic; i. e., it affects to a certain extent always both the parasites and the body tissue. The difference between a cancer cell and a normal body cell is much less than between a trypanosome and a body cell; consequently it

11. Orth: *Ztschr. f. Krebsforsch.*, 1904, 1, 399.

12. Levin, I.: *Ztschr. f. Krebsforsch.*, 1912, xl.

13. Blumenthal: *Med. Klin.*, 1910, vi, 1982.

14. Lewin, Carl: *Ztschr. f. Krebsforsch.*, 1912, xl.

15. Ehrlich, P.: *Festschr. f. Leyden*, 1898, 1.

16. Von Wassermann, A. and Von Hansemann, D.: *Berl. klin. Wchnschr.*, 1912, xlix, Nos. 1, 3, 5.

ought to be still more difficult to find a chemical substance which will be strongly toxic for the tumor cells and innocuous for the organ cells.

I am engaged at present in the comparative study of the action of various vital stains on normal rats and mice and on the same species of animals into which tumors were inoculated into parenchymatous organs. Of the different dyes used for the experiments eosin did not appear in my hands to stain selectively the tumors alone, but stains diffusely the whole organism. Furthermore, eosin itself without the addition of selenium appears to be extremely toxic and many animals die immediately or in a couple of hours after the intravenous injections of the eosin. Nagelschmidt¹⁷ also reported recently the fact that eosin is extremely toxic unless the precaution is taken of putting the animal in a dark room immediately after the injection.

Trypanblau, isaminblau and pyrrrolblau have had extensive use recently for vital staining. These dyes have a selective action on certain cells. It is not necessary to enter here into the details of the subject. The following fact is of interest for the present discussion. In the liver of a normal animal these dyes stain the so-called Kupffer's cells. If a sarcoma is inoculated into the liver a great deal of the vital stain is found in the cells of the tumor. But not all the cells of the sarcoma take the stain and furthermore Kupffer's cells are stained as strongly as in a normal animal. It would seem probable, then, that the dyes used for vital staining will not be of great aid in the chemotherapy of cancer. Recently C. E. Walker¹⁸ reported on experiments with treatment of tumors with different combinations of selenium and eosin with completely negative results.

None the less, negative results of one investigator cannot completely contradict the positive results of another, and von Wassermann's results seem to be the most successful of all those reported. The presence of immunity in the tumor animals makes it quite certain that ultimately a specific method of treatment in experimental cancer will be found. But it is impossible to predict whether the methods of chemotherapy, serotherapy or ferment therapy will be the most fruitful of results.

Chemotherapy, as stated above, is not the ideal specific method of treatment but seems the most promising of results at present. It is difficult to predict the chemical nature of the most successful drug of the future, though I believe that one does not need to search for a substance absolutely fatal to the life of the tumor cells. The end may be achieved when a substance is found that will possess the power to arrest the active proliferation of the tumor cells. I am at present engaged in work in that direction.

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ABSTRACT OF DISCUSSION

DR. WILLIAM SALANT, Washington, D. C.: What was the duration of the immunity which Dr. Levin induced by means of autolyzed tissue? A cure for cancer or for any other disease by means of a specific which is not toxic is, I believe, hopeless, since any substance when given in sufficient amount may exert a harmful effect.

DR. G. W. McCONNELL, Philadelphia: It seems to me that immunity in cancer tumors is one of the most difficult propositions, inasmuch as we know that it may also be given to

white mice, yet mice from different parts of the country will react differently to the same tumor. This winter, for example, in some tumor work in mice, I found, in a series of twenty mice, that only 3 per cent. showed a growth when inoculated with one kind of tumor, but when inoculated with a different form, they gave a percentage of 20.

I think that it is quite well understood that certain organs of the body have a distinct organ immunity. The spleen, for instance, is seldom the seat of primary tumors, and also quite rarely the seat of secondary ones. Metastasis from these tumors does not occur very frequently. Nevertheless, if the original growth is removed, we are more likely to get secondary tumors in other parts of the body following the original subcutaneous inoculation.

DR. V. C. VAUGHAN, Ann Arbor, Mich.: It seems to me that the ferment idea is the most reasonable one at present. Of course, there is nothing in sight as yet; but the fact that you can induce immunity by autolyzed tumors, it seems to me, indicates (I will not say proves, because it does not prove) a ferment action; and the autolysis is simply a change in the physical condition of the cancer protein. When autolyzed, it is soluble, and, therefore, more readily acted on by the ferments of the body. This, of course, is all hypothesis. Everything that we say about it is theoretical, as yet, but it is by means of hypotheses that we are ultimately enabled to do things. To say that the autolyzed cancer tissue, being soluble, is more readily acted on and calls out ferments that destroy that cancer tissue seems reasonable. It is undoubtedly true that there are two kinds of proteolytic ferments that the cells of the body are capable of forming, one of which may be called a general proteolytic ferment, and the other specific proteolytic ferment. Ferments have been extracted from the leukocytes and there is no doubt of their existence. This much of it is not hypothesis. The only question is about the possibility of developing in the body enough of a proteolytic ferment to destroy the cancer tissue without, in this destruction, liberating sufficient poison to be fatal.

DR. J. W. VAUGHAN, Detroit, Mich.: Dr. Levin said that he had a serum which he obtained from one animal injected with rat sarcoma which possessed a ferment that would split up the cancer cells in other animals with the same tumor. I should like to ask how long after the injection of the cancer tissue into the animal that serum was obtained. We are accustomed to consider a ferment as a stable product. For example, we look on the use of vaccine in small-pox as such, persons retaining immunity over several years. In the majority of cases of typhoid fever, the patients retain their immunity for a long time also. In cancer, a ferment is formed that is stable only for from six to ten hours. After that, it may be stored in small quantities in some other tissue of the body, but it is not active in the serum or the blood-cell.

DR. LEO LOEB, St. Louis: Experiments carried out in our laboratory proved that while the fowl spleen had a very active immunizing power against mouse carcinoma, the autolyzed spleen no longer had such an immunizing effect.

DR. ISAAC LEVIN, New York: In reply to Dr. Salant, I could not ascertain the duration of the immunity induced by treatment with autolyzed tissue. In order to prove that the animals are immune a piece of tumor is inoculated, which becomes absorbed. Thus the animals are rendered immune doubly, by the treatment with autolyzed tissue and through the inoculation of tumor. The latter immunity caused by an unsuccessful inoculation of tumor remains active all through the life of the animal and obscures the effect of the treatment with autolyzed tissue. No chemotherapeutic measure can be found which is toxic for a parasite and completely innocuous for the organ cells. Still more difficult would it be to find a chemical substance which will be toxic to the cancer cells and will not injure the organ cells. I stated, therefore, that in my opinion chemotherapy is not the ideal method of treatment in cancer, but for lack of better methods the research on lines of chemotherapy must continue. In my own investigations I am searching for a substance which will be toxic neither to the organ cells nor to the cancer cells, but will arrest the proliferating power of the latter. Such a substance would act in a manner antagonistic to those sub-

17. Nagelschmidt: Berl. klin. Wchnschr., 1912, xlix, 118.

18. Walker, C. E.: Lancet, London, 1912, clxxxii, 1337.

stances which, as Jacques Loeb has shown, enhance the proliferating power of the cell. While it is self-evident that no chemical will be absolutely innocuous to the cells of the organism, a chemical substance may arrest the proliferating power of a cell and not kill it. The influence of the racial differences on immunity is neutralized in our work by the great number of animals used. I stated that the question of organ immunity as well as general immunity in human cancer cannot be discussed at present for lack of properly analyzed material, but that my own investigations on eugenics in human cancer seem to indicate that there may exist a condition of resistance or immunity in human cancer. Metastases occur after an inoculation into a parenchymatous organ of tumors which do not metastasize on a subcutaneous inoculation. It is my personal belief that ferment activity underlies the condition of susceptibility as well as immunity in cancer. But at present the knowledge of the chemical nature of the ferments is so limited that it is impossible to ascertain their true functional significance.

FOUR CASES OF TYPHUS FEVER (BRILL'S DISEASE) IN ONE FAMILY

WITH SUCCESSFUL INOCULATION INTO GUINEA-PIGS
AND MONKEY *

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The recent work of Anderson and Goldberger of the Hygienic Laboratory at Washington establishing, experimentally, the identity of typhus fever and so-called Brill's disease, together with the mode of transmission of typhus fever by body-lice as shown by these writers, and Nicolle and his co-workers abroad, and by head-lice as lately shown by Anderson and Goldberger, greatly increase the interest in cases of what we must now regard as endemic typhus fever, so well studied by Drs. Brill, Louria and others as it occurs in this country and especially in New York City.

* From Research Laboratory, Department of Health, New York.

For many months before the occurrence of those reported, no cases of typhus fever had occurred in New York to the best of our knowledge. Those that we present are unique in the history of the endemic form of the disease as it has been studied in New York, in that they affected four members of one family, and that two of them were young children. These cases, furthermore, represent types of the disease varying from the comparatively mild, to an example of typhus fever such as is commonly seen in epidemics, thus giving, as it were, a clinical demonstration of the identity of the endemic (Brill's) and epidemic form. But one member of this family escaped the disease, a child of 1½ years of age.

A careful investigation of the premises (a large tenement house) in which these cases occurred failed to reveal the occurrence of any other cases previously, and an extensive inquiry among physicians and hospitals has brought to light but three additional cases of the disease up to the present time.

The patients were typical east-side residents, Russian Hebrews of the poorer class. They had been in the country for about eight months.

REPORTS OF CASES

CASE 1.—Ida K., aged 28, (Chart 1), the mother, was admitted to the Mar Moriah Hospital, April 9, 1912, with a temperature of 105 F. She had previously been healthy and there was nothing in her past history to throw any light on her present condition. About six days before admission she had a severe chill followed by fever, sweating and intense headache. She was obliged to take to her bed. Four days before admission she vomited some bilious material. These symptoms continued, together with a profuse watery diarrhea, up to the time of her entrance to the hospital. On admission the patient's condition was fairly favorable; a few hemorrhagic spots were noted on the abdomen. The general physical examination, together with two Widal tests, proved negative. On April 10, the leukocytes were 12,600 per c.mm. of which 66 per cent. were polymorphs. A second count on April 13, showed 11,200 leukocytes and 64 per cent. polymorphs. The case was regarded as one of intestinal toxemia, the true cause not being suspected until after the entrance to the same hospital of other members of the family.

Chart 1.—Pulse and temperature in cases of Israel K. (solid line) and Ida K. (line composed of dashes).