THE QUESTION OF ATHREPSIA.*

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In a recent number of this Journal[1] an article by I. Levin and M. J. Sittenfield, "Studies on Immunity in Cancers of the White Rat," appeared, which, as is indicated by its sub-title, "The Significance of Athrepsia," presented a criticism of the athrepsia hypothesis of cancer immunity as set forth by Ehrlich. In consideration of the lack of clearness concerning the nature and significance of athrepsia which is there indicated, the deductions drawn by the authors of this article should not remain unchallenged. The authors are in error in an early sentence, namely: "The most popular and most generally accepted theory of cancer immunity is the one advanced by Ehrlich and is commonly designated the athrepsia hypothesis." With much more justice it might be maintained that the athrepsia of Ehrlich is the most misunderstood and precisely on this account the most frequently misrepresented of all theories of cancer immunity. The work of Drs. Levin and Sittenfield offers a particularly striking proof of this.

On page 512 occurs the following sentence: "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. Immunity, then, to cancer growth consists in the lack of food athrepsia." How the authors arrive at this remarkable conclusion is incomprehensible; certainly it would be difficult to find verifica-

* On account of the importance of the questions involved as well as the eminence of the Institute from which this paper emanates, the Editor of the *Journal of Experimental Medicine* is departing, in this instance, from the policy of the *Journal*, which is to decline to publish articles purely critical of previous experimental papers appearing in its columns. Received for publication, July 12, 1911.

[1] Levin and Sittenfield, *Jour. Exper. Med.*, 1911, xiii, 511.

tion for it in the reports of the work which have been issued from the Institute at Frankfurt. They have simply confused the actively produced tumor immunity with that of athrepsia, and appear not to be aware that Ehrlich has always separated the two immunities sharply from one another. In one of his latest publications[2] on the subject he says, "The question naturally arises as to the foundation of the acquired immunity. Were it dependent on the formation of specific antibodies,—a possibility to be first considered,— then the production of passive immunization with the blood of immune animals would inevitably follow. Up to the present time only a few data on this point have been under discussion,—by Jensen[3] among others; and the figures, particularly those published by Clowes and Baeslack,[4] are not convincing. Since these authors did not work with tumors of maximum virulence, the possibility remains that the quantity of antibodies formed was insufficient for demonstration with certainty by the test of passive immunization. At any rate we should mention that in the various centres for cancer research, (the Rockefeller Institute, London, Frankfurt), attempts at the demonstration of such antibodies, either in experiments with animals, or *in vitro,* have turned out on the whole negatively. Although it is not yet possible completely to rule out antibodies, nevertheless still further experiments are necessary in order to gain a clear insight into this question. For various reasons, however, I consider it inadmissible to bring forward, on the basis of present knowledge, and without anything further by way of positive fact, the hypothesis that the immunity directed against mouse cells rests on isolysins." Thus not a word is uttered concerning athrepsia. On the other hand, he continues further on, "So much, gentlemen, concerning active immunization. You will permit me at this point to enter somewhat more fully into the question of another form of immunity, to the assertion of which I was led years ago by reason of many peculiarities of mouse tumors; namely, immunity by athrepsia." Here, therefore, immunity by athrepsia is brought into sharp contrast with active immunity, a fact which seems wholly to have escaped Drs. Levin and Sittenfield.

[2] *Verhandl. d. deutsch. path. Gesellsch.,* 1908, xii, 17.
[3] *Centralbl. f. Bakt., Orig.,* 1903, xxxiv, 28; 122.
[4] *Med. News,* 1905, lxxxvii, 968.

The remarks of these authors on the subject of panimmunity suffer in the same way. They begin this division of their paper with the sentence: "Ehrlich did not consider the phenomenon of panimmunity a direct proof of athrepsia," and continue immediately, "but there must undoubtedly be a certain relation between the general non-specific character of the former and athrepsia, which is merely a phase in intracellular nutrition. Indeed, if athrepsia is to have a general application it must be capable of explaining the conditions of panimmunity against the different tumors used in this research, and it may be stated that in a general way the fact of panimmunity was found to be correct for the majority of cases." It may be replied, that athrepsia does not have a general application, and that it has never been brought by Ehrlich into relation with panimmunity. Hence the authors' method of treatment leads to a misinterpretation of the theory of athrepsia, which thus becomes the object of criticism that could not apply to the theory correctly formulated. This error is to be deplored.

The case is different with the further divisions of the article, in which the authors raise objections to athreptic immunity, where according to Ehrlich they surely have weight, first in regard to the so called zigzag transplantations between mouse and rat. But here again we find a sentence which shows that they have again fallen into error: "On the basis of this supposition, Ehrlich created the general theory that whenever cancer cells fail to proliferate, it means that they fail to obtain the food x, either because the normal body cells have greater avidity for this food than the cancer cells, or else the cells with which the animals were immunized anchored all the specific food and the cancer cells inoculated subsequently could not obtain it."

The authors adduce against Ehrlich's explanation that the inoculation-yield by zigzag inoculations is considerably less than in the control inoculations in the same species, and hold that this fact is to be explained not by lack of specific food stuff, but merely by the presence of directly injurious substances. That the yield on inoculation in a foreign species is in the first place not so good as within the same species would appear to be not remarkable, since the conditions for proliferation in the first instance are naturally less favorable.

But if these zigzag inoculations are continued, which the authors in question seem not to have done, the results improve, and above all, the growth of the tumors, if they grow at all, shows no retardation. This is irreconcilable with the conception of injurious substances. In this case it is not the unsuccessful but the successful inoculations which point to the true explanation. If rats possessed preformed antibodies against mouse tumor cells, the latter would in no single instance grow in the rat to a transplantable tumor, which, even according to Levin and Sittenfield, is reinoculable into the mouse in twenty-five per cent. of the animals.

Moreover these authors do not allow to stand unqualified the second form of athrepsia postulated by Ehrlich, which is observed in the same animal after double inoculation. Neither with the Flexner-Jobling rat carcinoma, nor with the Ehrlich rat sarcoma did they fail to obtain takes of the second tumor graft. It is, however, noteworthy that the rat carcinomata possess far too slight a growth for the demonstration of this form of athrepsia. But even in the case of the considerably more virulent rat sarcoma the athreptic influence of the first tumor could be observed, primarily in the retarded growth of the subsequently inoculated tumor. Whether Drs. Levin and Sittenfield considered these facts and took into account the weight of the tumors which Ehrlich on his side has required, is not apparent.

Again, they deny a general value to my results with the inoculation of mixed tumors,—results which Ehrlich has explained in connection with athrepsia. I had been able to show, that by the inoculation of mixed but unlike virulent tumors only the more virulent component comes to development, and that, therefore, a true mixed tumor is only obtained when the stronger power of proliferation of the more virulent tumor is artificially set aside. Levin and Sittenfield corroborate my results for the mixture of mouse carcinoma and sarcoma, but not for the corresponding rat tumors, also with divergent degrees of virulence. From their very short and summary data, to which no protocols at all are added, it does not appear whether in the development of the two components no quantitative differences were present. For various reasons, not to be further dealt with in this place, the results of such inoculation of mixed

emulsions naturally vary within certain limits, so that it is permissible to draw positive conclusions only after very numerous experiments. Drs. Levin and Sittenfield do not state the number of inoculations made by them.

Finally, the authors concede that conditions of nutrition for the growth of the tumor grafts enter into the question, but the proof of this adduced,—namely, the stroma reaction postulated by Russell,[5] —shows plainly that these conceded nutritive conditions have nothing to do with the athrepsia of Ehrlich. It should also be mentioned that the value of Russell's investigations has become exceedingly problematic by reason of the subsequent very exact repetitions carried out by Goldmann. It should be further noted that Drs. Levin and Sittenfield misinterpret some of the facts and fail entirely to mention others which demonstrate the existence of athrepsia. The former applies to their presentation of the relation of tumor growth to pregnancy. They refer on the one hand to Haaland,[6] who first observed the resistance of gravid animals to tumor inoculation, and on the other to Herzog,[7] who described a more rapid growth of the tumor in the course of pregnancy. They conclude immediately from these observations that pregnancy simply inhibits the take of an inoculated graft, but that it stimulates the growing tumor to stronger proliferation. This conclusion is entirely arbitrary, and rests on a mistaken citation. For Herzog speaks not of tumor-bearing animals, which became pregnant, but of inoculation of pregnant animals. On the other hand, Cuénot and Mercier found that the beginning of tumor growth can be temporarily inhibited by the onset of pregnancy, and by lactation, only to proceed thereafter in a normal manner. The apparent inconsistencies in the observed relations between pregnancy and tumor growth are probably explained, as Fichera has already observed, by the fact that, if numerous embryos are present, the specific foodstuffs, which are often the same for embryos and for tumor cells, are almost wholly demanded by the former, but that, on the other hand, when only a few embryos are present, the production of the

[5] *Scientific Reports of the Imperial Cancer Research Fund,* 1908, No. 3, 341.
[6] *Berl. klin. Wchnschr.,* 1907, xliv, 713.
[7] *Jour. Med. Research,* 1902, viii, 74.

specific food stuffs, increased by pregnancy, comes to benefit the tumor cells also. It is reasonable and entirely consistent with the principle of athrepsia that occasionally an already strongly growing tumor should draw still more strongly on the food stuffs abundantly produced at the advent of pregnancy, and so grow still more quickly.

Drs. Levin and Sittenfield do not mention at all the experiments of Pierre Marie and Clunet, which are in direct verification of the theory of athrepsia. Ehrlich, in 1905, had already advanced the supposition that the rare occurrence of metastases in animals inoculated with very virulent tumors, in contrast to the relative frequency of secondary nodules in animals having slowly growing spontaneous tumors, was due to the fact that in the former case the specific food stuffs of the embolized cells were appropriated by the original tumor. Marie and Clunet have recently found that after operative removal of rapidly growing tumors, metastases occur in fifty per cent. of the animals; and they are of the opinion that the facts are best explained by Ehrlich's theory of athrepsia.

In conclusion we desire to urge that a theory as well founded as that of athreptic immunity be not subjected to discredit without the presentation of all the facts bearing upon its various sides, with a degree of fullness and clearness of interpretation that will permit of a convincing conclusion.