PRELIMINARY NOTE ON THE POSSIBLE EFFECTS OF THE NERVOUS SYSTEM UPON THE GROWTH AND DEVELOPMENT OF TUMORS

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It is one of those strange phenomena which are occasionally met with in the history of medicine, that what one might think were very obvious anatomical facts or physiological relations, are for a long time either entirely overlooked, or do not receive the attention which they deserve. Thus it has for an indefinite time been accepted as a fact that genuine tumors, with the exception perhaps of those directly originating from nerves, as the neuromata, and of those more indirectly connected with them, as the multiple neurofibromata described by Recklinghausen, are not supplied with any nervous apparatus, with the exception perhaps of some vascular innervation, and even this has not been definitely ascertained for every kind of tumor. The literature on the subject is extremely scanty and consists mostly of a casual remark scattered here and there. William Cullen (1) in his "First lines of the practice of physic," 1789, looks upon cancer as caused by some disturbance of the nervous system. This, however, is not based on any anatomical investigation, but is simply in accordance with the teachings of the school to which he and his master Alexander Monro belonged, according to which a majority of human disease was supposed to be due to perverted nervous influence. Virchow (2) does not seem inclined to recognize any influence of the nerves upon the origin and growth of tumors. This opinion, however, seems to be based rather upon general considerations and not upon histological investigations, which, after all, the microscopic technique of his time would
hardly have rendered feasible. John Marshall (3), in a very suggestive Morton lecture on "Cancer and cancerous diseases," urges the investigation of the relations of the nervous system to cancer as a very promising method of research. His own opinion is purely hypothetical and not based on any direct observation. To him, cancer is an "anarchical" growth of cells which perhaps have broken away from nerve control and thus can continue, stimulated probably by numerous other influences, in unlimited proliferation. He thus postulates a *biological* change in cancer cells by which they differ from the normal. At about the same time Klebs (4) remarks very briefly and without any further discussion, that the absence of nerves in tumors, especially malignant ones, may mean the diverting of normal inhibition from the tumor cells and thus may be made accountable for their unlimited proliferation. The great majority of the text books of pathology either make no mention at all of the question of the relation of nerves in tumors, or simply state that nerves in tumors have not been demonstrated. In 1897 Young (5), using the methylene blue supravital stain, made a rather extensive search for nerves in various kinds of neoplasms. He found nerve fibers, in some cases rather more plentifully than he expected, in about half of the cases he examined. He does not arrive at very positive conclusions, but is strongly inclined to the opinion that in several of his cases the nerves that he found were actual integral parts of the tumor. We are unable to consider this opinion as satisfactorily proven, especially as he does not show any constant relation of the nerve fibrils to the tumor cells, or to their possible functional activity. Since Young's paper we have not been able to find in the literature any other special research directed toward this problem. Borst (6) in his well known monograph reiterates the statement that nerves forming an integral part of genuine tumors have not been demonstrated, and points out the desirability of an exhaustive investigation of the subject. He says further, that it is quite obvious that in infiltrating tumors, nerves are very frequently found within the tumor tissue; that these, however, do not belong to the tumor itself, but are preexisting formations which are simply included
into the tumor in the course of its encroachment upon the surrounding tissues.

A further study of this problem has been in the mind of one of us for a long time, and many years ago a number of experiments were made, which, however, could not, owing to the state of our knowledge at that time, produce any results. We have now concluded to take up the subject again.

It seems to us that there are two methods available for attacking the problem. One method would consist in an anatomical, especially histological, study, as complete as possible, of the actual relations of the nervous system to neoplasms; and if it should turn out, as seems probable, that tumors have no nerves of their own, an attempt to discover the biological conditions which determine this lack of innervation. The other method would consist in taking some transplantable tumor, inoculating it into various organs whose connection with the nervous system has been completely severed, and noting if there are any recognizable differences in the growth and development of the tumors in such organs, as compared with the result of inoculations into similar organs whose innervation has remained intact. Like everything connected with the great cancer problem in its totality, this special investigation is by no means an easy one, and almost insurmountable obstacles seem to block the road to definite conclusions. Nevertheless it has seemed to us worth while to devote our energies to this in the hope of perhaps attaining some, though possibly only a minimal, result.

The following set of experiments of which we present here a very brief report, were done in the first half of 1916 and extended over a series of fifty white male rats. The tumor employed was the well known Flexner-Jobling carcinoma. The organ selected for inoculation was the testicle. It is very easy to get at this organ and bring it outside of the scrotum and thus deprive it of all possible little nerve fibrils which might perhaps enter the testicle from its environment. As is well known, the main nerve supply of the testicle runs along the vas deferens and the spermatic vessels. There is no difficulty in stripping this funiculus of everything but the bare vessels. Unfortu-
nately it was not possible to do this without interfering to some extent with the blood supply on account of the smallness and extreme fragility of the vessels. As a consequence, in practically every case in which the testicle was stripped of its nerves, blood vessels were also more or less damaged and a certain amount of atrophy of the glandular elements was pretty sure to follow. Of our fifty rats, six were denervated but not inoculated with tumor, because we wished to study the effect of the operation without any complicating circumstances. This, as stated before, resulted in a varying degree of atrophy of the glandular tissue, but we never encountered necrosis. Nine animals, including controls, denervated, and inoculated animals in about equal numbers, were found dead, and either so completely decomposed or eaten by their fellows, that nothing could be said about the result of the experiment, and they must therefore be excluded from the series. There remained then fourteen rats that had been inoculated in a testicle stripped of all its nerves. All these fourteen rats developed tumors, mostly exceptionally large. Of the twenty controls, that is to say, animals whose testicles were simply inoculated without interference with the nerve supply, either through the skin or more often through a very small incision into the skin, seventeen showed no signs of tumor whatsoever, but were perfectly normal. In one, the testicle was free from tumor, but there was some neoplasm in the omentum and sigmoid. It is doubtful whether this had any connection with the inoculation; at any rate, as the testicle was normal, it must count as negative in our series. In another rat there was a very small whitish-gray patch to be observed in the testicle, which however, under the microscope, did not show any signs of tumor formation, but was probably of inflammatory origin, and was distinguished by a great number of plasma cells. One other control showed an extremely small tumor. We can therefore state with confidence that all the rats that had been inoculated into testicles stripped of their nerves, very promptly developed exceptionally large and rapidly growing tumors, but that none of the controls, inoculated at the same time under the same conditions and with the same tumor, the testicle
having its normal nerve supply, developed any tumor, with perhaps one single and insignificant exception. This result is the more striking when it is remembered that all investigators agree that the testicle is not a very favorable site for tumor transplantation; Woglom (7), indeed, has shown that the Flexner-Jobling tumor of the rat is transplantable into the testis of the animal, though he also finds that the resulting growths do not often attain the usual size of subcutaneous tumors.

We wish to mention just incidentally that we also tried a number of experiments with the object of testing the effect of Scharlach R. upon denervated testicles. Concentrated solutions of the dye in olive oil were injected into the testicle, sometimes alone, sometimes with aleuronat in order to produce some mechanical irritation. The experiments led to no result. Only very insignificant quantities of the Scharlach could be injected into so small an organ and this it seems was rapidly carried away by the lymphatics. We obtained some very beautiful specimens of Scharlach injections through the great lymph trunks of the abdomen and into the centrum tendineum, and even into the thoracic cavity. What ultimately became of it we did not investigate.

Returning to our tumor inoculations, we realize that no very positive conclusions can be derived from them. The series is altogether too small, and must be extended over a considerably greater number of animals; other organs must be tested in the same way, and above all there is one obvious objection that must be overcome. A method must be found by which an organ can be completely severed from all its connections with the nervous system without at the same time interfering in the least with its blood supply, for it may well be conceived that the general atrophy following the operation on the rat's testicle lowers the normal tension and mutual balance of the tissues to such an extent as to give the implanted foreign tumor element more room and a better chance for development. That such a mechanism is possible or even probable has, as far as we can see, not yet been proven, but nevertheless the possibility must be taken into account. We offer this series of experiments, therefore, merely
as a preliminary notice and refrain from drawing any conclusions, desiring merely to place on record results which, at least, are somewhat encouraging.

REFERENCES

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