
*THE EFFECT OF PHYSICAL AGENTS ON THE RESISTANCE
OF MICE TO CANCER*

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The report which I wish to present today has to do with further progress in the work which I reported before the Academy in June, 1915. I will review that work briefly in order to orient you with the observations made since then.

The fundamental point in immunity to transplanted cancer is that there are two types of resistance, the so-called natural and induced immunity. Mice may be rendered resistant by an injection of a quantity of homologous living tissue given at least a week or ten days before the cancer inoculation; this is called induced immunity. A variable proportion of mice inoculated with a transplantable tumor will be resistant; this is called natural immunity. The histological manifestation of resistance about an introduced cancer graft in these two types of immunity is the same and

is characterized by a lymphoid infiltration of the tissues around, and later, an actual invasion of the graft.

We first showed that there was an actual increase in the circulating lymphocytes, accompanied by hyperplasia of the lymphoid elements following cancer inoculation into immune animals. If this crisis was prevented by the destruction of the lymphocytes the immunity of the animal was destroyed. Furthermore, animals with tested immunity could be rendered susceptible by a similar destruction of the lymphocytes. The method we used for the destruction of the lymphocytes was that of small repeated doses of X-rays. It was established that this procedure would practically deplete the animal of lymphoid tissue without apparent injury to other important structures and without detectable influence on the animal's general health.

In the course of this investigation of the action of X-rays it was noted that while repeated small or a single large dose would destroy the lymphoid tissue, a single, small exposure to a ray of suitable quality would stimulate the lymphocytes. The stimulation was judged by the numbers of circulating lymphocytes and the state of activity of the germinal centers in the spleen and lymph nodes as indicated by the number of mitotic figures present. This method of increasing the lymphoid elements of the body was first used in an attempt to increase the resistance of mice to replants of their own spontaneous tumors. By this treatment we increased the resistance from 3.4% in our control series to 50% in the treated series. By a similar induced lymphocytosis we have been able to develop a resistance to transplanted cancers which compares most favorably with the immunity following tissue injection. The procedure here was to expose a number of mice to a stimulating dose of X-rays and then inoculate them with a transplantable cancer a week later, at the same time inoculating a series of controls. The following table gives the result of these experiments:

EXPERIMENT NUMBER	I	II	III	AVERAGE
Takes in X-rayed mice.....	25.0%	29.0%	28.6%	27.5%
Takes in control mice.....	77.8%	87.5%	60.0%	75.1%

We next turned our attention to finding other methods of producing lymphoid stimulation. Several agents have been found other than X-rays, but only one so far which gives a reaction extensive enough and of sufficient duration for experimental purposes. Dry heat ranging from 55 to 65° C. applied to the whole animal for five minutes was found to produce a stimulation of the lymphocytes and of lymphoid tissue of marked intensity, the increase in the number of lymphocytes persisting for a number of days. Mice treated in this manner and then inoculated with cancer a week later showed a striking degree of immunity as compared with the control animals inoculated with the same tumor at the same time. The following table gives the result of these experiments:

EXPERIMENT NUMBER	I	II	III	AVERAGE
Takes in heated mice.....	30.0%	30.0%	50.0%	36.6%
Takes in control mice.....	77.8%	78.8%	94.5%	83.6%
Number of mice used.....	20	33	54	Total 107

The effect of heat stimulation was also tested on the resistance of mice with spontaneous tumors to replants of their own cancers. The result in this case was even better than that obtained with the small doses of X-rays. The heated mice had an immunity of 59.4% as compared with 50% in the X-rayed series and 3.4% in the untreated animals.

It will be noted that in our experiments with the transplanted tumors we made our transplantations one week after exposure to the heat or the X-rays. This time was selected at first because the greatest stimulation occurred then. Further experiments indicated that if animals treated by either of these methods were inoculated during the first two or three days after treatment there was either no immunity or very slight evidence of it. The following table illustrates this point:

	AVERAGE
Takes in mice X-rayed 1 week before inoculation.....	27.7%
Takes in mice X-rayed 1 to 3 days before inoculation.....	60.0%
Takes in control mice.....	67.0%
Takes in mice heated 1 week before inoculation.....	36.6%
Takes in mice heated 1 to 3 days before inoculation.....	77.7%
Takes in control mice.....	86.2%

This observation offers a very interesting parallel with that on immunity induced by tissue injection. The immunity is non-operative during the first few days and is at its best between seven and ten days after the injection. It seems to me of considerable interest that we are able to induce the same degree of immunity by the use of physical agents as by the use of what we may call a biological agent. The points in common are: the lymphocytosis induced by the physical agents, which occurs normally after the use of the biological agent, and the latent period before the immunity, become evident after the use of all three of the agents.

Summary.—It was first shown that animals immune to transplantable cancer showed a large increase in the circulating lymphocytes after cancer inoculation. This reaction is accompanied by hyperactivity of the lymphoid tissue of the spleen and lymph nodes. If the reaction is prevented by the destruction of the lymphoid tissue the immunity is destroyed, and the animal becomes susceptible to cancer inoculation.

Two methods have been found whereby the lymphocytes may be markedly increased along with a heightened activity of the germinal lymphoid centers: (1) by exposure to diffuse, small doses of X-rays; and (2) by exposure to dry heat. The lymphocytosis and lymphoid hyperplasia induced by these two physical agents are associated with an immunity to transplanted cancer equally as great as that arising from tissue injections.

Furthermore, these methods are capable of increasing the resistance of mice to replants of their own spontaneous tumors. From the evidence at hand it seems then that the immunity aroused by these two physical agents has at least one other point of similarity to that induced by tissue injection, namely, a period of latency after the exposure before the immunity becomes evident. Whether the tissue injection, the small dose of X-rays, or the dry heat induce changes in the organism other than those associated with increase in the lymphoid tissue which would account for the immunity, is impossible to state at the present time; but the evidence now at hand points at least to the lymphoid tissue as an important agent in the immunity reaction to transplanted cancer of mice.

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