

THE LYMPHOCYTES IN NATURAL AND INDUCED
RESISTANCE TO TRANSPLANTED CANCER.

IV. EFFECT OF DRY HEAT ON RESISTANCE TO TRANSPLANTED
CANCER IN MICE.*

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The striking histological difference between a cancer graft in an immune animal and in a susceptible animal is the early appearance of large numbers of lymphocytes in the former and the relative absence of these cells in the latter. This fact has led some observers to venture the opinion that the lymphocytes may be a factor in the resistance to these growths. Da Fano¹ carried out extensive histological studies of this reaction about the cancer graft in immune animals and also extended his observations to changes in the cells of the subcutaneous tissue of the body. He demonstrated a marked increase in the lymphoid elements about the cancer graft and in the tissues, and likewise showed an increase in the closely related group of plasma cells. Later Murphy and Morton² showed that mice potentially immune to cancer developed a marked lymphocytosis after inoculation with a cancer graft. These investigators also showed that potentially immune animals can be rendered susceptible to cancer inoculation if the lymphoid tissue is depleted by means of x-rays. Murphy and Taylor³ extended the latter observation and showed that immune animals of a tested resistance can be made again susceptible to inoculation after depletion of the lymphoid tissue.

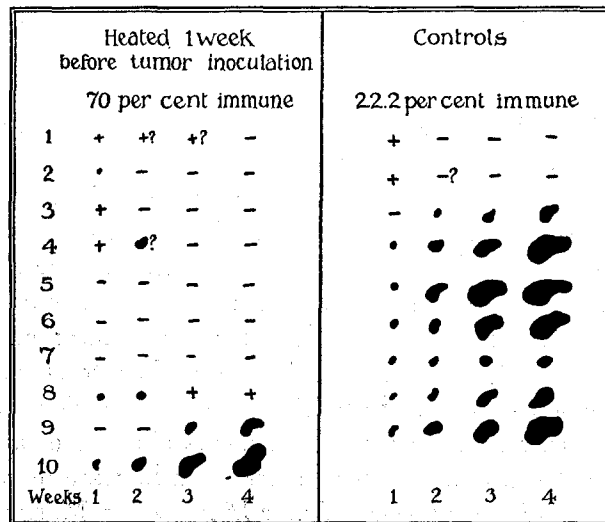
*This investigation was carried out by means of funds from the Rutherford Donation.

¹ Da Fano, C., *Z. Immunitätsforsch., Orig.*, 1910, v, 1.

² Murphy, Jas. B., and Morton, J. J., *J. Exp. Med.*, 1915, xxii, 204.

³ Murphy, Jas. B., and Taylor, H. D., *J. Exp. Med.*, 1918, xxviii, 1.

It has been deemed advisable to test the effect of induced lymphocytosis in the animal on resistance to inoculated cancer. The amount of stimulation of the lymphocytes induced by splenectomy⁴ and small doses of x-rays⁵ did not prove sufficient to influence markedly the course of these highly resistant transplantable tumors. However, with the development of the more extensive and enduring stimulation induced by heat we have an opportunity of testing the effect of such a reaction on cancer resistance.



TEXT-FIG. 1. Rate of growth of the Bashford Adenocarcinoma No. 63 in mice heated 1 week before inoculation contrasted with the rate of growth in control animals.

Experiment 1.—Ten mice of about the same age and weight were heated for 5 minutes at 55–65°C. over an electric heat lamp. 1 week later the animals, together with ten healthy controls, were inoculated subcutaneously in the groin with a strain of a 3 week old transplantable cancer (Bashford Adenocarcinoma No. 63). The rate of growth of the tumors was charted at weekly intervals thereafter. At the end of 4 weeks the heated animals showed only three tumors, with an immunity of 70 per cent. Of the nine control animals surviving, seven developed tumors, and only two were immune. This per cent of immunity (22.2)

⁴ Murphy, Jas. B., and Ellis, A. W. M., *J. Exp. Med.*, 1914, xx, 397

⁵ Murphy, Jas. B., and Morton, J. J., *J. Exp. Med.*, 1915, xxii, 800.

is in striking contrast to the 70 per cent in the heated animals. The results of this experiment are shown in Text-fig. 1.

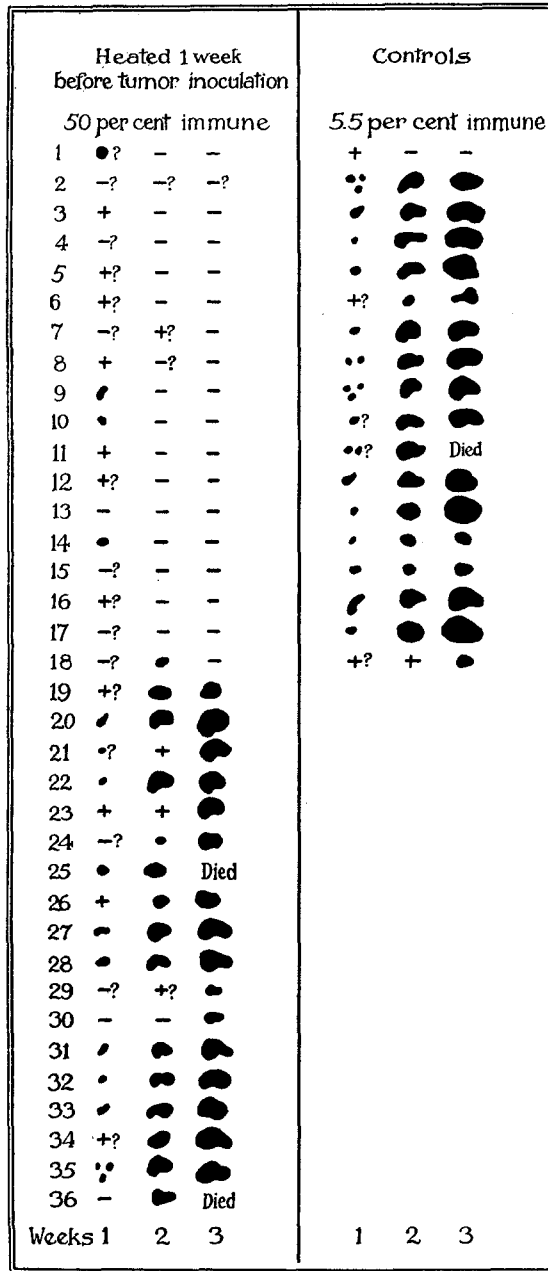
Experiment 2.—Seventeen mice were heated in the manner described in the previous paragraph. A week later these animals, with sixteen control mice, were inoculated with a strain of the Bashford Adenocarcinoma No. 63. Weekly measurements were made of the developing tumors. The heated animals showed five out of seventeen with tumors, or an immunity of 70 per cent. Eleven of the sixteen control animals developed tumors, the immunity being 31.3 per cent.

	Heated 1 week before tumor inoculation			Controls		
	70 per cent immune			31.3 per cent immune		
1	+	-	-	•	+	+
2	-	-	-	?	+?	-
3	+	-	-	-	-	-
4	-	-	-	-	-	-
5	+	-	-	•	+	+
6	+	-	-	•	+	•
7	•	-	-	+	•	•
8	+?	-	-	•	•	•
9	-	-	-	•	•	•
10	-	-	-	•	•	•
11	•	+?	-	+	+	•
12	•	-	-	-	+	•
13	+	+	•	•	•	•
14	-?	+	•	-	+	•
15	-	+	•	+	+	•
16	+	•	Died	+	•	•
17	+	+?	•			

TEXT-FIG. 2. The same as Text-fig. 1.

The difference in immunity between the heated animals and the controls presents a striking contrast. The result is shown in Text-fig. 2.

Experiment 3.—Thirty-six healthy mice of about the same age and size and from the same stock were heated for 5 minutes over an electric heat lamp at a temperature ranging from 55–65°C. A week later these animals, with eighteen normal mice, were inoculated with a 2½ week old Bashford Adenocarcinoma No. 63. After 3 weeks eighteen of the thirty-six heated animals had developed tumors, showing an immunity of 50 per cent, while seventeen of the eighteen con-



TEXT-FIG. 3. The same as Text-fig. 1.

trols had developed tumors, the immunity being only 5.5 per cent. This experiment is shown graphically in Text-fig. 3.

The three foregoing experiments, carried out on over 100 mice, show that animals whose lymphocytes have been stimulated by dry heat have a much higher resistance to transplanted cancer than control mice inoculated with the same tumor. The general health of animals subjected to this treatment did not seem in the least affected. There was no loss of weight, no roughening of the hair, or other indication of disturbance. This difference in resistance was manifest both when the tumor inoculated gave a relatively low per cent of takes, and when the tumor was highly virulent and gave a high per cent of takes.

DISCUSSION.

The absence of any acceptable demonstration of antibodies to explain cancer immunity suggests strongly that this type of resistance probably comes under the head of cellular immunity. The evidence connecting the lymphocyte with the resistance to transplantable cancer may be summed up briefly as follows: (*a*) the presence of lymphocytes and related cells about a cancer graft in immune animals, and the relative absence of these cells around such a graft in highly susceptible animals; (*b*) the general changes which take place in the cellular elements of the tissues of animals potentially immune to cancer (Da Fano); (*c*) the lymphocytic crisis in the circulating blood of potentially immune animals after inoculation with cancer; (*d*) destruction of potential cancer immunity by depletion of the lymphoid elements with x-rays; (*e*) destruction of established cancer immunity by the same means; (*f*) the marked increased resistance to cancer after artificial stimulation of the lymphocytes.

It would be difficult to adapt the foregoing facts so that they would fit either into the Ehrlich theory of cancer immunity or that of the Bashford school of stroma reaction. Neither of these explanations seems tenable in the light of the present results. That other factors than the lymphocytes are involved in the process of cancer immunity seems more than probable. It can at least be said with a degree of certainty that we have in the lymphoid elements an important link in the process of so called cancer immunity.

SUMMARY.

The marked and durable stimulation of the lymphoid elements induced by dry heat applied to the animal results in the establishment of a high degree of immunity to certain transplantable cancers in mice. This immunity is evident when the tumor used gives a low, as well as when it gives a high percentage of takes.