Immunity to Sarcoma 180 and the Induction of Leukemia

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SUMMARY

Sarcoma 180 was 100 per cent fatal in BALB and DBA mice. In the Rockland strain there was a 17 per cent spontaneous expulsion. In these, subsequent implantations, up to 11 times, yielded practically 100 per cent immune animals. Fifteen out of 47 immunized mice (32 per cent) which have died so far, presented a condition consisting of marked hepatosplenomegaly and lymph node enlargement with at times thymus hyper trophy, leukocytosis, and immature cells in the peripheral blood. The histological picture was that of leukemia with massive lymphocytic infiltration of spleen, thymus, liver, lymph nodes, and kidney. Transplants of cellular suspensions of spleen gave rise to a similar condition, serially reproducible. It is concluded that a subcellular agent escaping immunity is present in Sarcoma 180 and is capable of inducing leukemia.

A series of papers were published by Andervont from 1932 to 1937 (1-4) on the immunity induced by Sarcoma 180 in the mouse; the subject was extensively investigated then, and in 1957 it was brought up to date by the same author (5).

In this laboratory, serial transplants of Sarcoma 180 have been carried out for the last 3 years. Immunization was obtained by several methods; unexpectedly, one at a time, fifteen of these immunized animals presented leukemia, and one developed a metastatic sarcoma similar to Sarcoma 180. The sequence of the development of immunity to a sarcoma and the appearance of leukemia are the subjects of this paper.

MATERIALS AND METHODS

Sarcoma 180 was supplied to us in the Rockland mouse. It has been transplanted in 1297 Rockland mice in a total of 70 serial passages. Both males and females, ranging from 2 to 4 months of age when first transplanted, were used in approximate equal proportions. Our colony of Rockland mice has been inbred, by sister-brother matings for eight generations. BALB and DBA mice were also used in this study.

The tumor was transplanted by trocar subcutaneously in the axillary region, with pieces of tumor of approximately 5 × 5 mm. soaked in a penicillin solution. Subsequent transplants were carried out in alternate axillas. Some of the animals were immunized by surgical extirpation of the tumor.

RESULTS

Mouse Sarcoma 180 is a malignant tumor which grows rapidly in all strains of mice. It proved 100 per cent fatal in mice of DBA and BALB strains. In the Rockland strain, it soon became apparent, however, that some of the animals did not succumb to the tumor. Out of a total of 1297 mice during 70 serial passages, there were 97 per cent takes, 83 per cent deaths, and 17 per cent survival (Table 1). In the 217 animals which survived, the tumor either receded or, more frequently, was expelled spontaneously. These animals were reimplanted with Sarcoma 180. As can be followed in Table 1, the number of takes after the second transplant were minimal, yielding

1 BALB and DBA strains were sent to us by Dr. J. Burchenal of Sloan-Kettering Institute, New York City, and have been inbred for six generations in our laboratory.
96 per cent of immune animals; from the fourth to the eleventh transplants there were no more deaths, and all animals proved immune.

Out of a total of 203 mice that survived the second transplant of Sarcoma 180, 47 either died spontaneously or were sacrificed when apparently very sick. Out of these, fifteen, that is 32 per cent, exhibited a condition characterized by marked hepatosplenomegaly and lymph node enlargement; some had an enlarged thymus and immature cells in the peripheral blood. There were ten females and five males; their ages ranged from 8 to 25 months at the time of death, with a mean of 15 months, 22 days. They were immune to a mean of five implantations, with a range of 2 to 11; at the first implantation they averaged 4.5 months of age with a range of 1.5-10. Such a condition has never been seen in untreated Rockland mice of our colony, nor did it appear in 55 mice of both sexes which were sacrificed on purpose. These control animals belonged to the same stock and had the same inbreeding as the experimental ones (six to eight generations); their ages at the time of sacrifice averaged 15 months, 17 days, with a range of 8-25 months.

Histologically, the picture was that of lymphocytic leukemia; there was massive lymphocytic infiltration of spleen, thymus, and lymph nodes with loss of normal architecture; infiltration of liver and kidney was constant.

Attempts at transplanting cellular suspensions of spleen and thymus, intraperitoneally, to adult mice of the same strain were carried out in seven cases with a positive result in one of them. This transplant is now in its fifth passage.

Another immunized animal showed a tumoral infiltration of spleen and liver which closely resembled Sarcoma 180. Upon cellular transplantation, however, it proved very different, since no takes have been obtained so far.

**DISCUSSION**

The development of immunity to Sarcoma 180 in Rockland mice followed the general pattern described by Andervont (5). BALB and DBA mice always succumbed to Sarcoma 180 transplants, whereas 17 per cent of Rockland mice expelled the tumor spontaneously. Subsequent reimplantations in the surviving animals led to 100 per cent immunity from the fourth transplant onward. After variable time intervals some of these animals developed a condition characterized by marked hepatosplenomegaly, lymph node enlargement, and at times thymus hypertrophy, leukocytosis, and blasts in the peripheral blood. The histological appearance was that of lymphocytic leukemia, and, since this condition has been successfully transplanted to adult animals of the same strain, it seems safe to consider it as leukemia.

The induction of leukemia in nonleukemic strains of mice has been obtained by different investigators. Gross (8), using leukemia cell-free filtrates from AK mice administered to C3H newborn mice, obtained leukemia. Using cell-free filtrates of different mouse sarcomas and of Ehrlich carcinoma Graffi (7) described the appearance of myeloid leukemia 2-3 months after their administration in newborn mice of a nonleukemic strain. Friend (6) obtained a filtrable agent which consistently produced leukemia in adult mice and which originated in Swiss mice given inoculations, when less than 24 hours old, of a cell-free extract of Ehrlich tumor cells. Stewart _et al._ (10), in an attempt to confirm Gross' work, obtained a number of neoplasms in mice; they have proved that these are induced by the SE polyoma virus. Schwartz and Schoolman (11) have induced leukemia in adult nonleukemic mice with cell-free filtrates from brains of leukemic mice and of human patients rather than from leukemic tissues; Moloney (10) obtained 100 per cent leukemia upon injecting a cell-free preparation of Sarcoma 37. All these investigators, and others who have repeated their work (9), used newborn animals and/or cell-free filtrates. On the contrary, in this case, leukemia arises in adult mice immune to Sarcoma 180.

The explanation of the observed phenomenon is not easy. We favor the idea that both Sarcoma 180 and the leukemic condition are caused by a
cell-free agent, although proof is lacking. However, on this assumption, there are several possible explanations. Thus, (a) the immunity to the sarcoma cells may be referable to histocompatibility genes and not to a subcellular agent in the sarcoma; (b) more than one subcellular agent may occur in Sarcoma 180, and immunity to each may be developed independently; or (c) there is a single subcellular agent with two potentialities—the one which is responsible for Sarcoma 180 is inhibited by the immune reaction, and the other responsible for the leukemia is not. Evidence that immunity against a tumor may arise under conditions where histocompatibility genes are not operating has been obtained by Doménico. In studying a new sarcoma of the rat (E100) he found that immunity could be elicited by surgical removal and successive grafting of the tumor in the inbred strain of rats in which it had arisen. We feel that the possibility that the immunity against Sarcoma 180 may be related to immunity against a subcellular sarcoma-inducing agent merits further study. In any case there appears to be an agent in mice immunized against Sarcoma 180 which is capable of inducing leukemia.

A. D. Doménico, Instituto de Investigaciones Médicas, Rosario, personal communication.

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