Attempts at Tumor Adaptation by Serial Passage through Backcross Mice

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SUMMARY

A brief historical review of the technics available to effect "adaptation" of a transplatable neoplasm has been given. A mouse tumor was removed from the strain of origin and serially transplanted, for 25 generations, into F1 hybrid mice backcrossed to mice of the tumor-resistant strain. Several times during this process of serial transplantation the tumor was tested in the strain of origin and in mice of the resistant strain. The results indicate that this technic was ineffective in altering the transplantation potential of this transplantable anaplastic carcinoma.

The problem of adaptation of the transplantable tumor became assailable only after the establishment of the inbred strains of mice by Strong (10, 14-19, 22) and by other investigators (6). The development of genetically homogeneous strains of mice (genetic homozygosity) permitted serial transplantation of tumor tissue in the original ancestral mice and their derived hybrids on a reproducible and thus predictable basis and the consequent demonstration that susceptibility to transplanted tumors is under genetic control. This early work was performed by Strong (10-19), by Snell (8, 9), and by many others.

The adaptation or conditioning of tumor tissue to grow in mice of foreign strains as well as in animals of species other than that of tumor origin has had a long history. Only a brief review will be presented here. In 1926, Strong (11, 12), working with the dBrA and dBrB tumors, found that shortly after these tumors had grown progressively their transplantation potentials suddenly changed. He concluded that "mutations or genetic changes may occur within the tumor cell at least during the process of transplantation; and the tumor mass may deviate from the genetic constitution of the host tissue that gave rise to it, at least during the process of transplantation." Gorer (7), in 1948, concluded that tumors may undergo some antigenic simplification (alteration) during transplantation.

Barrett and Deringer (2) were able to induce a threefold increase in the incidence of "takes" when the tumor was transplanted into relatively resistant backcross mice following passage of the tumor through the F1 hybrid of an outcross between susceptible and resistant mice. These investigators reported that when the tumor went directly from the susceptible to the relatively resistant backcross only one-third as many backcross animals grew the tumor as from passage through the F1. Later, in 1952, Barrett and Deringer (3) reported, "The change in transplantability is induced by a single exposure (F1 hybrid passage) to the foreign environment and it is a permanent change in the character of the tumor tissue." The same authors also report that a stock tumor was transplanted for a single generation in the F1 hybrid and that when this tumor was returned to the strain of origin it was found to have a higher degree of transplantability than before its passage through the hybrid. At least for five generations of transplantation this "F1 hybrid effect" was obtained.

Strong (20, 21) grew a spindle-cell neoplasm, more recently called an anaplastic carcinoma (Stoll1) which originally arose in the forestomach of a mouse of the pBr descent. After the tumor grew predictably in mice of the strain of origin, it was transplanted into the partially related (ancestral) N strain of mice for nine transplant generations and then returned to the pBr mice for thirteen transplant generations. The tumor

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was then tested in F₁ hybrids (pBr × N) and in F₂ hybrids (pBr × N) and grew in all the F₁ mice and yielded a 9+:7— ratio in the F₂. The original pBr tumor (always having been grown in pBr mice) had grown in 100 per cent of the mice in the F₁ generation but had given a 15+:1— ratio in the F₂. The latter ratio implies that the growth of the tumor is possible in the presence of either one of two alternative dominant genes. The former ratio implies that the sojourn in the N mice altered the tumor in such a way that it subsequently depended upon two genes, both of which must be present, for progressive growth of the transplant.

The present authors (23) attempted to adapt a pBr-derived tumor to grow in mice of a totally unrelated resistant strain (F strain) by serial growth in the F₁ hybrid. Contrary to the foregoing reports of tumor adaptation by the various tech-nics described by other investigators, the tumor did not exhibit any tendency to "adapt." We were unable to ascertain any "hybrid effect" or enhancement of the tumor to grow in the resistant mice of F strain even after 27 serial transplants through the F₁ hybrid of a cross between F and pBr mice. We, therefore, concluded from the data that this tumor could not be "adapted" by the method of F₁ growth to grow subsequently in mice of the resistant parent.

This paper will report further attempts to adapt this same pBr-derived anaplastic carcinoma by serial transplantation through the backcross to the resistant parent (F₁ pBrF X F). MATERIALS AND METHODS

All animals used in this experiment were born and raised at the Biological Station of Roswell Park Memorial Institute, Springville, New York. The anaplastic carcinoma used in this study arose in the forestomach of a mouse of a highly inbred strain, the pBr. The origin of the pBr mice and the origin, genetics, and pathology of this tumor have been extensively studied by Bagshaw and Strong (1) and by Strong (21). It should be noted that the N strain is ancestral to the pBr, and there is no genetic relationship between mice of the pBr and the F strains.

The tumor was grown in mice of the original pBr strain for 75 transfer generations and was given the symbol Tp75b. Approximately 1 cu. mm. of tumor tissue was transplanted subcutaneously by the trocar method, into the right side of mice of the backcross to the resistant parent (F₁ pBrF X F) at intervals of 21-40 days for 25 serial transplant generations. At the time of each transplant the tumor was tested in pBr and F mice to determine if there were any change in the "transplantation potential" as measured by tumor takes.

RESULTS

Of 1145 backcross animals implanted with the pBr neoplasm there were 89 (7.8 per cent) that supported its growth; and 1056 (92.2 per cent) that rejected it.

Examination of the resulting curve based upon successive transplant generations (Chart 1) would lead one to suspect that there was a marked fluctuation from the mean average from time to time. However, when this curve was subjected to a significance test at a 12.5 per cent level (a three-gene "take" percentage for a F₁ pBr X F backcrossed to a resistant parent) it was found that only three points (Tp1, Tp13, Tp14) were significantly different from this level. One of these significant differences would be expected to occur by chance alone when working at the 5 per cent level of significance. Since all the significant values were below the expected value, this would not seem to indicate oscillating gene numbers or genic instability.

The tumor grown in the backcross mice when returned to the pBr parent mice grew as well as before passage through the backcross mice. When this tumor was tested in F mice there was no growth or even enhancement of the tumor's ability merely to sustain itself.

DISCUSSION

As has been previously reported by Strong (20, 21) this tumor has exhibited a fluctuating or variable characteristic when transplanted into the F₂ hybrid of a cross between the pBr and
N strains. It should perhaps be pointed out that, when the pBr tumor is transplanted into the pure N strain, it grows with greatly reduced vigor. The appearance of apparent rhythms has been investigated many times. Bashford et al. (4) in 1905 reported, “Success (in transplantation) is seen to increase through a series of successful inoculations till a maximum is reached. From this point onwards success diminishes till a minimum is arrived at, from which the curve again rises to a maximum. . . .” Strong in 1929 (13) concluded that rhythms are artifacts and may be explained by a genetic analysis of the mice inoculated. Bittner (5) performed several similar experiments and reached the conclusion that “rhythms of growth do not occur in the transplanted tumor cell.”

As might be expected, when the genetic makeup of the tumor does not change, neither does it change in its transplantability.

From these data and other published works (20, 21) it would appear safe to say that this tumor does not respond to any of the “adaptive” technics so far tested which have been reported by other workers. The pBr transplantable tumor has resisted all genetic and other biological attempts to alter its strain specificity. It remains constantly a strain-specific tumor.

REFERENCES
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