EFFECT OF BLOOD FROM IMMUNE ANIMALS UPON TRANSPLANTABLE TUMORS

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Even a cursory review of research in experimental cancer will reveal many inconsistencies, various workers having obtained contradictory results when attacking a problem with apparently similar methods. In many cases, however, patient repetition with careful checking up of the findings has brought to light factors which offer a satisfactory explanation for these puzzling variations. In this study an attempt was made to clear up one of the problems in which different workers have reached diametrically opposed conclusions.

Jensen (1) reported the disappearance of transplanted tumors in mice injected with serum from rabbits treated with carcinoma. In a later publication (2) he stated that while he realized that spontaneous retrogression would explain most of his “cures,” it did not account for the disappearance of several of the very large tumors.

von Leyden and Blumenthal (3) reported the successful outcome of the treatment of a dog with a carcinoma, the diagnosis of the growth having been verified by microscopical examination. The method was as follows: Several rabbits were given a series of subcutaneous injections of carcinoma emulsion over a period of several weeks, and the serum obtained from these rabbits was injected subcutaneously into the dog.

Clowes (4) reported the results of experiments with mice in which one half of the animals received injections of “immune” serum obtained from mice whose tumors had retrogressed spontaneously. The other half acted as controls and received normal
mouse serum. Of the twenty mice in the first series, only one failed to show the beneficial effect of the immune serum, and all were alive at the time of the report; while in the control series, five were dead and all the others had tumors exceeding in size those of the first series. Clowes and Baeslack (5) reported the results of experiments in which one lot of mice was treated with tumor mixed with immune serum, a second with tumor mixed with normal serum, and a third with tumor mixed with normal saline solution. The difference between the results obtained in the two latter groups was negligible. The difference between the results in the "immune" set and in the two control sets, however, was considerable, 31.6 per cent of tumors developing in the controls and only 12.3 per cent in the immune group. On the basis of these findings, they justified their assumption of the presence in the blood of immune bodies antagonistic to the development of carcinoma.

Crile and Beebe (6) reported a series of ten blood transfusions in dogs with an infectious lymphosarcoma, resulting in cure in seven cases and in marked improvement in two. In the remaining case, in which the treatment was a complete failure, it was later found that the donor was not an immune animal.

von Dungern (7) obtained serum from rabbits in which there has occurred spontaneous retrogression of a sarcoma. Seven rabbits were treated by intravenous injection of this serum before being inoculated with sarcoma. Nine other rabbits were employed as controls. Six of the control animals developed tumors; in none of the treated animals did a tumor develop. Uhlenhuth, Händel, and Steffenhagen (8), however, performed the same experiment and found that rats treated with "immune" serum gave 94 per cent of successful takes, whereas those treated with normal serum gave 83 per cent, and those that received no treatment at all gave only 66 per cent. In another series of experiments, these authors mixed an emulsion of tumor tissue with immune serum. The injection of this mixture gave 100 per cent successful takes. In their experience heterologous immune serum proved just as unsuccessful as the homologous serum.
Haaland (9) treated Berlin mice with the serum of immune Hamburg mice. On subsequent inoculation of the Berlin mice with a sarcoma to which they were normally susceptible the tumors grew just as well as they did in the untreated controls. He then repeated the experiments, employing the serum from immune Danish mice; but here again there was no difference between the growth of the tumors in treated and in untreated animals.

Russell (10) and Bashford, Murray, and Cramer (11) also failed to obtain positive results with the blood from immune animals.

Sisto (12) repeated the experiments of von Dungern (13) and others in attempting to influence tumor growth by the injection of splenotoxic, orchidotoxic, and hepatotoxic sera from rabbits into which emulsions of the fresh respective rabbit organ had been injected. His published charts show practically no effect of the injections one way or the other.

It would not be amiss in a paper of this character to make mention of a closely allied but not quite similar method of treatment that has been tried in man. In 1910 Hodenpyl (14) published a preliminary report of the treatment of carcinoma by the subcutaneous and intravenous injection of ascitic fluid from a patient who, he believed, had undergone a spontaneous recovery from carcinoma. All of his patients showed subjective improvement. It is, however, well known to those who have had experience in the treatment of inoperable carcinoma that every new form of therapy along this line is followed by a temporary subjective improvement, i.e., relief of pain, diminution of weakness, improvement in appetite, etc., only to be succeeded by the inevitably fatal termination. Hodenpyl stated that the tumors diminished in size and that some disappeared. No cures were obtained, however, and the donor of the ascitic fluid also died later from cancer.

Ill and Miningham (15) repeated Hodenpyl's treatment in a series of twenty-seven cases in which ascitic fluid was injected subcutaneously. The fluid was obtained from a patient who was apparently recovering from carcinoma of the liver; but
autopsy later on revealed widespread carcinoma of the liver, ovaries, and intestines. The authors noted marked subjective improvement, although they too failed to produce a single cure with this treatment.

In the experiments about to be reported, the procedure was as follows: The rats used were those known in the laboratory as the Marshall and the August breeds. The Marshall rats are susceptible to the Flexner rat carcinoma and refractory to the Jensen rat sarcoma. The August rats have the reverse characteristics in respect to these two tumors. To make doubly sure that the animals used were immune, a preliminary inoculation of the Flexner rat carcinoma (FRC) was made in the August, and of the Jensen rat sarcoma (JRS) in the Marshall rats. Only those animals were used which did not develop tumors or in which there was a small growth with subsequent complete retrogression. These animals constituted the stock from which the immune blood was taken.

One group of Marshall rats was treated by intraperitoneal injections of blood from the August rats which had showed a natural immunity against the Flexner rat carcinoma. A second group of Marshall rats received an intraperitoneal injection of blood from normal Marshall rats. A third group received no preliminary injection of blood. All three groups were then inoculated with grafts of 0.002 gram of the FRC in the right axilla. Exactly the same plan was followed with the August rats, the immune Marshall rats being used as the source for the immune blood, and the JRS being inoculated. The amount of blood injected varied from 2 to 3 cc. depending upon the size of the animal, the idea being to take as much blood as possible without killing the rat. The tumor inoculation was made synchronously with the blood injection or within a period of forty-eight hours after it.

In accordance with the theory of the workers cited, there should have been a complete absence of growth or at least a noticeable retardation of growth in those animals that had been treated with blood taken from the immune animals. Examination of the records, however, showed that the rats treated with the immune
blood not only did not show any absence or retardation of growth of the tumor, but actually showed tumors that were in most instances larger, and developed earlier than those in the untreated animals. Even the animals treated with normal blood showed this phenomenon though in a lesser degree. Gay (16) found that injection of blood from insusceptible or refractory animals lead to an increase in the number of takes of carcinoma implantation.

Another series of experiments was made in order to determine whether the blood or other proteins injected act as a food. Three sets of rats, 36 in each group, were employed. One group received 1 cc. of blood (18 rats subcutaneously, and 18 intraperitoneally) every three days over a period of six weeks. A second group received 1 cc. of egg-white (18 subcutaneously, and 18 intraperitoneally) every three days over a similar period. A third group was kept as controls. All these animals were inoculated with the JRS, and the tumors were charted every week for eight weeks. No appreciable difference was noted in the growth of the tumors in the three groups. Hence, the possibility that the injections acted as nutriment could be disregarded.

CONCLUSIONS

It is apparent from these experiments that:
1. If immune bodies do exist in animals that are refractory to tumor growth, they are not resident in the circulating blood.
2. The transfusion of blood, if it has any influence, accelerates the development of a tumor, as regards both time and intensity of growth; the inadvisability of transfusing human cancer cases is therefore evident.
3. The results obtained by those investigators who report successful cures after injections of blood or serum must be explained by the assumption that they were dealing either with infectious granulomata or with tumors that disappeared spontaneously.

In order to reduce the effects of extraneous factors as much as possible, the tests were conducted in eight successive series, each
set containing five test animals and ten controls. The test animals were those treated with preliminary injections of "immune" blood, the controls those that received injections of normal blood or nothing at all.

REFERENCES

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