Effects of Radiophosphorus and Cortisone on Transplanted Mammary Adenocarcinomas in Susceptible and Resistant Mice*

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MATERIALS AND METHODS

Test animals are described in Table 1. The mouse mammary adenocarcinomas included E 0771 (C3H/Bl6 stock) origin, and Z8352 of C3H (Bittner Z stock) origin, maintained for 42 passages in B6C mice.

Tumor implantation was accomplished mainly by subcutaneous injection of saline suspensions of tumor cells prepared from freshly excised tumors forced through a tissue press to yield a mince which could be passed through a 22-gauge needle. This mince was suspended in a ratio of 1 gm. of minced tumor to 19 ml. (Z8352) or 9 ml. (E 0771) of sterile 0.85 per cent NaCl solution, filtered through four layers of 19-ply gauze and allowed to sediment 10 minutes at room temperature. The supernatant suspension of cells was used for tumor implantation in a volume of 0.1 ml.; the sediment was discarded. The uniformity of the suspension was maintained by continuous mixing during tumor implantation. The 0.1-ml. challenge inoculum of tumor Z8352 contained approximately 2 million cells (counted in a hemocytometer), that of E 0771 contained about 3 million cells. In a few experiments fragments of tumor tissue were implanted subcutaneously by trocar; the fragments were selected for uniformity of size and weight. Aseptic technique was followed throughout.

Radioactive phosphorus (32P) was obtained from the Oak Ridge National Laboratory as H3PO4 in a weak HCl solution containing 0.025 mg. of carrier phosphorus (31P) per millieurie of radioactive phosphorus. The concentration of radioactivity in each shipment was determined by use of a Victoreen r-meter.1 The solution was diluted with sterile 0.85 per cent NaCl solution to the desired concentration of radioactivity, and 0.2 ml. was administered intraperitoneally to each test animal 3 days prior to the implantation of tumor cells.

Cortisone acetate (Cortone-Merck), 11-dehydro-17-hydroxyecorticosterone-11-acetate, 1.5 mg/ml, was diluted with sterile 0.85 per cent NaCl solution to a concentration of 1.0 mg/0.1 ml. Usually, a single injection of 2 mg. was given subcutaneously 1 day before the inoculation of tumor cells.

Following implantation of tumor tissue, test and control animals were observed daily until death or for 3 months after implantation.

Method of reporting results.—Since mouse mammary adenocarcinoma cells transplanted into susceptible mice regularly grow progressively to kill the host, the time from implantation to death is a convenient measure of the rate of development of the neoplastic process. The Percental Accelerant Index (PAI) devised by Shear et al. (55) was employed to compare the longevity of test and control mice. The PAI was calculated from the formula:

\[
PAI = \left( \frac{C}{T} \right) \times 100
\]

\(C\) represents the interval in days from challenge to death from cancer of 50 per cent of the control group of mice; \(T\) is the similar interval for the test group.

RESULTS

Effect of radiophosphorus and/or cortisone on transplantation in susceptible mice.—For the trans-
plantation of Z8352 tumor cells, ZBC mice were pretreated with 8 µc. of P³², 2 mg. of cortisone, or both; female C57BL/6 mice were prepared by intraperitoneal injection of 20 µc. of P³² followed 2 days later by subcutaneous injection of 2 mg. of cortisone. A 5 per cent suspension of E 0771 was used for challenge.

Table 2 summarizes three replicate experiments with Z8352 and one experiment with E 0771. Combined pretreatment of ZBC mice consistently accelerated the development of transplanted Z8352 tumor cells. The PAI in the three experiments varied from 21 to 35 per cent. In contrast, pretreatment with either P³² or cortisone alone failed to enhance tumor transplantation significantly. The PAI for groups given P³² alone varied from 3 to 23 per cent, while that for cortisone-treated groups of mice ranged from −5 to 23 per cent.

Chart 1 illustrates the combined data. The progressive influence of P³² and cortisone on tumor transplantation was observed by comparison of relative mortalities with time. The relative mortalities of test and control groups differed significantly by the "2 × 2" χ² test (13); 50 per cent of 57 pretreated mice versus 22 per cent of 55 untreated controls, χ² = 9.4, P < 0.003; 50 per cent of 55 control mice versus 88 per cent of 57 pretreated animals, χ² = 19.0, P < 0.001.

Pretreatment with radiophosphorus alone exerted an accelerative effect of 16 per cent. χ² analysis showed that P values were not significant (P > 0.01) until late in the course of the neoplastic process. Pretreatment with cortisone alone did not significantly affect the early stages of the malignant process, and its effect was of doubtful significance in the later stages of the disease.

In contrast to the effect with the Z system, combined pretreatment produced little if any acceleration with the C57BL/6 system (PAI = 5 per cent).
Effect of dosage of radioactive phosphorus in combination with cortisone upon enhancement of tumor development.—ZBC mice were prepared with from 8 to 50 \( \mu \text{c.} \) of \(^{32}\text{P} \) per animal, in combination with 2 mg of cortisone; 10–70 \( \mu \text{c.} \) of \(^{32}\text{P} \) with cortisone was given to C57BL/6 mice. All mice were challenged with viable tumor cells as in the preceding experiment. The results of this study are presented in Table 3. It can be seen that all test groups challenged with Z8352 exhibited the acceleration of tumor development previously noted in mice pretreated with radioactive phosphorus and cortisone. Although a slightly greater effect was observed in the test groups pretreated with concentrations of \(^{32}\text{P} \) in excess of the 8 \( \mu \text{c.} \) employed initially, the use of larger doses (20–50 \( \mu \text{c./animal} \)) did not appreciably increase the degree of tumor enhancement.

Little acceleration of E 0771 development in C57BL/6 mice was induced with from 10 to 40 \( \mu \text{c.} \) of \(^{32}\text{P} \) in combination with cortisone. Higher dosages of radiophosphorus produced enhancement evidenced by per cental accelerated indices of from 10 to 31 per cent.

Effect of combined pretreatment on transplantation of Z8352 in Zb mice.—Although the growth of the Z8352 tumor of inbred C3H origin occurs uniformly in ZBC mice, the back-cross animals do differ genetically from the C3H (Z) donor strain. It was possible that this incomplete homology of the Z system might account for the greater effectiveness of pretreatment with respect to dosage compared with that observed with the C57BL/6 system. The results of pretreatment and challenge of inbred Zb mice, genetically homologous to the Z8352 tumor, are presented in Table 4. Treatment with cortisone in combination with 8 or 20 \( \mu \text{c.} \) of \(^{32}\text{P} \) per animal before transplantation of Z8352 tumor cells produced enhancements of 40 and 30 per cent, respectively (PAI). Since enhancement was demonstrable in the homologous host-tumor preparation of test mice. Test and untreated control animals were challenged with 0.1 ml of a 2, 5, or 10 per cent suspension of viable E 0771 tumor cells. Table 5 shows that pretreated mice challenged with a 10 per cent suspension of tumor cells exhibited an acceleration of tumor development of 24 per cent (PAI). Mice similarly prepared but challenged with a 5 per cent suspension of tumor cells showed an acceleration of only 10 per cent; no
tumor enhancement was observed in pretreated mice challenged with a 2 per cent cell suspension. With this C57BL/6 tumor-host system, appreciable enhancement depended upon pretreatment with cortisone and at least 50 μc. of P⁴⁰, in combination with a challenge inoculum of approximately 3 million cells; with the Z system, in contrast, even greater acceleration was achieved with only 8 μc. of P⁴⁰ and an inoculum of approximately 2 million cells. The difference suggests that mice differ by strains with respect to the threshold level of radioactive phosphorus and cortisone required to so alter the host physiologically as to accelerate development of a subsequent homologous tumor transplant. An optimal challenge dose also is involved.

The enhancement obtained with higher dosages of pretreatment and challenge inoculum was verified in further experiments. Radiophosphorus, 50 μc., and 2 mg. of cortisone in combination with an inoculum of 0.1 ml. of a 10 per cent E 0771 cell suspension produced respective enhancement of 33 and 22 per cent. The compiled results are shown in Chart 2. The differences between test and control groups were significant by χ² analysis.

**Effect of radiophosphorus and cortisone on transplantation in heterologous mice.**—Male and female C57BL/6 mice were treated with graded doses of P⁴⁰ (10–80 μc/animal, ten animals/group) in combination with cortisone. After treatment the test and control mice were implanted with viable Z8352 tumor fragments. A large number of treated mice developed palpable nodules at the site of tumor implantation; untreated animals exhibited only a few small growths which regressed more rapidly than those in test mice. All tumors in test and control animals regressed completely 4 weeks after implantation. Evidently pretreatment modified temporarily but did not suppress the resistance of the C57BL/6 host to the foreign tissue.

In this study radiophosphorus pretreatment was followed 2 days later by a single dose of cortisone. Tumor implantation was carried out 24 hours later. Since the enhancement of heterologous tumor transplantation reported by Foley (14), Foley and Silverstein (15), and Howes (30) resulted from multiple injections of cortisone, the effect of such treatment in combination with internal irradiation was investigated. Two groups of male C57BL/6 mice were given 80 μc. of radiophosphorus intraperitoneally. Two days later all animals were given 1 ml. of cortisone subcutaneously; the dose was repeated every 2 days until the termination of the experiment. One day after the first injection of cortisone the mice of one experimental group were implanted with Z8352 tumor fragments.

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**TABLE 4**

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**TABLE 5**

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**Chart 2.**—The effects of radioactive phosphorus and cortisone in combination upon the development of transplantable mouse mammary cancer E 0771 in C57BL/6 mice.
hosts (14, 30). Female Zb mice were prepared by
administration of 80 μg. of cortisone. Moreover, under
the conditions of this experiment, treatment resulted
in marked weight loss and eventual death of all
test and control animals. The first death occurred
19 days after the initial injection, when each ani-
mal had received 10 mg. of cortisone. Forty-six
days after the start of experimentation, the last
animal in the test and control groups expired; this
mouse had received 22 mg. of cortisone.

The influence of pretreatment on heterotransplantation of the E 0771 tumor was of interest,
since it is transplantable to some extent in foreign
hosts (14, 30). Female Zb mice were prepared by
administration of 80 μg. of P32 and 2 mg. of corti-
sone; thereafter, test and untreated control ani-
mal were implanted with fragments of E 0771 tu-
mor tissue. The results in Table 6 show that E 0771
could be transplanted successfully in Zb mice witho
out pretreatment. Susceptibility was in-
creased by treatment, however, as evidenced by
the higher percentage of successful tumor trans-
plants and the decreased longevity of the tumors oc-
curred in three of these animals during the course of the experiment.

The effect of pretreatment on heterotransplantation of the E 0771 tumor was investigated fur-
ther with ZBC and CFW mice prepared with 50 μg. of P32 and 2 mg. of cortisone. Following prepa-
ration, test and control animals in groups of twelve
(ZBC) or ten (CFW) were challenged with 0.2 ml.
of a 10 per cent cell suspension. Of the ZBC mice,
nine of twelve treated animals died with tumors,
compared with six of twelve controls. Among
treated CFW mice six of ten died with tumors
compared with four of ten controls. The successful
transplantation into both treated and untreated
ZBC and CFW mice indicated that E 0771 lacked
genetic specificity. The higher incidence of suc-
cessful grafts in treated hosts was considered in-
sufficient to demonstrate enhancement by P32 and
cortisone.

Effect of radioactive phosphorus and cortisone,
singly and in combination, on unchallenged mice.—
Control groups of mice were included in the vari-
ous experiments to test the toxicity of the concen-
trations of radioactive phosphorus and/or corti-
sone employed for preparation of the test mice.
Following administration of radiophosphorus and cortisone, the mice were observed daily for 90
days. The compiled data from these studies are presented in Table 7. The sporadic deaths in control
groups do not suggest that the decreased longevity of the test mice resulted from direct
toxicity of the P32 and cortisone.

The possibility that preparatory treatment had
affected the test mice by predisposing to microbial
infection was considered in view of the known ad-
verse effects of ionizing radiation and cortisone
upon the resistance of animals to infectious agents
(60). In certain of the experiments representative
numbers of mice from each of the experimental
and control groups upon death from cancer were
examined at autopsy, and tissues were selected for
bacterial culture. Tissues from mice representa-
tive of all groups commonly yielded microorgan-
isms. The bacteria represented genera usually
found as secondary invaders rather than primary
pathogens. No significant differences were found
in the comparative frequency of isolation or in the
types of bacteria recovered from nonirradiated
control animals and test mice. It was considered that the isolation of microorganisms probably reflected bacterial invasion occurring during the agonal stages of the malignant process or after the animal had died from cancer. The organisms may have come from the intestines since they were members of genera known to be common inhabitants of the intestinal tract of animals. It was concluded that bacterial infection was not an important factor in the difference between test and control mice as to time until death from cancer.

DISCUSSION
The described experiments were conducted to assess the influence of pretreatment with internal radiation in combination with cortisone upon the response of mice to transplanted mouse mammary cancer. Adequate preparation under specified conditions was found to decrease the longevity of challenged mice. Although ionizing radiation and cortisone can be toxic or lethal to experimental animals, in these investigations the decreased longevity could not be attributed to direct toxic effects exerted by the P32 and cortisone. The possibility that preparatory treatment, by predisposing to bacterial infection, contributed to the decreased time until death from cancer of test mice was discredited by bacteriological examination at autopsy of representative test and control mice dead from cancer. No significant differences were noted in the comparative frequency or types of bacteria recovered from treated and untreated animals. The enhancement elicited by pretreatment agrees generally with the findings of some previous investigators (3, 7, 16-19, 34, 44, 45, 47, 51, 53, 66), who reported that treatment of recipient animals by single or repeated doses of whole-body x-radiation, prior to or immediately after cancer implantation, altered the response to implanted malignant tissue. The alternative effect generally was manifested by accelerated development of the malignant process as indicated by larger tumor growths, shortened time until death from cancer, and an increased percentage of successful grafts in test mice compared with nonirradiated control animals. Contrariwise, it has been reported that the resistance of recipient animals to tumor transplantation increased when the hosts had been exposed, prior to implantation of viable tumor tissue, to a single small dose of whole-body x-radiation 1 week previously (44, 47, 49), or to a series of small daily doses (58, 54). This increase in resistance resulted in fewer successful grafts and in inhibition of growth of successful tumor transplants. No such evidence of tumor transplant inhibition was obtained in this study. However, results of whole-body x-radiation cannot be compared properly with those of irradiation with radioactive phosphorus internally administered because of inability to compare true dosage levels of the two types of radiation. Internal radiation with radioactive phosphorus, largely localized, continues as long as the radioactive substance remains in tissues, or until its decay is complete, whereas external x-radiation, exerting general effects upon all tissues, continues only as long as the radiation source is applied.

Cortisone therapy instituted at the time of tumor implantation or shortly thereafter reportedly resulted in complete or partial inhibition of the growth of the malignant tissue (5, 6, 20, 24, 28, 29, 33, 58, 59). No inhibition of tumor transplantation here was observed whether recipient animals were treated prior to tumor implantation with cortisone alone or in combination with P32. This result disagrees with reported effects. In this study cortisone was administered as a single dose of 2 mg. 1 day prior to implantation of tumor cells, whereas in earlier investigations the hormone was employed in a series of injections beginning shortly after or at the time of cancer transplantation. Reported dosages of cortisone considerably exceeded 2 mg.; indeed, dosage was commonly so great as to injure and kill recipient animals (5, 6, 28, 33). Furthermore, the majority of these investigations concerned the effects of cortisone upon transplantable lymphomas or lymphosarcomas. Since cortisone exerts a marked atrophic effect upon lymphoid tissue (1, 2, 24, 28, 32) and inhibits the formation of granulation tissue (30, 31, 32, 37), it seems reasonable that the effect of this hormone upon lymphomas and lymphosarcomas would differ appreciably from that on mammary adenocarcinomas. Sugiura et al. (59) reported that cortisone markedly inhibited growth of three types of rat or mouse sarcoma but had little or no effect upon two types of mouse carcinoma.

The possibility that tumor enhancement in pretreated ZBC mice resulted from the suppressive effect of internal radiation and of cortisone upon resistance mechanisms reflecting immunogenetic differences between tumor and host (91) was discredited by the finding that pretreatment with P32 and cortisone accelerated ZB352 tumor development in Zb mice as well as in ZBC mice. Moreover, pretreatment of inbred C57BL/6 mice accelerated development of the transplanted E 0771 tumor which arose spontaneously in this mouse strain.

Although enhancement of homologous tumor transplantation by pretreatment was demonstrated for two different host-tumor combinations in these studies, the required experimental conditions
differed. Enhancement was observed with ZBC and Zb mice treated with cortisone and P\textsuperscript{32} at dosage levels from 8 to 50 μc prior to challenge with a 5 per cent suspension of viable Z8352 tumor cells. Similarly prepared C57BL/6 mice challenged with a 5 per cent suspension of E 0771 tumor cells failed to show enhancement until the dosage of P\textsuperscript{32} combined with cortisone had been increased to 50 μc or more/animal. Size of the challenge inoculum also was of considerable importance. Adequately prepared C57BL/6 mice showed marked tumor enhancement when challenged with 0.1 ml. of a 10 per cent suspension but not a 5 or a 2 per cent suspension of E 0771 tumor cells. For each host-tumor combination the demonstration of maximal tumor enhancement apparently depended upon an optimal relationship between preparatory treatment and concentration of challenging tumor cells. It seems likely that the amount of pretreatment required for adequate preparation is governed by the relative degree of radiosensitivity characteristic of the host strain of mice. Differences in the comparative concentration of Z8352 tumor cells required to demonstrate tumor enhancement in pretreated ZBC and Zb hosts, and of E 0771 tumor cells most effective for challenge of treated C57BL/6 mice, may reflect inherent growth characteristics of the two tumors. The finding that an optimal concentration of tumor cells is required for the elicitation of the tumor-enhance effect in pretreated hosts may indicate the mode of action of pretreatment. The prior administration of P\textsuperscript{32} and cortisone to recipient animals may induce temporary impairment of host resistance so that conditions more conducive to development of the implanted malignant cells are established for a limited time. Consequently, the concentration of cancer cells implanted must be sufficiently great to initiate and maintain maximal proliferation during this limited period of increased susceptibility of the treated host. This postulate assumes that accelerated development of the malignant process occurs for the most part before any appreciable re-establishment of resistance can occur from regeneration of the radiation-damaged defensive mechanisms of the treated host. Re-establishment of resistance upon the part of the treated host challenged with a suboptimal dose of cells conceivably would slow the initial accelerated development of the cancerous process so that finally no appreciable difference in the time until death of the test animals compared with untreated control mice would result.

All attempts to transplant the Z8352 tumor of Z origin to inbred C57BL/6 mice were unsuccessful despite utilization of various concentrations and combinations of radiophosphorus and cortisone for the preparation of the recipient animals. Apparently, the prior administration of P\textsuperscript{32} and cortisone under the experimental conditions employed was not sufficiently effective to overcome the “strain barrier,” which prevents the successful transplantation of specific tumors to genetically resistant hosts. The E 0771 tumor, on the other hand, was successfully transplanted to inbred Zb, hybrid back-cross ZBC, and random-bred CFW mice whether or not the recipient animals were pretreated. The ability of the E 0771 tumor to grow in inbred or heterozygous strains of mice without known genetic relationship to the inbred C57BL/6 strain of origin indicates that this neoplasm requires little genetic compatibility in host strains of mice. However, pretreatment of alien hosts with P\textsuperscript{32} and cortisone generally resulted in an increased percentage of progressive E 0771 tumor growths and fewer tumor regressions as compared with those of untreated control animals. The difference between the percentage of successful transplants in test and control animals possibly did not reach significance because of the high incidence of “takes” in the control animals. The finding that prior treatment of Zb mice with P\textsuperscript{32} and cortisone enhanced the development of heterologous E 0771 tumor transplants, as evidenced by decreased longevity of the test mice, provided further evidence of the alternative effect of P\textsuperscript{32} and cortisone. It appeared that prior administration of P\textsuperscript{32} and cortisone altered the resistance of recipient animals to the development of heterologous tumor implants, provided the tumor grew to some degree in the foreign strain of mice. This result is in accord with previous findings concerning the influence of radiation and/or cortisone upon transplantation of a variety of experimental neoplasms in foreign strains or species of animals (3, 7, 14–17, 19, 30, 35, 38, 42–45, 54, 56, 63, 64, 67, 68). Although employed successfully in the transplantation of mouse leukoses in resistant inbred mice (3, 16–19, 67, 68), these agents appeared relatively ineffective for inducing transplantation of other types of specific tumors to genetically resistant hosts.

Although much is known of the biological effects of ionizing radiation and cortisone, the mechanisms of interference resulting in altered resistance of the organism still are a subject for speculation. In the case of malignancies, attempts to determine the mode of action of these extrinsic agents are complicated by limited knowledge of factors responsible for the innate and acquired resistance of experimental animals to neoplasms. It is assumed that the tumor-enhancing effect of pre-
treatment with radiophosphorus and cortisone involves an increased growth rate of cancer cells in the susceptible treated host. The increased growth rate could result from either a direct stimulatory effect of P32 and cortisone upon the tumor cells or a depressive effect upon the resistance of the treated host. A direct stimulatory action seems improbable because (a) at the time of tumor implantation some of the P32 and cortisone administered previously has been excreted, and most of the remainder has been deposited in the liver, spleen, bone, bone marrow, and lymph nodes (4, 39); and (b) the selective deposition of P32 limits the radiation effects to the few millimeters of tissue penetrable by beta particles (4, 39). Under the conditions of these studies, then, the implanted cancer cells would be subject to little if any irradiation from the internally administered P32. The resistance-depression hypothesis seems more tenable in view of the known detrimental effects of ionizing radiation and cortisone upon factors associated with the resistance of animals. It has been reported that ionizing radiation and cortisone depress phagocytic activity (8–10, 12, 22, 37, 57, 61), destroy lymphatic tissue (2, 4, 23, 26, 27, 43, 44, 48, 50, 61), inhibit antibody formation (1, 2, 10, 11, 22, 25, 41, 48, 61), and interfere with the function of the reticulo-endothelial system (4, 8–10, 26, 27, 61). Damaging irradiation of the reticulo-endothelial system by selectively deposited P32 could conceivably inhibit the activity of this system for varying periods of time dependent on the extent of radiation injury. Another mechanism by which P32 and cortisone could adversely affect host resistance involves the known destructive action of these agents on lymphoid tissue and lymphocytes (2, 4, 23, 26, 27, 43, 44, 48, 50, 61). Murphy and associates (43–46) have presented evidence that lymphoid cells are important in host resistance to the growth of transplanted cancer cells. Since a correlation was observed between the number and activity of lymphocytes and resistance to transplanted tumors, these workers concluded that the decreased resistance of animals after irradiation resulted from destruction of lymphocytic tissue and lymphocytes. The studies of Furth (19) confirmed these findings. More recently, Kidd and Tooan (56, 65) have furnished additional evidence of the importance of lymphoid elements in the resistance of animals to transplanted tumors.

The finding that P32 and cortisone in combination could elicit the tumor-enhancive effect in ZBC mice, although either agent alone was ineffective, suggested that the combined agents functioned synergistically to alter the resistance of the treated host. The synergistic action could result from: (a) additive effects of these agents upon the physiology of the host or (b) potentiation of the effects of radiation by the cortisone, possibly by suppression of the regenerative processes associated with radiation damage (62).

SUMMARY

Pretreatment with radioactive phosphorus (P32) and cortisone in combination was found to enhance the development of implanted homologous Z835 tumor tissue in susceptible ZBC and Zb mice. Pretreatment with either P32 or cortisone alone failed to elicit the enhancive effect upon tumor transplantation obtained with these agents in combination. The enhancive effect was as readily demonstrable in the homozygous strain of mice in which the Z835 tumor originated as in hybrid back-cross ZBC animals. Preparation with radiophosphorus in combination with single or multiple doses of cortisone did not permit transplantation of the Z835 tumor in resistant C57BL/6 mice. Preparation of inbred C57BL/6 mice with radioactive phosphorus and cortisone accelerated development of subsequently implanted E 0771 homologous tumor transplants. Maximal tumor enhancement apparently depended upon an optimal relationship between the preparatory dose of P32 administered in combination with cortisone and the concentration of tumor cells in the challenging inoculum. The tumor-enhancive effect was demonstrable in pretreated inbred Zb mice implanted with heterologous E 0771 tumor tissue as evidenced by decreased longevity of test mice compared with untreated control animals. The E 0771 tumor was transplantable also in hybrid back-cross ZBC and heterozygous CFW mice, with or without pretreatment.

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