logical changes seen.

Summary. Forty-seven rabbits were given graded injections of bovine gamma globulin intravenously. These were bled frequently for antibody and complement studies and then sacrificed for histological examination. When amounts used were from .250 g to 1 g per kilo body weight, glomerular lesions attributable to hypersensitivity were seen in most animals, and regular depression of complement followed by the appearance of circulating antibodies was demonstrable. In smaller doses, no histological changes occurred and the serological alterations were inconstant.

The authors wish to express their appreciation to Dr. Charles A. Janeway and Dr. John F. Enders of the Children's Medical Center, Boston, Mass., for their help and criticism in the preparation of this manuscript.

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Received March 4, 1952. P.S.E.B.M., 1952, v80.

Induction of Necrosis in Mouse Mammary Carcinoma by Cortisone.* (19530)

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The use of 11 dehydro 17 oxycorticosterone (Cortisone) in attempts to produce regression of neoplasms is not new. Heilman and Kendall(1) reported temporary regression of a mesenchymal tumor in mice after administration of this agent in doses smaller than those used in the present study. They did not report on the nature of the damage to the neoplasms. Vrat(2) has reported that cortisone has no effect upon mouse mammary carcinoma. The dose levels he used were smaller than those employed in our studies. There has been extensive clinical use of cortisone in the treatment of various types of neoplasms in man. The results have been disappointing as to long-term effects in spite of evidence of temporary remissions.

There is a large literature(3) on the use of bacterial toxins, colloidal substances of numerous sorts and other toxic agents in producing intra-tumoral hemorrhage and necrosis in man and other animals. In general it can be said that numerous such agents induce injury to neoplasms, greater in extent and degree than that inflicted on the host, but that no agent is known which regularly causes total

* Aided by grants from the Minnesota Division American Cancer Society, the U. S. Public Health Service and the Graduate School Medical Research Fund.

TABLE I. Effects of Cortisone at Various Dose Levels on Mice with Spontaneous Mammary Carcinoma.

No. of mice	Cortisone, mg/mouse	Days of treatment	Tumor necrosis No.	Tumor necrosis %	Generalized reactions No.	Generalized reactions %
3	.50	10	0	0	0	0
12	1	4	2	17	1	8
12	2.50	4	3	25	1	8
41	5	4	14	34	12	29
14	10	4	8	57	6	43

TABLE II. Effects of Cortisone and of Terramycin upon ZBC Mice Bearing Transplanted Z-9168 Mammary Carcinoma.

Tumor transplant generation	No. of mice	Cortisone, mg/mouse /day	Days of treatment	Tumor necrosis No.	Tumor necrosis %	Generalized reactions No.	Generalized reactions %
2nd	17	5	4	5	29	5	29
3rd	12	5	4	4	33	2	17
4th	8	5	4[T]	6	75	0	0
4th[E]	13	5	4[T]	13	100	0	0
5th	17	5	4[P]	9	53	3	18

[T] Terramycin in drinking water .1%, 6 days beginning day prior to cortisone treatment.
[P] Penicillin inj. 1000 units/day, 6 days beginning day prior to cortisone treatment.
[E] Treated also with tumor extract (see text).

tumor destruction in non-fatal doses. In a few instances, both in man and in other animals, it appears that complete regression has occurred with host survival. A safe dose level for regular results of this type has not, however, been found for any substance or physical agent. Therefore further search for agents or combinations of agents capable of producing such results is not only warranted but urgently needed.

Methods and materials. Both transplanted and spontaneous mouse mammary tumors have been employed in these studies because in some respects the transplanted tumor allows more simple experimentation and interpretation. For work with transplanted tumors female ZBC animals were employed, using a spontaneous tumor derived from a Z animal. This tumor will be identified as Z-9168. Transplantations were made to the right axilla of ZBC mice by the cell suspension technic. The animals were employed for study when the tumors reached approximately 1 cm diameter. In other studies spontaneous mammary tumors from the A, Z, D, and ZBC stocks were employed. In general the tumors were more than 1 cm in diameter at the time of use. After experimentation mice were sacrificed at various intervals of time and subjected to gross and microscopic examination of their mammary tumors and their viscera. Other details of experimental procedure will be indicated in connection with the results.

Results and discussion. Table I presents the observations upon mice bearing spontaneous mammary tumors treated with various dose levels of cortisone. With increasing doses there is an increase in the proportion of mice showing gross tumor lesions. The character of the tumor lesion as seen on microscopic examination was a combination of hemorrhage and necrosis. The necrotized areas showed disorganization of tumor cell arrangements, detachment of cells, infiltration with leucocytes and nuclear pyknosis. The extent of the lesions varied from 25 to 90% of the tumor mass. Complete destruction was not observed.

In addition to the tumor injury the mice showed destructive lesions in lungs, liver and kidneys. Such effects, which are lethal unless treated as noted below, have been reported before(4). The frequency of these findings, listed as generalized reactions, also increased with cortisone dose level.

In Table II are shown the summarized results of experiments upon ZBC mice with transplanted tumors. In 25 such mice one case of spontaneous tumor necrosis was observed, therefore it would appear that any incidence higher than 4% in this tumor can be

ascribed to treatment. It will be noted that the proportion of animals showing gross tumor lesions ranges from 29 to 75%, excluding the case of mice which had in addition an intravenous injection of a Seitz filtrate of a 0.9% NaCl extract of homologous tumor tissue. Likewise as to generalized reactions the frequency was of the same order of magnitude as was found with spontaneous tumors at the same cortisone dose level, except where supplementary treatment was given.

When terramycin, 0.1% in the drinking water was given the incidence of generalized reactions fell to zero. Penicillin in the dose employed did not show such an effect. Two points are of interest in this connection. First, it is apparent that terramycin did not reduce the frequency of tumor necrosis following cortisone. Second, it is apparent that terramycin reduced the frequency of generalized reactions and allows long survival.

The fact that survival can be expected following tumor necrotizing doses of cortisone when accompanied by terramycin suggests that by combining with such treatment another agent differentially more damaging to tumor than to host tissues, more complete tumor destruction might be accomplished. Studies using radiation, chemical agents and antigenic materials to such an end are already in progress.

Conclusions. In mice bearing spontaneous and transplanted mammary carcinoma it is possible by treatment with cortisone to induce a high frequency of massive necrosis with or without hemorrhage in the tumors. Cortisone administration in necrotizing doses is also followed by inflammatory lesions in lungs, liver and kidneys, which are usually fatal. Terramycin treatment before and during cortisone administration resulted in an abolition of the above-mentioned generalized reactions. It has not been possible with cortisone alone or with terramycin to obtain complete tumor destruction. It is pointed out that cortisone necrotizing treatment in conjunction with some other agent having differential damaging effects upon tumor and host respectively, may yield better results.

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Received March 26, 1952. P.S.E.B.M., 1952, v80.

Differentiation of Growth Hormone from the Pituitary Factor Which Produces Diabetes. (19531)

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The diabetogenic effect of pituitary extracts, observed by Houssay(1), was attributed by Evans to the growth hormone(2). It is now generally accepted, despite earlier evidence to the contrary(3), that growth hormone is the factor in pituitary extracts which is responsible for the production of diabetes(4-7). Extensive experimentation has yielded clear evidence that the pituitary contains a potent diabetogenic agent, or combination of agents, which rapidly produces severe insulin-resistant diabetes when administered to susceptible animals, and which produces permanent diabetes with pancreatic damage after prolonged administration(2,8). The diabetogenic effect may be obtained in the

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