microns showed a moderate elevation in the number of fat particles. In 4 infusion studies with the 15% fat emulsion and in 3 with the 20% fat emulsion, positive reactions were obtained for acetone varying from 1+ to 2+ in 2 or 3 of the intermediate urine specimens examined during the course of the infusion. During the post-infusion phase the tests for acetone occasionally showed a faint trace and remained negative thereafter. There were no positive tests for diacetic acid. There were no indications by these tests of any greater acetone spillage occurring in recipients of the 20% fat emulsion as compared with recipients of the 15% fat emulsion.

Follow-up studies for hematologic complications in subjects who received either single or multiple infusions showed no signs of hemolytic anemia. Likewise x-rays of the lungs gave no evidence of fatty emboli or pulmonary irritation. Liver and lung biopsy specimens failed to show any organic lesions which could be attributed to the intravenous infusion of fat. Liver and kidney function studies showed no pathologic alterations which were attributable to the emulsions.

Comment. The effects of the intravenous infusion of either the 15% or 20% combined fat emulsions were in many respects similar to those noted in our clinical studies on the infusion of the 10% combined fat emulsion.(1) These pertained particularly to hematologic changes, blood pressure response and follow-up observations on liver, lung and kidney function. Constitutional reactions such as high temperatures or chills averaged 27% as compared with 9% with the more dilute fat emulsion. About 50% of the reactions encountered in this series were found to be due to the speed with which the emulsion was administered, the fast infusions being associated with the chill reaction. The temperature elevations could be accounted for on the basis of a sudden plethora of fat. In any case the concentrated fat emulsions required cautious careful administration.

Summary. Two types of combined fat emulsions, one containing 15% fat and the other 20% fat, were infused into 25 human subjects. A total of 51 of these concentrated fat emulsions were administered intravenously. The incidence of constitutional reactions was 27%. A variety of laboratory and clinical observations were made in conjunction with these infusions.

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Malignant Lymphoid Tumors in Orchidectomized Mice Receiving Hypophyseal and Ovarian Grafts at Various Ages.* (17493)

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While studying the effects of anterior hypophyseal and ovarian transplants on mammary growth in male castrate mice of strain A, we noted the occurrence of lymphoid leukemia and lymphosarcoma in a number of animals bearing these grafts.(1) The present report deals with the incidence of these tumors in the various experimental groups.

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1. Silberberg, R., and Silberberg, M., PROC. SOC. EXP. BIOL. AND MED., 1949, v70, 510.

Material and methods. The experiments have been described in detail in a previous paper.(1) Briefly, 161 male mice of the closely inbred strain A kept on a standard diet of Purina Laboratory Chow and water were castrated at the age of 3 weeks. The animals were divided into two age groups: *I. Younger age group* grafted at the age of one month: Twenty-eight castrates received four anterior hypophyses each; 26 received 2 or 4 ovaries each; 25 received a combination of 4 hypophyses and ovaries. *II. Older age group* grafted at the age of 7 months: Twenty-eight

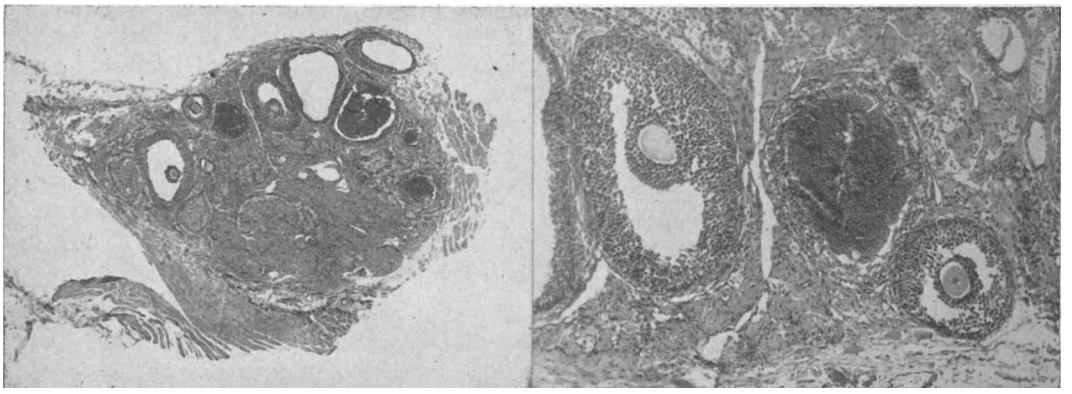

FIG. 1 and 2.
Section through an ovarian graft 21 months after transplantation. Fig. 1 (left) magnification 70×. Fig. 2 (right) magnification 345×.

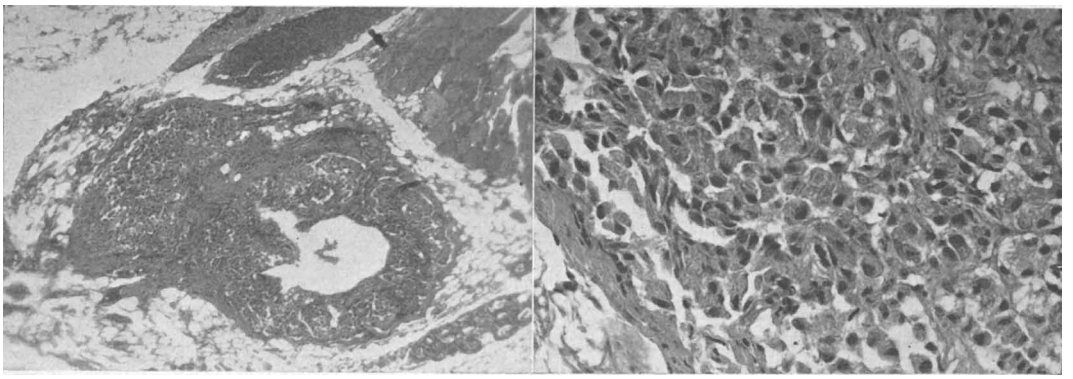

FIG. 3 and 4.
Section through an hypophyseal graft 14 months after transplantation. Fig. 3 (left) magnification 25×. Fig. 4 (right) magnification 93×.

castrates received anterior hypophyses; 25 received ovaries; and 29 received a combination of 4 hypophyses and ovaries. All grafts were obtained from freshly killed animals closely related to the host (syngenesiotransplants).(2) The glands were transplanted into a subcutaneous pocket of the chest wall.

Observations. In untreated mice of strain A which is known to have a 3.8% incidence(3) of spontaneous lymphoma only an occasional case of malignant lymphoid tumor was noted. These tumors with or without leukemia manifested themselves in large neoplasms of the mediastinum or mesentery, or in diffuse infiltration of lymph nodes, spleen, liver, kidney, lung or heart, leukemic blood picture, or in a combination of several of these findings. Only those cases were classified as malignant lymphoma in which gross and microscopic changes in liver, kidney, lung, heart, and frequently also in blood smears were sufficiently advanced to permit a clear cut diagnosis. Cases in which the microscopic findings were merely suggestive of lymphoma but not definite were listed as preleukemic. Since the present experiments were originally not designed to include observations on leukemia, the bioassay of suspected cases of malignant lymphoid disease, which would have been desirable, was not made. Mice showing merely hemopoiesis were grouped among the negatives. Microscopic examination showed

2. Loeb, L., *The Biological Basis of Individuality*, 1945, Charles C. Thomas.

3. Kirschbaum, A., and Kaplan, H. S., *Science*, 1944, v100, 360.

TABLE I.
Incidence of Malignant Lymphoid Tumors and Time of Appearance of the Neoplasms in the Various Experimental Groups.

Type of graft	Age at grafting (mo.)	No. of mice	Age at death of all mice (mo.)		Animals with lymphoma				Animals with preleukemia change			
			Mean	Range	No. of cases	%	Age (mo.) of appearance		No. of cases	%	Age (mo.) of appearance	
							Mean	Range			Mean	Range
I. Hypophysis	1	28	16.4	9–20	7	25.0	16.6	9–20	3	10.7	17.3	16–18
II. Ovaries	1	26	18.2	9–24	7	26.9	20.0	15–24	3	11.5	20.0	13–24
III. Hypophysis and ovaries	1	25	17.4	9–22	9	36.0	18.7	12–21	2	8.0	19.5	18–21
IV. Hypophysis	7	28	19.3	12–25	3	10.7	22.0	19–24	3	10.7	20.7	18–22
V. Ovaries	7	25	16.8	12–26	2	8.0	15.0	12–18	4	16.0	16.5	12–23
VI. Hypophysis and ovaries	7	29	15.7	12–24	4	13.8	17.5	12–24	3	10.3	17.7	14–22

that grafts may remain alive for a considerable length of time. The following photomicrographs 1-4 demonstrate well preserved hypophyseal and ovarian grafts. As had been found in regard to mammary cancers in these animals,(1) the development of malignant lymphoid tumors could not always be correlated to the state of preservation of these transplants at the time of necropsy. It must thus be assumed that grafts may exert an effect for some time and then undergo regression.

The incidences of malignant lymphoma, the mean age at death, and the age range at death in the various experimental groups are given in Table I.

Younger age group: Transplants of anterior hypophysis had a leukemogenic effect of about the same order (25%) as ovarian grafts (26.9%). However, ovaries were slower in calling forth this result than were hypophyseal transplants, the mean age at death of animals of the former series being 20 months as compared with 16.6 months in the latter group. Anterior hypophysis grafted together with ovaries produced malignant lymphoma about 40% more often, namely in 36% of the animals, than either hypophysis or ovaries alone, and the mean age at death in this group was 18.7 months.

Older age group: 10.7% of the castrates bearing transplants of anterior hypophysis had lymphomas at the mean age of 22 months; 8% of the animals bearing ovarian grafts alone developed lymphoid tumors at the age of 15 months, and neoplasms were observed in 13.8% of the mice bearing grafts of anterior hypophysis together with ovaries. In this group, the mean age at death was 17.5 months.

Discussion. In castrate male mice of strain A bearing anterior hypophyseal grafts, malignant lymphoid tumors were found to develop in increased numbers. This leukemogenic effect of anterior hypophysis was apparently not mediated through the ovaries since it was present in castrates which did not carry ovarian grafts. The mode of action of the anterior hypophyseal hormone in this type of leukemogenesis is unknown. Tentatively, however, the following explanation may be

offered: Anterior hypophyseal hormone by stimulating the adrenal cortex may cause a prolonged depletion and atrophy of the lymphoid tissue. This atrophy may become a stimulus to or may represent a step in leukemogenesis,(4-8) since malignant lymphoma is often preceded by atrophy of lymphoid tissue. The leukemogenic effect of the anterior hypophyseal hormone is probably not due to increased output of estrogen by the adrenals, because the mammary glands of these castrates failed to develop cancer or marked acinar proliferation in contrast to conditions found in the castrates carrying ovarian grafts.(1) As to the formation of lymphomas by transplanted ovaries, the results are in agreement with those obtained by the administration of estrogens in mice of various ages,(9) and may be attributed to the production of such hormones by the ovarian grafts. The increased incidence and the shortened latent period of lymphoma in mice bearing hypophyseal grafts together with ovarian transplants seem to represent a cumulative effect of the two hormones given off by the grafts. Whether or not the mechanism by which estrogens produce lymphoid tumors is in any way connected with that initiated by anterior hypophyseal hormone or whether two different mechanisms are involved, is unknown.

In the older age group, the incidence of lymphomas induced by anterior hypophysis fell to 10.7%. Thus the susceptibility to these neoplasms declined somewhat, as the age of the animal at the time of grafting advanced. However, the difference in the mean lymphoma age in the two age groups (5.4 months) agrees closely with the difference in age at the time when the transplants were made (6 months' difference). The latent periods of tumor formation were thus similar in both series. Of the castrates of the older age group carrying ovarian grafts 8% developed lymphoid tumors, and of those bearing ovaries together with anterior hypophysis 13.8% had these neoplasms. However, these tumor incidences are probably not truly representative of the effects of these two types of grafts in the older age group: There was a decrease in the lymphoma incidence and a lowering of the lymphoma age, whereas one would expect the lower lymphoma incidence to be associated with a prolongation of the latent period. This apparent discrepancy may, however, be explained by the relatively early age at death of the mice in these two groups. The total incidence of malignant lymphoid tumors and the mean lymphoma age would probably have been higher if the animals of these groups had reached an older age. There was no obvious cause for the relatively short life spans of these mice particularly since none of them developed mammary cancer. As to the possible role of an age factor it may be stated: However small the incidence of induced lymphoma in the older age groups, it was still larger than the zero incidence of mammary cancers observed in the same mice.

Conclusions. Mice of strain A orchidectomized before weaning and bearing grafts of anterior hypophysis, of ovaries, or of anterior hypophysis together with ovaries from the age of one month on, developed malignant lymphoid tumors. Anterior hypophysis seems to exert its leukemogenic effect (1) through the ovaries and (2) independently of the grafted ovaries, possibly through the adrenal cortex. Transplantation of ovaries together with anterior hypophysis resulted in the highest incidence of malignant lymphomas. The age factor plays in this type of leukemogenesis a less important role than in the production of mammary cancers by anterior hypophyseal and ovarian grafts.

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