method will permit measurement of considerably lower concentrations of C-reactive protein than 2 μg per ml. However, as sensitivity is increased, two limitations become progressively more important: incidence of anticomplementary activity in test specimens, and C-reactive protein interaction with normal serum constituents which affects its reaction with antibody.

Summary. A quantitative immunochemical method for determination of C-reactive protein concentration in serum is described. The sensitivity of this method, based on complement fixation, has been selected to measure the same concentration range of CRP as determined by microprecipitation. Two important features generally applicable to complement fixation methods are presented; namely, removal of anticomplementary activity from absorbed antisera and use of a reference standard to compensate for variations in fixability of complement.

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Pheochromocytomas of Adrenals in Male Rats Chronically Injected with Pituitary Growth Hormone.* (22667)

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Increased numbers of tumors of the types occurring spontaneously in the rat were observed during the course of chronic injection of normal female rats with pituitary growth hormone. Pulmonary and lymphatic tissues, reproductive organs, pituitary and adrenal glands were involved(1-6). Outstanding was the occurrence of adrenal medullary pheochromocytomas(2). Since none of this work had hitherto been done in male rats, the questions arose as to whether males would be equally responsive in body growth and similarly susceptible to tumor formation, especially as regards reproductive organs and adrenal glands.

Materials and methods. Male rats of the Long-Evans strain, of 2 different age groups, 6 and 14 months, were divided into experimental and control groups of 8 rats each. The purified growth hormone(7) was injected intraperitoneally in saline 6 days weekly. The initial daily dose of 0.5 mg was increased progressively during the first 160 days, reaching a maximum of 3.0 mg in the younger, and 3.5 mg in the older group. These doses were then maintained for the remainder of the 15-month injection period. Complete autopsies were performed on all rats. The weights of all organs were determined, and the entire organ or representative blocks were fixed and prepared for histological study.

Results. Body weight and length. The rats in the 6-month-old group weighed approximately 400 g at the beginning of the experiment and gained steadily, reaching a maximum of almost 700 g at 18 months (Fig.

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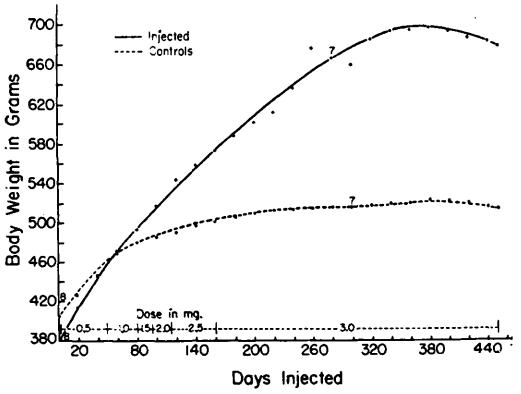

FIG. 1. Avg body wt of male rats inj. with growth hormone for 15 mo, beginning at 6 mo of age, compared with uninj. controls. Dosage shown in scale above abscissa. (No. of rats on which avg is based is indicated by numbers above curves.)

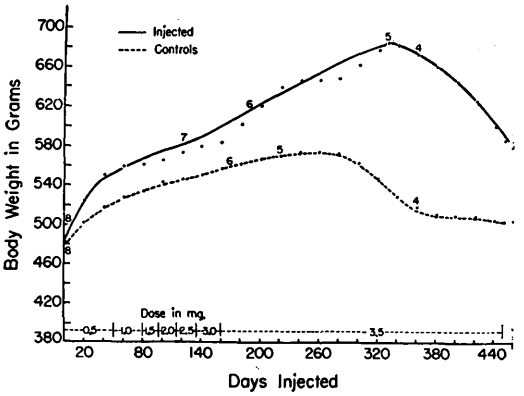

FIG. 2. Avg body wt of male rats inj. with growth hormone for 15 mo, beginning at 14 mo of age, compared with uninj. controls.

1). During the last 90 days there was cessation of growth and some loss of weight, despite the high daily dose. The rats of the 14-month group (Fig. 2) were heavier at onset (480 g) and their gain was slower and less regular, the maximum weight attained during the 15-month period being slightly less than that of the younger group, even though they received a higher dose. Both experimental groups increased in total length above their controls, and the greater increase occurred in the younger group.

Blood pressure. Because of the anticipated development of pheochromocytoma, a neoplasm which had occurred frequently in female rats similarly treated(3), determinations of blood pressure were made at intervals during the course of this experiment. A microphonic manometer for determination of the systolic blood pressure was used(8). The animals were anesthetized with ether for determination of blood pressure, and body length was determined at the same time. No significant differences were observed in the blood pressure of experimental and control rats.

TABLE I. Neoplasms in Growth Hormone Injected Male Rats and Controls (8 per Group).

	Age at onset of exp.			
	6 mo		14 mo	
Type of neoplastic lesion	Inj.	Controls	Inj.	Controls
Pheochromocytoma	4	0	5*	0
Adrenal cortical adenoma	0	1	0	1
Thyroid: Adenoma	3	4	3	1
Carcinoma	1	0	1	1
Pituitary, adenoma	4	6	4	5
Testis, Leydig-cell tumor	1	0	0	0
Thymus, squamous cell carcinoma	0	1	0	0
Lymphosarcoma, thoracic and abdominal	1	0	4	3
Mesenchymal sarcoma (synovioma)	1	0	0	0
Kidney, papillary cystadenoma	0	0	1	0

* Bilateral in 4.

Neoplastic lesions. Neoplasms occurred in lymphoid tissue, adrenals, pituitary and thyroid glands. There was nothing significant in regard to the reproductive system. The number of tumors in the growth hormone injected rats of the 2 ages was not significantly different from that in the controls,† except in the tumors of the adrenal medulla. Neoplasms of the adrenal medulla were the most outstanding lesions observed in the experimental animals. Even in the adrenals where no pheochromocytomas were present, there was enlargement of the medullas. None of the controls of either age group had pheochromocytomas; 3 had focal areas in the medulla composed of uniformly small cells adjacent to blood vessels. Pheochromocytomas were

† Numbers of tumors exclusive of pheochromocytomas, in the 6 months old group, 11 in experimental, 12 in control; in the 14 months old group, 13 in experimental, 11 in control.

present in 9 of the 16 rats treated with growth hormone; multicentric foci were present in some (Fig. 3-5). In the younger group, 4 of 8 rats showed unilateral tumors. In the older

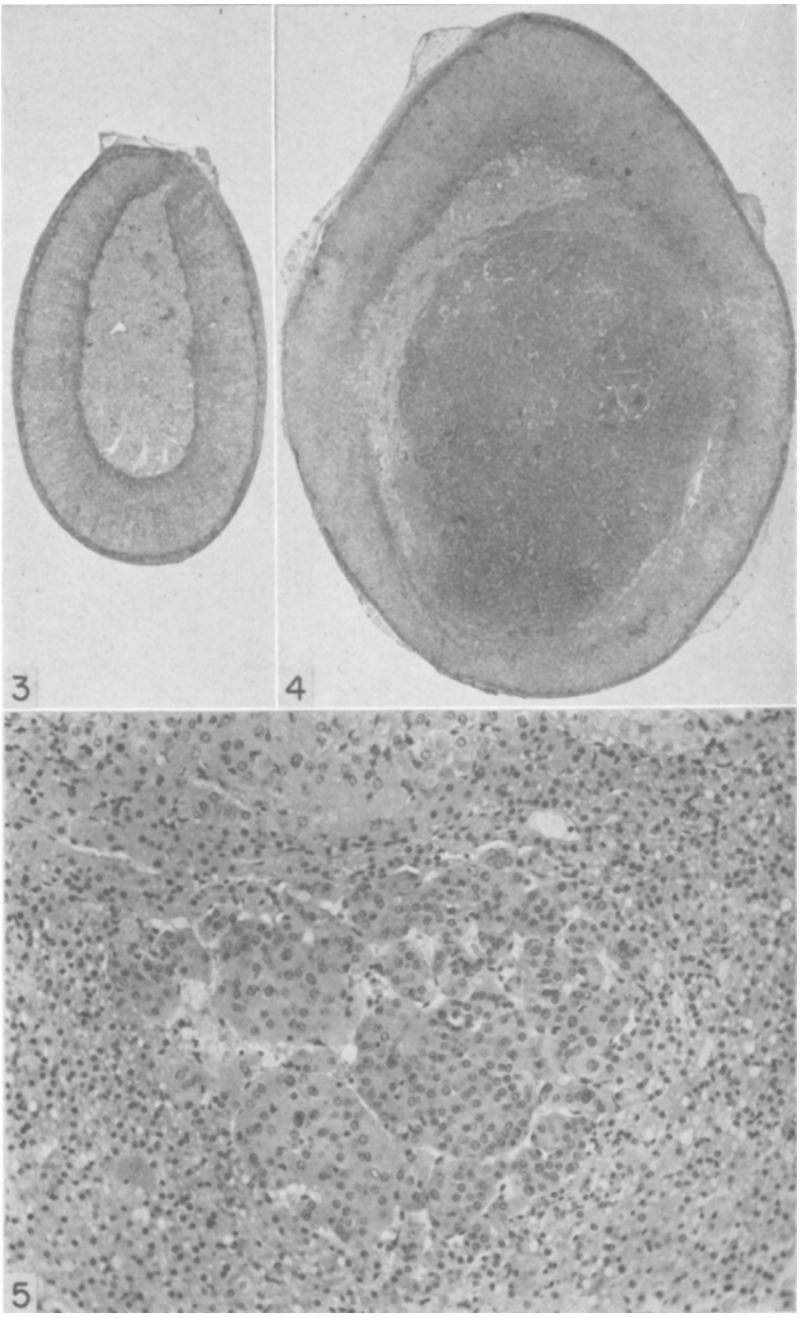

PLATE I (Fig. 3-5). Adrenals of adult male rats, control and exp. (H and E stain)

FIG. 3. Control, untreated. Age 21 mo. × 22.

FIG. 4. Large medullary pheochromocytoma. Note compression of normal medullary tissue. Growth hormone inj. begun at 6 mo of age. × 22.

FIG. 5. Small pheochromocytoma composed of large cell types; surrounded by cells of zona reticularis. Growth hormone inj. begun at 14 mo of age. × 250.

group there were lesions in 5 of 8 rats and in 4 instances these were bilateral. Invasion of blood vessels by neoplastic cells, as described by Gillman *et al.*(9) in spontaneous pheochromocytomas of the rat, was not observed.

Discussion. Analysis of the results of chronic administration of pituitary growth hormone to adult male rats indicates that growth response was similar to, but less striking than, that of females so treated. Growth response of the older of the 2 age groups tested (14 months old at onset) was inferior to that of the younger group (6 months old at onset), particularly in the later part of the experiment. This may have been due to a number of factors, such as aging, debility due to neoplasms, and recurrent infections. In the earlier studies on females injected with growth hormone, pheochromocytomas frequently occurred. There was no evidence of a prolonged hypertension in those animals, as judged by weight of the heart and histology of the arterioles. In the present study no significant elevations of blood pressure were observed in experimental rats subsequently shown to have pheochromocytomas. However, the possibility of transient episodes of hypertension cannot be excluded.

Summary. The long term administration of pituitary growth hormone to adult male rats of the Long-Evans strain resulted in progressive growth in body weight and length. Many neoplasms developed in the rats during this prolonged period, but the incidence in treated rats was not significantly different from that in controls, with the exception of tumors of the adrenal medulla. Pheochromocytomas occurred in 9 of 16 growth hormone injected rats and in none of the controls.

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Influence of Acetylcholine on Human Pulmonary Circulation under Normal and Hypoxic Conditions.* (22668)

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Short periods of induced hypoxia characteristically produce a moderate increase in the pressure in the pulmonary artery in normal man(1). In general, the rise in pressure is greater than might be expected to be due to the increase in cardiac output which occurs. Moreover, the possibility that the augmented pressure results from generalized systemic vasoconstriction seems unlikely, since the pulmonary wedge pressure does not change(2,3) the brachial artery pressure remains constant, and the "central blood volume" shows no consistent alteration(3,4). From these data it may be inferred that the

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