bile demonstrated DNase activity similar to that of the portal vein plasma. 4. Hepatic damage by anoxia or carbon tetrachloride injection suppressed the capacity of the liver to "extract" DNase from the blood. This hepatic function is abolished 24 hours after the injection of CCl_4; after 48 hours there appears to be partial recovery. 5. Hepatic duct obstruction for as long as 96 hours did not impair the liver's capacity to "extract" DNase. Thus, excretion of DNase in the bile is probably not the principal means by which it is "cleared" from the portal blood.

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Modification of Thyroid Activity in Absence of the Anterior Pituitary Gland.* (20732)

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It is generally stated that the principal, if not the only, regulatory factor governing the metabolic activity of the thyroid gland is hypophyseal thyrotrophic hormone (TSH). However, it is well known that thyroid function does not altogether cease after ablation of the hypophysis, for example, Morton *et al.*(1) noted that although the thyroids of hypophysectomized rats concentrated far less radioiodine than did those of intact animals, conversion of iodide to diiodotyrosine readily occurred. Synthesis of thyroxine did, in fact, proceed in the hypophysectomized rat, albeit markedly decreased.

Factors influencing this apparent "intrinsic activity" are, however, unclear. It has been reported that a diet low in iodine content exerts a stimulatory effect on the thyroid gland of the hypophysectomized rat. Chapman(2) stated that increased thyroid gland weight, acinar cell height, and vascularity occurred in hypophysectomized rats placed on an iodine-deficient diet. Because of the importance of this observation, relative to the elucidation of factors other than pituitary TSH affecting thyroid activity, it was deemed of interest to reinvestigate this problem, utilizing additional methods of study.

Experimental. Six-week-old male Sprague-Dawley rats, raised on Purina Lab Chow, were hypophysectomized by the standard parapharyngeal approach and maintained post-operatively on non-raised cages (following I^{131} injection, rats were placed on raised cages to prevent access to urine and feces). Five per cent sucrose in the drinking water was supplied *ad lib*. One week post-operative the rats were placed on Remington(3) diet No. 342 (containing 2% desiccated liver) which was (with the ingredients used here) found to contain 0.1 γ iodine/g by chemical analysis. Addition of iodine to the diet was carried out by preparation of an aqueous solution of NaCl and NaI; this was evaporated to dryness, pulverized to a fine powder with mortar and pestle, added to the basic diet, and distributed with a mechanical mixer. Final iodine content of the diet was further checked by analyses of random samples. In Exp. I, hypophysectomized rats

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TABLE I. Influence of Dietary Iodine on Thyroid Gland of the Hypophysectomized Rat.

Exp.	Iodine content of diet,* γ/g	No. of rats/group§	Thyroid gland: Wt, mg/100 g body wt	Thyroid gland: I^{131} content,‡ cts/mg/sec.	Thyroid gland: I^{127} content, mg/100 g	Thyroid gland: Acinar cell ht
I	2.5	9 (15)	5.2 ± .4†	22.4 ± 3.2†	—	3.68 ± .16
	.1	9 (15)	4.7 ± .4	126 ± 34	—	4.28 ± .43‖
II	1.0	9 (15)	6.0 ± .6	43.0 ± 12	57 ± 9†	—
	.1	9 (15)	6.2 ± .5	132 ± 75	59 ± 10	—

* On diets for 4 wk following 1 wk on Purina Lab Chow post-operatively.
† Mean ± S.D.
‡ Exp. I: Carrier free I^{131}.
Exp. II: I^{131} + 5.0 γ I^{127} carrier.
§ Figures in parentheses represent original No. of rats at start of exp.
‖ $P < .05 > .01$.

were placed on the low iodine diet and a similar diet augmented with 2.5 γ I^-g/m. In Exp. II, the low iodine diet was supplemented with 1.0 γ I^-/g. One month after inauguration of the special diets the rats were injected intraperitoneally with a 5 μc I^{131}. Carrier-free I^{131} was used in Exp. I. 5.0 γ I^{127} carrier was added in Exp. II. The rats were sacrificed under ether anesthesia 24 hours after injection. The thyroids were removed, and the lobes were weighed individually on a Roller-Smith torsion balance. In Exp. I, the left lobe was placed in formalin for histological examination. The other lobe was digested in 1 ml 2 N NaOH, diluted to a convenient volume and assayed for radioactivity with an end window G.M. tube. In Exp. II both lobes of the thyroid were digested in base; one aliquot was taken for I^{131} analysis and the remainder was analyzed for I^{127} content by the method described by Taurog and Chaikoff(4). The thyroids, prepared for histological study, were embedded in paraffin, sectioned at 4 μ, and stained with hematoxylin and eosin. Acinar cell heights were measured by horizontal projection of the image on a screen crossed by 3 vertical and 3 horizontal channels. All cells from a field through the center of the lobe falling within these channels were measured with a millimeter rule. Follicles cut tangentially were not included. An average of 240 cells were counted per gland. All measurements (made at x 1700) were made at one sitting by a single observer. Animals incompletely hypophysectomized were excluded from the study.

Results. It will be seen from Table I that in both experiments, maintenance of hypophysectomized rats on a diet low in iodine resulted in a significant increase in the I^{131} content of the thyroid gland 24 hours after injection of either carrier-free I^{131} (Exp. I) or I^{131} with 5.0 γ I^{127} carrier (Exp. II). No increase in the weight of the thyroid glands was observed in the groups on the iodine deficient diet (Table I). As can be seen from Table II, intact rats placed on the iodine deficient diets develop thyroid glands 60% larger than those of intact rats on the same diet augmented with 1.0 γ I^-/g. It will also be seen that a 3-fold increase in thyroid I^{131} content occurs in the former situation.

TABLE II. Influence of Dietary Iodine Content on Thyroid Gland of Intact Rats. 6 rats in each series.

Iodine content of diet, γ/g	Thyroid gland: Wt, mg/100 g body wt	Thyroid gland: I^{131},† % of inj. dose
1.0	7.0 ± .2*	15.0 ± 3.7*
.1	10.1 ± .2	40.5 ± 4.3

* Mean ± S.D.
† 24 hr after inj.

Gross examination of the thyroids failed to reveal any significant differences between the various groups of hypophysectomized rats in respect to vascularity, color, or consistency. By cytological examination, the thyroid glands from the hypophysectomized rats maintained on the low iodine diet were not distinguishable from those removed from rats given the iodine supplement, judging from vascularity, colloid content, and gross estimate of acinar cell heights. However, as seen in Table I, actual measurement suggests that

the height of the acinar cells was increased in the thyroids of rats maintained on the low iodine diet. The values for the acinar cell heights are given in mm (as measured at 1700x); the computed values would be 2.17 μ and 2.52 μ for the low and high iodine groups, respectively.

It should be noted that following one month on the low iodine diet, the total iodine content of the thyroid glands was not reduced (Table I).

Comment. It is evident that the maintenance of hypophysectomized rats on a low iodine diet results in an increase in thyroidal I^{131} content as compared to that of similar rats on an iodine augmented regime. This increase in thyroidal I^{131} was found 24 hours after the injection of either 5.0 γ I^{127} labeled with I^{131} or *carrier-free* I^{131}, the question of isotope dilution being obviated in the former condition. In these experiments the low iodine diet was not found to result in an increase in thyroid gland mass (in the hypophysectomized rats). Assuming that the renal clearance of iodide and the thyroidal blood flow were essentially the same in the 2 groups, one can reasonably infer that the efficiency of iodide extraction from the blood by the thyroid gland was increased(5). This apparent increase in extraction efficiency occurred in the absence of a concomitant reduction in thyroid iodine content. It was somewhat surprising to find that the total iodine content was not reduced after one month on the iodine deficient diet. As is well known, the secretion of thyroid hormone does proceed after hypophysectomy, although at a reduced rate. As pointed out recently by Money *et al.*(6), thyroid iodine content is halved in *intact* rats placed for one month on the Remington low iodine diet. It is of interest to recall here, Astwood's(7) speculation that perhaps a deficiency of iodine within the thyroid cell is, *per se*, a stimulus to it. It is possible that a relative *iodide* deficit could have existed which would not have been revealed by the determination of the *total gland iodine.*

Microscopic examination of the thyroids glands failed to reveal differences between the groups of hypophysectomized rats as judged by acinar cell height, colloid content, vascularity, follicle size, or amount of interfollicular fibrous stroma; actual measurement of the acinar cell height suggested, however, that there was a slight increase in height in the group on the low iodine diet. This change, if significant, was by no means of the order of magnitude reported by Chapman(2). Unfortunately his data do not reveal the range of values or the variation within groups.

Evidence of a different nature suggesting that the thyroid gland may be stimulated in the absence of hypophyseal TSH has also been presented by Turner and Turner(8) who noted that incubation at cold bath temperatures appeared to activate surviving thyroid slices, as judged by cytological appearance. On the other hand, *in vitro* studies in this laboratory(9) have indicated that while incubation of surviving thyroid slices at reduced bath temperature (26°C) results in no decrease in the efficiency of iodide extraction, the rates of iodinated-tyrosine and thyroxine synthesis were markedly depressed. Incubation at 41°C slightly reduced the efficiency of iodide extraction without affecting the rate of conversion of iodide to organic combination. Control values were taken at a bath temperature of 37.5°C.

Summary. Maintenance of hypophysectomized rats on a diet deficient in iodine resulted in 1) an apparent increase in the efficiency of iodine extraction from the blood by the thyroid gland; 2) no reduction in thyroid gland iodine content and, 3) a slight and questionably significant increase in thyroid acinar cell height accompanied by other morphological manifestations of increased activity. It is suggested that hypophyseal thyrotrophin is not the only factor capable of stimulating the thyroid gland.

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Effect of Pregnancy and Lactation on Granuloma Tissue Formation and Joint Permeability in Rats.* (20733)

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Hench confirmed and extended the general observation that pregnancy has a beneficial effect on rheumatoid arthritis in the human female(1). Subsequently he and his coworkers administered large doses of ACTH or cortisone to patients with rheumatoid arthritis and obtained a dramatic and prompt improvement(2). These results made it seem probable that adrenal cortical hormones of the gluco-corticoid type are the endocrine agents responsible for the improvement seen during pregnancy and stresses, although as Selye states, "the beneficial effect of pregnancy upon rheumatoid arthritis has repeatedly been confirmed, but the underlying mechanism is still obscure(3)."

In view of the complex endocrine mechanisms existing during pregnancy and their relationship to arthritis, it became of interest to make a quantitative study of the effect of pregnancy and lactation in the rat on connective tissue formation induced by the subcutaneous implantation of cotton pellets, and on the permeability of knee joint synovial membranes injured by the intra-joint injection of formaldehyde.

Materials and methods. Female rats 90-120 days of age were obtained from Sprague-Dawley, Inc., and maintained on Rockland Rat Diet. Males were placed with the females in the evening and vaginal smears were taken in the morning to detect sperm. The day on which sperm were found was considered as day 0 and the next day as day 1 after insemination. Lactation was standardized by maintaining the number of sucklings at 8 throughout the period of lactation. Cotton pellets weighing between 4-5 mg were selected from those supplied to the dental profession in package form. Each pellet was implanted through a small incision into the loose subcutaneous connective tissue according to the method reported by Meier *et al.*(4) and modified in our laboratory by Shipley and Meyer (5) who have shown that systemically or locally administered gluco-corticoids inhibit the formation of granuloma tissue around the implanted pellets. Care was taken to place the pellet in the subcutaneous pocket in such a way that connective tissues surrounded it on all sides. The skin incisions were closed with skin clips. Pellets were bilaterally implanted in both the pectoral and groin regions in one experimental series and in another experiment in the dorso-lateral neck region only. The pellets were implanted into rats on the day of insemination and on days 6, 12, 18, 24, 30, 36, and 42 after insemination. The pellets and their attendant granulation tissue (granulomas) were removed after having been in place for 120 $\pm$ 4 hours. Any one rat carried pellets during one stage of pregnancy or lactation only, and no pellet was in place more than 120 $\pm$ 4 hours. Control animals were non-pregnant female rats which were having regular estrous cycles and were implanted with pellets without regard to stage of cycle at the time of implantation. After the pellets had been in place for 5 days the rat was killed and each granuloma was dissected out of the surrounding loose connective tissue and weighed on a torsion balance. Granulomas which were

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