the amount of loading substance administered, while producing increasing urine flow, also resulted in higher plasma level of the solute so that the work remained constant. A maximum value in the same range was observed for the following solutes: glucose, sucrose, mannitol, xylose, sorbitol, creatinine, and sodium sulfate. Sorbose and *p*-aminohippurate were not used in sufficient amounts to produce adequate loads. Maximum work was not obtained with urea or sodium chloride.

From equation 2 it follows that under the conditions of hydropenia here considered, the U/P ratio is the main factor determining work. Given the observed limitations of urinary osmolarity, increasing values of P would necessitate greater rates of urinary flow to produce maximum work. The actual relation between urinary flow and osmolarity, with the osmolarity decreasing with rising flow, is such that beyond a certain level of loading solute in the plasma, which is approximately 100 milliosmols/liter, maximum work can no longer be obtained, no matter how great the amount of loading substance administered. As a matter of fact, the work value may decrease, despite increasing urinary flows, loads, and plasma levels. These relationships serve to explain the failure to produce maximum work with either urea or sodium chloride. On the basis of the work equation and the observed relation between osmolarity and flow of the urine one may also determine by graphic methods the minimal urinary volume at which maximum work will be reached for any plasma level of loading solute under the simplifying assumption that the loading solute accounts for the entire urinary osmolarity.

Substituting the value of flow from equation 5 and using the identity $U = \frac{\text{load}}{\text{flow}}$, an equation is obtained in which both U and V are expressed in terms of load:

$$(7)\quad W = RT\ \text{load}\left(\frac{\ln A'e^{-k\ \text{load}} + B}{P} + \frac{P}{A'e^{-k\ \text{load}} + B} - 1\right),$$

in which the symbols have the same meaning as before. This equation permits one to relate directly work and solute load, and, by definition, urinary volume, for any given plasma level of loading solute on the same assumption as before, namely, that the loading solute accounts for the entire urinary osmolarity. One may also calculate the minimal urine volume at which maximum work will be reached.

The studies of glucose diuresis in diabetic subjects, beyond offering an explanation of the polyuria of diabetes, have a bearing on the problem of the cause of electrolyte loss during uncontrolled glycosuria. It was found that the urinary losses of sodium and chloride increased 4-fold above control levels during glucose diuresis, whereas the potassium losses were unchanged. Urea diuresis, on the other hand, did not affect the rate of electrolyte excretion.

At present studies are planned on the osmotic limitations and the work of the kidney at the other extreme of the osmotic relationships, *i.e.* during diuresis of water loading when the work of electrolyte conservation is at maximum.

Details of the foregoing studies will be published shortly.

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Effects of the Antithyrotoxic Factor of Liver on Growth and Survival of Immature Rats Fed Massive Doses of Thyroactive Materials[1]

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Available data indicate that liver contains one or more factors other than the known B vitamins that prolonged survival and counteracted the growth retardation of immature rats fed massive doses of desiccated thyroid (*1, 3, 4*). Since liver feeding did not prevent the rise in oxygen consumption following thyroid administration (*3*), the question arises whether liver actually exerts an antithyrotoxic effect or whether it might not be counteracting other noxious substances present in the desiccated

TABLE 1

Dietary component	Diet A	Diet B
Extracted liver residue*	0.0	10.0
Casein†	22.0	22.0
Salt mixture‡	4.5	4.5
Sucrose	73.5	63.5

To each kilogram of the above diets were added the following synthetic vitamins: thiamine hydrochloride, 72 mg; riboflavin, 9 mg; pyridoxine hydrochloride, 15 mg; calcium pantothenate, 67.2 mg; nicotinic acid, 60 mg; 2-methyl-naphthoquinone, 5 mg; and choline chloride, 1.2 gm. (In view of the increased requirements for thiamine, pyridoxine, and pantothenic acid in the hyperthyroid rat (*2*), the B vitamins in the present experiment were administered in excessive amounts in order to assure an adequacy of these factors in the diet.) Each rat also received 3 times weekly the following supplement: cottonseed oil (Wesson), 500 mg; α-tocopherol acetate, 1.5 mg; and a vitamin A-D concentrate (Nopco Fish Oil Concentrate, assaying 800,000 U.S.P. units of vitamin A and 80,000 U.S.P. units of vitamin D/gm) containing 50 U.S.P. units of vitamin A and 5 U.S.P. units of vitamin D.

* Extracted Liver Residue, Wilson Laboratories, Chicago, Illinois.

† Vitamin Test Casein, General Biochemicals, Inc., Chagrin Falls, Ohio.

‡ Salt Mixture No. 1 (*6*).

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thyroid material. The present experiment was accordingly undertaken to determine the effects of the "antithyrotoxic factor" of liver on growth and survival of immature rats fed massive doses of thyroid, thyroxin, thyroglobulin, and iodinated casein.

Two basal rations, diet A and diet B, were employed (Table 1). Diet A was a purified ration containing the B-complex factors in synthetic form only. Diet B was similar in composition but contained Extracted Liver Residue (Wilson) in addition to the synthetic vitamins. Recent work from this laboratory (*3, 5*) indicates that the above material, consisting of the coagulated, water-insoluble material remaining after removal of the extractable water-soluble substances, is a potent source of "antithyrotoxic factor." Each of the above diets was supplemented with U.S.P. desiccated thyroid,[2] thyroxin,[3] thyroglobulin,[4] or iodinated casein.[5] Supplements were incorporated in the basal rations at the following levels: thyroid, 0.5%; thyroxin, 50 mg/kg of diet; thyroglobulin, 0.1%; and iodinated casein, 0.25% and 0.5%. Supplements were added in place of an equal amount of sucrose. One hundred and twelve female rats of the Long-Evans strain were selected at 21–23 days of age and with an average weight of 42.4 gm. These were kept in metal cages with raised screen bottoms to prevent access to feces and were fed the above diets *ad libitum*. Feeding was continued for 8 weeks or until death, whichever occurred sooner. Results are summarized in Table 2.

Findings indicate that the beneficial effect of Extracted Liver Residue on growth and survival of immature rats fed massive doses of desiccated thyroid is equally evident in rats fed massive doses of thyroxin, thyroglobulin, or iodinated casein. Effects were particularly striking in the thyroxin series, with a 100% survival over an 8-week period on diet B in contrast to a 30% survival on diet A; similarly, animals gained approximately twice as much weight on diet B as they did on diet A. Results were somewhat less marked in the iodinated casein series, possibly because of the greater thyroxin content of these rations.

TABLE 2

EFFECTS OF THE ANTITHYROTOXIC FACTOR OF LIVER ON GROWTH AND SURVIVAL OF IMMATURE RATS FED MASSIVE DOSES OF THYROID, THYROXIN, THYROGLOBULIN, AND IODINATED CASEIN

Dietary group	Thyroactive supplement	No. of rats	Initial body wt	Gain in body wt (gm) on following days of experiment: 14th	28th	42nd	56th	Avg. survival time* (days)
A	Desiccated thyroid	10	42.4	33.0 (6)†	61.0 (3)	87.5 (2)	97.5 (2)	28.2 ± 5.2
B	" "	10	42.5	51.8 (9)	96.4 (8)	123.8 (8)	136.4 (5)	49.4 ± 3.3
A	Thyroxin	10	42.0	29.9 (9)	57.3 (6)	70.7 (6)	80.7 (3)	37.5 ± 5.1
B	"	10	42.0	56.9 (10)	109.0 (10)	137.7 (10)	150.3 (10)	56.0 ± 0.0
A	Thyroglobulin	10	42.5	33.4 (9)	53.6 (7)	68.5 (2)	75.5 (2)	35.1 ± 4.0
B	"	10	41.9	58.8 (10)	109.3 (10)	132.1 (10)	145.4 (5)	51.7 ± 1.4
A	0.25% iodinated casein	10	43.1	30.0 (7)	33.3 (3)	57.0 (1)	....	22.6 ± 3.5
B	" " "	10	42.8	58.7 (9)	91.8 (5)	117.6 (5)	115.0 (1)	36.3 ± 4.4
A	0.5% iodinated casein	10	42.3	24.0 (7)	48.7 (3)	60.0 (2)	....	24.5 ± 4.2
B	" " "	10	42.3	46.3 (9)	90.5 (4)	116.5 (4)	113.0 (2)	35.9 ± 5.1
A	None	6	42.5	52.2 (6)	90.4 (6)	125.7 (6)	143.3 (6)	56.0 ± 0.0
B	"	6	42.3	63.0 (6)	107.0 (6)	137.3 (6)	154.8 (6)	56.0 ± 0.0

* Averages, computed on the basis of a 56-day survival time for animals alive at the termination of the experiment, include standard errors of the mean.

† Values in parentheses indicate number of animals that survived of which this is an average.

[2] Thyroid Powder, U.S.P., Armour & Company, Chicago, Illinois.

[3] Thyroxin (Synthetic Cryst.), Roche-Organon, Inc., Nutley, New Jersey. The material was dissolved in .1 N NaOH, adjusted to pH of 8.0, and diluted to a volume containing 50 mg in 12.5 cc.

[4] Endothyrin, Harrower Laboratories, Glendale, California, a commercially prepared, partially purified thyroid preparation containing 0.995% total iodine.

[5] Protamone, Cerophyl Laboratories, Kansas City, Missouri.

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