tion of the drug in average therapeutic amounts. Although animal experiments, theoretical considerations, and one report on human volunteers have indicated that reserpine can increase gastric acidity, under conditions of this study, no significant change of volume, free hydrochloric acid or output of hydrochloric acid was observed during reserpine administration.

It is possible that large doses of reserpine taken orally or parenterally over a short period of time may increase gastric acidity, since they have been shown to cause other severe side effects, as indicated by Noce *et al.* (7). It is also possible, however, that tranquilizing effect of well-tolerated doses of reserpine may bring about a secondary decrease in gastric acidity and may therefore be helpful in the management of the peptic ulcer patient.

Conclusions. 1. Basal gastric analyses were made in 20 patients with various gastrointestinal disorders, including peptic ulcer, before and during therapy with reserpine. 2. No consistent change in volume, free hydrochloric acid concentration or output of hydrochloric acid was observed after prolonged oral administration of 0.25 mg of reserpine 4 times daily.

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Effects of Liver Fractions on Thyroid Function of the Rat.*† (22120)

D. R. HIGHLEY AND H. E. PARKER. (Introduced by William A. Hiestand.)
Department of Biochemistry, Purdue University, West Lafayette, Ind.

Several investigators have reported that diets containing liver produced thyroid enlargement in different laboratory animals (1-5). Hou(5) was able to demonstrate that goitrogenic activity was present in the ethanol soluble portion of ox liver. Although substantial thyroid enlargement was obtained in the latter investigation, a search of the literature has failed to yield any further information concerning the substance(s) responsible for the goitrogenicity. Anselmino and Hoffman(6) found fetal blood and other animal tissues to contain an "antithyroid protective" substance capable of overcoming the increase in basal metabolic rate caused by thyroxine injection. More recently Ershoff (7-10) has studied the "antithyrotoxic" effect of liver in overcoming the growth retardation of rats fed thyroidactive materials.

The present investigation is part of a study designed to identify the substance(s) responsible for the goitrogenicity of liver and to determine whether its goitrogenicity is related to the "antithyroid protective" substance or the "antithyrotoxic" factor.

Experimental. Sixty male and 60 female rats of the Wistar strain (housed in individual wire cages) were divided equally into 12 groups of 10 each and treated as indicated in Table I. Pork liver fractions‡ were incorporated into an iodine deficient ration (Table II) and into the same ration containing adequate iodine. The liver fractions replaced

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‡ Desiccated pork liver and the water soluble and water insoluble fractions of pork liver were purchased from Wilson Laboratories, Chicago, Ill.

TABLE I. Effect of Liver Feeding on Thyroid Function.

Treatment	Iodine content of ration, p.p.b.	Thyroid wt /100 g body wt, mg*	Thyroid-iodine content†		Protein bound plasma iodine/100 ml, μg	Avg weekly gain, g
			Total, %	Protein bound, %		
Basal ration	58	7.44 ± 1.21	.0106 ± .0025	.0103 ± .0025	1.40	29.2
3% H_2O soluble liver	"	8.11 ± 1.36	.0133 ± .0032	.0117 ± .0032	1.62	29.2
6% " " "	"	8.52 ± 1.08	.0094 ± .0025	.0087 ± .0018	1.14	26.8
20% H_2O insoluble liver	"	12.28 ± 1.42	.0040 ± .0004	.0029 ± .0008	1.20	28.6
20% desiccated liver	"	12.15 ± 2.15	.0038 ± .0028	.0025 ± .0014	1.62	14.6
.01% thiouracil	"	15.83 ± 2.59	.0022 ± .0009	.0013 ± .0007	1.21	27.3
Basal ration	400	5.77 ± 1.49	.0545 ± .0080	.0463 ± .0148	1.77	28.2
3% H_2O soluble liver	"	5.52 ± .76	.0616 ± .0115	.0579 ± .0120	2.45	29.8
6% " " "	"	6.44 ± 1.47	.0576 ± .0120	.0567 ± .0179	2.71	26.2
20% H_2O insoluble liver	"	6.58 ± .70	.0639 ± .0307	.0541 ± .0295	2.70	28.8
20% desiccated liver	"	6.39 ± 1.01	.0615 ± .0291	.0594 ± .0288	3.02	16.2
.01% thiouracil	"	10.39 ± 1.30	.0096 ± .0029	.0082 ± .0023	1.89	27.4

* Mean ± stand. dev., 10 animals/group.
† Mean ± stand. dev., from analyses of thyroids from 4 animals/group.

wheat germ in the diet and the percentage composition of the diets was adjusted by varying the quantity of corn and wheat germ until each contained the same percent protein. Diets containing 0.01% thiouracil were used to compare the goitrogenic activity of the liver fractions with that of a known goitrogen. After the animals had been on the experimental diets for 39 or 40 days they were starved for 20 hours after which basal metabolic rates were determined using a modified Haldane apparatus. On the 42nd day blood samples were taken and pooled according to treatment. Thyroid glands were excised, weighed and reserved for analysis. Protein bound plasma iodine determinations were made using the procedure of Barker (11). The following determinations were made on thyroid samples: total fresh weight, dry matter content, total iodine content, and protein bound iodine content.

TABLE II. Composition of the Basal Diet.*

Ingredient	%
Corn	58.6
Wheat germ†	35.0
Cottonseed oil	2.0
DL methionine	.4
Mineral mixture‡	4.0

* The following amounts of vitamins were added to this diet (expressed in mg/100 g): riboflavin 1, thiamine hydrochloride 0.75, niacin 5, *i* inositol 30, pyridoxine hydrochloride 1, choline chloride 200, biotin 0.01, folic acid 0.01, calcium pantothenate 5, *p*-amino benzoic acid 30, vit. B_{12} 0.002, 2-methylnaphthoquinone 0.50, α-tocopherol 10, vit. A acetate 0.05, and calciferol 0.005.

† Wheat germ which had been partially defatted, dehydrated and pulverized was purchased from Viobin Corp., Monticello, Ill.

‡ The mineral mixture had the following percentage composition: sodium chloride 4.43, magnesium sulfate (anhydrous) 6.78, disodium phosphate 8.86, monopotassium phosphate 19.03, potassium chloride 10.40, calcium phosphate monobasic 13.75, calcium lactate 33.07, ferrous ammonium sulfate 3.63, manganese sulfate 0.016, copper sulfate 0.024, and zinc carbonate 0.024.

Results. The goitrogenic activity of pork liver was found to be present in the water insoluble fraction and, with rats fed low iodine diets, was of nearly the same magnitude as that produced by 0.01% thiouracil. When the iodine intake was adequate the goitrogenicity of water insoluble liver was completely overcome. Desiccated liver exhibited the same degree of goitrogenicity as water insoluble liver and rats fed the former grew poorly. The concentration of iodine in the thyroid glands of rats fed the goitrogenic liver fractions and low dietary iodine was approximately one-third that of the corresponding controls. This decrease appeared to be due to lowered protein bound thyroid iodine. However, when adequate iodine was included in the diet the thyroid iodine of animals fed the goitrogenic liver fractions was the same as, or slightly higher than, that of the control animals fed the same level of iodine. Thiouracil reduced thyroid iodine concentration at both dietary iodine levels. Histological examination of thyroid sections indicated that

water insoluble liver was as active as 0.01 percent thiouracil in causing loss of colloid, and epithelial hypertrophy and hyperplasia. Slight variation was observed in protein bound plasma iodine values at the low dietary iodine level, but adequate dietary iodine resulted in increased plasma protein bound iodine values with rats fed all the liver fractions. This was not accompanied by an increase in basal metabolic rate. No significant differences in basal metabolic rate were observed between treatments when expressed either as a function of body weight or of body surface area.

Discussion. Rats fed low dietary iodine and water insoluble liver had greatly reduced protein bound thyroid iodine stores but when the liver fed animals received adequate dietary iodine not only did thyroid protein bound iodine return to normal but plasma protein bound iodine values were nearly doubled. This appears to indicate an increased synthesis and secretion of thyroxine rather than a decreased rate of thyroxine synthesis as is observed with thiouracil. The effects of the liver fractions on thyroid size and the level of protein bound iodine in the thyroid and in blood plasma seem to be dependent upon the level of iodine available to the thyroid. It would also appear that whatever causes this effect on thyroid and plasma protein bound iodine is either partially water soluble or different than the agent responsible for the thyroid enlargement observed in rats fed water insoluble or desiccated liver. In either case it appears that the mode of action of the goitrogenic factor(s) in liver is unlike that of thiouracil.

Summary. The present study is part of an investigation initiated in order further to purify and evaluate the goitrogenic substance (s) present in liver. The activity was found to be in the water insoluble portion of pork liver. Increased dietary iodine completely overcame its effect on thyroid size and iodine content. The decreased thyroid iodine of rats fed this material and inadequate iodine appears to be due to a fall in the protein bound fraction. This may be caused by an increased thyroxine secretion rate. Further experiments are in progress further to purify and study the metabolism of the active principle.

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