For additional evidence that the syndrome was due to cardiac insufficiency, 2 of the dogs were sacrificed for study in heart-lung preparations. Cardiac output was low for both hearts. To obtain cardiac outputs approaching the normal range for fresh heart-lung preparations required extremely high auricular pressure, *e.g.*, 150 to 200 mm of saline. Calculation of the "competence index"(7) also indicated marked cardiac impairment.

The animals were sacrificed 1½ to 3 months after pulmonary stenosis was produced. Autopsies revealed dilatation and hypertrophy of the right auricle and ventricle in each dog. The pleural cavity was dry and the lungs normal. The liver was markedly enlarged and congested, and 2 to 5 liters of serosanguinous fluid were found in the peritoneal cavity.

7. Wollenberger, A., *Am. J. Physiol.*, 1947, v150, 733.

Summary. A form of progressive, chronic, "right-sided" cardiac failure has been produced in dogs by tricuspid valve avulsion and pulmonary artery stenosis. Three dogs so treated developed congestive failure with elevated auricular pressure and distended veins, decreased work tolerance, hepatomegaly, ascites, tachycardia at rest, and a relatively fixed heart rate during exercise. Studies of 2 of the hearts in the heart-lung preparation indicate clearly that cardiac insufficiency was present.

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Thyroid Function in the Alarm Reaction. (17596)

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The response of the body to stress of various kinds has received considerable attention in recent years; the majority of investigations have been concerned with the role of the pituitary-adrenocortical system under such conditions. It appeared *a priori* probable that the pituitary-adrenocortical system would not be the only one involved. Some rather specific forms of stress, "alarming stimuli", are quite well known to involve also the pituitary-thyroid system, *e.g.* reduced oxygen pressure (high altitude), and changes of environmental temperature. In an interesting and stimulating speculation, Means(1) considered the possibility that Graves' disease might in some way be related to an alarm reaction, a thought which he discusses in the first edition of his monograph. However, this speculation appears to have lost its appeal to its author, because it is omitted from the second edition. We decided to investigate the response of the thyroid to alarming stimuli. While our work was in progress, two reports on this subject appeared,(2,3) indicating the general interest in the complicated response to stress on the one hand, and in the adrenocortical-pituitary-thyroid interrelationship on the other hand.

Materials and methods. A total of 106 adult male rats was used in this study. Animals were kept on a stock diet of Purina dog chow. Intramuscular injection of 10% formalin was used as the stress or alarming stimulus. Thyroid function was gauged by uptake of tracer doses of I-131.* The latter

1. Means, J. H., *The Thyroid and Its Diseases*, 1st edition, 1937.

2. Reiss, R. S., Forsham, P. H., and Thorn, G. W., *Assn. Study of Int. Secretions*, 1949.

3. Soffer, L. J., Gabrilore, J. L., and Jailer, J. W., PROC. SOC. EXP. BIOL. AND MED., 1949, v71, 117.

TABLE I.
Uptake of I-131 and Thyroid Weight Following Formalin Injection.

Exp. No.	Thyroid: counts/mg/sec. Controls	Formalin (10%)	Diff.	"p" of Diff.	Thyroid wt (mg/100 g body wt) % decrease
1	55.3 (3)*	36.2 (3)†	19.1	<.4	18
2	145.7 (5)	54.9 (5)‡	90.8	<.01	32
3	137.4 (5)	70.2 (6)§	67.2	.01	17
4	59.4 (10)	33.9 (10)‡	25.5	<.001	21
5	78.1 (10)	63.4 (10)‖	14.7	<.01	36

* Fig. in parentheses = No. of rats.
† 1 inj. of 2 cc, tracer 48 hr later (4 μc).
‡ 4 inj., .5 cc each, in 2 days, tracer 24 hr after last inj. (4 μc).
§ 3 inj., .5 cc each, in 2 days, tracer 24 hr after last inj. (4 μc).
‖ 1 inj., .5 cc, tracer 17 hr later (4 μc).

TABLE II.
Uptake of I-131 Following Injection of Cortical Hormone.

Exp.	Treatment	Thyroid: counts/mg/sec. Treated	Controls	Difference ("p" of Diff.)
6	D.O.C.A., 2 days* 40 mg/day	69.7 (9)‡	59.4 (10)	10.3 (<.1)
7	Aqu. Adr. Extr.† (Upjohn) 1 cc every hr. 7 inject.	39.8 (9)	29.5 (8)	10.3 (<.1)

* 4 μc I-131 given 24 hr after last inj. of D.O.C.A.
† 4 μc I-131 given 1 hr after last inj. of Adr. Cort. Extr.
‡ Figures in parentheses indicate number of rats.

was administered by intraperitoneal injection as sodium iodide without carrier. Rats were killed four hours after injection of I-131; the thyroid glands were dissected out, weighed rapidly on a Roller-Smith Torsion balance, and were immersed in 2% sodium hydroxide solution. Aliquots were taken for determining radioactivity by means of a Geiger-Muller Counter. Because the application of an alarming stimulus is followed by increased secretion of adrenocortical hormone, an attempt was made to duplicate results obtained with injection of formalin by injection of adrenocortical hormone. No crystalline C-11 oxygenated compound was available to us. Aqueous adrenocortical extract (Upjohn) was employed, assayed by us to contain approximately 350 μg equivalents of compound A acetate. In another experiment desoxycorticosterone acetate was used.

Results. Results are summarized in Tables I and II. As can be seen from Table I, the uptake of I-131 was decreased in every instance following injection of formalin; this decrease was statistically significant in all but one experiment; in the latter only 3 rats were used, and a large dose of formalin given in a single injection had proven very toxic rendering the animals exceedingly sick at the time the tracer dose was administered. The weight of the thyroid gland (mg per 100 g body weight) was decreased in all experiments.

As can be seen from Table II, the uptake of I-131 was increased slightly following treatment with desoxycorticosterone acetate and with aqueous adrenocortical extract, but the increase is statistically not significant.

Discussion. Before discussing the results obtained, two points in our procedure require brief mention.

Diet. Many authors, using the rat in tracer studies with I-131, have employed a diet slightly deficient in iodine (Steenbock diet with added potassium iodide), as suggested by

* Radioactive Iodine (I-131) was supplied by the Atomic Energy Commission, Oak Ridge, Tenn.

Rawson *et al.*(4) The latter authors chose this diet in order that animals might not be protected by iodine against the effects of thiocyanate. At the same time, the uptake of I-131 by the rats' thyroid is increased under this iodine deficient regime. At least within certain limits, the uptake of I-131 is inversely proportional to the amount of potassium iodide added to the stock diet.(5) Whereas use of the iodine-poor diet offers the technical advantage of increased uptake, it introduces a further metabolic variation, the significance of which for the problem under study could not be foretold. For this reason we have used a laboratory stock diet and tap water.

Calculations of Uptake. It is customary to report the uptake of I-131 by thyroid glands, and to compare the total uptake by control animals with that obtained under conditions of an experiment. It appears to us that this is a valid indication of altered thyroid function only if the experimental procedure does not involve a change of thyroid weight. Otherwise the possibility exists that increased or decreased uptake of the tracer might be due to changes in the amount of functioning tissue only, without necessarily indicating alteration in function. We have therefore calculated the uptake per milligram of thyroid tissue, expressed in the table as counts per milligram per second.

Thyroid Function Under Conditions of Stress. The observations presented in this paper indicate that thyroid function is depressed in a condition of acute stress (formalin injection). This finding is similar to that reported by Soffer *et al.*(3) who found decreased uptake of I-131 following injection of epinephrine in the intact animal; however, epinephrine increased the uptake in adrenalectomized rats and this increase could be prevented by treating the adrenalectomized rat with compound E. The authors concluded that the adrenal cortex exerts an inhibitory effect on the thyrotrophin-stimulating effect of epinephrine. In our formalin-treated rats the thyroid weight was decreased, confirming Selye's statement(6) that thyroid "atrophy" is observed early during the alarm reaction. The finding of decreased thyroid function under conditions of stress (formalin injection: present authors; Epinephrine: Soffer *et al.*) (3) is at variance with observations in humans reported by Reiss *et al.*(2) who found increased uptake of I-131 following epinephrine injection in normal individuals and following injection of compound E in Addison patients.

At the present time little can be gained by attempting to explain these apparent discrepancies, which might conceiveably be due to species differences, to differences of timing or to a number of unknown factors. Both in Soffer's and in Reiss's observations, 11-dehydro-17-hydroxycorticosterone (Compound E) influenced the uptake of I-131 by the thyroid, although the effect was in opposing directions. In our experiments, desoxycorticosterone acetate (40 mg daily) failed to influence significantly uptake of I-131 by the rat's thyroid, nor did it have any effect upon inhibition of thyroid function induced by stress. No influence of aqueous adrenocortical extract (Upjohn) upon uptake of I-131 was observed in the intact rat.

Summary. Rats under the influence of an alarming stimulus (formalin injection) showed decrease in thyroid function, the latter evidenced by diminished uptake of I-131 per milligram of thyroid tissue. Desoxycorticosterone acetate and adrenal cortical extract failed to influence thyroid uptake of I-131 significantly.

4. Rawson, R. W., Tannheimer, J. F., and Peacock, W. C., *Endocrinol.*, 1944, v34, 245.

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6. Selye, H., *J. Clin. Endocr.*, 1946, v6, 117.

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