

## THYROID FUNCTION IN EXPERIMENTAL STREPTOCOCCAL PNEUMONIA IN THE RAT\*

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PLATE 27

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Since the first report of Sokolow in 1895 (1), many authors have drawn attention to pathologic alterations in the thyroid glands of patients dying of infectious diseases (2-7). The conventional interpretation of these findings (6, 7) has been that there is an increased requirement for thyroid hormone during infection, which leads to an early, intense stimulation of the thyroid gland that is followed in some instances by "functional exhaustion." More recently, however, as a result of the introduction of more precise quantitative methods, evidence has been accumulated which indicates that the usual effect of various types of trauma is to bring about a reduction in thyroid activity (8-13). The apparent contradiction between the conclusions based on the one hand on histologic findings, and, on the other, on a large body of experimental data concerning the effect of trauma on thyroid activity in animals, has stimulated the following study in which the effect of experimentally induced pneumonia upon thyroid activity in rats was determined. In these experiments it was demonstrated that severe pulmonary infection usually resulted in a reduction in thyroid function. This finding in turn led to inquiries into (a) the mechanism by which this reduction was brought about, and (b) the functional importance of the inhibitory thyroid response for the resistance of the animals to infection.

### *Material and Methods*

Male albino rats of the Sprague-Dawley strain, weighing 170 to 300 gm., were used for all experiments. The animals were housed in a controlled temperature room at  $21 \pm 1^\circ\text{C}$ ., exposed to constant photo-periods, and fed a standard rat diet<sup>1</sup> and tap water *ad lib*. Uniform iodine intake was insured during the course of the experiments on the effect of pneumonia

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<sup>1</sup> Purina Laboratory Chow.

on thyroid activity, by feeding the animals an iodine-free diet<sup>3</sup> and providing them, once daily by subcutaneous injection, with 15  $\mu$ g. of potassium iodide in 0.2 ml. of NaCl solution. Thyroxine<sup>3</sup> was dissolved in 2 N NaOH solution and brought to the desired concentration with 0.9 per cent NaCl solution. The goitrogenic diet employed in some experiments was prepared by mixing *n*-propylthiouracil<sup>4</sup> in a concentration of 0.1 per cent with ground Purina laboratory chow.

Thyroid activity was determined by the measurement of the rate of release of  $I^{131}$  from the thyroid gland, utilizing an external counting technique in unanesthetized rats (14). A scintillation counter (Nuclear, Chicago) and conventional scaling equipment were employed, and counts were corrected for physical decay by comparison with a radioiodine standard at the time of each count. The specially constructed lead shield used was 2.5 cm. thick, and counting was done over an oval aperture measuring 12 by 18 mm. Metal guides, or a brass yoke, were used to insure constant position in relation to the counter. The animals were injected with 40  $\mu$ c. of  $I^{131}$  intraperitoneally and placed in individual metabolism cages. Forty-eight hours later, the neck region was counted for 15 seconds in each of 4 positions and this count was repeated twice daily thereafter. At 48 hours, 5 to 10 per cent of the administered dose was present in the thyroid region, as indicated by readings of approximately 15,000 c.p.m. The value obtained at the initial observation was taken as 100 per cent, and subsequent counts were calculated as per cent of initial count. Neck counts repeated at any given time were usually reproducible within  $\pm 2$  per cent. Tissue background in the neck region was found to constitute less than 5 per cent of the total neck radioactivity at 48 hours, and hence no corrections for this artifact were made.

Intrabronchial inoculation was carried out under ether anesthesia using the technique described previously by Glaser and Wood (15). The inoculum consisted of 700 chains of group A type 17 streptococci, contained in 0.1 ml. of 6 per cent gastric mucin at pH 7.3.

#### EXPERIMENTS

##### *Experiment I: The Effect of Streptococcal Pneumonia on Thyroidal $I^{131}$ Release.—*

In duplicate experiments, carried out 1 week apart, a total of 43 rats was injected with radioiodine and neck counts were obtained 48 hours later. The animals were then divided into 2 groups of equal average weight. Both groups were subjected to ether anesthesia and intratracheal intubation; the first group was inoculated with streptococci, and the second with 0.1 ml. of sterile mucin. The release of  $I^{131}$  from the thyroid gland was then determined for both sets of animals. A few animals died prior to the termination of the experiment 4 days after intrabronchial intubation at which time all survivors were sacrificed.

##### *Experiment II: The Effect of Pneumonia on Thyroidal $I^{131}$ Release in Adrenalectomized Rats.—*

This experiment was similar in outline to Experiment I, with the following exceptions: (a) bilateral adrenalectomy was performed in both groups 3 days before the injection of  $I^{131}$ . Beginning the day of adrenalectomy and continuing throughout the experiment, all animals received 1.0 mg. of cortisone acetate twice daily subcutaneously; on the day of intrabronchial intubation they received an additional dose of 2.0 mg. of cortisone acetate, and 10

<sup>3</sup> Low iodine test diet, Nutritional Biochemicals, Cleveland.

<sup>3</sup> Obtained through the kindness of Dr. L. D. Bechtol, Travenol Laboratories, Morton Grove, Illinois.

<sup>4</sup> Kindly supplied by Dr. Stanton M. Hardy, Lederle Laboratories, Pearl River, New York.

ml. of 5 per cent glucose in 0.9 per cent NaCl solution subcutaneously. Isotonic saline solution containing 5 per cent glucose was available *ad lib.*; (b) At the time of intrabronchial intubation, mucin was not introduced in the control rats. A total of 8 control and 7 infected animals survived inoculation and were used in the experiment.

*Experiment III: The Role of Undernutrition in the Thyroid Response to Infection.*—

It was noted in Experiment I that infected rats ate less than normal animals, and since fasting has been shown to reduce the rate of release of  $I^{131}$  from the thyroid gland (14), 2 additional studies were performed.

In the first of these (III a) rats were pair-fed with infected rats, and both groups compared with normal control animals receiving food and water *ad lib.* Forty-eight hours after the injection of radioiodine in 29 rats, an initial neck count was made, and the animals divided into 3 groups:

Group 1, numbering 12 animals, was subjected to intrabronchial inoculation with virulent streptococci. Group 2, also numbering 12, was made up of rats matched for weight with the animals in group 1. Group 2 rats were pair-fed and pair-watered with their opposites, but received an intrabronchial inoculum of sterile mucin only. Five rats constituted group 3; they were anesthetized, and intrabronchial cannulation was performed without introduction of any inoculum. Subsequently they were given food and water *ad lib.* Observations on rats in groups 2 and 3 were begun on the day following inoculation of the group 1 animals. Infected animals from groups 1 and 2 were observed carefully at frequent intervals. Any animal that appeared to be moribund was sacrificed by injection of sodium pentobarbital; blood culture was obtained immediately and the extent and character of pulmonary involvement was determined. The adrenal and thyroid glands were removed and their weights determined to within 0.1 mg. on a torsion balance.

In the second part of this experiment (III b) 20 rats were fed increasing amounts of liquid diet by gastric tube for 10 days until they were receiving 26 ml. per day. Radioiodine was injected and initial neck counts determined after which 12 of the animals were inoculated intrabronchially with streptococci. The other 8 served as controls. Eleven injected and 7 control rats survived the cannulation procedure. Both groups were maintained twice daily with tube feedings for the duration of the experiment.

*Experiment IV: The Effect of Increased and Decreased Thyroid Activity upon the Resistance to Streptococcal Pneumonia.*—

These experiments were designed to determine the effect of varying levels of thyroid activity upon the resistance of rats to streptococcal infection.

Following a modification of the method of Dempsey and Astwood (16), animals were fed a ground Purina laboratory chow diet containing 0.1 per cent propylthiouracil (PTU)<sup>6</sup> and given water *ad lib.* In experiment IV a 36 rats were divided into 3 groups and matched by weight. Initially the average weight was 245 gm. The animals were injected once daily subcutaneous with a solution of *L*-thyroxine throughout the course of the experiment. The dose of *L*-thyroxine for each of the 3 groups was respectively 1.0, 6.0, and 18.0  $\mu\text{g.}/100$  gm. body weight. After 3 weeks of this regimen all the animals were inoculated intrabronchially with streptococci. A total of 30 animals in 3 groups (9, 10, and 11 respectively) survived the inocu-

<sup>6</sup> PTU, propylthiouracil.

ation procedure. During the period following inoculation the animals were offered a diet free of propylthiouracil, and a constant dosage of propylthiouracil was administered parenterally (0.5 ml. of 3 per cent PTU suspended in 0.01 N NaOH solution containing 0.9 per cent NaCl). The animals were observed twice a day, and the time of death noted. At autopsy, the animals were examined as in Experiment III.

In Experiment IV *b* a total of 50 rats survived inoculation. The procedure was otherwise identical with that in Experiment IV *a*.

*Experiment V: The Effect of Induced Hypothyroidism on the Resistance to Infection.—*

In this experiment, cumulative mortality curves, determined in rats infected with streptococci after hypothyroidism had been induced by PTU feeding for 3 weeks prior to inoculation, were compared with mortality curves for control animals subjected to the same infection.

The 18 rats fed propylthiouracil received the drug by injection after inoculation. The control group, fed a normal diet, numbered 17, and were given injections of 0.01 N NaOH in 0.9 per cent saline.

The observations made prior to and after sacrifice of animals were identical with those described in Experiment III.

#### RESULTS

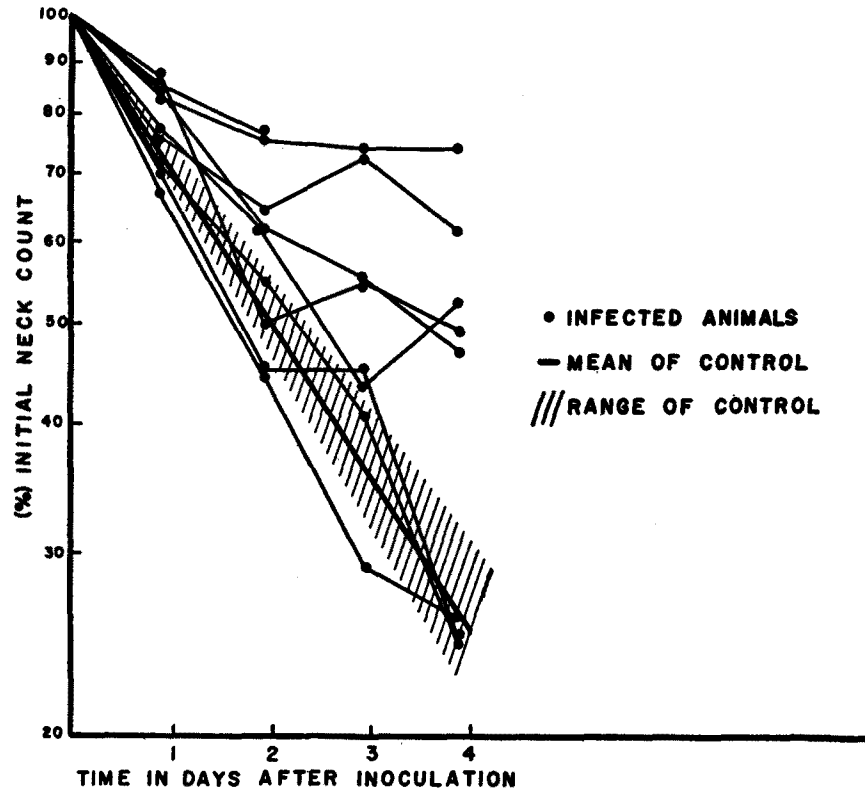
*The Effect of Streptococcal Pneumonia on Thyroidal I<sup>131</sup> Release*

In 2 duplicate experiments (Experiment I), carried out 1 week apart, I<sup>131</sup> release rates were compared in animals which had been inoculated intrabronchially with virulent streptococci, and control animals receiving only sterile mucin intrabronchially. In the first experiment a total of 21 rats was used, 11 of which received the infectious inoculum. Nine control and 9 infected animals survived the immediate 16 hour period following the intrabronchial cannulation; in these animals, the radioiodine release curve was followed for the next 4 days, the neck region of the animals being counted only once per day. Although all the infected animals became extremely ill, only 1 rat died before the conclusion of the 4 day observation period at which time the survivors were sacrificed. At autopsy, all the infected animals demonstrated extensive pneumonia, usually involving the entire left lung, often associated with extension to the right lung, pleural effusion, pericarditis, and mediastinitis. The findings were thus similar to those previously described by Glaser and Wood (15), and examples of the gross changes are illustrated in Figs. 1 and 2. Impression smears of cut sections of the lungs in each instance demonstrated the presence of many streptococci and of a polymorphonuclear cellular response. In contrast, the control animals, injected intrabronchially with sterile mucin, were found to exhibit only small wedge-shaped areas of atelectasis.

At some time during the course of the I<sup>131</sup> release curve, (Text-fig. 1), 8 of the 9 infected animals showed rates of discharge which were slower than the mean control value, and in 5 of the 9 animals the rates were slower than the slowest of the control group. There was striking variation in iodine release rates amongst the animals in the pneumonia group, the values ranging from almost 0 to 35 per cent per day. The

control group, on the other hand, showed little variation in slope, with a mean of  $31 \pm 1.4$  per cent/day and a range of 26 to 33 per cent per day. In general, the animals which appeared clinically to be the most ill showed the most striking reduction in the rate of iodine discharge.

The second test, in which 12 animals were infected and 10 served as controls, was less satisfactory in that only 3 of the infected animals survived beyond the 3rd day.



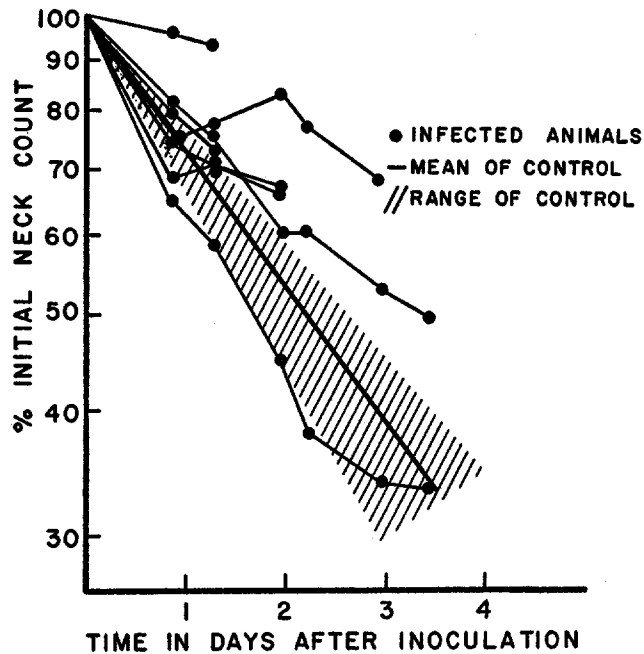
TEXT-FIG. 1. Thyroidal  $I^{131}$  release curves in rats suffering from streptococcal pneumonia. The initial neck count was determined 48 hours after the injection of radiiodine. Immediately after the first count, intrabronchial inoculation with streptococci was carried out. There were 9 infected and 9 sham-inoculated controls.

However, 4 of the 7 rats that survived 2 days after inoculation showed release rates persistently slower than the average of the control rats, a finding consistent with the observations in the first experiment.

#### *The Effect of Pneumonia on Thyroidal $I^{131}$ Release in Adrenalectomized Rats*

Adrenal hypertrophy was a striking finding in infected rats. Since large doses of ACTH or cortisone inhibit thyroid  $I^{131}$  release in rabbits (17) and in rats (18), it appeared possible that the thyroid inhibition seen in rats suffering from pneumonia was

a consequence of increased adrenal cortical activity. Thyroid  $I^{131}$  release curves were measured, therefore, in 7 infected and 8 sham-inoculated animals, subjected to adrenalectomy 3 days before  $I^{131}$  administration, and maintained on a constant parenteral dose of cortisone (Experiment II). The effects of streptococcal pneumonia on thyroid activity in adrenalectomized animals (Text-fig. 2) was similar to that seen in animals with intact adrenals (Text-fig. 1) in that 5 of the 7 infected animals displayed release curves which were at some time during the course of the experiment slower than the average of uninfected animals.



TEXT-FIG. 2. Thyroidal  $I^{131}$  release curves in adrenalectomized rats suffering from acute streptococcal pneumonia. Both infected and sham-inoculated animals were maintained on cortisone injections, 2 mg. per day.

#### *The Role of Undernutrition in the Thyroid Response to Infection*

In the foregoing experiments, it was noted that most sick animals consumed less food and water than did normal ones. Since it is well known that fasting *per se* leads to a reduction in thyroid activity and that this reduction is also reflected in a decreased rate of discharge of radioiodine from the thyroid gland (14), it was necessary to determine the importance of self-induced fasting in bringing about the changes in thyroid activity observed during the course of the infection. The role of undernutrition was evaluated first by measuring thyroid activity in infected animals and in pair-fed controls and then by

measuring thyroid activity in infected and control animals maintained on tube feedings.

#### *Thyroid Function in Infected and Pair-Fed Controls*

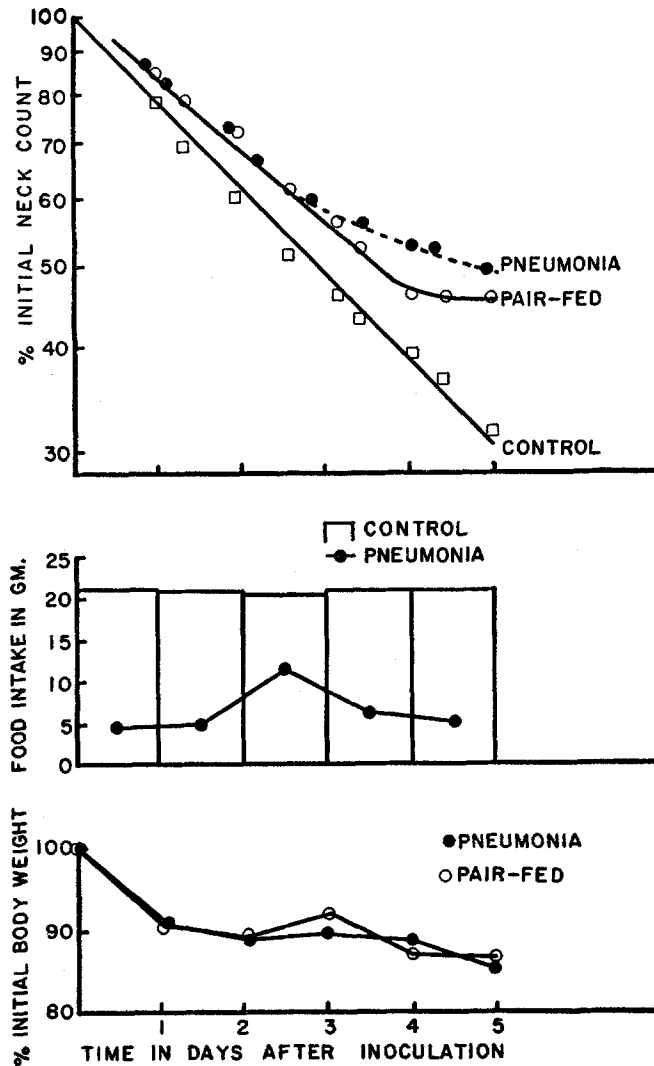
$I^{131}$  release curves were determined in 12 infected animals, 12 pair-fed controls, and 5 animals given food and water *ad lib.* (Experiment III a). Observations in the control animals were instituted 1 day after those in the infected animals to permit pair-feeding, and whenever an infected animal died, its pair was killed at a corresponding interval after inoculation. Six of the 12 infected animals were dead by the 3rd day and 9 were dead by the 5th day after inoculation.

Release curves were plotted for individual rats, and a release curve was derived for each group by calculating the average per cent of initial neck count at each observation. The group average curve was thus made up of a changing number of rats as deaths occurred.

Curves plotted from average values for the neck counts of the 3 groups of animals (Text-fig. 3) indicated that both infected and pair-fed animals displayed release rates slower than the average normal rate. In the last 2 days of the experiment there was a progressive further slowing in these groups. For the first 3 days the average of neck counts in infected animals was identical with that of the pair-fed controls, and thereafter, the curves of the infected animals appeared to flatten out slightly sooner than did those of the fasted animals, but the differences at each time interval were not significant statistically.

Despite the fact that the difference in average slope was not significant by statistical test, there was evidence that infected animals showed a more marked decrease in thyroid activity than did their pair-fed controls. Comparison of release rates in individual pairs indicated that in 7 of 11 pairs, the release rate in the infected animals was slower than in its semifasted control, in 2 pairs the rate was equal, and in 2 pairs only did semifasted animals display slower rates than those of the infected animals. Moreover, the thyroid glands in the 7 rats dying of pneumonia on the 3rd day and thereafter were significantly smaller ( $P < 0.02$ ) than their pair-fed controls ( $14.6 \pm 1.0$  mg. *vs.*  $18.8 \pm 1.5$  mg.).  $I^{131}$  release rates in infected animals ranged from 16 to 95 per cent of the normal rate, (3.5 to 20.0 per cent per day) and in 2 of the animals release rates fell to the levels observed in a group of 9 hypophysectomized rats previously studied in this laboratory (4.3 per cent per day with a range of 3.0 to 6.2 per cent per day). None of the pair-fed controls had release rates within the range characteristic for hypophysectomized rats.

Depression of thyroid function in infected animals was only a little more marked than in pair-fed controls despite the greater severity of the stress to which the infected animals had been subjected. When compared with pair-fed controls the pneumonic animals appeared much sicker clinically, had a higher mortality rate (75 per cent by the 5th day *vs.* 0 per cent) and showed striking adrenal hypertrophy ( $70.3 \pm 5.6$  mg. *vs.*  $44.6 \pm 1.4$  mg.). It was noteworthy that adrenal hypertrophy was marked even in rats dying 24 hours after inoculation. An interesting and somewhat surprising finding was that rate of loss of weight was the same in both pair-fed and infected animals (Text-fig. 3).



TEXT-FIG. 3. Thyroidal  $I^{131}$  release curves in a group of 12 rats suffering from streptococcal pneumonia, in their pair-fed controls, and in a group of 5 control animals given food and water *ad lib*. Food intake and body weight are also illustrated.

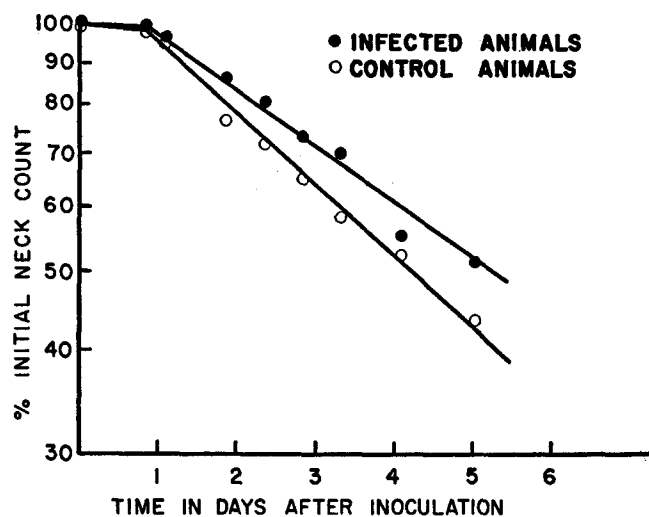
#### *Thyroid Function in Force-Fed Infected Animals*

The rate of  $I^{131}$  release was determined in 11 infected and 7 control animals to which constant food and water intake was administered twice daily by gastric tube (Experiment III *b*) (Text-fig. 4). Three of the 11 infected animals died by the 3rd day and 7 of the 11 died by the 5th day after inoculation. Curves plotted from average values for neck counts (Text-fig. 4) indicated that tube-fed infected animals showed a slower



rate of release of  $I^{131}$  than did uninfected pair-fed controls. The differences between mean neck counts at 45 hours and thereafter (with the exception of counts at 98 hours) were statistically significant at the 95 per cent level of confidence. Differences in thyroid function between normal and infected animals were revealed more clearly by consideration of individual neck curves (Text-fig. 5); thus  $I^{131}$  release rate in 7 of the 11 infected animals was slower than the slowest rate exhibited by control animals.

An initial slow release rate was observed in both groups, and probably was due to an excessively high room temperature during the first 18 hours after inoculation because of failure of air-conditioning apparatus in the animal room.



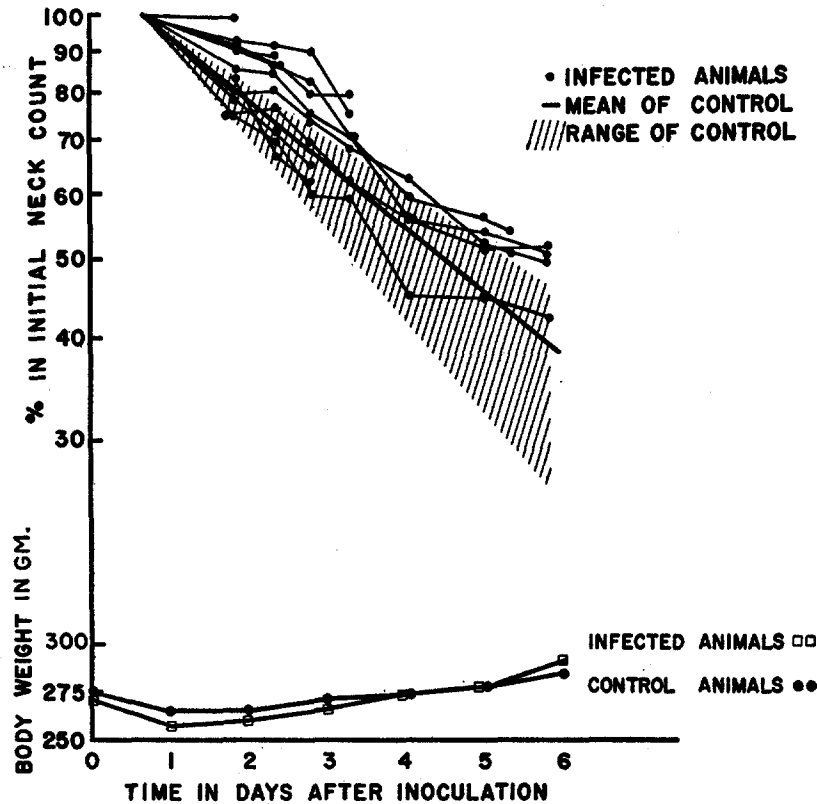
TEXT-FIG. 4. Thyroidal  $I^{131}$  release curves in groups of 11 infected and 7 control rats to which constant food and water was administered twice daily by gastric tube.

Despite the fact that there were significant differences in release rates in these animals, there was no significant difference in thyroid weight (22.3 mg. in infected animals and 21.4 mg. in control animals). By contrast, the average weight of the adrenal glands in infected animals was 74.2 mg. as compared with 48.3 mg. in control animals. As in the previous experiment, changes in body weight for both groups were virtually identical.

*The Effect of Increased and Decreased Thyroid Activity upon the Resistance to Streptococcal Pneumonia*

The demonstration that experimental pneumonia caused a decrease in thyroid activity led to consideration of the possibility that this response might serve a useful adaptive function. This hypothesis was tested by feeding rats a goitrogenic diet and providing appropriate thyroxine supplements by parenteral injection preceding and following inoculation. The effects of hyperthyroidism were also studied.

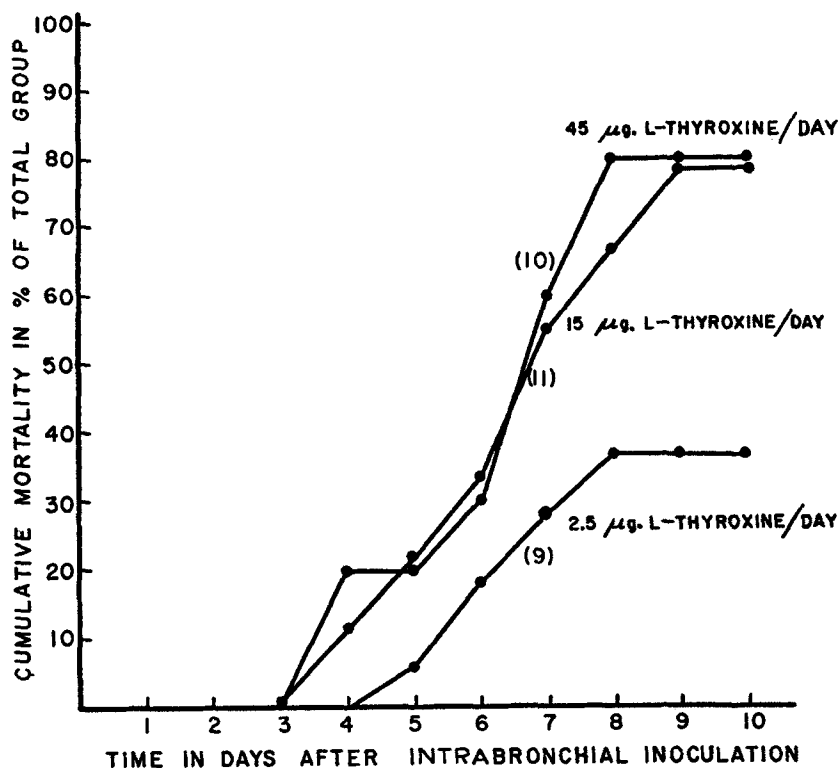
Two similar experiments were carried out, the 3 groups of animals in each experiment (Experiment IV) receiving 1.0, 6.0, and 18.0  $\mu\text{g}$ . of *l*-thyroxine per 100 gm. body weight. Thirty rats were used in the first experiment and 50 in the second. Intrabronchial inoculation of all rats in each group was carried out 3 weeks after starting the goitrogenic diet, and the time of death was noted and recorded by days.



TEXT-FIG. 5. Individual thyroidal  $I^{131}$  release curves in 11 rats with pneumonia maintained on tube feedings. The mean curve and range of curves in a group of 7 similarly fed uninfected controls is also shown.

The cumulative mortality curves of the rats in the 3 groups (Text-figs. 6, 7) indicate that hypothyroid rats died at a slower rate than did either normal or hyperthyroid animals. In the first experiment (Text-fig. 6) the total mortality in the hypothyroid group was less than in the other groups, while in the second experiment (Text-fig. 7), despite the decreased rate at which the animals died, the total mortality in the 3 groups was very nearly the same. Hyperthyroid rats appeared to die sooner than did normal or hypothyroid animals in the second but not in the first experiment. The weights of the thyroid glands of these animals (Table I) were indicative of the degree of suppression of goiter formation exerted by the dosage of thyroxine used;

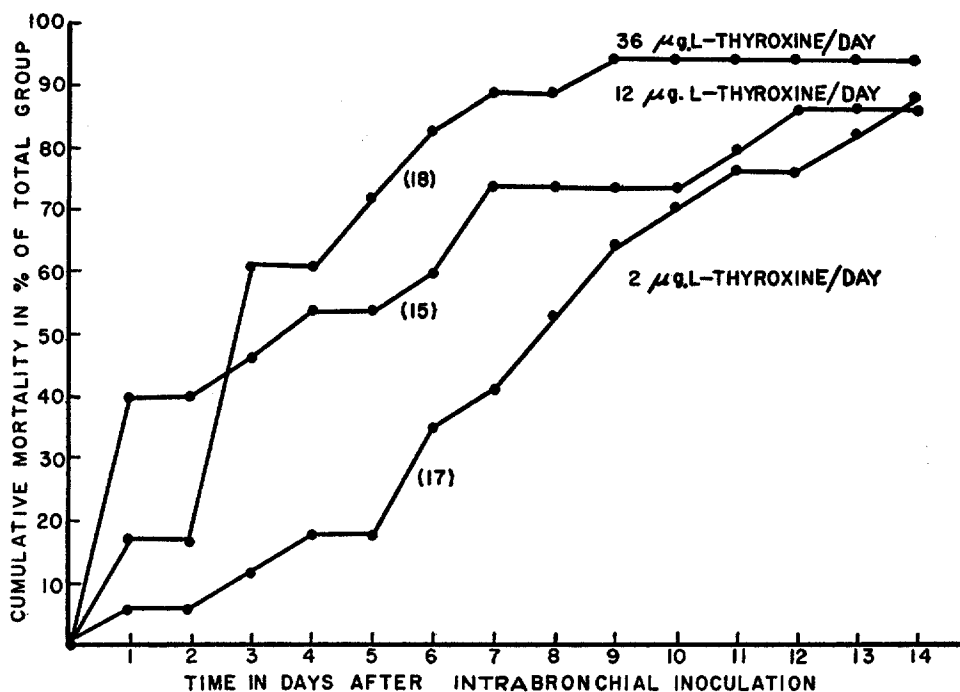
it is apparent that the rats on low thyroxine dosage were receiving a supplement which kept them in the hypothyroid range. The thyroid weights of rats in the normal and high dosage range indicate adequate suppression of endogenous thyroid activity, but the difference in thyroid weights of animals receiving normal and high dosages was not significant. In addition to the effects on survival time and total mortality, in-



TEXT-FIG. 6. Cumulative mortality curves in 3 groups of rats with streptococcal pneumonia. The animals were maintained on 0.1 per cent propylthiouracil in their feed, and given graded doses of *l*-thyroxine by subcutaneous injection. This therapy was given for 3 weeks preceding and following intrabronchial inoculation. After infection, propylthiouracil was administered parenterally. In brackets are shown the number of animals in each group.

ected rats with induced hypothyroidism appeared less ill than did hyperthyroid or euthyroid animals. This was most clearly demonstrated in the first experiment comparing general appearance, degree of weight loss, and adrenal hypertrophy.

By gross inspection there was no apparent difference in extent of the infection in the 3 groups. The effects of thyroxine on the course of infection was not due to direct stimulation of bacterial growth, as it was shown in *in vitro* experiments that *l*-thyroxine, added to broth cultures of streptococci, exerted no effect on multiplication of the organisms.



TEXT-FIG. 7. Cumulative mortality curves in 3 groups of rats with streptococcal pneumonia. The animals were maintained on 0.1 per cent propylthiouracil in their feed or by injection and given graded doses of *l*-thyroxine by subcutaneous injection. This therapy was given for 3 weeks preceding and following intrabronchial inoculation.

TABLE I

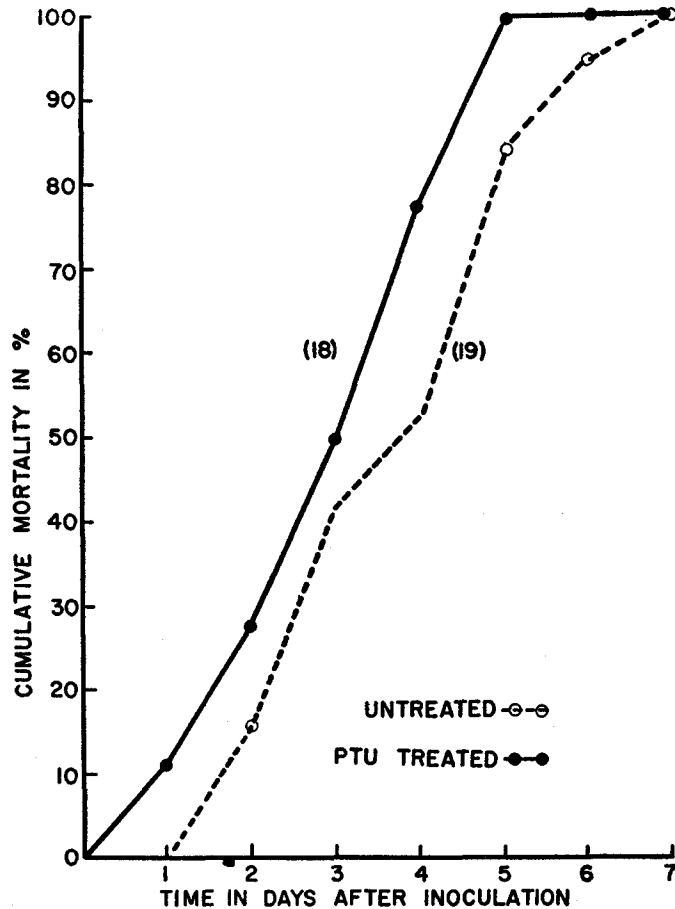
*The Effect of Various Levels of Thyroid Activity on Body, Adrenal, and Thyroid Weight in Rats with Streptococcal Pneumonia*

Experiment (dose of thyroxine per day in µg.)	No. of animals	Body weight			Thyroid		Adrenal		
		Initial	At time of infection	At death	Weight	s.e.*	Weight	s.e.*	
		gm.	gm.	gm.	mg.	mg.	mg.	mg.	
I	2.5	11	242	272	242	40.1	2.0	58.5	6.0
	14.0	9	245	276	229	18.8	1.0	73.5	5.8
	45.0	10	237	257	218	19.0	1.2	84.7	5.3
II	2.0	15	205	254	212	41.5	3.7	78.6	3.9
	12.0	13	201	242	203	18.5	2.9	64.6	4.3
	36.0	17	195	235	195	17.0	0.8	76.3	4.5

\* Standard error.

*The Effect of Induced Hypothyroidism on the Resistance to Infection*

In the preceding experiment, in which varying levels of thyroid activity were maintained at predetermined levels, resistance to streptococcal pneumonia was



TEXT-FIG. 8. Cumulative mortality curves in 2 groups of rats with streptococcal pneumonia. The propylthiouracil treated animals had been on 0.1 per cent propylthiouracil in their diet for 3 weeks prior to inoculation, and propylthiouracil was administered intraperitoneally after infection.

generally least in hyperthyroid and greatest in hypothyroid animals. This finding suggested that the decreased thyroid function which occurs in infected rats might act to increase resistance to infection. The following experiment (Experiment V) was performed in order to determine whether a further lowering

of the already reduced thyroid activity of infected animals would exert a favorable effect on resistance:—

Mortality from streptococcal pneumonia was determined in 19 untreated animals and in 18 rats given propylthiouracil in the diet for 3 weeks preceding inoculation and by injection for the survival period thereafter (Text-fig. 8). No thyroxine supplements were administered. Although the slopes of the 2 mortality curves were approximately parallel, the initially hypothyroid rats evidenced decreased resistance to infection as indicated by earlier deaths of animals in this group.

In interpreting these data it should be pointed out that pretreatment of rats with propylthiouracil led to decreased weight gain as compared to control animals (15 per cent as against 25 per cent). Moreover, the hypothyroid rats appeared less fit physically as judged from the condition of their coats and the lack of muscular tone.

#### DISCUSSION

In these studies, severe pulmonary infection was found to cause an inhibition of thyroid activity as measured by decrease in the rate of discharge of  $I^{131}$  from the thyroid gland, and by a decrease in gland weight. Acute infection, therefore, like most other stressful conditions in the rat is associated with a depression of thyroid function. A number of other observations support this conclusion.

It was shown by Williams *et al.* (8) that the injection of a pyrogenic substance led to a decreased thyroid iodine uptake, and Goldberg *et al.* (22) demonstrated that pyrogenic substances in the rabbit resulted in a lowering of the blood protein bound iodine concentration. Low thyroid activity following the development of a large abscess in a rabbit has been described (13). Three studies in humans are of particular interest. Gordon and Rabinowitch (23) reported the case of a male patient who developed severe hypothyroidism following an attack of lobar pneumonia, and Schick *et al.* (24) observed low basal metabolic rates in children following their recovery from pneumonia. More recently, Walker (25) demonstrated that there is a variable degree of depression of the blood protein bound iodine at some time during the course of non-fatal lobar pneumonia. Especially in the presence of malnutrition, chronic debilitating disease in man was found to be associated with low levels of serum-precipitable iodine (26). Functional studies in man clearly indicate, therefore, that thyroid function may be reduced during the course of an infection. The histological changes described in patients dying of infection (1-7) should be reinterpreted in this light.

The mechanism by which thyroid activity is reduced during the course of infection has not been elucidated. The demonstration that thyroid inhibition occurs even in adrenalectomized animals on constant cortisone intake excludes the adrenal gland as an essential factor in this response.

Voluntary food restriction was undoubtedly a major factor in causing the thyroid inactivity seen during infection. Fasting influences thyroid function by bringing about a decreased output of pituitary thyroid-stimulating hormone

(TSH) (27); this decrease in TSH is reflected in thyroid atrophy (14, 19, 20), depressed  $I^{131}$  uptake (8, 12, 21), and decreased rate of release of thyroidal  $I^{131}$  (14). The mechanism by which fasting brings about a decrease in TSH release is still a matter of conjecture. Although fasting was important in the animals studied in this investigation, it was not the sole factor leading to thyroid inhibition during the course of acute bacterial infection. From the observations of Brown-Grant *et al.* (28) it has been inferred that severe physical stress may reduce the responsiveness of the thyroid gland to TSH, and depress pituitary TSH output as well. Even in the hypophysectomized animal, severe physical stress has been shown to reduce thyroid activity (29), suggesting the participation of local metabolic or vascular factors independent of TSH. Similar factors probably are operative in the thyroid inhibition associated with infection.

Consideration was given to the possibility that reduction in thyroid activity induced by infection exerted a protective effect. This effect, if indeed real, was probably fortuitous since thyroid inhibition was generally most severe in rats that were the most seriously affected by pneumonia (and hence the least resistant); conversely, rats showing the greatest resistance usually had thyroid activity within the normal range.

In the studies herein reported, it was shown that severe hypothyroidism as well as hyperthyroidism lowered resistance to infection. On the other hand, a moderate degree of hypothyroidism appeared to increase resistance. Mortality rose with increasing thyroid activity when thyroid function was maintained artificially at three levels.

With respect to the effect of thyroxine overdosage on resistance to infection, the findings in this study are similar to those previously reported in experiments on mice infected with hemolytic staphylococci (30), tubercle bacilli (31), eggs of *Hymenolepis nana* (32), and murine pneumonitis virus (33).

In mice infected with poliomyelitis, there was an increased incidence of deaths without previous paralysis in hyperthyroid animals (34). On the other hand, a protective effect of increased thyroid activity has been observed in tuberculosis of rabbits (35) and perhaps in man (36). Experimental poliomyelitis infection in mice (37) was less virulent in thyroxine-treated animals.

There are fewer observations on the effect of hypothyroidism on resistance to infection. Reduced thyroid activity resulted in increased resistance of mice to murine pneumonitis virus (33) and to infestation by *Hymenolepis nana* (32). On the other hand, induced hypothyroidism resulted in reduced resistance of mice to poliomyelitis virus (37), and of rats to infestation with *Notodres muris* (38). There seems to be a measure of agreement that hypothyroidism reduces resistance to tuberculosis in rabbits (35), and perhaps in man (36).

The relation of thyroid activity to the specific mechanisms of immunity is the subject of a large literature which cannot be considered here.

## SUMMARY

In order to study the effects of a severe bacterial infection on thyroid function rats were subjected to group A streptococcal pneumonia, and thyroid activity determined by measurement of the rate of discharge of  $I^{131}$  from the thyroid gland.

Decreased thyroid activity of moderate to marked degree was observed in the majority of infected animals. Infected animals ate less than normal animals. Since fasting leads to decreased thyroid function,  $I^{131}$  release rates were measured in control animals pair-fed with infected animals and in control and infected animals force-fed a normal intake. The reduction in thyroid activity seen in acute infection was found to be partly but not entirely due to the associated voluntary food restriction.

Although the adrenal glands of rats dying of pneumonia were very large, the thyroid inhibition occurring during the course of experimental pneumonia was not secondary to increased adrenocortical function since infected, adrenalectomized animals, receiving injections of cortisone, showed thyroid inhibition comparable to that observed in intact infected animals.

The possible influence of the level of thyroid activity on resistance was evaluated. In two experiments a total of 80 rats in 3 groups was pretreated with propylthiouracil and injected daily with 3 dosage levels of *l*-thyroxine for 3 weeks prior to inoculation. Under these conditions mortality rates in infected animals fell with decreasing levels of thyroid function. However, induced hypothyroidism was found to afford no protective effect in comparison with untreated infected animals.

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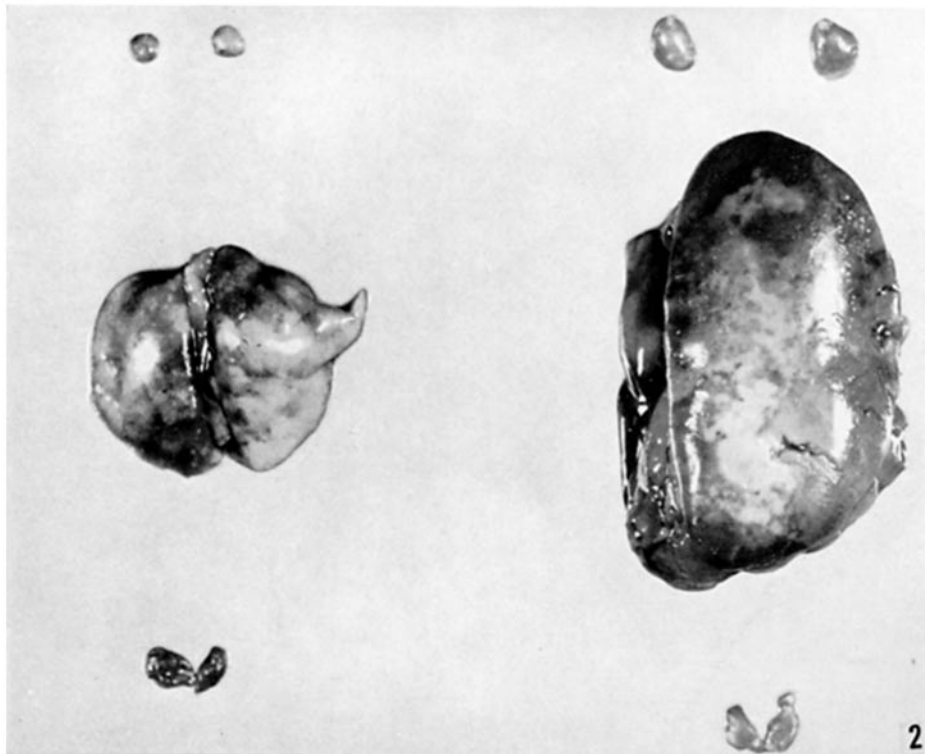
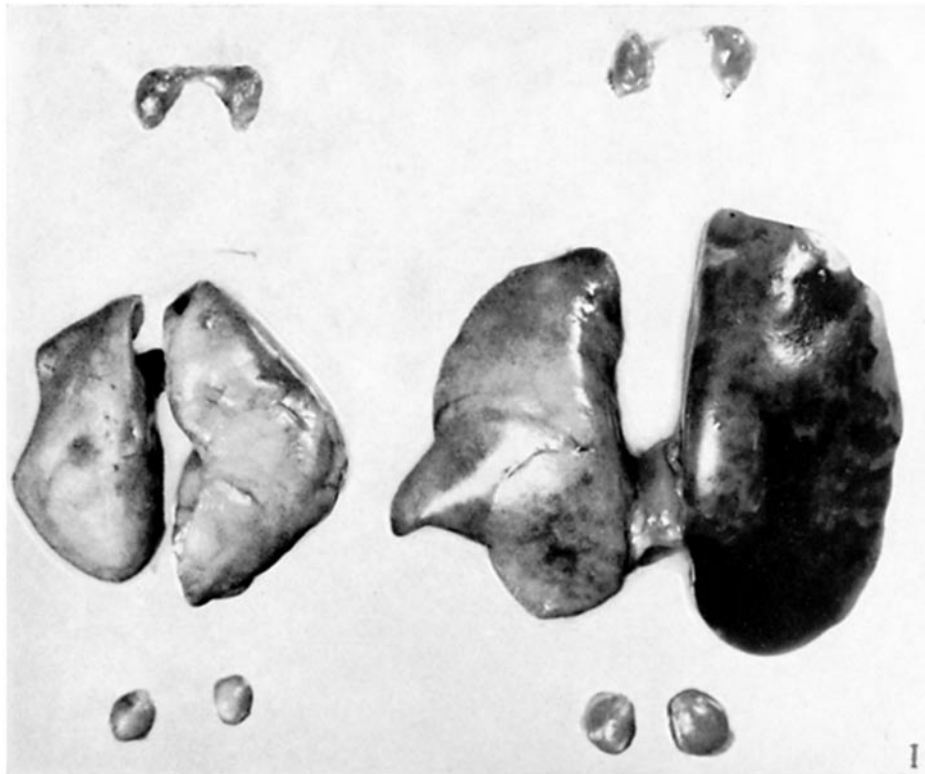
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## EXPLANATION OF PLATE 27

Gross photographs of the lungs and of the adrenal and thyroid glands of normal rats and rats with streptococcal pneumonia. Approximately  $1\frac{1}{2}$  times life size. The photographs were made by Mr. K. Cramer Lewis, Department of Illustration, Washington University School of Medicine.

FIG. 1. Hemorrhagic pulmonary consolidation in a rat dying of pneumonia 24 hours after intrabronchial inoculation of type 17 beta hemolytic streptococci in mucin. Note the size of the infected lung as compared with that of a control animal, the striking adrenal gland hypertrophy (bottom) and the congested thyroid gland (top).

FIG. 2. Pulmonary consolidation with abscess formation in a rat with pneumonia killed 4 days after intrabronchial inoculation of type 17 beta hemolytic streptococci (right). In the lung of a control rat (left) note the wedge-shaped area of atelectasis which followed intrabronchial inoculation with sterile mucin. There is striking adrenal hypertrophy in the infected animal (top).



(Reichlin and Glaser: Thyroid function in streptococcal pneumonia)