The Relationship of Iodine to the Basal Metabolic Rate and to Changes in the Thyroid in Pregnant Rabbits; An Experimental Study.

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Preface.

This paper is the end result of three and one half years of study of the thyroid gland and certain of its changes. During the first year the immediate problem was not undertaken. Other experiments were being done that gradually led up to the present investigation. Dogs were used in the first attempt to study the effect of iodine on the basal metabolic rate and the structure of the thyroid, during pregnancy. These animals required careful training to fulfil the conditions of correct B.M.R. recordings. No suitable breathing mask could be found and the artificial conditions of life in cages rendered the animals relatively sterile and the induction of pregnancy became a real difficulty. After a thorough trial with rather poor results, this experiment was abandoned. Rabbits were selected because of their gentle nature and small size. The major portion of the work presented here was done during the past one and one half years. The experiments not reported were nevertheless, of great value, contributing to the perfection of technique and the evaluation of results.

This work would not have been possible except for the very able guidance and counsel of Dr. Frank R. Menne under whom I have had the great pleasure of working for the past four years. I am also indebted to Dr. F. R. Menne and Dr. W. C. Hunter for their very learned criticism and correction of this paper, and to Miss Basler, the secretary of this department for her very kind and careful stenographic assistance.

The Relationship of Iodine to the Basal Metabolic Rate and to Changes in the Thyroid in Pregnant Rabbits, An Experimental Study.

James D. Stewart, Jr. A.B. *

The changes in the thyroid gland during pregnancy have held the interest of Clinicians and Pathologists for many years. The problem is especially recognized in the goiter districts, where without early prophylaxis, thyroid disturbances are inevitable. By clinical observation and laboratory tests, these variations in thyroid function during pregnancy have been estimated. Iodine is given during pregnancy to minimize such functional disturbances. That such administration is justified, is common knowledge and is supported by the mass of current literature dealing with this subject.

It is an established fact that pregnancy is associated with a considerably exaggerated metabolic rate. This has been recognized by clinical observation for many years but was not established definitely until recently. Root and Root (1) in a very complete review of the

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(1) Root, H.T. and Root, H.K.: Arch. Int. Med., 32:411-424 (Sept) 1923

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literature, state that Magnus and Levy (1904), Zunts (1910), and Hasselback (1912) noted the basal metabolic rate before conception and during pregnancy in one individual each. A relative and absolute increase in the oxygen consumption, per kilogram body weight, was noted as early as the third month by Magnus and Levy who also reported an average

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increase of 17 per cent during the entire period of pregnancy. These observations represent only a few cases and were recorded with the early types of apparatus then available for determining the basal metabolic rate.

In 1921, Baer (2) published the results of a series of basal

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(2) Baer, J.L.: AM. J. Obst. and Gynec., 2:249-256 (Sept) 1921.

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metabolic determinations during pregnancy and the puerperium. He reports the readings in forty-four cases of normal pregnant women. Using standard equipment and the Aub-Dubois tables he noted that during the thirty-sixth week of pregnancy, the basal metabolic rates in these women, were 26 per cent higher than those for non-pregnant women of equal surface area. The increase was 33 - 35 per cent during the fortieth week. Three days post-partum these rates fell to 15 per cent above the normal or predicted normal, and at the end of ten days returned to normal. Baer concludes that the increase in the basal metabolic rate, late in pregnancy is due to the rapidly growing demands of the fetal organism and its placenta. The incomplete and delayed return to normal, after delivery, is due to the involutionary changes in the uterus and the onset of lactation. Similar observations were made by Cornell (3), who

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(3) Cornell, E.L.: Surg. Gynec. and Obst.,36:53-58 (Jan) 1923.

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noted an ante-partum rise of the basal metabolic rate and a post-partum fall, almost identical with those of Baer, (2). He recorded the ante- and post-partum rates, in eighty four pregnant women. The average ante-partum rise in this series was 29 per cent, compared with non-pregnant women of the same surface area, age, etc., the age varied from 20 to 40

years and the average increase was greater in the older patients. The average range for individuals from 20 and 25 years being 23.73 per cent and 33 per cent for those between 35 and 40 years. The post-partum average rates were 27.3 per cent for the first three days and 17.3 per cent at the end of nine days. He concluded that there are wide variations in the degree of increase in rate and that many factors in pregnant women are responsible for such changes. Cornell found no relationship between the increased metabolism and the toxemias of pregnancy.

In the detailed study of a 29 year old primipara, made by Root and Root (1), the determinations were rigidly controlled, being made every fortnight until the last three weeks of pregnancy, when they were taken weekly. The course of pregnancy was normal in all respects. They obtained normal readings up to the fourth month, after which time there was noted a gradual increase to 23 per cent above normal eleven days before term. The patient's weight increased only 7.6 per cent. After term the B.M.R. declined to 9.6 per cent, or to about the level at the fourth month of pregnancy. Although there is some disagreement as to the exact time of the onset, and the percentage of increase in the basal metabolic rate, there appears to be uniformity of opinion as to the occurrence of a considerable increase in the latter half of pregnancy and a rapid return to normal post-partum in all of the 135 instances studied. Most of the authors agree that the percentage increase in the rate of metabolism is out of proportion to the actual rise in weight due to the fetus and membranes. It may be that the increased rate is indicative of an accentuated metabolism in the rapidly growing fetus. This in turn would overload the thyroid and cause a dysfunction in the presence of inadequate iodine in the diet.

The response of abnormal glands, compared with those considered normal in pregnant women, was studied by Plass and Yoakman (4) in 1929.

(4) Plass, E.D. and Yoakman, W.A.: Am. J. Obst. and Gynec., 18:556-568, (Oct.) 1929

They detailed the basal metabolic rates in 72 pregnant women. Of these, 51 were considered to have abnormal thyroids and were classed as: small endemic goiter, adenomatous goiter, and large colloid goiter. The remaining 21 women were normal. Their study indicates that pregnancy places an extra burden on the thyroid gland. The normal gland was found to compensate while the abnormal one was disturbed. They found that the greater the original pathology of the gland, the greater the hyperthyroidism associated with pregnancy. These authors further concluded that iodine does not protect against gestational hypertrophy in normal glands but prevents further changes in the abnormal ones. However it does prevent enlargment of the thyroid of the fetus. In general the ante-partum rise and the post-partum fall in the basal metabolic rates conformed with those of previous reports.

The relationship between gestation and the basal metabolic rate is well illustrated in the report of Litzenberg and Casey (5). They found

(5) Litzenberg, J.C. and Casey, J.B.: Am. J. Obst. and Gynec., 17: 550-552, (April) 1929.

that moderately low metabolism is associated with menstrual disturbances, sterility, and interrupted pregnancies in a large per cent of cases. One-third of all the women studied had a low basal metabolic rate and one-half of these were sterile. Two-thirds of the women with low metabolic rates, had menstrual disturbances. One-fourth of those with low rates, who conceived, aborted, some repeatedly. The restoration of the normal metabolism and general hygienic measures, in many cases improved menstruation, aided conception, and prevented abortion. Earlier observations were presented by Kraul and Halter (6). They used roentgen rays to stimulate

(6) Kraul, K. and Halter, G.: Ab., J.A.M.A., 83:570 (Aug. 16) 1924.

or destroy genital function. Two days after a stimulating dose was administered there occurred an increase in the basal metabolic rate. This effect at times persisted for a period of six weeks. Roentgen ray castration was followed by decreased metabolism.

If the basal metabolic rate may be taken as an index of thyroid activity, a fact generally accepted, the foregoing references present positive evidence of the existence of increased activity during the latter months of pregnancy and early in puerperium. But there are still other evidences supporting such a view. The observations of Braun (7)

(7) Braun, I.: Am. J. Obst. and Gynec.,3:352-358, (April) 1922

substantiate the trend shown by the basal metabolic recordings. He discussed all phases of pregnancy in cases with exophthalmic goiter and refers to the possibility of aggravated symptoms in the latter months. Exophthalmic goiter is not considered a contra-indication to pregnancy, but he believes that if it occurs, attempts should be made to carry the pregnancy through to term in order to avoid an upset in endocrine function. He advises against prolonged labor, repeated pregnancies, and lactation because of the possibility of exhaustion of the thyroid gland by repeated overstrains. It is Braun's belief that Graves' disease is a manifestation of toxins produced in the body with a compensatory thyroid activity. Raycraft (8) states

(8) Raycraft, J.L: Ohio State Med. J., 26:559-561, (Sept) 1930

that an increase in the size of the thyroid during normal pregnancy is a well established fact. He called attention to the greater frequency of

glandular enlargement in endemic goiter regions and makes a plea for rigid iodine prophylaxis.

There is abundant evidence of the existence of thyroid hypertrophy during normal pregnancy in the writings of Cornell (3), Plass and Yoakman (4), Braun (7), Davis (9), and Straus and Daley (10). There are investigators

(9) Davis, C.H.: J.A.M.A., 84:1004, (Sept. 15) 1926

(10) Straus, S. and Daley, P.A.: Wisconsin Med. J.,25:325-328, (July) 1926

who do not agree however, notably Kraus (11) of Berlin. He states that the

(11) Kraus, H.: Arch. fur Gynakologie, 126:1-336, (Dec.15) 1924. J.A.M.A. 84:558, Feb. 14, 1925

results of ephedrin injection tests for thyroid function, show a depressed rather than an intensified thyroid activity during pregnancy. In support of this view he reports three cases dying intra-partum in which the histological picture of the thyroid gland was that of hypothyroidism. Kraus reports that certain of his associates have made similar observations. No such observations are found in the American literature. It is difficult to evaluate the findings and conclusions drawn from the ephedrin injection tests and possibly limited histological studies. It is a well known fact that in different areas of the thyroid gland the microscopic picture may vary markedly.

Experimental studies of thyroid activity and associated abnormalities are probably more numerous than strictly clinical investigations. In the great mass of animal experimentation reported in the current literature concerned with the thyroid and its function, there are a few dealing with the problem presented here. In 1917, Smith (12) reported the results of

(12) Smith, G. E.: J. Biol. Chem., 29:215 (March) 1917

feeding iodine and thyroid to pregnant sows. He found that five grains of potassium iodide daily throughout pregnancy, increased the number and vigor of the young. Sheeps thyroid, five grains daily, had little effect, and those sows not receiving potassium iodine or thyroid had few young and many of these died. The effect of large doses of potassium iodide on pregnant ewes, as given by Eward (13) does not support Smith's observations.

(13) Eward, J.M.: Endocrinology, 12:539-540 (Sept. and Oct) 1928

He found that large doses of potassium iodide decreased the resistance of the young, increased fetal mortality, but lowered the incidence of goiter. Carefully controlled experiments indicated that the larger the dose the greater the deleterious effect. Schlotthauer (14) varied the protein

(14) Schlotthauer, C.T.: Pro. Staff Meeting Mayo Clinic, 4:184, (June) 12, 1929.

and carbohydrate content of the diet of pregnant, thyroidectomized, Duroc sows. He found that thyroidectomized sows on a low protein diet did not develop the signs and symptoms of myxedema.

The effect of iodine by mouth on the heat production of individuals with high metabolic rates, is well known. According to Marine et al (15)

(15) Marine, David: Deutsch, Max: and Cipra, Anna: Proc. Soc. Exp. Biol. and Med. 24:657-662, 1927

Loewry and Zondek, in 1921, first showed that iodine lowered the basal metabolic rate in cases of Grave's disease. In 1924, Plummer and Boothby (16)

(16) Plummer, H.S., Boothby, W.M.: J. Iowa Med. Soc. 14:66-73 (Feb) 1924

reported 600 cases of Grave's disease in which the oral administration of Lugol's solution, minims ten to fifteen, three times a day, caused the basal metabolic rate to drop from dangerous heights to a point compatible with an excellent surgical prognosis. Marine (15) stated that iodine in any form will involute physiologic hyperplasia of the thyroid and prevent its occurrence in all orders of animals studied. He attributes this involution to increased colloid storage, distention of the acini, and an acute blocking of the peri-acinar capillaries and lymphatics, thus damming back the secretion. In studying the effects of large doses of iodine on the heat production in rabbits, Marine found that a decrease in five instances, no change in eleven, and an accentuation in two animals. He found no distinct microscopic changes in the thyroid. Cordonnier (17) fed

(17) Cordonnier, J.: Proc. Soc. Exp. Biol. and Med., 26:636-639 (May) 1929

dessicated thyroid to guinea pigs and produced an increased metabolic rate. These animals were then given potassium iodide but this did not effect the return of the metabolic rate to normal after the thyroid feeding was discontinued.

Still other criteria of thyroid activity such as the size of the acinar cells, the number of mitoses, the size of the acini, and the character of the colloid$, have been studied experimentally. In 1927 Gray, Haven, and Loeb (18) studied the effects of potassium iodide and

(18) Gray, S., Haven, F.L., Loeb, L.: Proc. Soc. Exp. Biol. and Med. 24: 503-565 (March) 1927

and dessicated thyroid by mouth on the thyroid glands of guinea pigs. They removed a large portion of the gland and administered potassium iodide, dessicated thyroid, and anterior pituitary substance to these animals. The potassium iodide seemed to increase the compensatory hypertrophy by increasing the size of the cells, the number of mitoses, and the fluidity of the colloid. Thyroid extract and anterior pituitary substance had opposite effects. Potassium iodide had no effect on the normal gland during the first thirty days except an increase in the cellular mitotic activity. After forty days the cells became small and the colloid abundant and firm. Gray and Loeb (19) in 1928 reported further results along these same lines.

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(19) Gray, S.H. and Loeb, L.: Am.J.Path., 4:257-270 (May) 1928

They found in control guinea pigs, low cuboidal acinar cells, vacuolated colloid, and irregular sized acini. The animals receiving 0.05 mg. of potassium iodide daily for 16 days, had acini lined with tall columnar epithelium, fluidified colloid, and were in a state of compensatory hypertrophy. Those receiving potassium iodide for a longer period of time had glands with low acinar epithelium, firm abundant colloid, and were in a state of depression. The administration of thyroid extract produced no effect in ten days, then the acinar epithelium became flattened, indicating a depressing effect.

There can be no doubt of the clinical value of iodine administration during pregnancy, as is witnessed by the many reports in the current literature. There is however, a lack of controlled animal experiments and observations regarding the use of iodine. For this reason it seems justifiable to report the results of experiments by the writer in which iodine was given to animals during pregnancy and puerperium.

Experimental Study.

The object of the study was to determine whether or not iodine has

any significant effect on the thyroid glands of rabbits during pregnancy. It was deemed advisable to establish certain conditions to be fulfilled during the course of the study. (1) The quantity of iodine to be administered calculated according to the physiological optimum, and multiples of this amount given daily by mouth. The exact doses are listed in the more detailed description below. (2) Frequent basal metabolic rates were taken to note the effect on the oxygen consumption and the heat production. (3) Lobectomies were done at term and at the end of lactation to determine the influence on the structure of the thyroid gland. Such data should give some indication of the changes, if any, in the thyroid gland during pregnancy and the effect of iodine, in varying amounts, upon it.

Two series of six and seven rabbits each were used. To these animals, multiples of physiologic iodine requirements were administered daily. Pregnancy was induced in as many animals as possible and these were followed through pregnancy and puerperium with frequent basal metabolic readings. The animals were kept in clean cages, in a moderately warm room with good light, adequate food, and plenty of water. The feeding time was at 2:00 P.M. and the basal metabolic determinations were taken the following morning so that eighteen to twenty hours elapsed after feeding. The rabbits were carefully transported to the apparatus to avoid any increased activity. A McKesson Metabolor, with circulating motor and water sealed breathing chamber were used to determine the oxygen consumption. (See figure 1, page 11) This apparatus was tested before each series of estimations and readings were only taken when it was found to be air tight. This test period lasted fifteen minutes. Wilson soda lime for metabolors was used in the lime chamber. Fresh air and one liter of oxygen were used for each estimation. The rabbit remained in the breathing chamber for fifteen minutes before the readings were taken. The weight in kilograms, the temperature, barometric pressure, and cubic centimeters of oxygen used, were noted on a separate

Figure No. I. Photograph of the McKesson Metabolor and the water sealed breathing chamber used in the experiments.

chart for each rabbit. Notes were also made regarding the condition of the animal and the probable approach to a basal condition. The animals soon became adjusted to the breathing chamber and remained in it for thirty minutes without a move.

The calculations were done with logarithmic tables reading to the sixth place. Meeh's formula for the surface area of animals was used. It is $S = K\sqrt[3]{Wt^2}$, when S is the surface area, K is a constant, and the weight is in kilograms. The constant for rabbits is 0.128. The surface areas of these animals averaged 0.25 square meters. Hayden's table of temperature and barometric pressure corrections were used in the calculation of the basal metabolic rates. The B.M.R. may be defined as the calories produced per hour, per square meter body surface area at standard conditions. The actual calculations were as follows: cubic centimeters of oxygen used per minute, times the correction factor in Hayden's table, divided by the fraction of a square meter body surface area. The rates for each animal are given in tables I - VII inclusive.

Each rabbit received one to five times the physiologic iodine requirement. This was administered in the form of Lugol's solution diluted 1/10000. Physiologic iodine is based on the quantity given by Sollmann (19)

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(19) Sollmann, Torald: A Manual of Pharmacology, 3rd Ed., W.B. Saunders Co. 884-908, 1927.

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as about 0.045 mg. of iodine for an adult in 24 hours. If the average adult weighs 70.0 kilograms, then the iodine per kilogram is 0.045/70.0 which is 0.00065. In each minim of Lugol's solution there is 6.5 mg. of iodine. Then in each minim of a 1/10000 solution of Lugol's, there would be 0.00065 mg of iodine or the requirement for each kilogram body weight in 24 hours. Thus for each kilogram of body weight the rabbit was given 1,2,3,4, or 5 minims of 1/10000 Lugol's solution. One rabbit (R VI)

in the first series and two rabbits (R VI and R VII) in the last series received no iodine and acted as controls.

On the day following delivery one lobe of the thyroid was removed surgically. The other lobe was extirpated at the end of the lactation period when the animals were sacrificed. There were no ill effects noted from the operation at term. The glands were fixed in Zenker's fluid, embedded in paraffin and stained with hematoxylin and eosin. The histologic description of each thyroid is included in the individual protocols.

The basal metabolic determinations for the first series are given on a composite chart, Table I. This is followed by more detailed charts for each rabbit.

Series I.

RABBIT NO. I: Received physiologic iodine according to the amount given above. This was administered daily over a period of 231 days. Repeated attempts were made to induce pregnancy without success. The periodic basal metabolic readings are given on the table for R-I, also remarks regarding the condition of the animal. At the end of the period the rabbit was killed and the thyroid removed for study. Grossly the thyroid consisted of two small reddish-brown lobes, one on either side of the trachea. The microscopic sections of the thyroid, reveal small, uniform sized acini, lined with low cuboidal epithelium. These acini contain pinkish blue colloid which is free of vacuolization. The gland appears inactive. The B.M.R. readings and data are given on Table II, page 15.

Table I. First Series - B.M.R. Recordings for entire series.

Date	R-I	R-II	R-III	R-IV	R-V	R-VI
6-20-28	21.153	37.7	23.115			
6-27-28	19.665	23.517	18.924	20.83	25.296	20.354
7-2-28	24.77	23.6	19.01	20.8	25.59	19.41
7-5-28	18.875	26.83	22.01	20.02	25.34	21.54
7-9-28	23.91	28.404	21.76		24.77	19.6
7-11-28	23.665	23.78	19.42	20.03		18.98
7-14-28	21.65	27.55	20.61	20.15	21.98	18.49
7-17-28	26.85	25.926	20.734	21.76	23.446	22.02
7-21-28	24.223	28.485	19.5	21.635	24.714	21.77
7-25-28	22.534	27.653	22.896	19.8	27.05	19.57
7-31-28	20.99	27.486	25.75	20.553	27.514	21.8
8-8-28	27.276	25.12	22.884	24.44	27.11	23.6
8-14-28	24.999	25.95	21.73	30.52	24.54	23.54
8-22-28	23.82	24.712	22.14	30.31	23.81	21.7
9-8-28	27.8	26.7	20.63	33.99	24.93	21.95
10-1-28	25.063	23.04	20.19	28.71	21.58	21.7
10-11-28	22.59	24.16	20.62		24.15	21.611
10-24-28	21.31	23.97	20.64		22.555	21.3
10-30-28	21.78	22.886	19.08		26.13	23.47
11-7-28	17.93	22.371	23.39		33.288	22.62
11-14-28	21.813	21.91	22.285		27.37	24.7
11-28-28	17.42	19.065	22.0		27.37	23.41
12-31-28	27.22	26.2	18.62		21.86	23.35
1-31-29	21.87		19.01			24.2
2-7-29			21.8			23.74
Average Rate			21.25		25.59	21.767
Recent Increase			21.17 %		37.6 %	

Table II. Rabbit No.I: Physiologic iodine.

Date	Bar. Press.	Temp.	C.C. of O_2 per min.	Wt. in Kg.	B.M.R.	Remarks
6-20-28	754	21.1	16.66	2.0	21.153	Quiet
6-27-28	756	22.2	16.0	2.1	19.665	"
7-2-28	753	20.0	20.0	2.1	24.77	Restless
7-5-28	761	22.1	15.66	2.2	18.875	Quiet
7-9-28	760	21.7	21.66	2.5	23.91	Slightly restless
7-11-28	756	23.0	21.66	2.5	23.665	"
7-14-28	762	20.0	20.0	2.6	21.65	Quiet
7-17-28	760	22.0	25.0	2.6	26.85	Very restless
7-21-28	755	25.8	22.5	2.5	24.223	Restless
7-25-28	752	27.2	22.5	2.7	22.534	Quiet
7-31-28	760	21.5	20.0	2.7	20.99	"
8-8-28	756	20.2	26.0	2.7	27.276	Warm, has snuffles
8-14-28	760	18.9	23.0	2.8	24.999	Still sniffling
8-22-28	764	20.5	22.0	2.8	23.82	Good test
9-8-28	762	23.0	26.0	2.8	27.8	Restless
10-1-28	758	20.9	25.0	2.9	25.063	Slightly restless
10-11-28	764	22.0	23.0	3.0	22.59	Quiet
10-24-28	760	24.0	23.4	3.2	21.31	"
10-30-28	756	22.8	24.0	3.3	21.78	"
11-7-28	757	21.5	20.0	3.4	17.93	"
11-14-28	751	20.0	22.0	3.0	21.813	"
11-28-28	768	19.6	19.0	3.4	17.42	"
12-31-28	769	15.0	30.0	3.5	27.22	"
1-31-29	752	13.8	24.0	3.5	21.87	"

RABBIT NO. II was given 2.0 minims of a 1/10000 Lugol's solution per kilograms of body weight, daily, from 6-20-28 until 1-31-29 or 266 days. This animal was apparently in estrus several times but did not become pregnant until the last month of the experiment. She delivered late in January, 1929 but owing to snuffles was not operated upon at this time. She was found dead the next day. The thyroid gland removed at autopsy presented no noteworthy macroscopic changes. Other findings were generalized acute passive hyperemia and bilateral pneumonia. Microscopically the thyroid gland is made up of relatively uniform small acini filled with pale blue colloid. The colloid is peripherally vacuolated. The acinar cells are cuboidal and are not infolded. The stroma is scant and there are many inter-acinar cells present. The B.M.R. and other data for this rabbit are listed on Table III, page 17.

Table III. Rabbit No. II:-, twice physiologic iodine.

Date	Bar. Press.	Temp.	C.C. of O_2 per min.	Wt. in Kg.	B.M.R.	Remarks
6-20-28	754	21.5	26.66	1.7	37.7	Restless
6-27-28	756	22.8	16.66	1.7	23.517	Quiet
7-2-28	753	20.2	16.66	1.71	23.6	"
7-5-28	761	23.0	19.0	1.72	26.83	Restless
7-9-28	760	22.0	20.0	1.72	28.404	In estrus
7-11-28	756	23.5	17.5	1.8	23.78	Quiet
7-14-28	762	21.5	20.0	1.8	27.55	Restless
7-17-28	760	23.0	20.0	1.95	25.926	Slightly restless
7-21-28	755	26.1	22.5	1.95	28.485	In estrus
7-25-28	752	27.9	22.5	1.98	27.653	Still excited
7-31-28	760	21.5	22.5	2.15	27.486	" "
8-8-28	756	22.0	21.5	2.27	25.12	Quiet
8-14-28	760	19.8	21.0	2.29	25.95	"
8-22-28	764	21.0	21.0	2.3	24.712	"
9-8-28	762	23.5	23.0	2.3	-26.7	Frightened
10-1-28	758	21.0	22.0	2.7	23.004	Quiet
10-11-28	764	26.5	24.0	2.8	24.16	"
10-24-28	760	25.0	24.0	2.8	23.97	"
10-30-28	756	23.5	23.0	2.8	22.886	"
11-7-28	757	22.1	23.0	3.0	22.371	"
11-14-28	751	23.1	22.4	3.0	21.39	"
11-28-28	768	20.5	22.5	3.1	21.91	"
12-31-28	769	16.2	20.0	3.3	19.065	"
1-31-29	752	15.2	28.0	3.3	26.2	Died at delivery

RABBIT NO. III, received three times the physiologic iodine according to the above calculations. This was administered daily, during the experiment or for a period of 233 days. Pregnancy occurred in the second month of this period and the animal delivered on 7-31-28 shortly after the B.M.R. recording for that day. The thyroid removed the following day was reddish brown but not enlarged. This gland is inactive microscopically. The acini are small and of irregular caliber. The colloid stains a deep blue and is free of vacuoles. The acinar cells are of the low cuboidal type. There are but few inter-acinar cells and the stroma is scant. (See Fig. 2., page 20). This rabbit devoured her young so that the thyroid at the end of lactation could not be studied. She did not become pregnant again. At the end of the experiment the remaining lobe of the thyroid was removed. This was unchanged grossly. Microscopically it is similar to the one seen at term except that the colloid is slightly vacuolated and there are a few more inter-acinar cells. (See Fig. 3, page 21). The B.M.R. readings and the data concerning this animal are listed in Table IV, page 19.

Table IV. Rabbit No. III: 3 x physiologic iodine.

Date	Bar.Press.	Temp.	C.C. of O_2 per min.	Wt. in Kg.	B.M.R.	Remarks
6-20-28	754	22.5	25.0	3.2	23.115	Quiet
6-27-28	756	23.0	20.0	3.1	18.924	"
7-2-28	753	20.4	20.0	3.0	19.01	"
7-5-28	761	22.0	22.5	3.0	22.01	"
7-9-28	760	24.0	22.5	3.0	21.76	"
7-11-28	756	21.7	20.0	3.0	19.42	"
7-14-28	762	26.2	22.0	3.1	20.61	"
7-17-28	760	27.9	22.5	3.1	20.734	"
7-21-28	755	22.2	20.0	3.0	19.5	"
7-25-28	752	22.8	24.0	3.0	22.986	Building a nest
7-31-28	760	20.0	25.0	2.8	25.75	With young, all well.
8-8-28	756	21.5	23.5	3.1	22.884	Good recording
8-14-28	760	24.0	23.5	3.2	21.73	Quiet
8-22-28	764	21.1	23.5	3.2	22.14	Devoured young
9-8-28	762	26.0	23.0	3.2	20.63	Quiet
10-1-28	758	25.5	22.0	3.2	20.19	"
10-11-28	764	23.0	22.0	3.2	20.62	"
10-24-28	760	23.5	22.0	3.2	20.64	"
10-30-28	756	27.0	21.0	3.2	19.08	"
11-7-28	757	20.9	26.0	3.4	23.39	"
11-14-28	751	16.5	24.0	3.3	22.285	"
11-28-28	768	18.8	23.0	3.2	22.0	"
12-31-28	769	15.0	16.0	3.0	18.62	"
1-31-29	752	16.7	17.0	2.8	19.01	"
2-7-29	766	15.0	22.0	2.8	21.8	Sterile, killed.

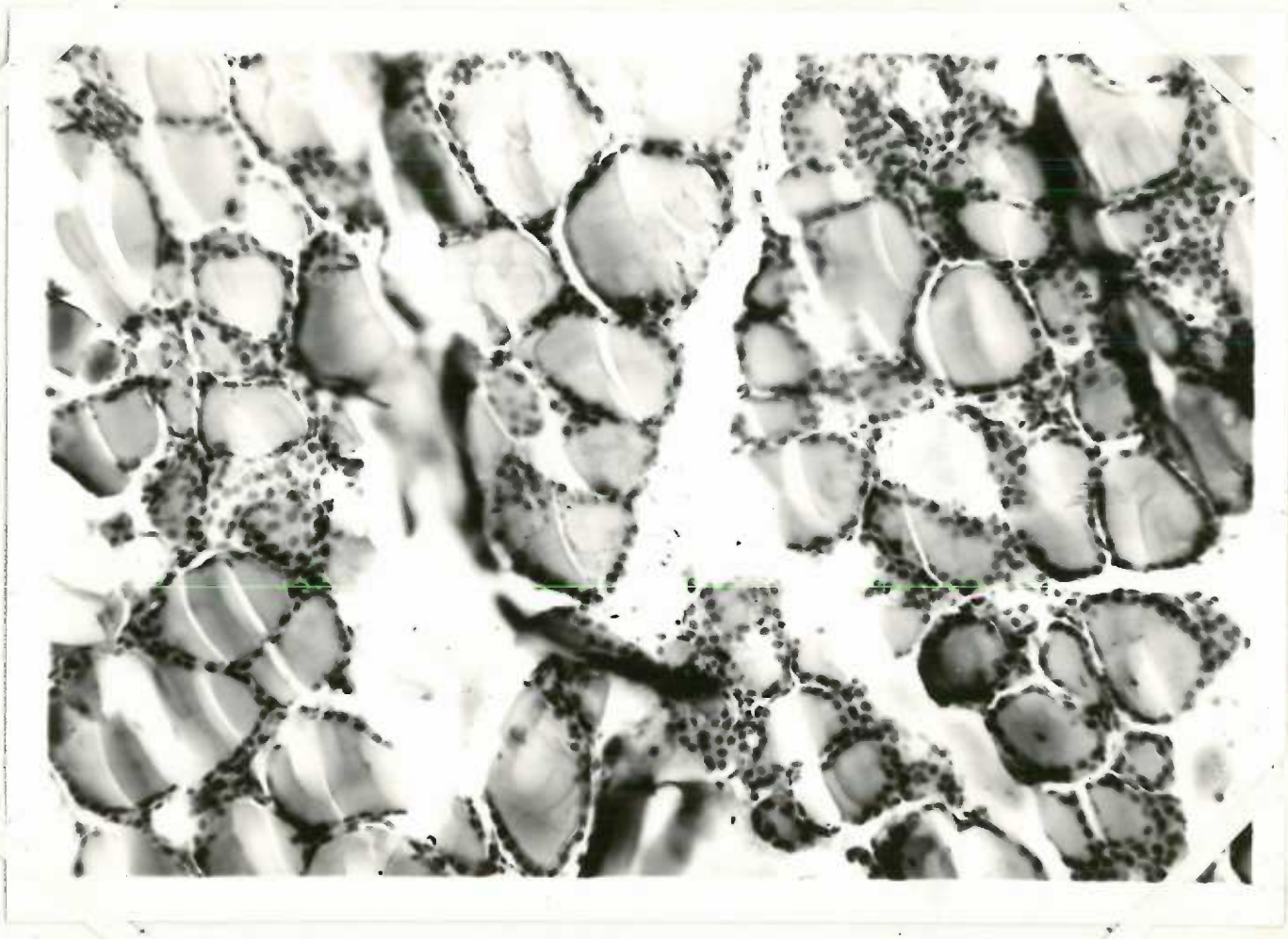

Fig. 2. R-III. Series 1. Microphotograph of thyroid gland removed at term. Note large colloid filled acini, low cuboidal epithelium and lack of vacuolization. No evident excess activity.

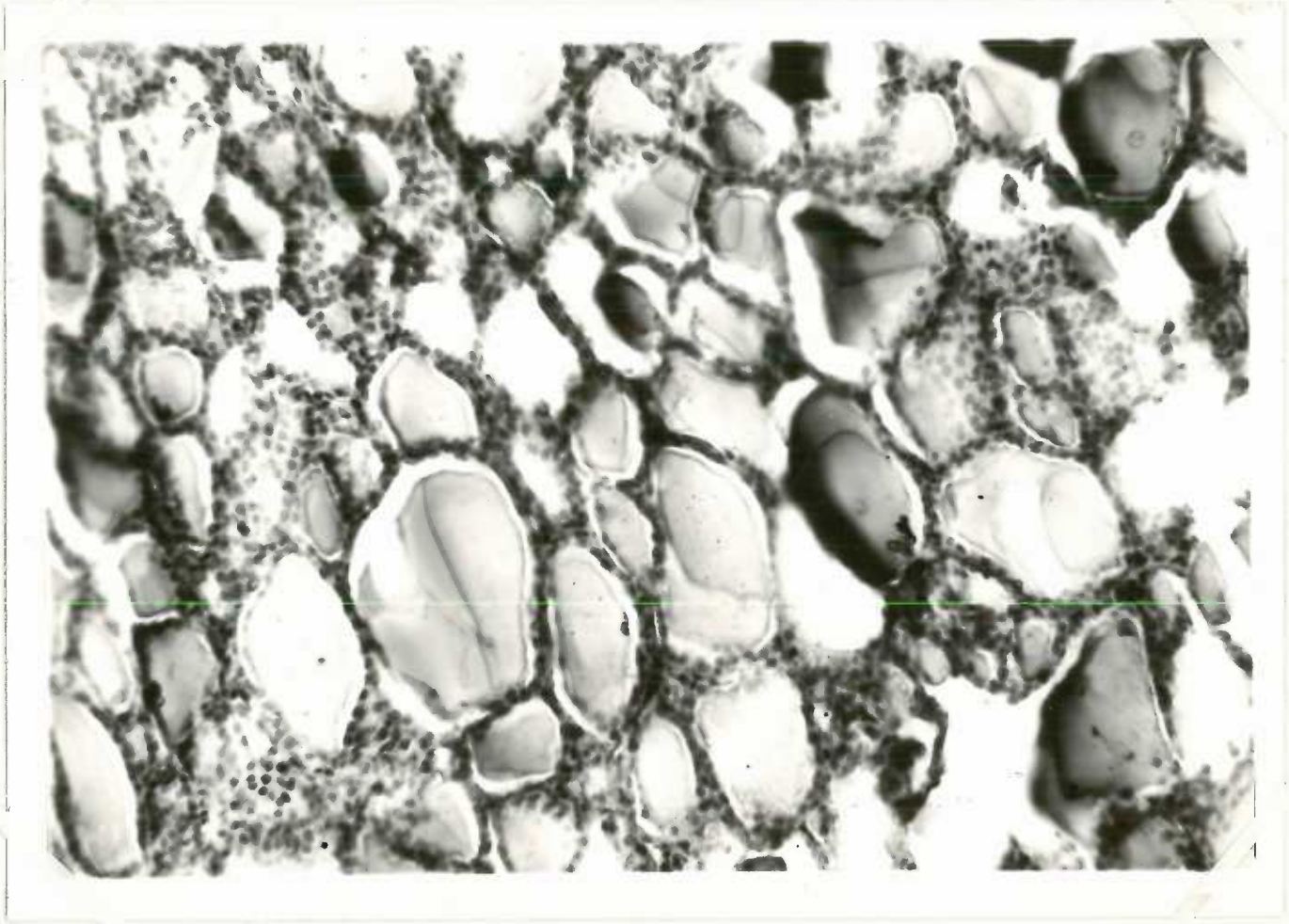

Fig. 3. R-III, Series 1. Photomicrograph of the thyroid at the end of lactation. Note large colloid filled acini, low cuboidal epithelium and no vacuolization. No evidence of increased activity.

RABBIT NO. IV., was given four time the physiologic iodine or 4.0 minims of 1/10000 Lugol's solution per kilogram of body weight daily for a period of 3 months and 23 days. This doe never became pregnant. She was always quite restless and seemed in estrus several times but never took the male. Early in the course of the experiment the animal developed several furuncles and died after being ill for 4 days. Autopsy revealed a septicopyemia with a purulent peritonitis, purulent pleuritis, and bilateral broncho-pneumonia. The thyroid removed at autopsy was small, reddish-brown, and smooth externally. The lobes measures 2.0 by 5.0 mm. Microscopic sections of the thyroid tissue reveal it to be very cellular. The acinar cells are cuboidal and closely compact, forming very small acini. The colloid is scant, deep blue, and presents marked peripheral vacuolization. The inter-acinar cells are abundant. The stroma is scant and the blood vessels are filled. The B.M.R. recordings and other data are given on Table V, page 23.

Table V. Rabbit No. IV: 4 x physiologic iodine.

Date	Bar.Press.	Temp.	C.C. of O_2 per min.	Wt. in Kg.	B.M.R.	Remarks
6-27-28	756	23.4	13.0	1.4	20.83	Quiet
7-2-28	753	20.3	13.0	1.4	20.8	"
7-5-28	761	23.7	12.5	1.4	20.02	"
7-11-28	756	21.7	13.0	1.5	20.03	"
7-14-28	762	22.2	13.0	1.5	20.15	"
7-17-28	760	21.3	14.0	1.5	21.76	"
7-21-28	755	26.5	15.0	1.6	21.635	"
7-25-28	752	21.5	12.5	1.7	19.8	"
7-31-28	760	22.4	15.0	1.8	20.553	"
8-8-28	756	21.0	16.5	1.8	24.44	Infection
8-14-28	760	18.6	25.0	2.2	30.52	Fever, dyspnea
9-8-28	762	22.0	25.0	2.3	30.31	Still warm
10-1-28	764	21.9	30.0	2.4	33.99	Abdomen doughy
10-11-28	760	27.0	28.0	2.7	28.71	Apathetic

RABBIT NO. V, received five times the physiological iodine, per kilogram of body weight, daily, for 226 days. Attempts to obtain pregnancy were unsuccessful. Although placed with the male several times the doe never showed much evidence of being in estrus. Except for a period of fever and dyspnea during the latter part of the second month of the experiment, this rabbit was very well until the sixth month of the experiment when it developed the snuffles. Fever, dyspnea, and general malaise, were quite marked during the entire sixth month. The rabbit remained restless and finally died on 2-4-29. At autopsy it was found to have unresolved pneumonia and empyema. The B.M.R. was very high during this period. Macroscopically the thyroid gland showed no changes. Microscopically the acini are small and uniform size. The acinar cells are cuboidal and not hyperchromatic. The colloid is peripherally vacuolated and takes an irregular pale pink to dull blue stain. The inter-acinar cells are abundant. The stroma is scant and the blood vessels are engorged. The B.M.R. readings and other data are given on Table VI, page 25. Photomicrograph of thyroid on page 26, Fig. 4.

Table VI, Rabbit No.V:- 5 x physiologic iodine.

Date	Bar.Press.	Temp.	C.C. of O_2 per min.	Wt. in Kg.	B.M.R.	Remarks
6-27-28	756	23.6	20.0	2.0	25.296	Quiet
7-2-28	753	20.7	20.0	2.0	25.59	"
7-5-28	761	24.0	20.0	2.0	25.34	"
7-9-28	760	22.0	20.0	2.1	24.77	"
7-14-28	762	23.5	18.3	2.2	21.98	"
7-17-28	760	20.5	20.0	2.3	23.446	"
7-21-28	755	26.9	22.5	2.4	24.714	Excited
7-25-28	752	22.0	25.0	2.5	27.05	Very restless
7-31-28	760	22.1	25.0	2.5	27.514	Fever & dyspnea
8-8-28	756	19.1	26.0	2.75	27.11	" "
8-14-28	760	22.0	24.0	2.8	24.54	Restless
8-22-28	764	22.6	25.0	3.1	23.81	Quiet
9-8-28	763	22.0	26.0	3.1	24.93	"
10-1-28	758	28.2	24.0	3.2	21.58	"
10-11-28	764	27.0	28.0	3.5	24.15	"
10-24-28	760	25.0	26.0	3.5	22.555	"
10-30-28	756	24.2	28.0	3.6	23.886	"
11-7-28	757	23.5	30.0	3.5	26.13	Restless and sniffling
11-14-28	751	19.5	38.0	3.5	33.288	Marked dyspnea and fever
11-28-28	768	17.0	31.0	3.6	27.37	Very restless
12-31-28	769	20.0	31.0	3.6	27.37	" "
1-31-29	752	20.0	25.0	3.5	21.86	Listless

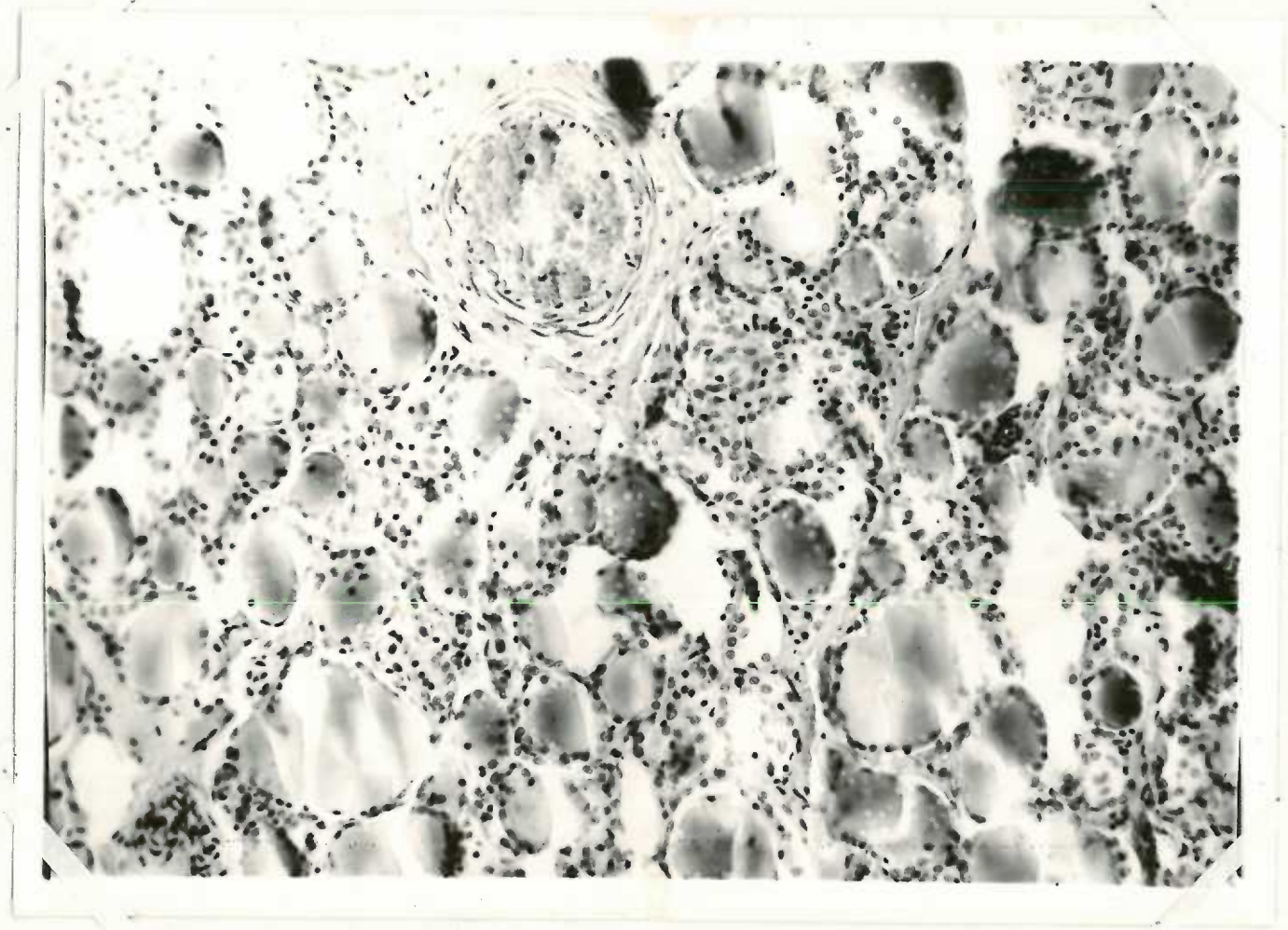

Fig. 4. R-V. Series 1. Photomicrograph of the thyroid taken after death from infection. Note many small circular acini containing vacuolated colloid. Blood vessels engorged. Definite evidence of increased activity.

RABBIT NO. VI, served as a control, received no iodine, and was under observation from 6-20-28 until 2-7-29 or 233 days. This rabbit was treated similar to the other rabbits in all respects, except that iodine was not administered. It did not become pregnant in spite of all efforts to induce conception. It was in estrus several times and placed with the male but did not take. At autopsy no demonstrable cause for sterility was found. The thyroid was small and pinkish gray. Microscopically the acini are small and closely compact. They contain but little non-vacuolated colloid. The gland is grossly and microscopically inactive. (See Fig. 5, Page 29). The B.M.R. recordings and the other data will be found in Table No. VII, page 28.

Table VII. Rabbit No. VI :- Control Animal.

Date	Bar.Press.	Temp.	C.C. of O_2 per min.	Wt. in Kg.	B.M.R.	Remarks
6-20-28	754	28.4	25.0	3.58	20.354	Quiet
7-2-28	753	21.0	22.2	3.5	19.41	"
7-5-28	761	23.7	25.0	3.58	21.54	"
7-9-28	760	22.6	23.0	3.5	19.6	"
7-11-28	756	22.0	21.66	3.5	18.98	"
7-14-28	762	24.0	20.0	3.5	18.49	"
7-17-28	760	22.0	25.0	3.5	22.02	Slightly restless
7-21-28	755	27.1	25.0	3.4	21.77	" "
7-25-28	752	22.5	22.5	3.5	19.57	Quiet
7-31-28	760	23.5	25.0	3.4	21.8	"
8-8-28	756	22.8	27.0	3.5	23.6	"
8-14-28	760	20.2	27.0	3.5	23.54	"
8-22-28	764	22.4	25.0	3.6	21.7	"
9-8-28	762	23.0	26.0	3.6	21.95	"
10-1-28	758	23.0	26.0	3.75	21.7	"
10-11-28	764	22.0	26.0	3.75	21.611	"
10-24-28	760	27.0	26.0	3.75	21.3	"
10-30-28	756	25.0	30.0	3.7	23.47	"
11-7-28	757	24.0	28.0	3.74	22.62	"
11-14-28	751	23.6	30.0	3.6	24.7	"
11-28-28	768	23.6	27.0	3.6	23.41	"
12-31-28	769	17.5	27.0	3.6	23.35	"
1-31-29	752	20.2	28.0	3.7	24.2	"
2-7-29	766	16.2	27.0	3.7	23.74	"

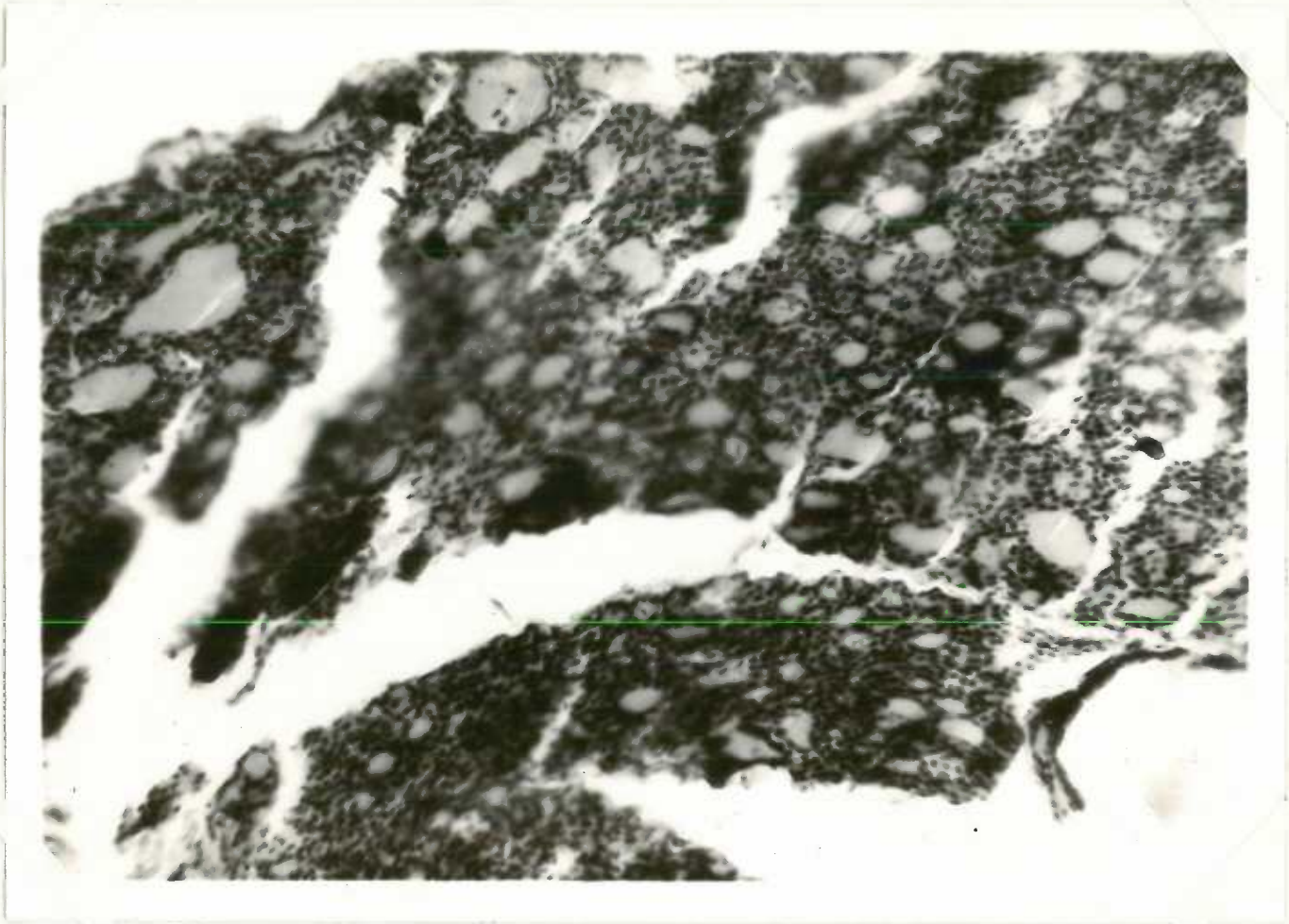

Fig. 5, R-VI. Series 1. Photomicrograph of the small thyroid removed from the control rabbit. This rabbit did not become pregnant. B.M.R. consistently low. Note small acini, absence of colloid, absence of vacuolization. This is an inactive atrophic gland.

In this first series of six rabbits all of the experimental conditions enumerated at the outset could not be carried out. The correct dose of iodine was given to each rabbit daily and frequent basal metabolic readings were taken but sterility and infections modified the results. These difficulties were contemplated and young healthy animals were selected and kept in clean cages in healthful surroundings but such precautions were of no avail. Rabbit No.I did not become pregnant and suffered no acute infections. Its basal metabolic rate fluctuated from 20.0 to 27.0 during the first 2 months, and then gradually came down to an average of 22.0. Its thyroid was grossly and microscopically inactive. Rabbits No. II and III became pregnant. Rabbit No. II died of pneumonia soon after delivery and before a basal metabolic reading could be obtained so that the actual increase of heat production is not known. Rabbit No. III, delivered early in the experiment. She ate all of her young soon after delivery thus making it impossible to obtain a gland at the end of lactation. This animal did not become pregnant again so was killed at the end of the period. The thyroid removed at autopsy of R - II was microscopically inactive. The lobe removed at term in R- III was inactive but the one removed at the end of the experiment showed slight evidence of activity. Both of these rabbits exhibited rather high basal metabolic rates at term. R - III soon came down to an average of 20.0 which she maintained throughout. Rabbits No. IV and V had very severe infections sufficient to cause death. Both exhibited a sudden marked elevation of the heat production at the time of the acute stage of their infection with a slight drop until death. In the case of R - IV the thyroid removed at autopsy was quite active. That of R - V was histologically very active, and if the gland could have been examined during the height of the curve it probably would have shown even greater activity. R - VI, the control rabbit failed to

become pregnant and did not develop an infection. The B.M.R. in this case fluctuated around 22.0 to 23.0 without any sharp rise or fall. The thyroid is microscopically inactive and in this respect is similar to that of R - I. The microscopic picture in case of R - I corresponds to the results given by Gray and Loeb (18) who found that the prolonged administration of potassium iodide caused a depressed state in the gland with abundant firm colloid and low acinar epithelium. None of the glands showed marked activity microscopically, although in certain instances the heat production was considerably increased. The abundance of iodine in the diet may be responsible for the lack of histological response. If so it does not correspond to the conclusions of Plass and Yoakman (4), who state that iodine does not prevent gestational hypertrophies but merely aids the abnormal gland.

A graphic representation of the Basal Metabolic Rates for certain of the rabbits, is given on Chart No. I, page 32. The B.M.R. curves of R-III, R-V, and R-VI are given, as a composite chart of all curves is very confusing. Rabbit No. III came to term and was not satisfactory for the illustration of such a curve. Rabbit No. V had a severe infection from which it died. The curve shows the marked rise in the B.M.R. under such conditions. Rabbit No. VI the control maintains a fairly constant level throughout.

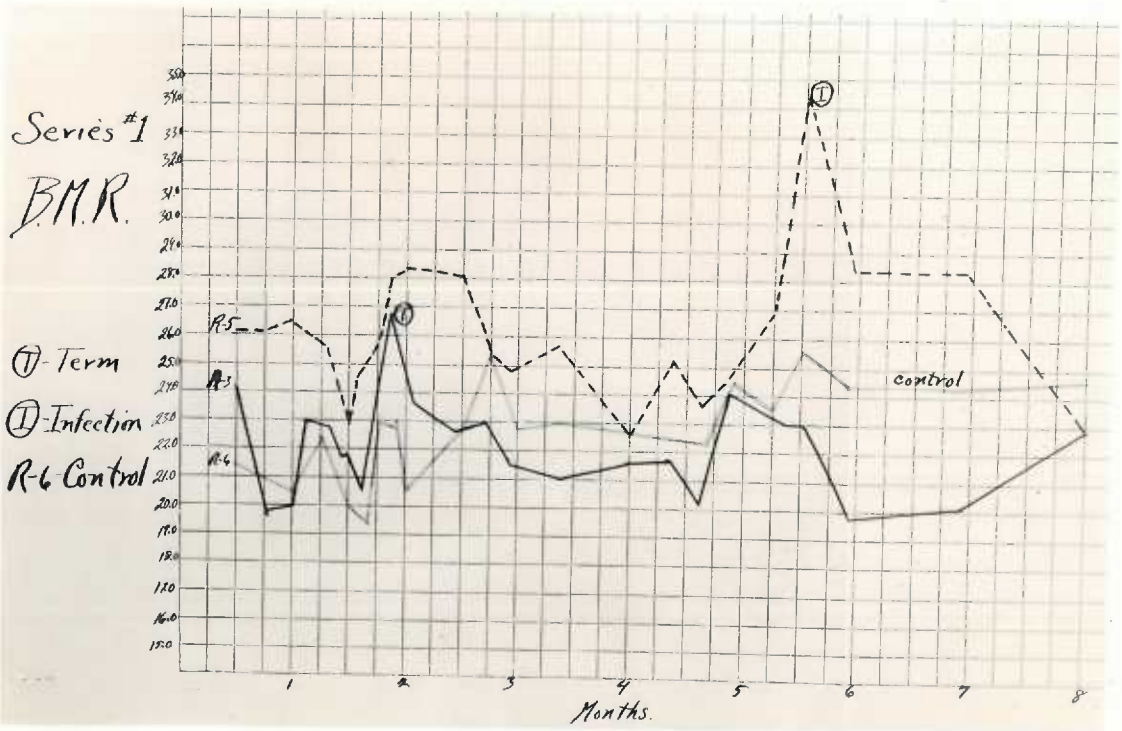

Chart No. I. Showing curves of B.M.R. of R-III, R-V, and R-VI of series 2.

Series 2.

Seven rabbits were treated similar to the ones in series 1. In this group there are five rabbits receiving iodine similar to R-I, R-II, R-III, R-IV, and R-V of the above series and two controls, R-VI and R-VII. All became pregnant and all except R-IV and R-VI were carried to the end of the lactation period. The recording and calculation of the basal metabolic rates are similar to the methods given on page 12 for series 1 and are charted in the same manner (Table VIII, page 34).

Table VIII. Series 2. All B.M.R. recordings of this series.

Date	R-I	R-II	R-III	R-IV	R-V	R-VI	R-VII
5-1-30	26.344	36.496	33.663	25.545	29.34	24.324	26.88
5-8-30	22.073	27.115	26.662	25.514	29.017	21.425	24.816
5-15-30	23.44	29.065	34.50	23.724	30.52	18.767	24.906
5-22-30	23.04	34.62	38.10	26.96	30.61	20.9	25.142
5-29-30	22.583	23.71	29.537	29.283	25.312	18.96	31.101
6-6-30	22.965	23.52	27.41	29.28	29.088	22.04	26.586
6-12-30	21.003	22.636	30.53	23.596	24.297	20.711	27.05
6-20-30	21.295	20.34	27.17	23.24	22.987	23.93	26.624
6-26-30	23.87	-	30.23	30.202	25.066	27.837	37.66
7-3-30	23.98	-	32.16	24.196	25.713	28.59	26.816
7-17-30	33.38	-	32.24	25.985	31.27	-	25.117
7-25-30	30.35	-	32.05	23.046	29.63	-	22.342
8-1-30	29.35	-	30.32	22.934	28.92	-	19.152
8-8-30	26.506	-	-	19.6	20.25	-	17.251
8-15-30	-	-	-	18.943	-	-	
8-21-30	-	-	-	18.0	-	-	
8-29-30	-	-	-	17.6	-	-	
Average	24.963	27.188	31.121	23.98	27.287	20.5	25.81
At term	33.38	34.62	32.24	30.202	31.227	28.59	37.66
Per cent increase	32.9	27.3	3.6	27.2	14.4	39.2	45.1

RABBIT NO. I, received 1.0 minim of 1/10000 Lugol's solution per kilogram body weight, daily, for fifteen weeks. It was in estrus the seventh week and delivered the tenth week. The following day one lobe of the thyroid was removed. She had four young, all well formed and healthy. They became independent of her at the end of the fifteenth week and she then was killed and the other lobe of the thyroid removed. The young were all healthy at the age of 2 months when they were disposed of.

Grossly the thyroid removed at term presented no noteworthy changes. The microscopic section of this thyroid reveals irregular sized acini lined with low cuboidal epithelium and filled with pink vacuolated colloid. The stroma is edematous and the blood vessels are engorged. (See Fig. 6, page 37.) At the end of lactation the thyroid is made up of closely arranged small acini lined with cuboidal epithelium and with very bright pink colloid. The sections appear very cellular due to the compact small acini with practically no lumen. A microphotograph of this gland is on page 38, Fig. 1. The B.M.R. recordings and data are given on Table IX, page 36.

Table IX. Rabbit No.I:- Physiologic Iodine.

Date	Bar.Press.	Temp.	C.C. of O_2 per min.	Wt. in Kg.	B.M.R.	Remarks
5-1-30	744	24.1	19.0	1.7	26.334	Trial test
5-8-30	750	21.5	20.66	1.85	22.073	Quiet
5-15-30	749	21.7	19.0	2.04	23.44	Good reading
5-22-30	755.7	21.6	20.0	2.17	23.04	" "
5-29-30	743.2	21.3	18.66	2.1	22.583	Quiet. Good test.
6-6-30	750	22.8	20.0	2.17	22.965	In estrus.
6-12-30	753	20.6	18.33	2.25	21.003	Quiet
6-20-30	746	21.0	19.0	2.37	21.295	"
6-26-30	747.1	19.8	21.33	2.41	23.87	Slightly restless
7-3-30	748	21.0	21.33	2.42	23.98	Restless
7-17-30	753.7	21.7	30.0	2.41	33.38	Delivered of young 7-10-30
7-25-30	752.9	21.4	27.33	2.41	30.35	Mother and young are well
8-1-30	750.9	22.1	26.66	2.42	29.33	"
8-8-30	745.4	21.8	24.33	2.42	26.506	"

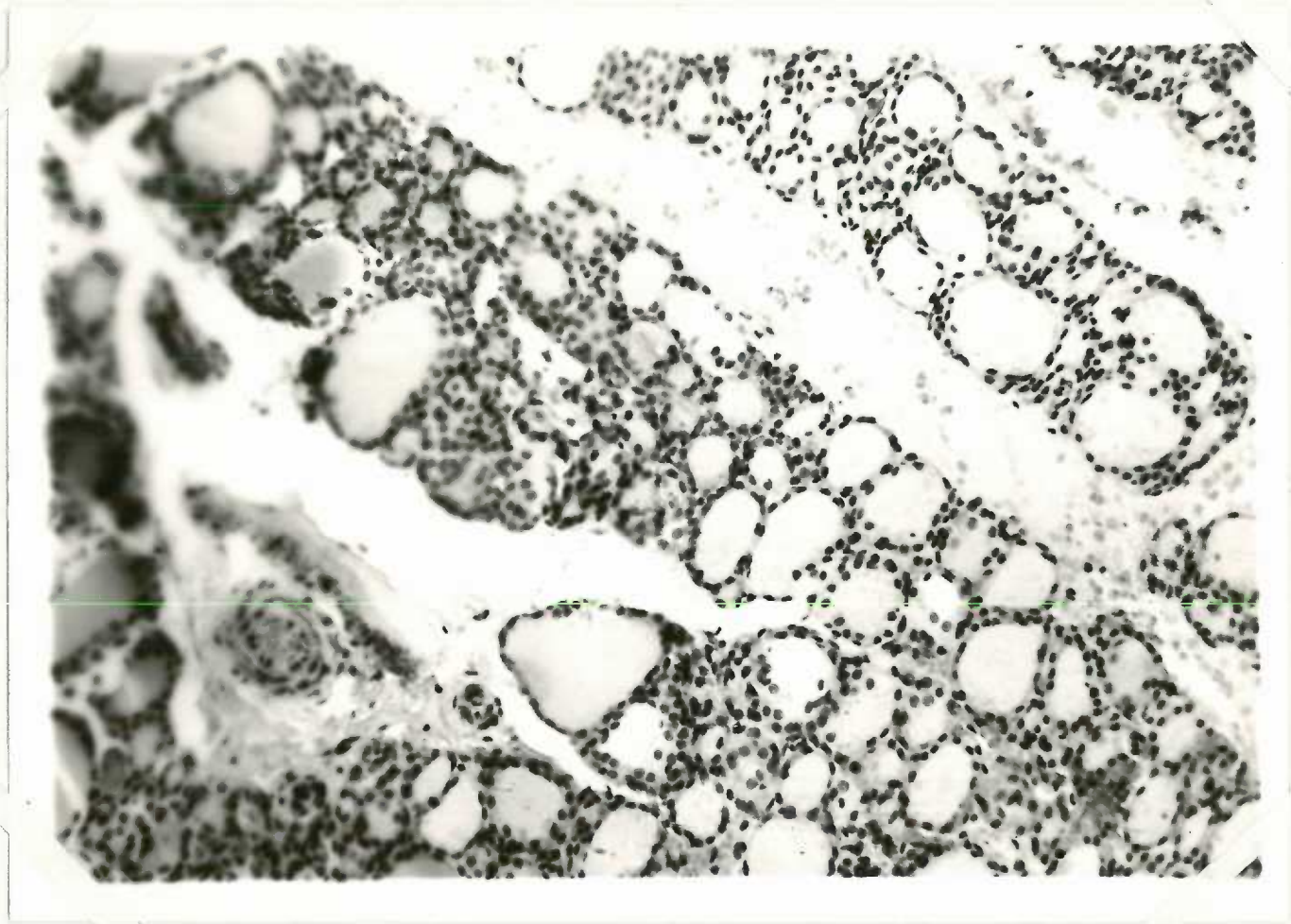

Figure 6, R-I, Series 2. Note that the acini are lined with low cuboidal epithelium. The colloid is pale and non-vacuolated. The stroma is edematous and the blood vessels engorged.

Figure 7, R-I, Series 2. Microphotograph of the thyroid removed at the end of lactation period. The acini are small and lined with cuboidal epithelium. The colloid is not vacuolated. No evidence of increased activity.

RABBIT NO. II. This animal received twice physiologic iodine according to the calculations mentioned previously. It became pregnant early in the experiment and delivered seven healthy young on 5-21-30. One lobe of the thyroid was removed at this time with no ill effects. She was killed 6-25-30 at the end of lactation and the remaining lobe removed.

Macroscopically the gland at term was reddish-brown and not enlarged. The microscopic sections reveal it to be made up of irregular small acini lined with low cuboidal epithelium and filled with pale pink colloid. The inter-acinar cells are abundant. The blood vessels are engorged and the lymph spaces are widened. The colloid is not vacuolated. (See Fig. 8., Page 41).

The thyroid removed at the end of lactation is microscopically essentially the same as that at term except that the inter-acinar cells are more abundant. There are many small acini present with little or no lumen and the scant colloid is sull deep pink staining. A microphotograph is given on page 42, Fig. 9. The B.M.R. readings and data are given on Table X, page 40.

Table X. Rabbit No. II :- 2 x Physiologic Iodine.

Date	Bar.Press.	Temp.	C.C. of O_2 per min.	Wt. in Kg.	B.M.R.	Remarks
5-1-30	744	24.3	31.0	2.19	36.486	Trial test
5-8-30	750	21.2	24.0	2.335	27.115	Good test.
5-15-30	749	22.4	26.6	2.45	29.065	Restless. Building a nest.
5-22-30	755.7	21.5	30.56	2.31	34.62	Young born 5-21-30 all well.
5-29-30	743.2	21.2	21.06	2.35	23.71	Good test.
6-6-30	750	23.8	24.0	2.38	23.52	" "
6-12-30	753	21.7	19.66	2.3	22.636	Young all well. Mother OK.
6-20-30	745	22.2	18.33	2.31	20.34	Good test. Killed 6-25-30

Fig. 8. R-II, Series 2. Photomicrograph of the term thyroid. The acini are small, lined with cuboidal cells and filled with pale slightly vacuolated colloid. Moderate increased activity.

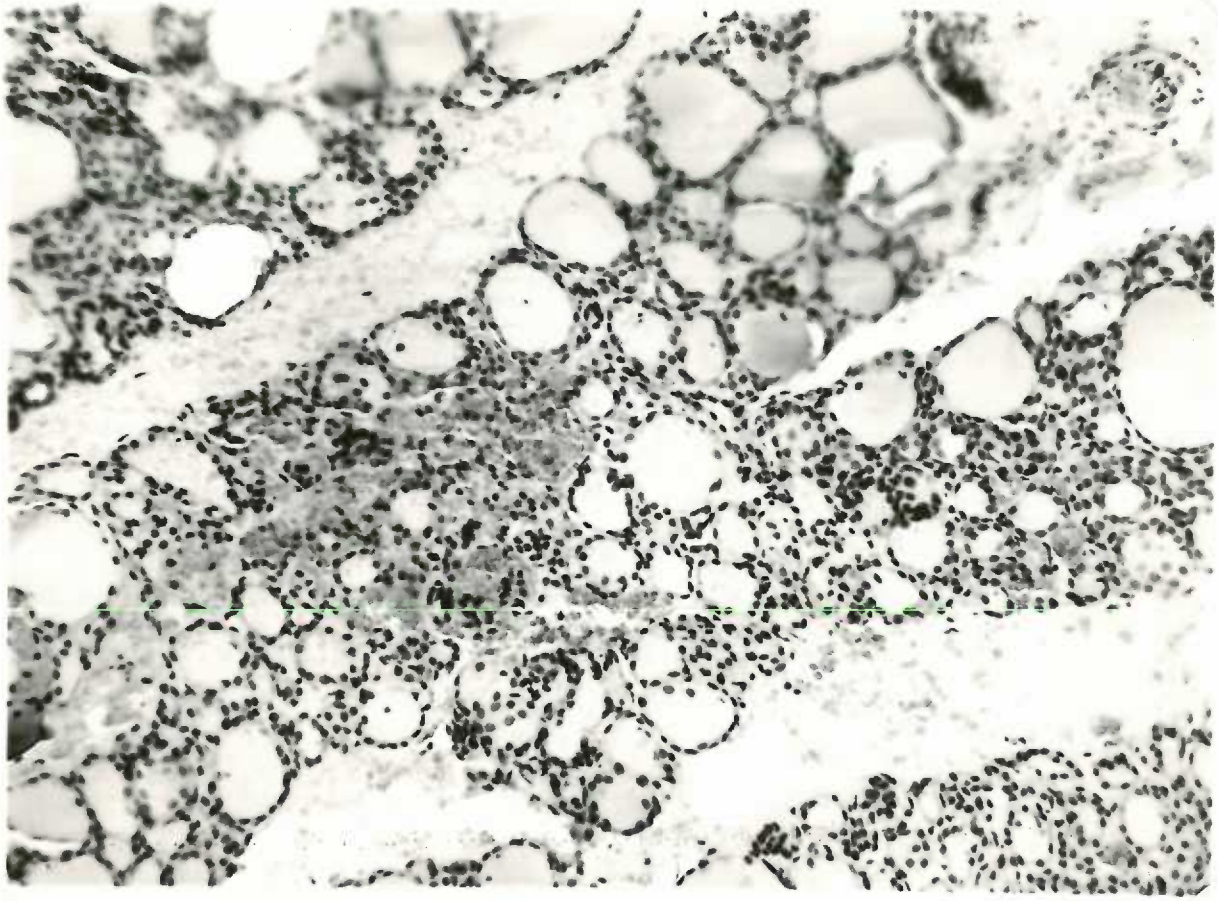

Fig. 9. R-II, Series 2. The microscopic picture is very similar to that of the gland removed at term. Note that there is no peripheral vacuolization of the colloid and that the colloid is pale. The acinar cells are cuboidal. This gland presents no evidence of increased activity.

RABBIT NO. III, received three times physiologic idoine per kilogram of body weight daily for seventeen weeks. This rabbit became pregnant about 6-12-30 and delivered eight well formed healthy young on 7-7-30. One lobe of the thyroid was removed the following day. The mother and young were well at the end of lactation. The other lobe was removed after killing the mother.

The thyroid removed at term presented no noteworthy gross changes. Microscopically the sections are seen to be made up of irregular sized acini lined with low cuboidal epithelium. The colloid is pink and exhibits only slight peripheral vacuolization. The blood vessels are engorged. The inter-acinar cells are abundant. A photomicrograph of this gland is shown on page45, Fig. 10.

The gland at the end of lactation was slightly enlarged. It is made up of uniformly small acini lined with low cuboidal epithelium. The colloid is pale pinkish-blue and not vacuolated. The blood vessels are moderately engorged and the inter-acinar cells are scant. See Fig. 11, page 46. The B.M.R. and data are given on Table XI, page 44.

Table XI. Rabbit No. III :- 3 x Physiologic Iodine.

Date	Bar.Press.	Temp.	C.C. of O_2 per min.	Wt. in Kg.	B.M.R.	Remarks
5-1-30	744	24.7	29.33	2.23	33.663	Trial test
5-8-30	750	21.5	24.0	2.4	26.662	Good test
5-15-30	749	22.5	31.66	2.45	34.54	Restless
5-22-30	755.7	21.9	38.33	2.75	38.10	In estrus
5-29-30	743.2	22.7	29.66	2.8	29.537	Quiet
6-6-30	750	24.1	26.0	2.83	27.41	Good test
6-12-30	753	22.5	33.3	3.09	30.53	In estrus
6-20-30	746	20.6	30.0	3.235	27.17	Good test
6-26-30	747.1	20.6	35.0	3.4	30.23	Restless
7-3-30	748	22.0	37.0	3.45	32.16	Building a nest
7-17-30	753.7	22.5	35.0	3.18	32.24	Delivered 7-7-30 young all well (8)
7-25-30	752.9	22.7	34.0	3.01	32.05	Mother and young all well
8-1-30	750.9	22.9	33.33	3.02	30.32	" " " killed 8-2-30

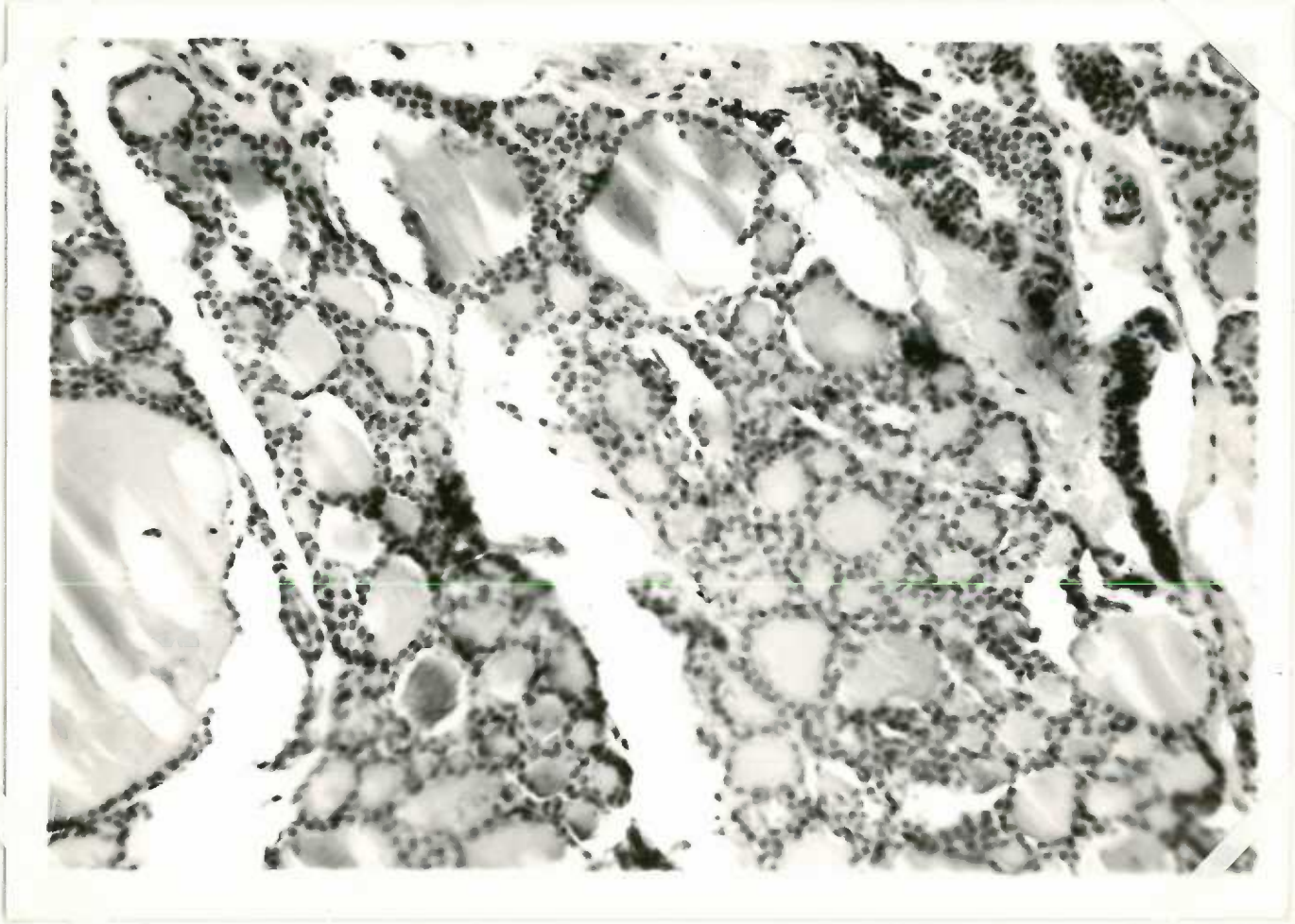

Fig. 10, R-III, Series 2. Microphotograph of the thyroid removed at term. It presents irregular sized acini with slightly vacuolated colloid. Acinar cells, cuboidal and columnar. Slight evidence of increased activity.

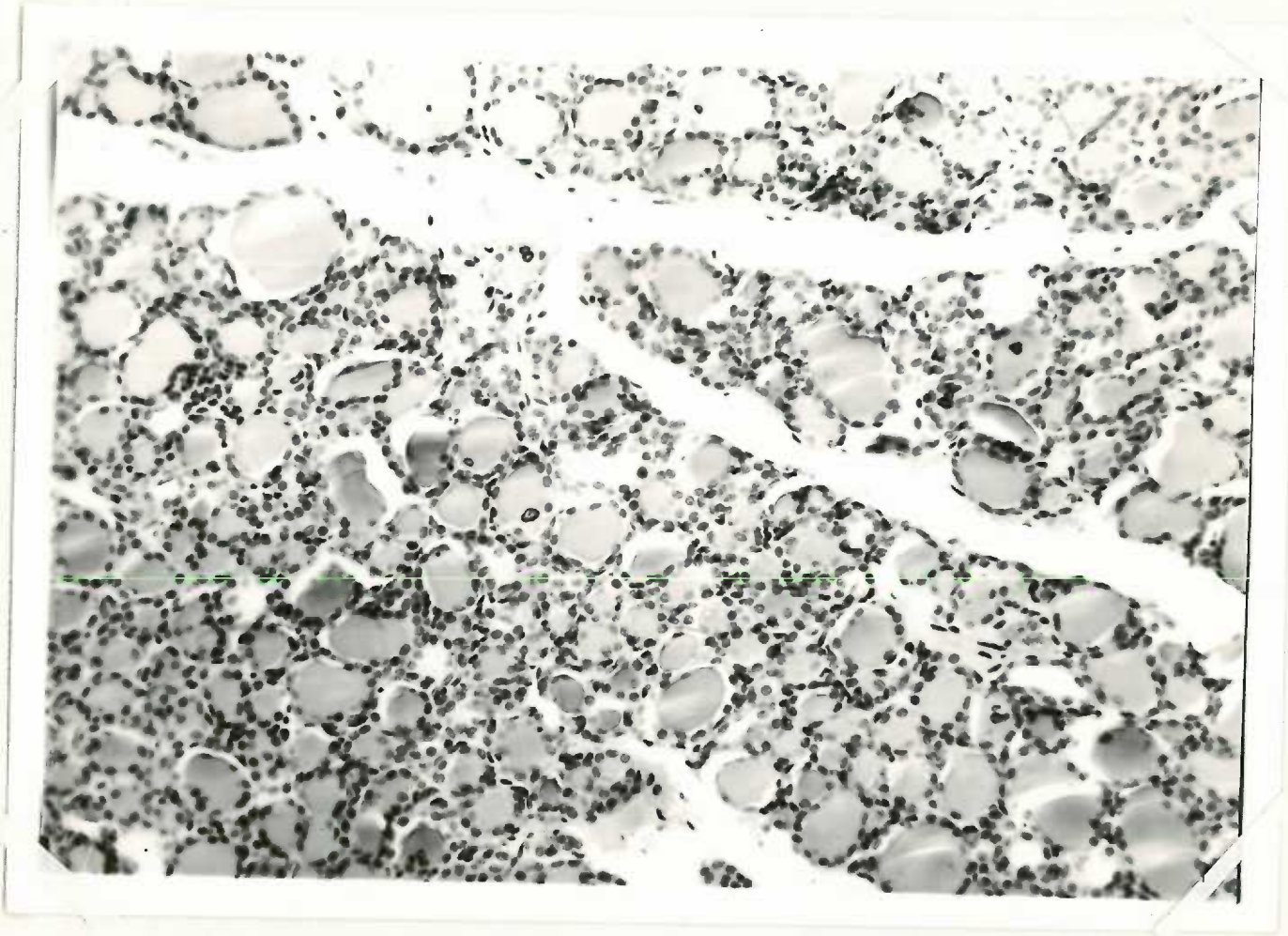

Fig. 11. R-III. Series 2. Microphotograph of thyroid removed at end of lactation period. Uniform small acini lined with cuboidal epithelium. Slight vacuolization of the colloid. Some evidence of activity.

RABBIT NO. IV. This animal received 4.0 minims of 1/10000 Lugol's solution per kilogram body weight daily, for seventeen weeks. It became pregnant early, delivered 3 young, 5-26-30, and killed them all soon after the thyroidectomy at term. It was decided to try to carry her through another pregnancy as the lactation period would be abnormal. She did not become pregnant again and was killed 8-30-30.

The thyroid removed at term was grossly unchanged. The microscopic sections of this gland are seen to be made up of uniform small acini lined with low cuboidal epithelium. The colloid is pale pinkish-blue and free of vacuoles. The stroma is scant as are also the inter-acinar cells. The blood vessels are slightly engorged. The photomicrograph of this gland is given on page 49, Fig. 12.

At the end of the experiment the gland was small, firm, and pale gray. It is made up of collapsed closely arranged acini containing no colloid giving the gland a very cellular appearance. The acinar epithelium is disintegrating, the cytoplasm is granular and fragmented and the nuclei are pale. Fibroblasts are proliferating in and about the acini but are not abundant. The blood vessels are empty and collapsed. See Fig. 13, page 50. The B.M.R. recordings and data are given on Table XII, page 48.

Table XII. Rabbit No IV :- 4 x Physiologic Iodine.

Date	Bar.Press.	Temp.	C.C. of O_2 per min.	Wt. in Kg.	B.M.R.	Remarks
5-1-30	744	21.5	21.33	2.14	25.545	Trial test
5-8-30	750	21.2	21.33	2.15	25.514	Trial test
5-15-30	749	22.8	20.0	2.14	23.724	Good test
5-22-30	755.7	20.8	20.0	1.860	26.96	Breasts large. Building nest.
5-29-30	743.2	22.8	21.33	1.8	29.283	Delivered 5-26-30
6-6-30	750	24.8	21.66	1.8	29.28	3 young, mother killed all.
6-12-30	753	22.5	18.3	1.89	23.596	Good test
6-20-30	746	22.3	18.0	1.97	23.24	" "
6-26-30	747.1	20.8	24.0	2.0	30.202	Restless. In estrus
7-3-30	748	22.7	19.66	2.05	24.196	Quiet
7-17-30	753.7	22.8	21.66	2.160	25.895	"
7-25-30	752.9	22.5	20.0	2.28	23.046	"
8-1-30	750.0	23.0	20.0	2.27	22.934	"
8-8-30	745.4	25.3	18.0	2.27	19.6	"
8-15-30	757.2	22.9	16.66	2.361	18.934	"
8-21-30	747	20.0	16.0	2.39	18.0	"
8-29-30	752	18.9	16.0	2.4	17.6	Did not become pregnant. Killed 8-30-30

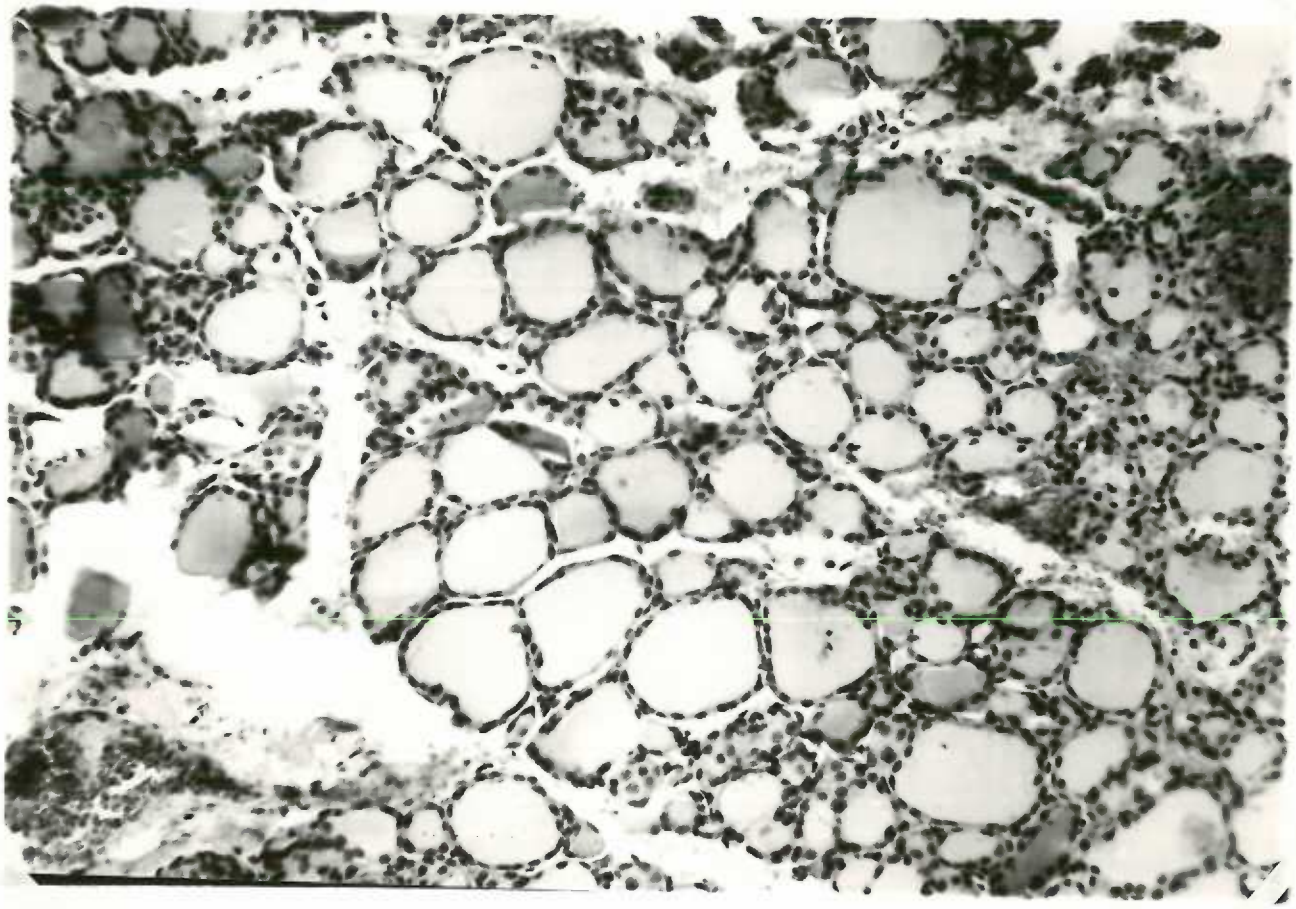

Fig. 12. R-IV. Series 2. Microphotograph of the thyroid gland removed at term. Note relatively large colloid filled acini lined with low cuboidal epithelium. No evidence of increased activity.

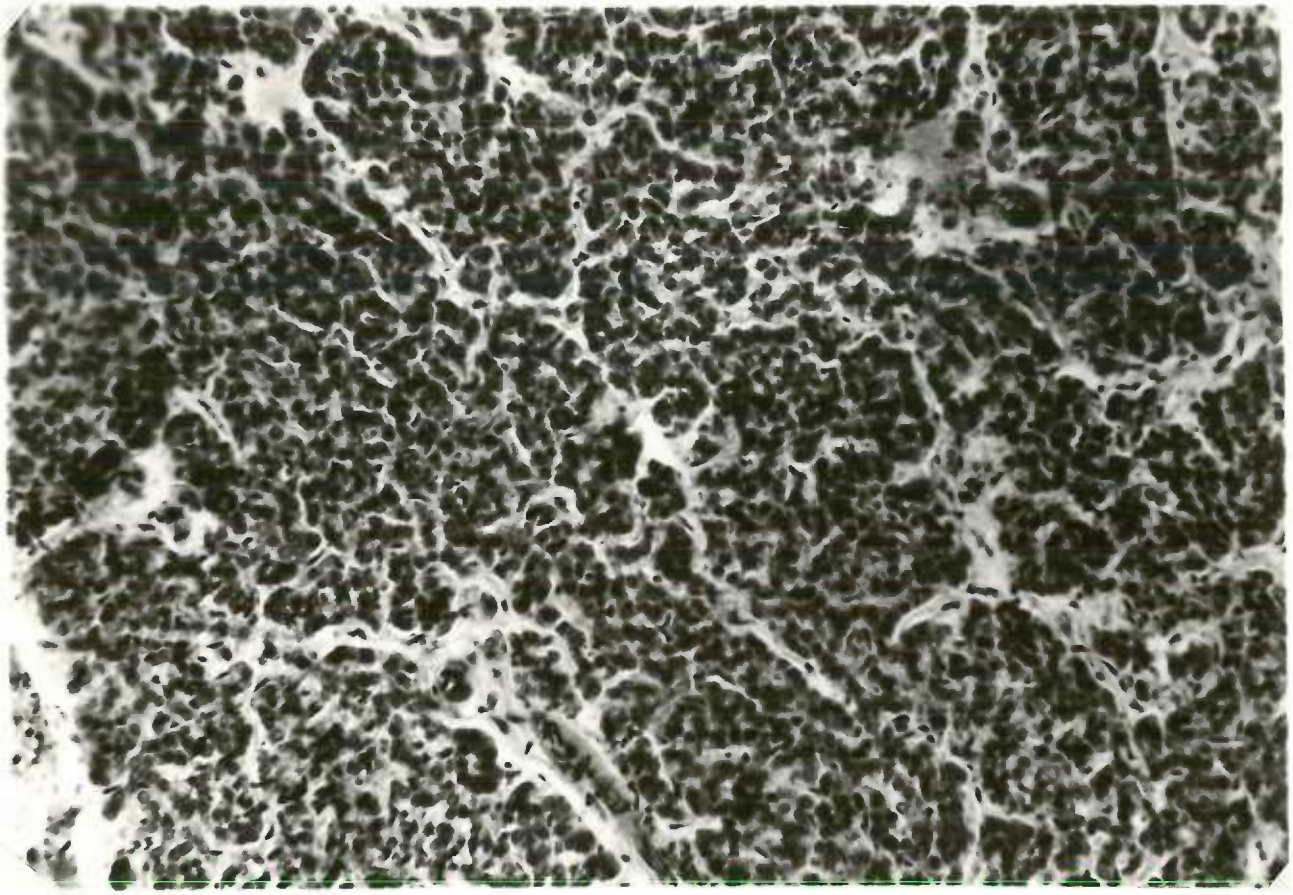

Fig. 13. R-IV, Series 2. Note the dense cellular character of this gland with no evident colloid in the collapsed acini. Little structure left that is suggestive of thyroid. Prolonged iodine administration, 4 times physiological.

RABBIT NO. V. This animal received five times physiologic iodine per kilogram body weight, daily for fourteen weeks. She became pregnant about 6-12-30 and delivered 7-9-30. She had nine young, all of which were well formed. The mother and young remained well throughout the lactation period and the mother was killed 8-9-30.

At term the thyroid was reddish-brown and smooth externally. The section revealed very irregular acini some containing abundant colloid and others none. The colloid is pink and contains no peripheral vacuolization. There are localized areas in which the inter-acinar cells are abundant. At one pole there is a small accumulation of lymphoid tissue. See Fig. 14, page 53.

At the end of lactation the gland is made up of thin walled acini containing bright pink colloid. There is no vacuolization present. The vessels are of small caliber. The microphotograph is given on page 54, Fig. 15. The B.M.R. recordings and data are given on Table XIII, page 52.

Table XIII. Rabbit No. V :- 5 x Physiologic Iodine.

Date	Bar.Press.	Temp.	C.C. of O_2 per min.	Wt. in Kg.	B.M.R.	Remarks
5-1-30	744	21.9	25.0	2.2	29.34	Trial test
5-8-30	750	21.3	24.66	2.2	29.017	" "
5-15-30	749	23.0	26.66	2.27	30.52	Restless
5-22-30	755.7	22.3	26.66	2.27	30.61	Restless
5-29-30	743.2	22.9	22.66	2.41	25.312	Quiet
6-6-30	750	25.0	28.0	2.41	29.88	In estrus
6-12-30	753	23.2	24.33	2.73	24.297	Quiet
6-20-30	746	22.7	23.33	2.85	22.987	"
6-26-30	747.1	21.0	26.66	3.07	25.006	"
7-3-30	748	22.7	28.33	3.16	25.713	Restless
7-17-30	753.7	22.5	31.66	2.89	31.27	Delivered 7-9-30 9 young all well
7-25-30	752.9	22.5	30.0	2.8	29.63	Mother and young all OK
8-1-30	750.9	22.5	28.66	2.75	28.92	Quiet
8-8-30	745.4	25.6	20.0	2.7	20.25	Good recording. Killed 8-9-30

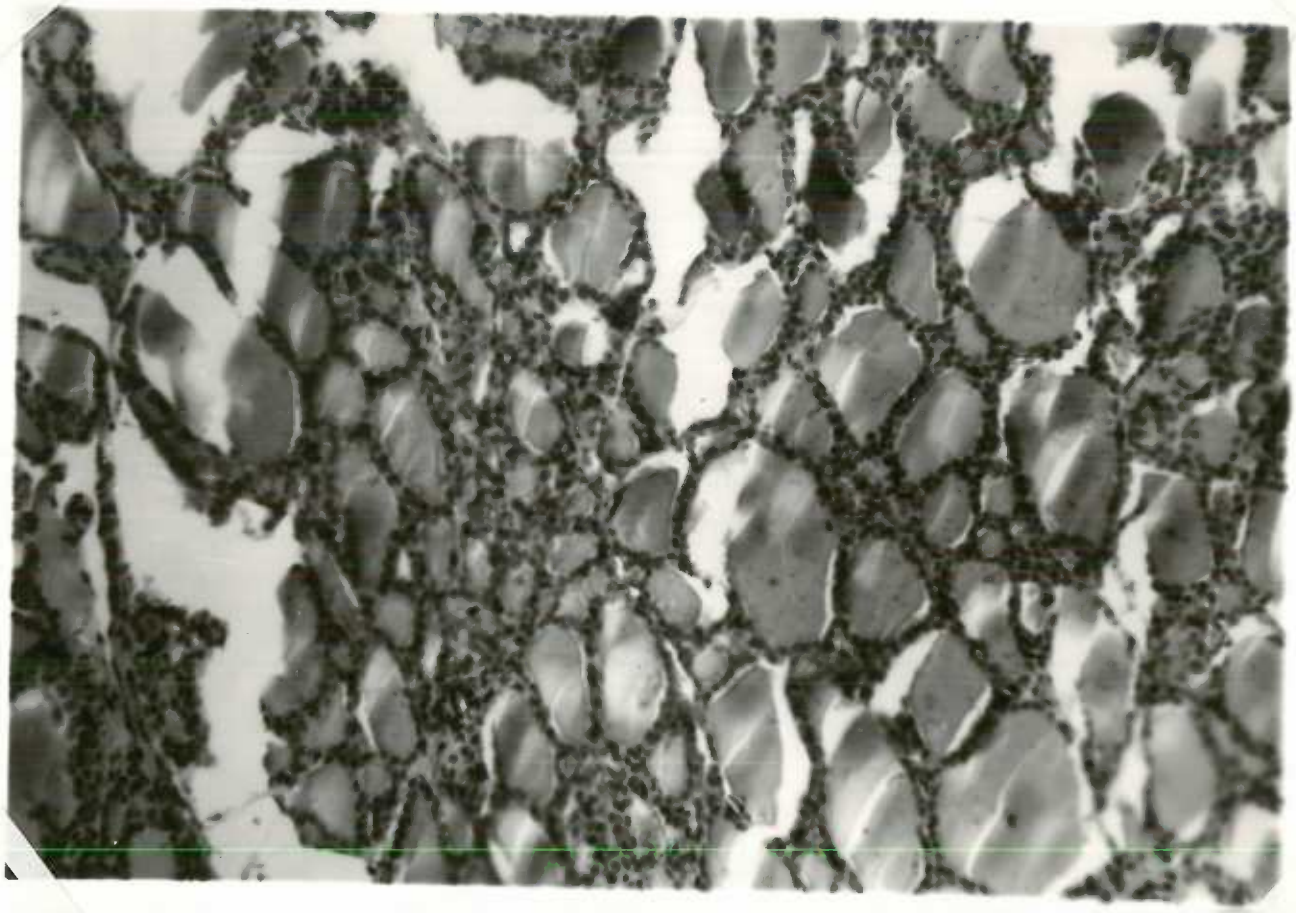

Fig. 14. R-V. Series 2. Microphotograph of the thyroid gland removed at term. Note relatively large colloid filled acini lined with low cuboidal epithelium. No evidence of increased activity.

Fig. 15, R-V. Series 2. This is the photomicrograph of the gland removed at the end of the lactation period. Note thin walled acini with no vacuolated colloid. There is no evidence of increased activity.

RABBIT NO. VI, one of the control animals of this series, was treated similar to the other five rabbits but received no iodine. This was a young healthy animal which became pregnant in the second month of the experiment and delivered six young early in the third month. The young were not properly cared for and all died. For this reason only the thyroid at term was studied. This is grossly unchanged. Microscopically this gland is made up of small acini lined with cuboidal and columnar epithelium. The colloid is dark and moderately vacuolated. It presents definite evidence of increased activity. The microphotograph is given on page 57, Fig. 16. The B.M.R. table and remarks are given in Table XIV page 56.

Table XIV. Rabbit No VI :* Control.

Date	Bar.Press.	Temp.	C.C. of O_2 per min.	Wt. in Kg.	B.M.R.	Remarks
12-23-30	756	23.8	25.0	2.99	24.324	Trial test
12-31-30	751	20.6	22.33	3.06	21.425	Good test
1-7-31	762	24.2	20.0	3.13	18.767	" "
1-14-31	750	25.3	23.33	3.21	20.9	" "
1-21-31	745.4	18.8	21.66	3.4	18.96	" "
1-27-31	751.2	24.6	25.33	3.4	22.04	Mated 1-23-31
2-4-31	747	17.0	23.33	3.5	20.711	Good test
2-11-31	750	20.3	28.33	3.65	23.93	Good test
2-18-31	741.2	16.2	33.33	3.8	27.873	Building nest.
2-25-31	741.2	20.0	30.0	3.41	28.59	Rate taken just after delivery of 6 young.

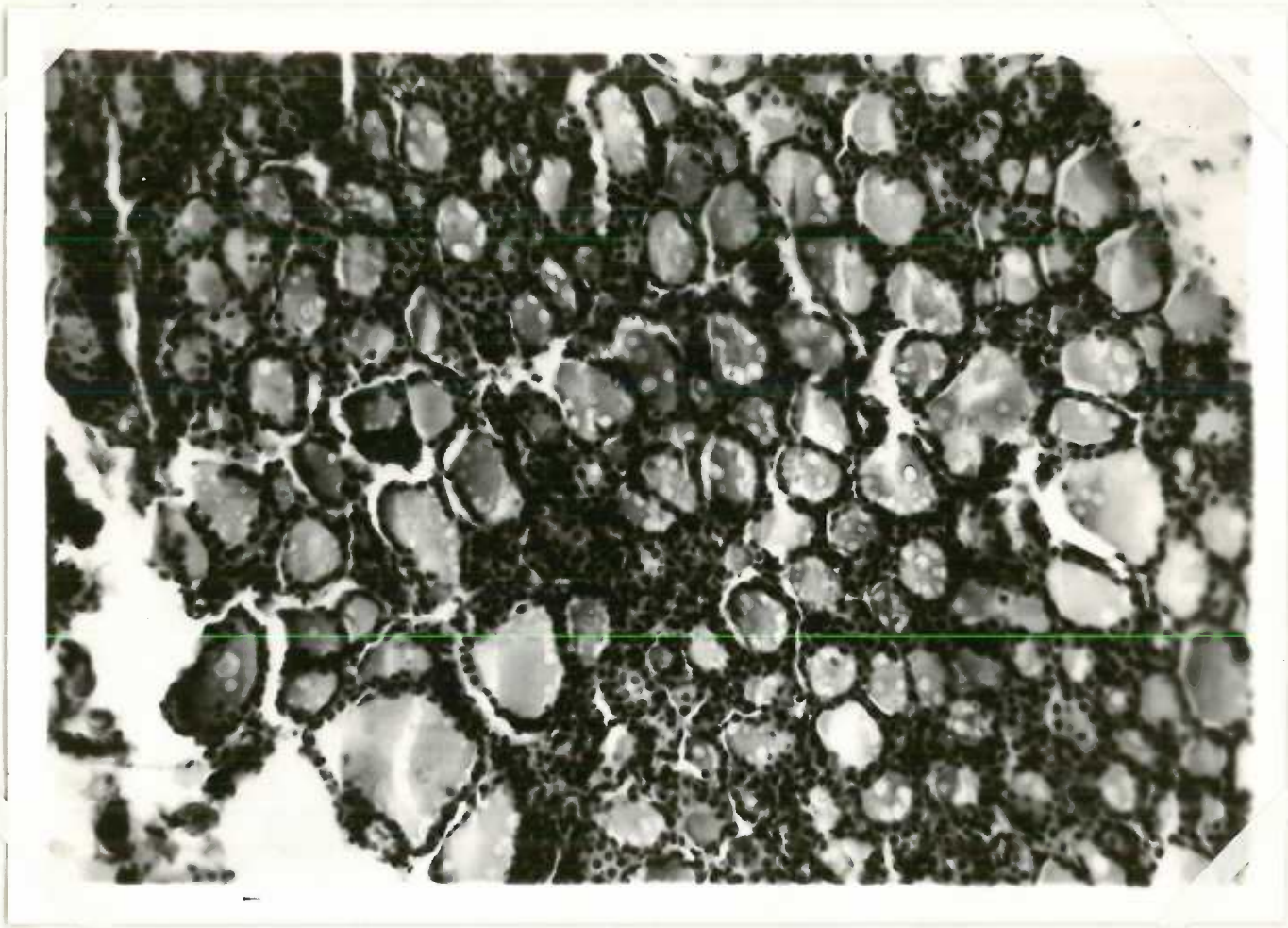

Fig. 16. R-VI, Series 2. Note the small circular acini lined with cuboidal and columnar epithelium. The colloid is moderately vacuolated. Definite evidence of increased activity.

RABBIT NO. VII, the second control animal of this series, was kept under conditions similar to the other five and was treated identically except that iodine was omitted. It was carried through pregnancy and lactation. She delivered two young early in the third month of the experiment. The term gland was removed the day following delivery. This procedure caused no evident effect and she went through the puerperium uneventfully. The term thyroid was slightly hyperemic, grossly. Microscopic sections reveal a very cellular gland made up of small circular acini. These acini are lined with tall cuboidal epithelium and contain vacuolated, scant colloid. There is evidence of well marked increased activity. See fig. 17, page 60.

The gland removed at the end of lactation had the same macroscopic appearance. The microscopic examination reveals a gland less cellular than at term but with evidence of well marked activity. The acini are large and lined with tall cuboidal epithelium. The colloid is pale but markedly vacuolated. See fig. 18, page 61. The B.M.R. table is given on page 59, Table XV.

Table XV, Rabbit No. VII :- Control

Date	Bar.Press.	Temp.	C.C. of O_2 per min.	Wt. in Kg.	B.M.R.	Remarks
12-23-30	756.7	25.5	26.66	2.76	26.88	Trial test
12-31-30	751.2	20.8	25.0	2.86	24.816	Good test
1-7-31	762	24.7	25.25	3.06	24.906	" "
1-14-31	750	26.7	27.0	3.06	25.142	" "
1-21-31	745.4	18.5	33.66	3.25	31.101	Mated 1-21-31
1-27-31	751.2	25.0	30.0	3.3	26.586	Good test
2-4-31	747	17.5	30.0	3.4	27.05	" "
2-11-31	750	20.7	31.33	3.6	26.624	" "
2-18-31	741.2	16.6	45.00	3.78	37.66	Term 2-23-31
2-24-31						Thyroidectomy. Mother and young O.K.
2-25-31	741.2	21.0	30.00	3.31	26.816	
3-4-31	739.0	21.3	28.0	3.40	25.117	Good test
3-11-31	745.0	22.0	25.5	3.41	22.342	" "
3-18-31	751	23.2	22.0	3.42	19.152	" "
3-25-31	752	23.0	20.0	3.50	17.251	" "

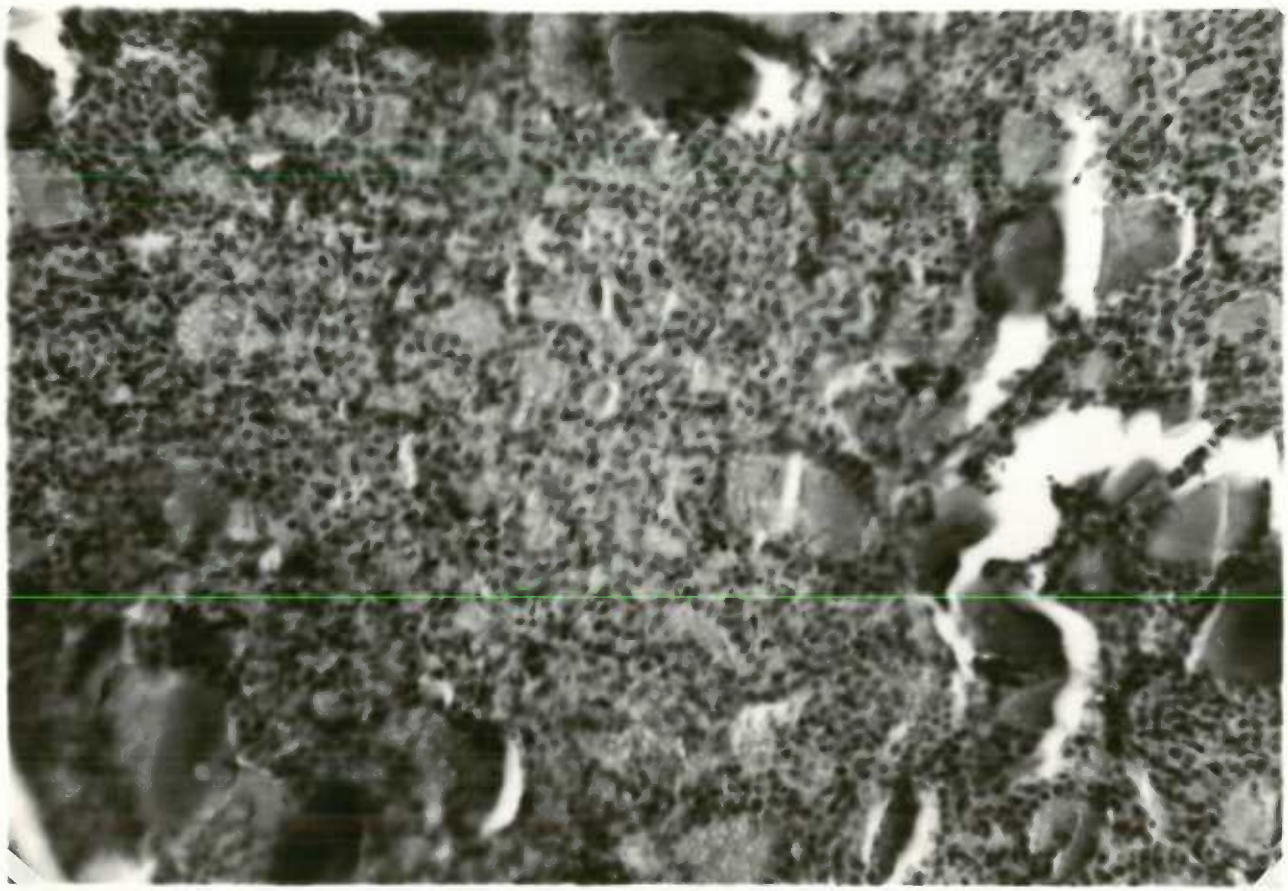

Fig. 17. R-VII, Series 2. Photomicrograph of the thyroid removed at term. This is a very cellular gland with scant and vacuolated colloid and small acini lined with tall cuboidal epithelium. Considerable evidence of increased activity.

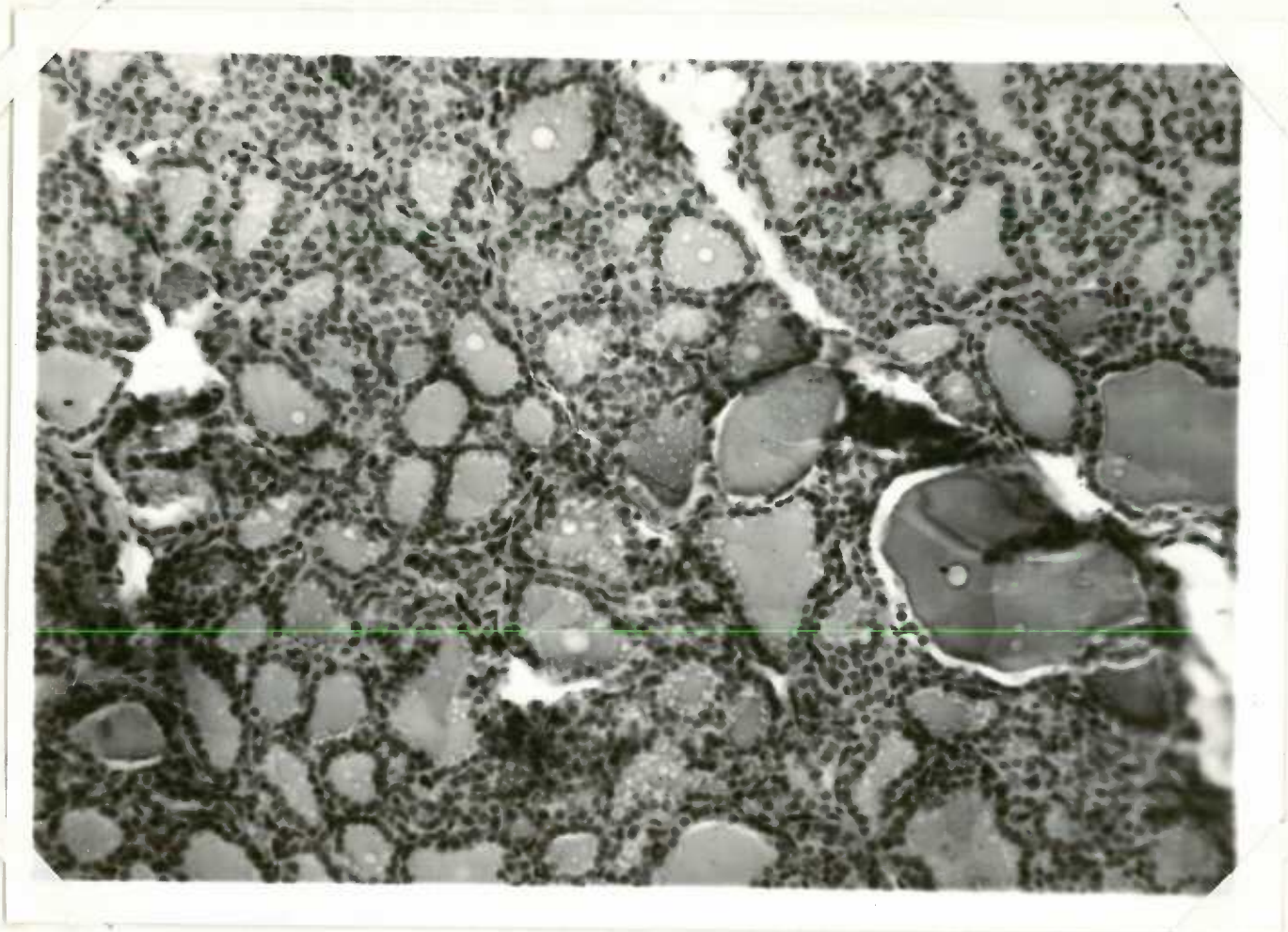

Fig. 18. R-VII, Series 2. Thyroid removed at the end of the lactation period. Note the marked vacuolization of the colloid. Small acini lined with cuboidal epithelium. Marked evidence of increased activity.

The second series (Series 2) is of greater value than the first, for the reason that the conditions enumerated at the outset are more nearly fulfilled. All of the animals became pregnant and were delivered of young. Two, R-IV and R-VI, did not complete the required lactation period. The recorded metabolic rates for these rabbits show some interesting results. Refer back to Table VIII, page 34, it will be noted that there is a definite rise of the B.M.R., above average, in the latter part of pregnancy. The greatest per cent rise occurs in the control rabbits; 39.2 per cent for R-VI and 45.1 per cent for R-VII. These animals received no iodine. The next greatest per cent increase, occurred in R-I receiving physiologic iodine with a 32.2 per cent rise above average, at term. Those given multiples of the required physiologic iodine, present lower figures ranging from 27.3 per cent to 3.6 per cent. It is significant that those animals having physiological iodine or multiples of it, should also present basal metabolic rates at term relatively lower than those recorded for the control rabbits, receiving no iodine.

This variation in metabolism is well illustrated in the curves pictured in Chart II, page 63. Here are three representative basal metabolic rate curves selected for the purpose of simplification from seven instances. The peaks of the curves, occurring at term are marked "T". This point is highest in R-VII, the control rabbit, next highest in R-I, receiving the minimum iodine, and lowest in R-V, which ingested five times the physiological requirement.

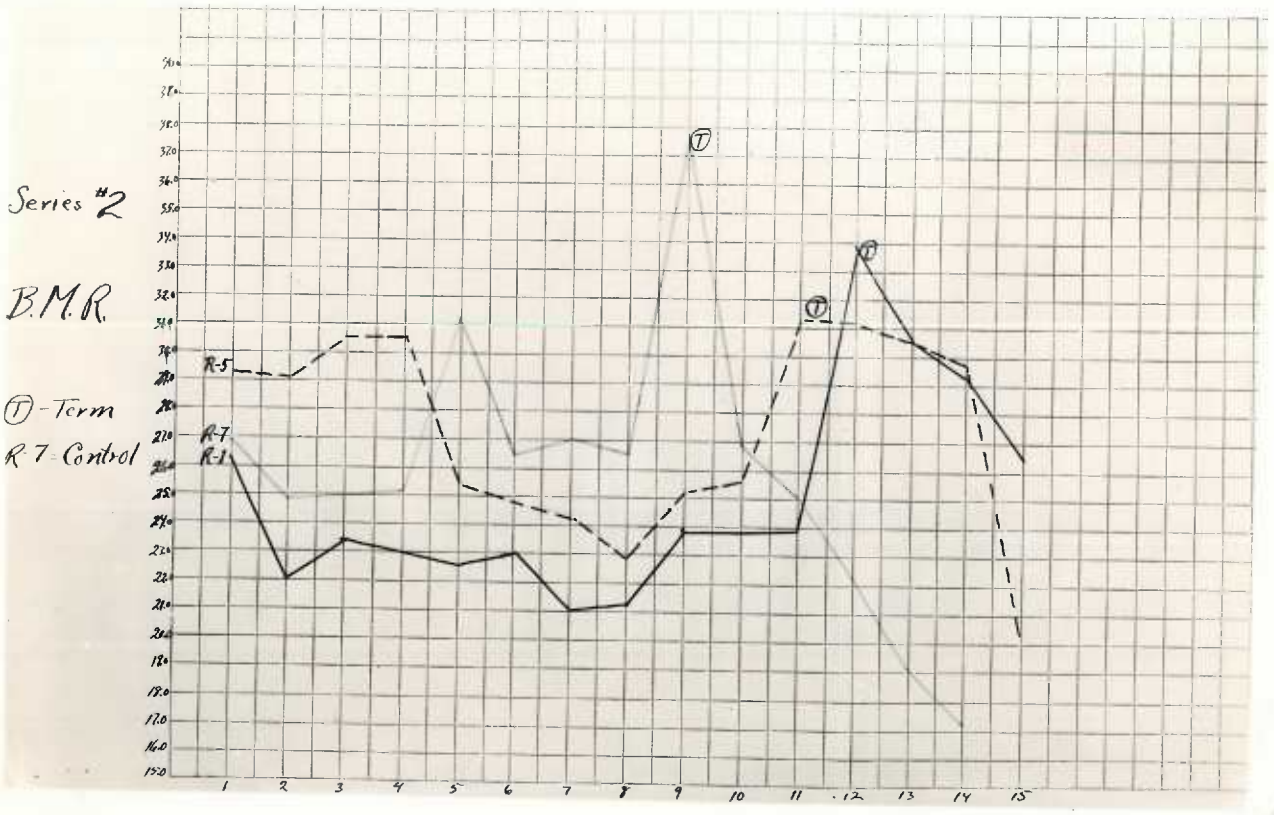

Chart II. Showing B.M.R. curves of R-I, R-V, and R-VII.

Discussion of Results.

The factors modifying the results in the first series of six rabbits have been pointed out previously and for this reason the information is of relatively little value. Certain data recorded during the course of the experiments may be of interest and have some bearing on the more complete Series 2. Rabbit No. III of Series 1 at term showed a significant elevation of the basal metabolic rate. The per cent increase corresponds very well with the figures for rabbits receiving multiples of physiologic iodine in Series 2. The thyroid gland removed at term is histologically inactive, presenting another point of similarity. The greatest per cent increase in this group was that of Rabbit No. V. dying of an infection. The histologic picture in this case is that of a very active gland, simulating the thyroids of the control rabbits of Series 2. The curve plotted, representing the basal metabolic rates of the control rabbit does not rise with the other curves, indicating rather definitely that the elevation must be due to the difference in condition of the animals rather than some common factor.

Although the second series is small, it is quite complete, and shows certain uniform definite trends. The rabbits receiving iodine exhibit lower B.M.R's, smaller per centage increase over the average, and less histologic evidence of thyroid activity. The animals ingesting more than the physiological optimum iodine within certain limits, show less metabolic response to pregnancy, judging from the rates recorded and the microscopic structure of their thyroid glands. These statements become obvious when the composite B.M.R. table No. VIII and the curves on Chart II are examined. The per centage increase of the basal metabolic rate, in this latter group, and of R-III of Series 1, is in every case less than 28.0 per cent. R-I of Series 2 is slightly higher,

being 32.2 per cent. However those animals not receiving iodine show rates 10 - 12 per cent higher, and the corresponding thyroid glands are without doubt much more active.

In view of the foregoing results there would appear to be limited but definite evidence that in rabbits iodine has a sustaining effect on the thyroid gland during pregnancy, and also possibly lowers the metabolic shock incident to the pregnant state. The above assertion is based upon the lower basal metabolic rates and less active thyroid glands recorded for the animals receiving iodine daily.

Summary.

1. Clinical observations indicate that there is an increase in metabolism during pregnancy but a review of the literature has failed to reveal any animal experiments supporting this belief.

2. With the object of testing out the validity of the above mentioned belief, two carefully controlled series of rabbits were studied.

3. The results obtained in the first series were not satisfactory but those of the second group allow of certain conclusions.

4. The basal metabolic rates and histologic picture of the thyroids, indicate that from 1 to 5 times the physiologic iodine requirement, stabilizes the B.M.R. and the thyroid gland during and following pregnancy.

5. The control rabbits, receiving no iodine, show high per centage increase in metabolism and more histologic evidence of increased thyroid activity, compared with those receiving iodine.

AN ABSTRACT OF THE THESIS OF

James D. Stewart Jr. (Name) for the Masters (Degree) in Pathology (Major)

Date of graduation June 15, 1931

Title The Relationship of Iodine to the Basal Metabolic Rate and to Changes in the Thyroid in Pregnant Rabbits; An Experimental Study.

Approved: (Adviser in charge)

In this study two series of six and seven rabbits each were used. These animals were given multiples of physiologic iodine requirements daily. Pregnancy was induced in as many animals as possible and these were followed through pregnancy and puerperium with frequent basal metabolic readings. At term one lobe of the thyroid was removed surgically. The remaining lobe was removed at the end of lactation. The histologic structure of these glands was studied and compared with the B.M.R. recordings and the iodine dosage.

The results of the first series of six rabbits were modified by sterility and infection and for this reason the information is of relatively little value. Certain data recorded during the course of the experiments may be of interest and have some bearing on the more complete Series 2. Rabbit No. III of Series 1 at term showed a significant elevation of the basal metabolic rate. The per cent increase corresponds very well with the figures for rabbits receiving multiples of physiologic iodine in Series 2. The thyroid gland removed at term is histologically

inactive, presenting another point of similarity. The greatest per cent increase in this group was that of Rabbit No. V. dying of an infection. The histologic picture in this case is that of a very active gland, simulating the thyroids of the control rabbits of Series 2. The curve plotted, representing the basal metabolic rates of the control rabbit does not rise with the other curves, indicating rather definitely that the elevation must be due to the difference in condition of the animals rather than some common factor.

Although the second series is small, it is quite complete, and shows certain uniform definite trends. The rabbits receiving iodine exhibit lower B.M.R's, smaller per centage increase over the average, and less histologic evidence of thyroid activity. The animals ingesting more than the physiological optimum iodine within certain limits, show less metabolic response to pregnancy, judging from the rates recorded and the microscopic structure of their thyroid glands. These statements become obvious when the composite B.M.R. table No. VIII and the curves on Chart II are examined. The per centage increase of the basal metabolic rate, in this latter group, and of R-III of Series 1, is in every case less than 28.0 per cent. R-I of Series 2 is slightly higher, being 32.2 per cent. However those animals not receiving iodine show rates 10 - 12 per cent higher, and the corresponding thyroid glands are without doubt much more active.

In view of the foregoing results there would appear to be limited but definite evidence that in rabbits iodine has a sustaining effect on the thyroid gland during pregnancy, and also possibly lowers the metabolic shock incident to the pregnant state. The above assertion is based upon the lower basal metabolic rates and less active thyroid glands recorded for the animals receiving iodine daily.

RABBIT NO. VI, one of the control animals of this series, was treated similar to the other five rabbits but received no iodine. This was a young healthy animal which became pregnant in the second month of the experiment and delivered six young early in the third month. The young were not properly cared for and all died. For this reason only the thyroid at term was studied. This is grossly unchanged. Microscopically this gland is made up of small acini lined with cuboidal and columnar epithelium. The colloid is dark and moderately vacuolated. It presents definite evidence of increased activity. The microphotograph is given on page 57, Fig. 16. The B.M.R. table and remarks are given in Table XIV page 56.