

Missouri Section.

St. Louis University School of Medicine, December 10, 1930.

5334

Effect of Intraperitoneal Injections of Potassium Iodide on Proliferative Activity of Thyroid Gland in Rats.

JACOB RABINOVITCH. (Introduced by L. Loeb.)

From the Department of Pathology, Washington University School of Medicine.

It has been shown that contrary to the action of thyroid substance, administration of potassium iodide to guinea pigs in which the greater part of the thyroid gland had previously been extirpated, does not prevent the occurrence of compensatory hypertrophy and that in normal guinea pigs it has a noticeably stimulating effect on this organ. It also produces a slight increase in the size of the epithelium, a certain degree of softening of the colloid and an increase in the number of phagocytes in the colloid.¹⁻⁹ Furthermore, the degree of cell proliferation and the intensity of the histological changes in the gland vary in accordance with the amount of iodide given, and the length of time during which it is administered, is also of importance.

Irsigler¹⁰ has shown that very similar changes take place also in the thyroid gland of white rats when treated with potassium iodide.

¹ Loeb, Leo, *J. Med. Res.*, 1920, **41**, 481; *Am. J. Pathol.*, 1926, **2**, 19; 1929, **5**, 79; *Endocrinology*, 1929, **12**, 49

² Gray, S. H., Haven, F. L., and Loeb, Leo, *PROC. SOC. EXP. BIOL. AND MED.*, 1927, **24**, 503.

³ Gray, S. H., and Loeb, Leo, *Am. J. Path.*, 1928, **4**, 257.

⁴ Rabinovitch, J., *Am. J. Path.*, 1928, **4**, 601; 1929, **5**, 87 and 91.

⁵ Gray, S. H., and Rabinovitch, J., *PROC. SOC. EXP. BIOL. AND MED.*, 1929, **26**, 468.

⁶ Rabinovitch, J., and Gray, S. H., *Am. J. Path.*, 1930, **6**, 75.

⁷ McCordock, H. A., *Am. J. Path.*, 1929, **5**, 171.

⁸ Silberberg, Martin, *Krankheitsforschung*, 1930, **8**, 171.

⁹ Loeb, Leo, *Am. J. Surg.*, 1929, **7**, 12.

¹⁰ Irsigler, F. H., *Beitr. z. Path. Anat.*, 1930, **85**, 221.

However, the amount of iodide necessary to produce these changes in the rat was considerably smaller than that used in the guinea pig; moreover, when somewhat larger doses were administered for the same or for longer periods of time, the increase in mitotic activity of the acinar epithelium was either diminished or completely prevented. As to the intensity of the mitotic proliferation produced by the administration of iodine, Irsigler makes only general statements without giving any definite figures comparable to those in the case of guinea pigs in the investigations from this laboratory.

Chouke¹¹ showed that when doses of potassium iodide corresponding by weight approximately to those which have been found active in the case of guinea pigs, or somewhat higher doses, are given to rats they do not produce an increased activity of the thyroid gland. Not only were the doses given greater but the time of examination was somewhat later than in Irsigler's investigations.

It was of interest to determine (1) whether the differences in the results obtained by these 2 investigators were due to the difference in the dosage and in the time of examination, and (2) to supply exact data as to the increase in mitotic activity caused by KI in rats. Twenty-four white rats with weights varying approximately between 120 and 190 gm. were divided into 4 sets. Each animal in the first set received daily injections of 0.0005 gm. KI dissolved in 1 cc. of sterile distilled water; the animals of the second set were similarly injected with 0.002 gm. KI and those of the third set received 0.01 gm. KI. The fourth set, serving as controls, did not receive KI. The injections were given in each set for periods of 5, 10 and 15 days respectively. At the end of each period the animals were killed by chloroform, the thyroids removed and studied in the same manner described in previous reports.

Table I indicates the number of mitoses observed in the various

TABLE I.—MITOSES.*

Time days	Control		0.0005 gm. KI		0.002 gm. KI		0.01 gm. KI	
5	0	22+	5472	30—	2980	0	200	15—
5	0	10—	4300	25—	2354	0	285	38+
10	48	30+	954	10+	350	40—		
10	0	6+	380	0	688	5+	150	10+
15	36	40+	300	95+	2124	13+	104	0
15	24	20+	180	0	100	10—	100	0

* + gain in weight; — loss in weight.

¹¹ Chouke, K. S., *Endocrinol.*, 1930, **14**, 169.

animals under the different experimental conditions. The highest proliferation activity is found in animals that have received the smallest amount of KI for the shortest period of time, namely 0.0005 gm. for a period of 5 days. As the amount of iodide is increased and the period of time is lengthened, there follows a corresponding reduction in the number of mitoses. Accordingly, we find in animals that have received the largest dose of KI for the longest period of time, namely 0.01 gm. KI for 15 days, the smallest number of mitoses. Occasional individual variations are noted; the animal that received 0.002 gm. KI for 15 days had 2124 mitoses while the other animals that received a similar small amount of KI had a markedly lower mitotic count. Occasional variations of this kind merely indicate that the thyroids of different animals respond with somewhat varying intensity to the stimulating effects of potassium iodide. If we consider, however, the experimental results obtained as a whole, there remains no doubt that KI exerts a marked stimulation on the thyroid gland of the rat and causes an increased proliferative activity when used in appropriate amounts. In this respect therefore, our experiments agree with the results obtained by Irsigler, and we feel that the cause of the different results obtained by Chouke and Irsigler are due to the difference in doses of KI and also in the periods during which it acted in the experiments of these 2 investigators.

In addition to the increased mitotic proliferation induced by suitable doses of KI, there were other microscopic changes in the thyroid gland likewise indicative of stimulation. Reference has already been made to such changes which briefly consist of a moderate softening of the colloid, an increase in the number of phagocytes in the colloid as well as a slight increase in the height of the acinar epithelium. In the present series of experiments these changes were also found and were most definite where the increase in proliferative activity was most marked. Where this increase was lacking or very slight, the thyroid retained its normal characteristics; the colloid tended to remain solid, the number of phagocytes was relatively small and the epithelium was low columnar or cuboidal. In some cases the diminished number of mitoses was associated with a distension of the acini due to an accumulation of colloid, and almost complete flattening of the lining epithelium. The latter changes are very similar to those previously observed by Gray and Loeb and by ourselves in guinea pigs receiving potassium iodide over a very long period of time.

Definite changes in body weight in the individual animals during

these experiments did not seem to be associated with the changes in cell proliferation. In previous investigations, on the other hand, it was noted^{4, 6} that a considerable loss in body weight in the animal interfered with the stimulating effects of potassium iodide and caused a diminution in gland activity. In our experiments with rats 2 of the animals that showed the largest mitotic count suffered from a moderate loss in body weight. It is quite possible that this loss of weight was secondary to the heightened activity of the thyroid gland resulting from the stimulating effects of the iodide.

Conclusions. Our experiments tend to reconcile the differences between the results obtained by Chouke and Irsigler, and our results confirm those of Irsigler as to the necessity of using relatively small doses and short periods of time in order to obtain stimulating effects on the thyroid of the rat by the administration of KI. There seems to exist a quantitative relation between the increase in mitotic proliferation and the quantity of KI used and the length of time during which it acted. In the case of the guinea pig we have shown previously that within the limits tested the larger doses are more effective than the smaller ones. Whether a similar relation exists also in the case of the rat thyroid remains to be seen. It is of interest that the maximum number of mitoses observed in the rat under the influence of optimal conditions of stimulation is very similar to that formerly established in the case of the guinea pig.

Associated with this increased proliferative activity of the acinar epithelium, there are observed the other structural changes in the thyroid gland indicative of increased metabolic activity, previously noted in the case of the guinea pig. The average index of mitotic proliferation which we found in the thyroid gland in the control rats is somewhat lower than that observed by Chouke. This may possibly be due to differences in the season of the year; however, this point needs further investigation.