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## Effect of Feeding Small Doses of Potassium Iodide on the Thyroid Gland.

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In previous experiments reported from this laboratory it has been shown that the oral administration of 0.01, 0.05 and 0.1 gm. KI daily for a period of 15 to 20 days to normal guinea pigs results in a very marked proliferative activity of the thyroid epithelium,[1, 2] which, as estimated by the number of mitoses, was directly proportional to the size of the dose.[2] The smallest dose of iodide used in the earlier experiments in the guinea pig, corresponded approximately to a therapeutic dose used in the human being, but 0.05 gm. and 0.1 gm. exceed considerably the quantities used in patients. Yet, even when the largest doses of potassium iodide were used none of our animals showed any injurious effects; they usually gained in weight, and appeared perfectly normal in every respect. It was, nevertheless, of interest to study the effects of very small doses of potassium iodide upon the thyroid glands and the following experiments were therefore performed.

Twenty-two guinea pigs, weighing between 325 and 450 gm. were divided into 4 groups, the first of which served as controls and received no iodide; the other 3 groups were fed respectively with daily doses of 0.01, 0.001 and 0.0001 gm. KI for a period of 20 days, at the end of which time, the animals were killed and the thyroids removed and studied in a manner already described in the previous communications.

I. *Estimation*

[1] Gray, S. H., and Loeb, Leo, *Am. J. Path.*, 1928, iv, 257.

[2] Rabinovitch, J., *Am. J. Path.*, 1928, iv, 601.

Table I shows the results obtained, as far as the mitotic activity is concerned.

TABLE I. *Tabulation of Mitoses.*

| | Control | 0.0001 gm. KI | 0.001 gm. KI | 0.01 gm. KI |
|---|---|---|---|---|
| | 72 | 486 | 140 | 924 |
| | 232 | 288 | 524 | 1814 |
| | | 56 | 430 | 1172 |
| | | 48 | 196 | 1296 |
| | | 520 S | 1018* | 160*S |
| | | 2000*S | 20*S | 906 S |
| | | | 220 S | |
| Total average | 152 | 566 | 507 | 1045 |
| Average if figures with * are omitted | 152 | 280 | 302 | 1224 |

(a) Control animals. Only 2 animals were used in the control group because the results obtained conformed closely to those observed in a very large number of control guinea pigs previously studied. The number of mitoses in the whole thyroid gland of these 2 animals were 72 and 232. These figures are within the control limits.

(b) Animals fed with 0.0001 gm. KI. The number of mitoses in this series of animals varied considerably. The figure 2000 found in our guinea pig is exceptionally high. When this number is omitted, the average number of mitoses is 280, which is slightly above the average of the control. However, at best this increase in the average of mitoses is very slight.

(c) Animals fed with 0.001 gm. KI. The mitotic activity found in this series also showed considerable variations. The average number of mitoses was 302, which is somewhat greater than in the controls although not very markedly so. This figure is obtained if we omit the 2 extremes (1018 and 20); otherwise the average exceeds that of the controls more decidedly.

(d) Animals fed with 0.01 gm. KI. The number of mitoses per gland in this group, with the exception of one (160), is much more constant than in the preceding 2 groups. We may omit this figure as an individual variation due to an unknown variable factor. The remaining animals present a marked increase in mitotic activity considerably greater than that found in the controls, or in the animals fed with smaller doses.

Although the feeding of 0.0001 and 0.001 gm. KI does not produce a pronounced increase in mitoses, it calls forth a slight increase above that found in the untreated control animal. This is especially true of some individual animals in which the increase was quite pro-

nounced. When we omit from our average the extreme figures obtained (marked in the table by *) the number of mitoses in the animals treated with the very small doses of KI, approaches closely the upper limits obtained in the controls. A markedly stimulating effect of the iodide on the mitotic proliferation becomes quite noticeable when a dose of 0.01 gm. KI is used. These figures also indicate that the larger the dose of KI administered to the animal, the greater is the resulting mitotic activity.

Some of these experiments were carried out in the summer months of 1928, while others were carried out during winter months. The ones done during the summer months are designated in the table by the letter "S". The results obtained during the warm season are more irregular than those obtained at other times; in general, they have the tendency to be low in animals fed with KI. This latter conclusion is borne out also by additional experiments not included in this table.

II. Changes in the character of the acini, epithelium and colloid. The histological structure of the average control gland may be described briefly, as follows: The acini are of medium size, lined by low cuboidal epithelium, but variations occur in different parts of the gland. The colloid is solid, but occasionally shows areas of softening and may or may not be infiltrated with phagocytes. In the interstitial tissues are found at times lymphocytic or leucocytic accumulations, although these latter findings are unusual.

The structural picture of the thyroid obtained from animals fed with 0.0001 gm. KI is very similar to that found in the control. These findings therefore indicate that the thyroid gland of guinea pigs does not respond to doses as small as 0.0001 gm. KI.

When doses of 0.001 gm. KI were administered, the glands showed a greater response. The acini tended perhaps to become slightly larger and somewhat more irregular in shape, and the epithelium was on the average slightly higher, than in normal glands. The colloid showed more softening and was more densely infiltrated with phagocytes. Such a structure of the thyroid is very similar to that observed in cases in which larger doses of iodide (0.01-0.1 gm.) were used and where mitotic activity was very pronouncedly increased. These structural changes in the gland correspond to a certain extent, with the mitotic cell activity of the acinar epithelium, inasmuch as they are found only in such guinea pigs as have been fed doses of KI which on the average increase the mitotic activity, and inasmuch as a very low number of mitoses is not usually associated with a softening of colloid, increase in phagocytes and slight increase in the size of the acinus cells. But if 0.001 gm. KI is fed

these changes may be visible even in cases where there is no definite increase in the number of mitoses, and there is moreover no direct parallelism between the doses of KI given, the increase in mitotic activity and the characteristic structural changes. The thyroid gland of normal guinea pigs may show marked structural variations which, in some cases, closely resemble the gland of animals fed with KI in that the colloid is soft and infiltrated with phagocytes while the epithelium is high and acini somewhat larger and of irregular shape.

Discussion. These experiments show that the oral administration of very small doses of KI (viz. 0.0001 gm. KI) to the normal guinea pigs for a period of 20 days, evokes no marked response on the part of the thyroid gland in so far as proliferation of the epithelium or structural appearance of the gland are concerned. When the dose is increased to 0.001 gm. KI, mitotic activity is still low, but there appear in the gland definite structural changes, found usually in gland of animals which have been fed larger doses of KI. These changes consist mainly in larger and more irregular acini, higher epithelium and softer colloid infiltrated with phagocytes. As small a dose as 0.001 gm. KI may stimulate the thyroid gland without necessarily causing an increased mitotic activity. This presents the first variation of what heretofore has been thought to be a parallelism: The greater the number of mitoses the more marked the other histological signs of thyroid activity.

When still larger doses of KI are administered, viz., 0.01 gm. KI, the number of mitoses in the gland increases considerably above the normal control. Associated with the rise in the number of mitoses, we also find the larger, irregular acini, the higher epithelium and softer colloid.

Summary. 1. The daily feeding of 0.001 gm. KI to guinea pigs does not increase the number of mitoses and does not affect the structure of the thyroid gland. 2. Feeding daily 0.001 gm. KI to guinea pigs produces only a slight increase in mitoses but at the same time produces an otherwise histologically active thyroid gland. 3. The feeding of 0.01 gm. KI stimulates the thyroid in all its histological phases.

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