STUDIES IN THE ETIOLOGY OF SIMPLE GOITER *

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INTRODUCTION

In a previous communication [1] we have reported the occurrence of goiter in a colony of rabbits maintained upon a diet consisting almost exclusively of cabbage. The condition was identified as simple or endemic goiter. The microscopic picture usually presented was that of the typical *struma diffusa parenchymatosa*. In view of the multiplicity of etiological factors with which simple goiter is commonly accredited, it was considered advisable to attempt to rule out some of these as contributory factors in the present epidemic. This communication deals with a series of experiments which were carried out in an effort to determine whether or not the cabbage diet was the sole etiological factor in this instance and, if not, what rôle certain other factors played in the production of goiter. Since goiter occurred with great regularity in all stock rabbits kept under standard conditions in our laboratory, it is considered advisable to describe these standard conditions briefly.

The rabbits were housed in quarters on the eighth floor of the dispensary building of the Johns Hopkins Hospital. The room is well ventilated and well lighted, having a southern and eastern exposure. The cages are supported on metal racks, three tiers high with ample ventilation space between individual cages. The standard cage is of metal and measures 45 by 30 by 30 cm. The front and top are made of wire mesh. The bottom of the cage is covered with shavings which are changed once or twice weekly. The standard diet consists of a daily ration of approximately 250 gm. of cabbage and a weekly ration of approximately 20 gm. of hay and 50 gm. of oats. The cabbage was procured from various regions in the Eastern United States, ranging between Florida and New York state with the season. Water was not given on the standard diet. No special breed of rabbits was used, the stock being procured

* Received for publication February 3, 1930.

largely from dealers in Maryland and Pennsylvania. All animals were examined on admission and were found to be clinically negative as regards thyroid enlargement.

All of the animals used in the experiments described below were of known stock and age. The animals in each experimental and control group were of the same age and the groups were so arranged that the number of males and females was the same in each group. Because of this uniformity of experimental material, absolute thyroid gland weights are given throughout, instead of thyroid gland, body weight ratios.

Experimental

Experiment No. 1: In view of the extensive work of McCarrison [2] and others on the relationship of food contamination to the etiology of goiter, an attempt was made to determine whether or not this factor played any part in the present epidemic. Accordingly, a special system of caging was instituted with the idea of removing, as far as possible, the factor of fecal contamination of the food. These cages were of metal and measured 61 by 46 by 31 cm. The top and front were of wire mesh. The bottom consisted of a removable metal pan over which was placed a grid of coarse wire mesh. Through this grid the urine and feces dropped to the pan below. The pans were so arranged that they drained into a central drainage system. In this way, the bottom of the cage, on which the animal rests, was always clean and dry. At frequent intervals the rabbits were removed and the interior of the cages was washed by means of a hose. Food was placed in glazed earthenware cups, 3 inches high. These cages were placed in a well ventilated, well lighted part of the animal room. By this manner of caging, fecal and urinary contamination of the food was almost entirely eliminated.

Five litters, consisting of thirty-two rabbits of approximately the same age, were used for this experiment. Sixteen rabbits were placed in the special cages described above. The remainder were housed in standard cages and were intended to serve as a control series. The litters were divided into approximately equal parts. The diet in both instances was identical, the standard laboratory diet being used. The mortality from intercurrent infections was high during the course of this experiment. At the end of approxi-

TABLE I

Incidence of Goiter in Rabbits Maintained in Two Types of Cages

Group I — Special Cages					Group II — Standard Cages				
Rabbit number	Weight of thyroid	Days in laboratory	Cause of death	Microscopic appearance of thyroid	Rabbit number	Weight of thyroid	Days in laboratory	Cause of death	Microscopic appearance of thyroid
	gm.					*gm.*			
2111	2.5	345	sacrificed	marked hyperplasia	2107	1.2	345	sacrificed	marked hyperplasia
2112	14.0	345	"	" "	2108	1.3	345	"	" "
2113	2.8	345	"	" "	2109	8.4	345	"	" "
2114	2.8	345	"	" "	2110	3.5	345	"	" "
2136	0.8	330	"	hyperplasia	2140	2.5	345	"	" "
2188	0.5	325	"	"	2190	1.2	345	"	" "
2189	0.9	325	"	"	2191	0.8	345	"	" "
2182	0.4	325	"	"	2185	2.7	345	"	" "
2195	1.8	325	"	"	2139	3.8	276	pneumonia	" "
2196	1.2	270	pneumonia	"	2192	0.65	258	"	hyperplasia
2138	0.3	97	diarrhea	slight hyperplasia	2137	0.6	172	"	"
2135	0.4	87	caseous abscess	" "	2197	0.6	141	"	"
2183	0.3	75	diarrhea	" "	2199	0.4	88	diarrhea	slight hyperplasia
2187	0.3	72	"	" "	2198	0.2	55	"	normal
2184	0.1	60	"	normal	2186	0.7	52	"	hyperplasia
2194	0.2	50	pneumonia	"					

mately three hundred and forty days, the animals still living were sacrificed and autopsied. Table I shows the results of the above experiment.

It will be observed from an inspection of Table I, that goiter developed in the animals kept in the special cages where fecal and urinary contamination was reduced to a minimum (Group 1), as readily as in the animals kept in cages where there was abundant opportunity for fecal and urinary contamination. The average weight of the thyroid glands at the termination of the experiment was 2.83 gm. for the group housed in the special cages, and 2.70 gm. for those housed under standard laboratory conditions.

Experiment No. 2: Since water has been associated with the etiology of simple goiter by all peoples from the remotest times [3] it was considered advisable to determine whether or not the absence of water was a factor in the present epidemic, and at the same time to find out if the traces of iodine contained in Baltimore city tap water * were sufficient to protect the animals against a powerful goitrogenic influence such as we were dealing with in this instance. Thirty rabbits of approximately the same age and from the same source were divided into three equal groups. All were placed on the standard cabbage diet and were housed under the standard laboratory conditions. Group 1 was constantly supplied with freshly distilled water in glazed earthenware containers. Group 2 was similarly supplied with Baltimore city tap water. Group 3 served as a control series and was given no water to drink. At the end of one hundred and twenty-five days all the animals were sacrificed and autopsied. Table II shows the results of this experiment.

This experiment was terminated at an earlier date than in the case of the preceding one, hence the thyroid weights were smaller. Previous experience had shown that time is an important factor in the development of the larger goiters in rabbits maintained on the goiter-producing diet. The table shows that the average weight of the thyroid gland in Group 1 (which received distilled water) was 0.57 gm., while the average weight in Group 2 (which received tap water) was 0.53 gm. In the control series the average weight of the thyroid gland was 0.67 gm. Microscopic sections of the thyroid glands of all animals sacrificed at the termination of the experiment showed varying degrees of hyperplasia.

* Two parts per billion, as estimated in laboratories of City Water Department.

TABLE II

Effect of Adding Water to the Diet on the Incidence of Goiter in Rabbits

Group 1 — Distilled Water Series					Group 3 — Control Series					Group 2 — Tap Water Series				
Rabbit number	Weight of thyroid	Days in laboratory	Cause of death	Microscopic appearance of thyroid	Rabbit number	Weight of thyroid	Days in laboratory	Cause of death	Microscopic appearance of thryoid	Rabbit number	Weight of thyroid	Days in laboratory	Cause of death	Microscopic appearance of thyroid
	gm.					*gm.*					*gm.*			
2397	0.80	125	sacrificed	hyperplasia	2400	0.70	125	sacrificed	hyperplasia	2390	0.25	125	sacrificed	slight hyperplasia
2380	0.80	125	"	"	2401	0.60	125	"	"	2391	0.30	125	"	"
2382	0.40	125	"	"	2402	0.90	125	"	"	2392	0.55	125	"	hyperplasia
2383	0.30	125	"	slight hyperplasia	2404	0.50	125	"	"	2393	0.55	125	"	"
2384	0.40	125	"	hyperplasia	2405	0.50	125	"	"	2394	0.65	125	"	"
2385	1.40	125	"	"	2406	0.65	125	"	"	2395	1.00	125	"	"
2386	0.45	125	"	"	2407	0.60	125	"	"	2396	0.30	125	"	slight hyperplasia
2387	0.55	125	"	"	2408	0.50	125	"	"	2397	0.60	125	"	hyperplasia
2389	0.50	125	"	"	2410	1.40	125	"	"	2398	0.65	125	"	"
2388	0.10	20	pneumonia	normal	2409	0.40	34	pneumonia	slight hyperplasia	2399	0.45	125	"	"

Experiment No. 3: An attempt was made to demonstrate the effect of iodine prophylaxis against an active goitrogenic agent such as the cabbage diet. Four litters consisting of sixteen rabbits, were divided into two equal groups containing representatives of each litter. These animals were all placed in standard cages and maintained on the standard cabbage diet. Group A received 7.5 mg. of iodine per week by mouth. Group B served as a control series and received no iodine. At the end of approximately four hundred days, all of the surviving animals of Group B had visible and readily palpable goiters, while in none of the Group A animals could the thyroid gland be felt at this period. The rabbits were then sacrificed and autopsied. Table III shows the results of this experiment.

Here it can be seen that all of the animals in Group A had thyroid glands which were within the normal weight range (average 0.25 gm.), while all those in Group B had moderate-sized goiters, the average thyroid gland weighing 2.3 gm.

During the course of the above experiments, several striking aspects of the disease manifested themselves. There was considerable individual susceptibility on the part of certain animals toward the goitrogenic agent. Thus, in Table III, Group B, one sees that rabbit No. 2029 had a thyroid gland which weighed 7.3 gm. while numbers 2028, 2030 and 2031, which were from the same litter and were kept under identical conditions, had thyroid glands weighing 1.8, 1.4 and 1.4 gm. respectively. This same variation may be noted in many of the other tables. A marked seasonal variation was also noted. In animals brought into the laboratory in the late autumn or winter, clinically detectable goiters developed much more quickly than in those procured in the spring or summer months. Similarly, some of the large goiters tended to decrease in size slightly during the spring and summer. Throughout the present epidemic no greater incidence in females than in males has been noted. There is suggestive evidence that young rabbits are more susceptible to the goitrogenic influence than adult ones. No variation in the incidence of goiter has been noted among the different breeds of rabbits.

TABLE III

Showing the Effect of the Addition of 7.5 mg. of Iodine Per Week to the Diet on the Incidence of Goiter in Rabbits

Group A — Standard Diet plus 7.5 mg. Iodine per week					Group B — Standard Diet				
Rabbit number	Weight of thyroid	Days in laboratory	Cause of death	Microscopic appearance of thyroid	Rabbit number	Weight of thyroid	Days in laboratory	Cause of death	Microscopic appearance of thyroid
	gm.					*gm.*			
1994	0.30	420	sacrificed	colloid increased, no hyperplasia	1998	1.75	420	sacrificed	extreme hyperplasia
1996	0.25	420	"	"	2000	2.0	420	"	" "
1997	0.30	420	"	"	2001	1.6	420	"	" "
2033	0.20	400	"	"	2028	1.8	400	"	" "
2035	0.30	400	"	"	2029	7.3	400	"	" "
1995	0.20	200	pneumonia	"	2030	1.4	400	"	" "
2032	0.30	130	"	"	2031	1.4	400	"	" "
2034	0.10	25	none found	"	1999	1.1	225	pneumonia	" "

Discussion

The experiments outlined above appear to indicate that the major etiological factor in the epidemic of simple goiter under investigation, is a nutritional one. The cabbage diet, on which the animals were maintained, apparently exerted a very active goitrogenic influence.

These experiments are not in accord with the extensive investigations of McCarrison,[2] in which he attempted to show that unhygienic surroundings and fecal contamination of food were important causative factors in endemic and experimental goiter. In Experiment No. 1 there was no greater tendency to thyroid hyperplasia when the animals were kept under conditions permitting easy contamination of food than when they were maintained in the special cages under the best possible conditions.

Drinking water has been associated with the etiology of simple goiter by countless writers on the subject.[3] In this instance, since goiter occurred when the animals were given no water to drink, one might conceive of the goitrogenic factor as being due to the absence, rather than the presence of, some water-borne substance. Experiment No. 2, however, shows that the addition of either tap or distilled water to the diet has little or no effect on the goitrogenic factor. The slightly lower level of the average thyroid gland weights of the groups receiving water (0.57 and 0.53), as compared with those of the control group (0.67), is well within the range of accuracy of such a method of observation. The amount of iodine or other inorganic substances in the tap water of Baltimore city apparently is not sufficient to cause any detectable effect different from that given by distilled water.

As Marine has repeatedly shown, iodine in sufficient quantities will protect against all known goitrogenic agents. Experiment No. 3 shows clearly that 7.5 mg. of iodine per week was sufficient to afford the animals complete protection for a period of over one year. It is probable that much smaller amounts would have sufficed. The traces of iodine contained in the drinking water exerted no demonstrable effect. The exact amount necessary to protect lies somewhere between those two extremes.

The experiments outlined above appear to rule out fecal and urinary contamination of food, and deficiency in water-borne sub-

stances as accessory factors in the etiology of the present epidemic of simple goiter. It would appear that the cabbage diet on which the animals were maintained contains some powerful goitrogenic agent. Further, our experience has been that there is considerable seasonal variation in the incidence of goiter in these animals. This could be due to seasonal increase in the goitrogenic factor or to variation in the animals' susceptibility at certain time periods. The extreme variation in susceptibility of individual animals from the same litter is of great interest. One has to presuppose a so-called "constitutional factor" here which may conceivably operate through other endocrine glands and exert a protective influence, in certain instances, against the goitrogenic agent.

Since the above experiments were concluded, Marine, Baumann and Cipra [4] have added considerable light to our knowledge of cabbage as a goitrogenic agent. They have confirmed our observation that a cabbage diet will produce thyroid hyperplasia in rabbits, and have further shown that other members of the Brassica group will also produce goiter. They have suggested that cabbage acts as a goitrogenic agent by depleting the thyroxin store in the thyroid, thus producing a relative iodine insufficiency in the animal, which in turn causes hyperplasia of the thyroid gland. Marine's suggestion that this is brought about by some powerful reducing substance contained in the cabbage seems probable, and offers a possible explanation of many of the hitherto seemingly unrelated etiological factors of simple goiter.

Summary

Further investigations into the etiological factors involved in an epidemic of simple goiter in rabbits are reported. A diet which consists almost exclusively of cabbage appears to be the major etiological factor. Fecal and urinary contamination of food seemingly play no rôle in the present epidemic. The addition of water (either tap or distilled) to the diet exerts no appreciable protective influence against the goitrogenic agent. Iodine, administered orally in quantities of 7.5 mg. per week will completely protect the animal against the goiter-producing factor. There is no evidence that the minute traces of iodine contained in Baltimore city tap water exert any detectable protective influence. The goitrogenic agent is much

more active in winter than in the summer months. This goiter-producing factor appears to be a nutritional one and may act through the oxidation-reduction systems of the body.

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