THE OCCURRENCE OF SEASONAL VARIATIONS IN THE GOITER OF RABBITS PRODUCED BY FEEDING CABBAGE

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During observations by Chesney, Webster and Clawson (1, 2, 3, 4) in 1927, 1928 and 1929 on the production of goiter in rabbits by the feeding of cabbage, it was suspected that in the winter months (October to March) goiter was more easily produced than during the summer (April to September). It was further observed that there appeared to be a tendency toward involution of the thyroid in rabbits with very large goiters during the summer. Thus, individual animals kept in the laboratory for a year or more developed large goiters during the winter season which receded or involuted, to some extent, during the summer. No definite attempt was made at that time to demonstrate seasonal variation. In repeating the work of Chesney, Webster and Clawson on goiter produced by feeding cabbage, Marine, Baumann and Cipra (5) noted furthermore that "summer cabbage" was practically non-goitrogenic.

The present paper deals with an analysis of the data on which the earlier impressions of seasonal variation were founded, together with further experiments designed to demonstrate more systematically this phenomenon.

Observations at the Johns Hopkins Hospital.—An analysis was made of the thyroid gland weights of 247 rabbits fed on a cabbage diet and used for stock and control purposes in the department of medicine of the Johns Hopkins Medical School during the years 1927 to 1929. These animals were obtained from dealers in Maryland and Pennsylvania and in no instance was the thyroid gland clinically palpable upon admission to the laboratory. Immediately upon arrival the rabbits

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were placed on a diet consisting 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. No water was given the animals to drink and they were maintained under standard laboratory conditions which have been fully described in a previous communication (4). The thyroid gland weights were obtained at the termination of the period of observation.

In the present analysis, the animals of this series were classified in two groups, namely, those entering the laboratory after September 15 and those entering after April 15. They were subdivided into groups according to the time period during which the cabbage diet had been fed. The results have been summarized in Table I.

TABLE I

Seasonal Variations in the Goiter-Producing Power of Cabbage (Baltimore), 1927–1929 Inclusive

Days on cabbage diet	Entering laboratory autumn and winter beginning Sept. 15		Entering laboratory spring and summer beginning Apr. 15	
	Number of rabbits	Average weight thyroid gland in gm.	Number of rabbits	Average weight thyroid gland in gm.
1–30	8	0.25	6	Less than 0.1
31–60	18	0.49	13	0.38
61–90	10	0.93	17	0.24
91–120	33	1.08	24	0.75
121–150	24	1.16	15	0.77
151–180	18	1.37	23	1.17
181–210	20	1.73	18	0.96

From Table I it can be seen that, in each group, the average thyroid gland weight of animals entering the laboratory during the autumn and winter months and kept on the cabbage diet was nearly twice as great as in the corresponding group which entered during the spring and summer months. This table suggests that the average goitrogenic power of cabbage was nearly twice as great during the 6 months period beginning September 15 as during the remaining months of the year. During the winter months the cabbage was derived largely from Maryland, Delaware and New York State and consisted of so-called "winter cabbage," *i.e.*, varieties which grow slowly and are allowed to

mature fully before being harvested and placed in cold storage. During the spring and summer the cabbage used was of the early varieties. In the spring this was obtained from Florida and the Carolinas. As the season progressed, the source moved northward. This cabbage was of the rapidly growing, loose, immature "summer" varieties.

It was further evident that lots of cabbage from the same geographic location varied in their goiter-producing power from year to year,

TABLE II

Yearly Variation in Goiter-Producing Power of Cabbage, 1927–1929

Days on cabbage diet	1929				1928				1927			
	Autumn		Spring		Autumn		Spring		Autumn		Spring	
	No. rabbits	Average thyroid weight in grams	No. rabbits	Average thyroid weight in grams	No. rabbits	Average thyroid weight in grams	No. rabbits	Average thyroid weight in grams	No. rabbits	Average thyroid weight in grams	No. rabbits	Average thyroid weight in grams
1–30	4	0.15	2	0.10	—	—	2	0.10	4	0.35	2	0.10
31–60	5	0.47	4	0.47	6	0.40	5	0.35	7	0.60	4	0.33
61–90	5	0.49	3	0.10	3	1.60	8	0.33	2	0.70	6	0.28
91–120	8	0.55	10	1.21	12	1.49	7	0.40	13	1.20	7	0.63
121–150	10	1.17	4	0.66	8	1.20	6	0.90	6	1.10	5	0.75
151–180	6	1.10	12	1.30	7	1.30	5	1.18	5	1.70	6	1.05
181–210	6	1.40	7	0.95	7	1.10	6	1.10	7	2.70	5	0.94
Average...		0.76		0.68		0.80		0.61		1.19		0.58

apart from the seasonal variation described above. For example, it was observed that cabbage harvested in northern New York State during late October in 1928 was fully twice as active in goitrogenic power as the same variety of cabbage from the same locality in October, 1929, when tested in a standard way. Although no systematic effort had been made to compare this yearly variation during the early years of the work, nevertheless, data in the form of thyroid gland weights of control animals on the cabbage diet were available since 1927. These rabbits were maintained on the standard cabbage

diet and under the standard conditions summarized above. Table II summarizes these weights. Although the series is not large enough to justify definite conclusions, it would appear that in 1927, the year in which goiter was first observed among the rabbit colony at the Johns Hopkins Hospital, the cabbage was higher in goitrogenic activity than in 1928 or 1929.

Data from Montefiore Hospital.—Marine, Baumann and Cipra in repeating the experiments of Chesney, Webster and Clawson in the spring of 1928, used the following diet:

1. Fresh cabbage—60 cal. per kilogram daily (the food value of cabbage figured as 3.1 gm. being equivalent to 1 cal.).
2. Whole oats—35 gm. weekly.
3. Alfalfa hay—20 gm. weekly.

All the rabbits used were reared in the laboratory from a single strain (Belgian). For the past 10 years this rabbit colony has been maintained on the following stock diet: Alfalfa hay—20 to 30 gm., oats—35 gm. and fresh water daily. Greens twice weekly.

The data of representative experiments are given in Table III.

In Experiment 1, imported raw Holland winter cabbage was fed from March 15 to June 5, 1928—81 days. At the end of this period the thyroids were readily palpable clinically and at operation they were from 2 to 2½ times the normal size, dark red in color and very vascular. On June 12 the 4 rabbits of Experiment 1 without iodization were started on whole summer cabbage (from New Jersey) together with 8 new rabbits as Experiment 2a. All 12 of these rabbits were fed for the following 55 days and on direct surgical examination, 11 of them were found to have thyroids only slightly enlarged and slightly more hyperemic than normal. Even the 4 that had large vascular goiters at the beginning of this experiment had regressed markedly as had been observed in Baltimore.

Experiment 4 was started October 8, 1928, in which 4 rabbits were fed for the next 56 days with whole winter cabbage from northern New York. At the end of this period all 4 had thyroids readily palpable clinically and on direct surgical examination were from 3 to 4 times normal size and very hyperemic.

Experiment 5 was started November 20, 1928, in which the 8 rabbits were fed for the following 28 days with the same northern New York winter cabbage. All the animals of this experiment had palpable thyroids on the 21st day and on direct examination they were about twice normal size, very vascular and dark red.

On April 17, 1929, experiment 41 was started, 2 rabbits being fed on imported winter Holland cabbage and 2 on Carolina summer cabbage. These were examined surgically after 22 days and those on the Holland winter cabbage had

thyroids more than 3 times normal size and very hyperemic, while in those on summer cabbage, one was slightly enlarged and the other about normal size and slightly hyperemic. Another experiment, No. 55, was started August 7, 1929, and the 4 rabbits were fed with Long Island and New Jersey summer cabbage. On direct examination at the end of 41 days the thyroids were possibly slightly enlarged and slightly hyperemic, *i.e.*, the cabbage used had little or no goitrogenic activity.

These data include the study of the goiter-producing power of cabbage during 2 winter periods and 2 summer periods. The winter periods include data on both imported Holland and New York State cabbage, while in the summer periods only cabbage grown along the Atlantic seaboard was used. The data obtained independently in Baltimore and in New York therefore are in agreement and clearly show that there is a tremendous seasonal variation in the capacity of cabbage to produce goiter in rabbits. Cabbage marketed in the fall of 1927 and 1928, whether grown in Holland or in the United States, was extremely effective, while cabbage grown along the Atlantic seaboard during the spring and summer of these years was almost ineffective.

In the light of these findings we began in the autumn of 1929 a systematic survey in an effort to demonstrate more completely the seasonal variation in the goitrogenic power of cabbage and to establish a standard with which surveys in subsequent years could be compared.

Arrangements were made so that lots of northern New York State cabbage, from the vicinity of Rochester and Syracuse, were procured at weekly intervals from September 12 to December 15. The goiter-producing power of each lot of this cabbage was tested by feeding for a period of approximately 3 weeks to rabbits with normal thyroid glands. At the same time, the iodine absorbing power of each lot was determined at frequent intervals by iodometric titration. Table IV shows the results of this survey.

It will be noted that the goiter-producing power was very low until November 8, 1929. The batch received on this date showed an abrupt increase in goiter-producing power. Although batches were tested at weekly intervals until January 4, 1930, the goitrogenic activity remained nearly constant. A similar increase in the goitrogenic activity had been noted early in November, 1928. However, one very striking difference was noted, namely, that all the winter cabbage,

TABLE III

Seasonal Variations in the Goiter-Producing Power of Cabbage

Experiment No. and kind of cabbage fed	Rabbit No.	Sex and weight gm.	Daily amount cabbage fed gm.	Thyroid weight gm.	Feeding period	Condition of thyroid found at operation
			60 cal. per kg.		*1928*	
1						
Winter cabbage (Holland)	618	M 3335	600		3/15 to 6/5	2 times normal size, very vasc.
	619	F 2755	500		"	2½ " " " " "
	620	F 3510	650		"	2½ " " " " "
	621	F 2878	550		"	2½ " " " " "
2a						
Whole summer cabbage	618	M 3436	630		6/12 to 8/7	2 times normal size, very vasc.
	619	F 2610	490		"	Not enlarged, slightly hyperemic
	620	F 3103	521		"	" " " "
	621	F 2631	490		"	" " " "
	627	F 3050	568		"	2 times normal size, very vasc.
	628	F 2838	510		"	Slightly enlarged, mod. vasc.
	629	F 2086	388		"	" " " "
	630	F 3081	574		"	" " " "
	631	F 2685	500		"	Normal size, not vasc.
	632	F 2804	522		"	" " " "
	633	F 2238	419		"	Slightly enlarged, slightly vasc.
	634	F 3039	565		"	" " " "
4						
Whole winter cabbage	653	F 2644	506		10/8 to 12/4	3 times normal size, very vasc.
	638	F 3339	621	1.40	"	4 " " " " "
	639	F 2911	543	1.02	"	3 " " " " "
	640	M 2765	515	1.50	"	3 " " " " "

5						
Whole winter cabbage	654	M 1636	305	0.46	11/20 to 12/18	2 times normal size, very vasc.
	661	F 2196	409		"	2 " " " " "
	655	M 1774	330	0.62	"	2 " " " " "
	656	M 1736	323		"	2 " " " " "
	657	M 1550	288		"	2 " " " " "
	658	F 2257	420		"	1½ " " " " "
	659	F 1594	297		"	2 " " " " "
	660	F 1945	362		"	2 " " " " "
			75 cal. per kg.		*1929*	
41						
Whole summer cabbage	723	M 1826	425		4/17 to 5/9	Normal size, slightly vasc.
	738	F 1030	242	0.14	"	Slightly enlarged, slightly vasc.
Holland winter cabbage	740	F 1110	260		"	3 times normal size, very vasc.
	657	M 1865	434		"	3 " " " " "
55						
Summer cabbage	773	M 1205	280		8/7 to 9/17	Normal size, slightly hyperemic
	775	M 910	212		"	" " " "
	789	F 1135	264		"	Slightly enlarged, mod. "
	790	F 975	227		"	Normal size, slightly "

whether domestic or imported Holland, procured in the fall and winter of 1928–29, was powerfully goitrogenic (producing palpable goiters in from 7 to 10 days), whereas the cabbage obtained during the fall and winter of 1929–30 was, at its best, only moderately goitrogenic, that is, the thyroids were not palpably enlarged after 21 days feeding.

TABLE IV

Seasonal Variation in Goitrogenic Activity of Cabbage, Autumn 1929

Cabbage lot No.	Source of cabbage	Experiment begun	No. rabbits used	Duration of exp. in days	Goitrogenic activity	No. cc. N/100 I absorbed by 10 gm. cabbage
		1929				
1	Onandaga Co., N. Y.	Sept. 12	8	19	Low	2.8
2	"	" 20	4	18	Very low	4.0
3	"	" 28	4	18	Moderately low	3.7
4	Westchester Co., N. Y.	Oct. 9	4	16	Low	2.4
5	Monroe Co., N. Y.	" 12	6	18	"	3.9
6	Genesee Co., N. Y.	" 19	6	18	Very low	3.5
7	Cortland Co., N. Y.	" 26	4	17	" "	3.9
8	Madison Co., N. Y.	" 31	4	19	Low	3.9
9	Genesee Co., N. Y.	Nov. 8	4	18	Moderate	3.0
10	Monroe Co., N. Y.	" 15	6	20	Moderately marked	2.7
11	"	" 22	6	15	" "	2.4
12	Dutchess Co., N. Y.	" 27	4	21	Moderate	3.0
13	Monroe Co., N. Y.	" 29	4	19	Moderately marked	2.8
15	"	Dec. 5	10	17	" "	2.5
16	"	" 12	4	18	" "	Red cabbage
17	"	" 12	4	18	" "	2.8
19	Niagara Co., N. Y.	" 19	4	22	" "	2.6
20	Monroe Co., N. Y.	" 20	4	18	" "	Red cabbage
		1930				
21	"	Jan. 4	6	18	" "	2.9

In view of the demonstration of an apparently antigoitrogenic substance in plants that is roughly measurable by iodometric titration (6), we made from 6 to 11 iodometric titrations on each batch of cabbage received and the averages of these titrations are given in Table IV. In general they show what had been previously demon-

strated—that the higher the iodine absorbing power the lower the goiter-producing power, that is, that the goitrogenic index varies inversely with the iodine absorbing power. Red cabbage from the same source had approximately the same ability to produce goiter as did the white variety. The possibility of climatic conditions influencing this seasonal variation in goitrogenic activity was considered. Accordingly, meteorological data were obtained from the United States Weather Bureaus at Syracuse and Rochester, New York. The normal mean temperature for October and November, 1929, was considerably higher than in 1928, as was the total number of hours of sunlight. On the other hand, the total precipitation was less in 1929 than in 1928. Continuous frosts occurred from October 10 in 1929, although the first killing frost was not until October 18. This was 10 days earlier than in 1928. Nothing was found in the climatic variations in the autumns of 1928 and 1929 that could be correlated with the great differences in goiter-producing power of the cabbage grown in these two years. It is hoped, however, that by collecting data in this standard way for at least 5 years some correlation will be possible.

In the autumn of 1928, it was found that cabbage imported from Holland, where the growing season is essentially long and slow, was high in goitrogenic activity. The same variety from approximately the same region was found to be only moderately active in 1929.

Although it has been apparent from the beginning that the variations in the goiter-producing power of cabbage were far beyond the range of anything which could depend on the iodine content, nevertheless determinations of the iodine content of samples of New York State and South Carolina cabbage were made.* The dried whole New York cabbage was found to contain 98 parts of iodine per billion. On this basis the fresh leaves would contain approximately 10 parts per billion. The iodine content of dried cabbage grown near Charleston, S. C., was 109 parts per billion. The goitrogenic activity of these two lots, with approximately the same iodine content, was found to differ widely. The Charleston sample had little or no goitrogenic activity, while the New York State sample, when tested under the same conditions, was moderately goitrogenic.

* We are indebted to Dr. Roe E. Remington of the South Carolina Food Research Laboratory, Charleston, for making the iodine determinations.

DISCUSSION

The seasonal variations in the goiter-producing power of cabbage, and also the variations from year to year, offer extensive fields for further investigation. The existence of such variations is indicated by the data contained in Table II, which were collected in the early period of the work at the Johns Hopkins Hospital. It is further confirmed by Marine, Baumann and Cipra's observation of a marked difference in goitrogenic power of cabbage from the same locality in 1929 as compared with 1928. The evidence at hand suggests that this seasonal variation is in part dependent upon the variable amounts of a goitrogenic factor and an antigoitrogenic factor. The existence of the latter substance seems to be established. Although in all probability climate rather than soil is the influence determining the amount and proportions of these two factors, it is not possible at present to correlate the meteorological data for the years 1927, 1928 and 1929 with the variations in goitrogenic activity of cabbage in the same time period. The nature of the annual variations is still unknown. The survey made in 1929 and summarized in Table IV marks the beginning of a systematic attempt to determine the extent and nature of these variations and it is our intention to continue these observations over a period of years. At the end of a sufficient time period, comparison of these results with meteorological and other data may throw some light on the factors responsible for the variations noted.

SUMMARY

The evidence presented indicates that cabbage maturing in the spring and summer months has little goiter-producing power. Cabbage maturing in the late autumn has much greater goiter-producing power, although this shows considerable variation in different years. It has not been possible to correlate available meteorological data with these variations.

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