FURTHER OBSERVATIONS AND EXPERIMENTS ON GOITRE (SO CALLED THYROID CARCINOMA) IN BROOK TROUT (SALVELINUS FONTINALIS).

III. Its Prevention and Cure.*

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Plates 13 to 17.

Investigations (1) made at the trout hatchery of the Blooming Grove Hunting and Fishing Club during 1909 and 1910 showed that all the fish were then goitrous. It was found that the thyroid hyperplasia began in the fry as soon as feeding was instituted, and advanced overgrowth was present at the fourth month of extra-oval life; that the overgrowth progressively increased to the stage of clinical detectability, as ascertained by the reddening of the pharyngeal floor over the thyroid area, about the tenth month in this hatchery; that visible goitres usually manifested themselves about the beginning of the second year, though they may be present as early as the sixth month, depending on the favorableness of conditions for overgrowth, and progressively increased during the second and third years; that older fish were more resistant and tended toward spontaneous recovery; that the water in which these fish lived was not naturally goitre-producing, since fish living wild in the stream and raceways did not develop thyroid overgrowth.

It was further shown that overcrowding and overfeeding with the highly abnormal and incomplete diet of hog's liver and heart were the major gross etiological factors, and of these the food was the more important factor in bringing about a fault of nutrition which stimulated the thyroid to compensatory overgrowth. No evidence was obtained that the disease was either infectious or contagious, or that a direct *contagium vivum* could account for the phenomenon.

The above summary of the work of 1909 and 1910 will serve as an introduction to the observations included in this report, which were made during August, 1913, and deal with the effect of changing the food from liver to fresh sea fish.

Comparison of the General Conditions Prevailing in 1909, 1910, and 1913.—The water supply has remained unchanged as regards source and volume (text-figure 1). The Club is holding more trout in each pond than in 1909 and 1910, hence the untoward factor of

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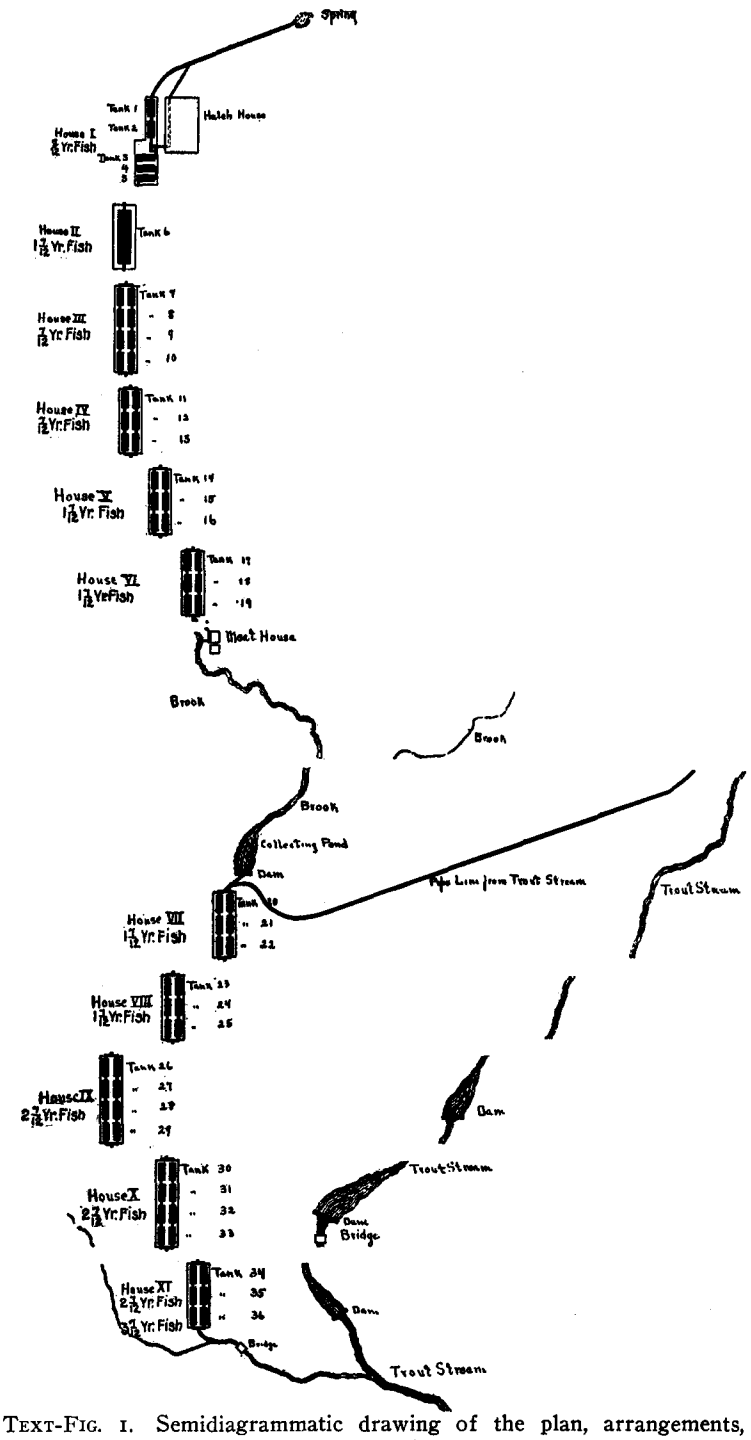

TEXT-FIG. 1. Semidiagrammatic drawing of the plan, arrangements, and location of the hatchery, water supplies, houses, and retaining tanks.

overcrowding is increased. The distribution of the fish is in general the same (text-figure 1),—the fry (hatch of 1913) in the upper, the nineteen months old trout in the middle, and the thirty-one months old trout in the lower ponds. The fry have always been scrupulously cared for by daily cleaning and sweeping the troughs and ponds. With the older fish (nineteen and thirty-one months) there is clearly less detritus in the ponds than in 1909 and 1910, although little additional attention has been paid to these ponds, the difference being due mainly to the change of food. Therefore, apart from the increased number of fish being held in the same pond space and the water supply, the only important change has been in the food.

The Food.—Beginning with October, 1911, fresh sea fish (butter fish (*Stromateus triacanthus*) and occasionally weak fish (*Cynoscion regalis*)) have been fed six times weekly to the older fish to the exclusion of all other foods. The fry are fed two to three times daily as in previous years, with finely divided hog's liver for the first four to five months of life, then heart muscle (hog) is added to this diet. This is continued until October (*i. e.,* nine months), when all the fry are removed to the ponds. At this time the change to fish diet is also made and maintained during the remainder of their stay in captivity.[1]

[1] It is as yet impossible to change to the fish diet earlier than the ninth month on account of the inability to hash the fish finely enough with the present machinery. This will soon be remedied, however, and then much of the thyroid overgrowth that now occurs during the period of liver feeding will be prevented. Several kinds of fish have been tried as food, among which are sea bass (*Centropristes striatus*), herring (*Clupea harengus*), weak fish (*Cynoscion regalis*), and whiting (*Merlangus americanus*). All have been found unsuitable either on account of bones or scales and have been abandoned. The fish scales being unaffected by digestion form rouleaux in the gut and produce intestinal obstruction followed by the usual sequelæ of enteritis, distention peritonitis, and death. I had the opportunity of examining two mild cases of partial intestinal obstruction, although for the past year only an occasional large scaled fish has been included in the food. In the two fish examined the obstruction was intermittent, as the scales were small (from weak fish) and could only obstruct when arranged transversely in the gut. There was well developed enteritis of the straight gut with extension through to the mesentery. Bones, if fine and rigid as in herring, are not broken up by the hasher and often perforate the stomach wall before the gastric acid can decalcify them. Fish with cartilagenous endoskeletons, such as skates, rays, sharks, etc., have not been tried owing to the difficulty as yet in

Comparison of the Gross Appearance of the Fish of 1913 with Those of 1909 and 1910.—Very striking differences are apparent. The nineteen months and the thirty-one months old fish are active and alert, while those of corresponding ages in 1909 and 1910 were sluggish and lumbersome. In handling large numbers of them in each of these three years, the 1913 fish are clearly stronger, show more fight, fatigue less easily, and do not die so quickly when removed from the water.

The fish are now more trout-shaped, that is, they have lost the pot-bellied appearance of 1909–1910. The skin pigments are brighter and better differentiated. It will be recalled from the descriptions of 1909–1910 that in all the fish the black pigment was excessively developed. The greenish grey marbling of the back was absent and the orange and pink color spots of the sides were wholly invisible. So also the orange and yellow colors of the fins and ventral surface were nearly absent. The silvery sheen of the sides was masked by the black pigment. In the fish of 1913 the colors approach closely those of the normal trout. The greenish marbling of the dorsum is detectable. The lateral color spots are well differentiated and the yellow and orange pigment of the ventral surface and fins are developed. The silvery sheen of the sides is perhaps better developed than in the average wild trout.[2]

As regards weight I have no exact data, although the impression is distinct that they are a trifle smaller on the average than in 1909 and 1910. The fry of 1913 are to all appearances the same as on previous examinations.

obtaining them in the markets. There seems no objection to their use since they would obviate the two great objections, scales and sharp perforating bones, and in addition might be less expensive than the usual market fish. Butter fish (*Stromateus triacanthus*) have been found least objectionable of the obtainable fish and are now used almost exclusively. They are received frozen and therefore in better condition than usually obtains with liver.

[2] These colors being readily adaptable to environment are modified by the color of the water, hence native trout from the brook are slightly darker than trout living in the spring water of the hatchery. It may also be recalled that in the experiments of 1910 the excessive black pigment diminished rapidly upon changing the food and removal of the fish from the ponds to troughs or to the trout stream. It would therefore appear that the food was a factor in the excess of the black pigment developed.

Of other diseases independent of goitre, as the myxosporidian infection (Taumelkrankheit, cramps), fungus, and enlarged gills (so called sore gills), there is a definite decrease.

Comparison of the Gross Thyroid Condition of 1909 and 1910 with That Obtaining in 1913.—These data are obtained from the clinical examination of the thyroid areas of a series of fish from the ponds for the presence of (*a*) reddening of the pharyngeal mucosa between the first and third gill segments as the first clinical evidence of thyroid overgrowth, and for (*b*) visible goitres projecting either dorsally in the floor of the mouth or in the gills, or ventrally in the angle of the attachment of the operculum as a late sign. The fry were not thus examined.

TABLE I.

	October 12, 1909.				June 27, 1910.				August 10, 1913.			
Pond No.	Age in yrs.	No. of fish examined.	Reddening of pharyngeal mucosa.	No. with goitre.	Age in yrs.	No. of fish examined.	Reddening of pharyngeal mucosa.	No. with goitre.	Age in yrs.	No. of fish examined.	Yellowish discoloration of pharynx.	No. with goitre.
6					1.5	41	10	0	1.7	25	1? trace	0
14					1.5	51	45	1	1.7	32	2? trace	0
19	1.8	210	197	7	1.5	60	51	2	1.7	22	2 trace	0
20	1.8	210	175	3	1.5	54	40	0	1.7	30	0	0
21									1.7	25	0	0
25	1.8	67	61	2	1.5	48	41	1	1.7	24	1 trace	0
26									2.7	22	3 trace	0
32	2.8	60	58	2	2.5	50	38	1	2.7	29	3 trace	0
35					2.5	40	28	2	2.7	32	4 trace	0
36	1.8	210	183	4					3.7	16	3	0
Totals		757	89%	0.23%		344	74%	0.17%		257	0.07%	0.0%

From the above tabulation it is seen that in 1909 89 per cent. of the fish had distinct reddening of the pharyngeal floor, and 0.23 per cent. had visible goitres. In 1910 a similar examination of fish from the same ponds and of nearly the same ages showed distinct reddening of the pharyngeal floor in 74 per cent. and visible goitres in 0.17 per cent. In 1913 a third examination of the fish from the same ponds and of approximately the same ages as those of 1909 and 1910 showed only a slight yellowish discoloration of the pharyngeal floor[3] in 0.07 per cent., and visible goitres in none.

[3] The reddening of the pharyngeal floor is due to the vascular thyroid tissue growing up to the pharyngeal mucosa. The yellow discoloration of the same region is due to the thyroid follicles rich in colloid and decreased vascularity, *i. e.*, recovery or colloid stage of a preceding hyperplasia.

These percentages illustrate the average condition of all the fish at the time of the examinations and are controlled by the histological examination of specimens removed at the same time from all the ponds during each of these years. The differences in the gross condition of the thyroids for the years 1909 and 1910 are unimportant but illustrate the severity and extent of the disease. The differences in the thyroid conditions of 1909–1910 and of 1913 were beyond what I had expected and demonstrate clearly that the disease in the 1913 fish had been completely arrested. There were none with reddening of the floor of the pharynx nor with goitre, hence none with any active overgrowth of the thyroid. The few instances where slight yellowish discoloration was present is indicative of colloid-filled follicles beneath the mucosa. How can this most striking difference in the thyroid condition be accounted for? The only noteworthy determinable factor of difference between the conditions prevailing in 1909 and 1910 and those of 1913 is the food,—sea fish in 1913 and liver in 1909 and 1910. That the change of food accounts for the differences in the thyroid condition will become more apparent from the following observations and comparisons of the histological conditions of the thyroids of the entire pond series for the three years.

Observations on the Histological Condition of the Thyroids from Specimens from All Ponds.—(Figures 1, 2, and 3, and table II.) For comparison I have tabulated the anatomical state of the thyroids in 1909 and 1910 with that of 1913. In this table all the fish are included: (1) the fry, (2) the one to two years old, and (3) the two to three years old fish.

In the case of the fry for 1909–1913, all conditions, including food, water, crowding, cleaning, and general hygienic conditions are as nearly identical as it is possible to keep them. This is most fortunate in that it makes comparisons of the thyroid conditions for each year possible under constant conditions. It also gives a broad foundation for estimating the average thyroid hyperplasia present in the fry and is therefore valuable for checking any changes found in the older fish. With the one to two years old trout and the two to three years old trout of 1913 all conditions except the food are similar to those of 1909 and 1910. The one to two years old trout of 1913 have been fed sea fish for the past ten months. The two to three years old trout have been fed sea fish for twenty-two months, while the one to two years and two to three years old trout of 1909 and 1910 had been fed with liver only.

All the fry of 1909, 1910, and 1913 exhibited the same general thyroid condition of active hyperplasia (figures 4, 5, and 6). The thyroid area is completely filled with thyroid tissue and extension to the adjacent bone and muscle is present

in all. The differences in the different years are only of slight degree and are probably dependent on the slight age differences at the time of examination: 1909, 8 to 9 months old; 1910, 6 months old; 1913, 7 months old. The individual variations within a given year are also slight and in general the same for all years. The examinations in each year comprised two specimens taken without choice from the twenty-one troughs in the hatch house and thirteen pairs of ponds of the pond series for the fry and also two specimens for each pond of the remaining twenty-three pairs for the older fish. From the examination of the fry in 1910, which, in addition to the above, included a series taken at weekly intervals from the time of hatching (January 15) to October, it was shown that the thyroid overgrowth began as soon as the fish began feeding and was easily detectable at the fourth month of extra-oval life, whence it progressively increased through the following months of the first and second years, rarely becoming clinically detectable before the tenth month at this hatchery. In some hatcheries the overgrowth has been clinically detectable at the sixth to the seventh month, depending on more favorable conditions for thyroid overgrowth. The fry of 1911 and 1912 were not examined, but these same fish were included in the 1913 examination as thirty-one months and nineteen months old fish, respectively, and from this examination there is complete evidence that their thyroids had undergone changes identical with those in the years 1909, 1910, and 1913. Passing now to the nineteen months old fish, one finds a most striking change also noted in the gross examination of the thyroid area. All the follicles are in the colloid state, although their distribution extends into the bone and muscle and often up to the pharyngeal mucosa. The fish from the same ponds and of approximately the same age in 1909 and 1910 all had well marked active hyperplasia (figures 7 and 8) greater in amount and more widely distributed in muscle, bone, gills, and pharyngeal mucosa than those of 1913.The growth in nineteen months old fish of 1913 (compare figures 9 and 10 with figures 11 and 12) was found to be completely arrested, and the hyperplasia had completely involuted, while in the fish of 1909 and 1910 of the same age the growth was extending rapidly. As the arrest of the growth corresponds in time with the change in food, and as no other factor of difference is present, one is forced to the conclusion that the food is the major cause of the change. While the fish have grown rapidly during the ten months since the feeding of fish began, their thyroid tissue is no greater in amount nor more extensive in distribution than that reached during the first ten months of life. So also with the thirty-one months old fish which have been fed fish for twenty-two months the thyroids are completely involuted to the colloid state and the amount and distribution of the follicles are the same as those of the nineteen months old fish, and hence no greater than that attained during the first ten months of life, although the fish have made their normal annual growth. One sees, therefore, fish nineteen months and thirty-one months old with thyroids identical in all particulars and no greater in amount nor more extensive in distribution than those of liver-fed fry of ten months in this hatchery. That the growth was arrested and involution started at the time of the change from liver to sea fish cannot be doubted, although for the sake of completeness it will be necessary to make a series of weekly examinations beginning before and continuing for some months after the change of food to fresh sea fish. This is now being done. Additional proof that change

TABLE II.

Pond or trough No.	1909. Age of fish in months.	1909. Condition of thyroid. Extent of overgrowth.	1909. Condition of thyroid. Classification.	1910. Age of fish in months.	1910. Condition of thyroid. Extent of overgrowth.	1910. Condition of thyroid. Classification.	1913. Age of fish in months.	1913. Condition of thyroid. Extent of overgrowth.	1913. Condition of thyroid. Classification.
Trough 1	8	All subpharyngeal structures,—bone and muscle	Marked hyperplasia	6	Entire aortic area; no invasion of bone or muscle	Moderate hyperplasia	7	Entire aortic area; invasion of bone and muscle	Marked hyperplasia.
Trough 5	8	All subpharyngeal structures,—bone and muscle	Marked hyperplasia	6	Entire aortic area: no invasion of bone or muscle	Moderate hyperplasia	7	All subpharyngeal structures in bone and muscle	Marked hyperplasia.
Trough 10	8	Entire aortic area including bone and muscle	Marked hyperplasia	6	Entire aortic area; invasion of bone and muscle	Marked hyperplasia	7	All subpharyngeal structures in bone and muscle	Marked hyperplasia.
Trough 15	8	Entire aortic area including bone and muscle	Marked hyperplasia	6	Entire aortic area; invasion of bone and muscle	Marked hyperplasia	7	Entire aortic area	Moderate hyperplasia.
Trough 20	8	Entire aortic area including bone and muscle	Marked hyperplasia	6	Entire aortic area; invasion of bone and muscle	Marked hyperplasia	7	Entire aortic area	Marked hyperplasia.
Normal above all ponds	20	Scattered follicles about aorta, filled with colloid	Normal	18	Scattered large follicles in aortic area, filled with colloid	Normal	19	Scattered large follicles in aortic area filled with colloid	Normal.
Pond 1	8	Entire thyroid area packed with follicles, in bone and muscle	Marked hyperplasia	6	Entire aortic area filled; invasion of bone and muscle	Marked hyperplasia	7	Entire aortic area filled; invasion of bone	Moderate hyperplasia.
Pond 2	8	Entire thyroid area packed with follicles, in bone and muscle	Marked hyperplasia	6	Thyroid area filled	Moderate hyperplasia	7	Entire aortic area filled; invasion of bone	Moderate hyperplasia.
Pond 3	8	Entire thyroid area filled	Moderate hyperplasia	6	Thyroid area filled; invasion of bone	Moderate hyperplasia	7	Entire aortic area filled; invasion of bone	Marked hyperplasia.
Pond 4	8	Entire thyroid area filled	Moderate hyperplasia	6	Thyroid area filled; invasion of bone	Moderate hyperplasia	7	Entire aortic area filled; invasion of bone	Moderate hyperplasia.
Pond 5a	8	Entire thyroid area filled	Moderate hyperplasia	6	Thyroid area filled; invasion of bone	Moderate hyperplasia	7	Entire aortic area filled; invasion of bone	Moderate hyperplasia.

TABLE II.—*Continued.*

Pond or trough No.	1909.			1910.			1913.		
	Age of fish in months.	Condition of thyroid.		Age of fish in months.	Condition of thyroid.		Age of fish in months.	Condition of thyroid.	
		Extent of overgrowth.	Classification.		Extent of overgrowth.	Classification.		Extent of overgrowth.	Classification.
Pond 5b	8	Entire thyroid area filled	Moderate hyperplasia	6	Thyroid area filled; invasion of bone	Moderate hyperplasia	7	Entire aortic area filled; invasion of bone	Moderate hyperplasia.
Pond 6	8	Entire thyroid area filled	Moderate hyperplasia	18	Entire thyroid area filled, in bone and muscle; infoldings; no colloid	Marked hyperplasia	19	Numerous small and large colloid-filled follicles in entire thyroid area	Colloid goitre.
Pond 7	8	Entire thyroid area filled, in bone and muscle	Marked hyperplasia	6	Entire thyroid area filled, in bone	Moderate hyperplasia	7	Aortic area filled; extension to bone	Moderate hyperplasia.
Pond 8	8	Entire thyroid area filled, in bone and muscle	Marked hyperplasia	6	Entire aortic area filled, in bone and muscle	Marked hyperplasia	7	Aortic area filled; extension to submucosa	Marked hyperplasia.
Pond 9	8	Entire thyroid area filled, in bone and muscle	Marked hyperplasia	6	Entire aortic area filled, in bone and muscle	Marked hyperplasia	7	Aortic area filled; extension to submucosa	Marked hyperplasia.
Pond 10	8	Entire thyroid area filled, in bone and muscle	Marked hyperplasia	6	Entire aortic area filled, in bone and muscle	Marked hyperplasia	7	Aortic area filled; extension to submucosa	Marked hyperplasia.
Pond 11	8	Entire thyroid area filled, in bone and muscle	Marked hyperplasia	6	Entire aortic area filled, in bone and muscle	Marked hyperplasia	7	Aortic area filled; extension to submucosa	Marked hyperplasia.
Pond 12	8	Entire thyroid area filled, in bone and muscle	Marked hyperplasia	6	Entire aortic area filled, in bone and muscle	Marked hyperplasia	7	Aortic area filled; extension to submucosa	Marked hyperplasia.
Pond 13	8	Entire thyroid area filled, in bone and muscle	Marked hyperplasia	6	Entire aortic area filled, in bone and muscle	Marked hyperplasia	7	Aortic area filled; extension to submucosa	Marked hyperplasia.
Pond 14	20	Entire subpharyngeal space filled, in bone and muscle	Marked hyperplasia	18	Entire subpharyngeal space filled, in bone and muscle	Marked hyperplasia	19	Numerous colloid-filled follicles in entire aortic area	Colloid goitre.
Pond 19	20	Entire subpharyngeal space filled, in bone and muscle	Marked hyperplasia	18	Entire subpharyngeal space filled, in bone and muscle	Marked hyperplasia	19	Numerous colloid-filled follicles in entire aortic area	Colloid goitre.

Pond or trough No.	1909.			1910.			1913.	
	Age of fish in months.	Condition of thyroid.		Age of fish in months.	Condition of thyroid.		Age of fish in months.	Condition of thyroid.	
		Extent of overgrowth.	Classification.		Extent of overgrowth.	Classification.		Extent of overgrowth.	Classification.
Pond 20	20	Entire subpharyngeal space filled, in bone and muscle	Colloid, moderate hyperplasia (hyperplasia involuting)	18	Entire subpharyngeal space filled, in bone and muscle	Marked hyperplasia	19	Numerous colloid-filled follicles in entire aortic area	Colloid goitre.
Pond 21	20	Entire subpharyngeal space filled, in bone and muscle	Colloid, moderate hyperplasia (hyperplasia involuting)	18	Entire subpharyngeal space filled, in bone and muscle	Marked hyperplasia	19	Numerous colloid-filled follicles in entire aortic area	Colloid goitre.
Pond 25	20	Entire subpharyngeal space filled, in bone and muscle	Colloid, moderate hyperplasia (hyperplasia involuting)	18	Entire subpharyngeal space filled, in bone and muscle; visible goitre	Marked hyperplasia	19	Numerous colloid-filled follicles in entire aortic area	Colloid goitre.
Pond 26	32	Entire subpharyngeal space filled, in bone and muscle	Marked hyperplasia, small visible goitre	30	Entire subpharyngeal space filled, in bone and muscle	Marked hyperplasia	31	Numerous colloid-filled follicles in entire aortic area; number of follicles same as in 19 mos. old fish	Colloid goitre.
Pond 32	32	Entire subpharyngeal space filled, in bone and muscle	Marked hyperplasia	30	Entire subpharyngeal space filled, in bone and muscle	Marked hyperplasia	31	Numerous colloid-filled follicles in entire aortic area; number of follicles same as in 19 mos. old fish	Colloid goitre.
Pond 35	32	Entire subpharyngeal space filled, in bone and muscle	Marked hyperplasia, slight general fibrosis	30	Entire subpharyngeal space filled, in bone and muscle; visible goitre	Marked hyperplasia	31	Numerous colloid-filled follicles in entire aortic area; number of follicles same as in 19 mos. old fish	Colloid goitre.
Pond 36	20	Entire subpharyngeal space filled, in bone and muscle	Marked hyperplasia	30	Entire thyroid area filled, extension to skin, bone and muscle	Marked hyperplasia	43	Entire subpharyngeal area filled with colloid follicles, in bone and muscle; number of follicles much greater than in the 19 or 31 mos. old fish	Colloid goitre.

of food is the cause of the arrest of thyroid growth is the preservation of 250 forty-three months old fish which had been fed liver for the first twenty-one months of life and sea fish for the last twenty-two months. In these I found three out of the sixteen examined having distinct yellowish discoloration of the pharyngeal floor, and in the two specimens examined histologically the thyroid was completely involuted to the colloid state; but the amount and distribution were far more extensive than in the thirty-one and nineteen months old fish, showing that the thyroid overgrowth had progressed much farther before the involution began, and corresponds to the extra year of liver as food.

It is well known that foods influence the mammalian thyroid to a marked degree. Baumann (2) noticed that flesh diets stimulate the thyroid in dogs to active hyperplasia. I have repeatedly made such observations, liver being the most important food in this regard. Reid Hunt (3) in his acetonitrile experiments noted that liver stimulates the thyroid of white mice. Watson (4) has described the effect of different diets on rat thyroids and also noted that meats produce hyperplasia, while mixed diets do not. I have made similar observations. Dogs spontaneously recover from goitre on a mixed diet, while meats, especially liver, maintain hyperplasias. In zoölogical gardens where carnivores are held and bred in captivity and the diet is for the most part beef, goitre, rickets, and osteomalacic states are quite common. Foods modify the thyroid slowly, involution extending over months, while iodin involutes hyperplasias much more rapidly. Iodin administered to dogs, sheep, pigs, and human beings often induces involution in a month, and in Lake Erie pike the involution of mild degrees of hyperplasia takes place in twenty-six days (5). In brook trout with extensive thyroid overgrowth and visible goitres involution occurs in forty days.

To summarize, it is seen that the ages of the fish held at the hatchery in August, 1913, are seven months, nineteen months, thirty-one months, and forty-three months. The seven months old fry all have active hyperplasia not different in degree or extent from the fry of 1909 and 1910. The nineteen, thirty-one, and forty-three months old fish all have completely involuted or colloid thyroids, and the amount and distribution of the thyroid tissue in the nineteen and thirty-one months old fish are the same and represent the degree of thyroid overgrowth reached during the first nine months of life when liver and heart only are fed. The forty-three months old fish had been fed with liver and heart for the first twenty-one months of life, and the thyroids both on gross and microscopical examinations were much larger and more widely distributed than in the nineteen and twenty-one months old fish.

DISCUSSION.

These data afford supplementary proof for several of the conclusions deduced from the earlier work, and in addition establish another simple and certain means for the cure and prevention of goitre in fish.

The view previously held by some observers that this disease was closely related to true carcinoma is now only of theoretical interest,

since, in addition to the facts already reported, it establishes the fact that the feeding of fresh sea fish also readily arrests the disease. No tissue overgrowth that presents the biological phenomena described for this disease, which are also identical with those of mammalian goitre, can be considered malignant. It was urged by some observers that the reaction with iodin could not be utilized as proof that the disease was not cancer since arsenic, mercuric chloride, and colloidal copper were reported to have the same thyroid effects (6). I have not been able to affect these changes with arsenic in canine goitre. I (7) have also failed to modify the growth of the mammalian thyroid carcinoma by the use of iodin, and from an extensive experience with human thyroid adenomata the conclusion was reached that they also are rarely affected by iodin (8). On the other hand, simple physiological hyperplasias of all animals are readily and invariably modified by iodin.

This disease should be classified as endemic goitre or endemic thyroid hyperplasia. One must recognize all degrees of the overgrowth in fish, just as in mammals, from the slightest departure from normal, detectable only microscopically, to the most extensive infiltration of the thyroid region and the formation of external goitres. Whether this form of goitre is similar to ordinary goitre in birds and mammals is not known. As mentioned above, they are identical anatomically, physiologically, and pathologically in all their known reactions, but inasmuch as goitre is only the symptomatic manifestation of a nutritional disturbance it is possible that many agents are capable of exciting the thyroid to this single and only known anatomical manifestation of increased activity, compensatory hypertrophy and hyperplasia.

From our knowledge of mammalian goitre it would seem probable that the thyroid reaction in infectious diseases, puberty, pregnancy, cretinism, Basedow's syndrome, etc., are not due to the same exciting cause. The fundamental fault in nutrition is probably the same in all, but the immediate exciting agent is probably different. In mammalian goitre the localization in certain districts is most obvious, while in fish and in birds this is not so apparent although it is present. Goitre, however, occurs wherever favorable conditions are created whether in mammals or in the lower animals. It is

therefore the increased susceptibility of mammals to goitre that brings out the localization of endemicity. Fish are very resistant to goitre and only acquire the disease when subjected to conditions incompatible with prolonged life in mammals.

The nearest approach to the etiology of goitre in fish was made when it was shown that food is the major etiological factor. Fish fed exclusively with liver always acquire thyroid hyperplasia, while fish of the same age, breed, and environment readily recover or escape goitre when fed with whole sea fish.

It is almost certainly a biochemical reaction, but whether it is due to the presence or absence of some substance normally needed by the organism is not known. A comparison of liver as a food with fish as a food seems to indicate that the liver lacked something normally needed by the developing fish which the diet of fish contained.

It is also probable that the liver contains some substances in excess, in attempting to utilize which, the animal exhausts other elements necessary for nutrition which are not present in the liver in sufficient amounts. As to the nature of this chemical fault one cannot reasonably speculate. From time to time most of the inorganic and many of the organic substances have been specified as etiological factors, but without foundation. Some observers have called it a toxin, but work based upon this hypothesis has added nothing to our knowledge of the etiology.

Iodin is certainly reduced in fish with thyroid hyperplasia, as in all other animals, and iodin certainly prevents and involutes hyperplasia, but the conclusion that goitre is due to a deficiency of iodin is not justified since there is considerable evidence to show that some other factor or factors are operating to divert or deplete an otherwise sufficient amount of iodin. On the other hand, the beneficial effects of feeding fish may be due to the iodothyreoglobulin that it contains, since only exceedingly small amounts are necessary, and the whole fish including the thyroid gland is used. Sea fish may also contain traces of iodin apart from the thyroid. Therefore much careful work must still be done to exclude iodin as the cause of the beneficial effects. I have made two iodin determinations on

mixed specimens of whole butter fish, and two determinations on mixed specimens of fish from which the thyroid areas had been removed. The results are as follows: (1) whole fish, slightest trace; (2) exclusive of thyroid area, no trace of iodin.

The possibility of a *contagium vivum* in fish goitre can, it seems to me, be eliminated since there is not the slightest evidence that it is either contagious or infectious. It obeys none of the laws which we associate with true infectious processes. No evidence of natural or acquired immunity has been obtained, though different species of fish exhibit different degrees of resistance (carp, trout).

Gaylord (9) has reported the finding of evidences of immunity, but this evidence does not exclude the following important factors: (1) Age is an important factor in all animals; the young are more susceptible to goitre and the old tend toward spontaneous recovery. (2) When the active hyperplasia involutes to the colloid state it is more difficult to produce again active hyperplasia (*a*) because of the increased age of the animal, and (*b*) because of the increased factor of safety due to the increased number of thyroid follicles over what obtains normally. For example, if a dog has fifty grams of colloid thyroid it is more difficult, apart from any age factor, to induce active hyperplasia in it than if the dog has three grams of normal thyroid; but other things being constant, three grams of colloid will undergo hyperplasia as readily as three grams of normal thyroid. (3) The food is probably the most important factor in determining the onset or cessation, progression or regression of the hyperplasia. (4) Water supply has some influence on the resistance of fish to active hyperplasia, reduced and much used water favoring, and large amounts lessening it. (5) The different Salmonidæ vary greatly in their susceptibility. I have seen none that were not susceptible, but the brown trout and rainbow trout in my experience have been more resistant than the silver salmon or brook trout.

The water supplied to this hatchery has little if anything to do with the development of goitre, since the fish have never developed the disease unless the single factor of overfeeding with the highly abnormal diet of liver and heart is also operating. The following observations bearing on the relation of water to the etiology and spread of goitre may be mentioned: (1) Within the hatch house are

twenty-one troughs,—twelve hatch troughs and nine nursing troughs. The twelve hatch troughs receive water directly from the spring, while the nine nursing troughs receive the water from the twelve hatch troughs. Every summer these troughs are used to hold extra fry. They are kept remarkably clean, yet all the fry have shown equally marked thyroid overgrowth in each of the years that they have been examined. Fish living outside the troughs and ponds (hence not directly fed with liver), whether above, below, or between the troughs and ponds, never develop active hyperplasia, although in most instances they have some degree of colloid goitre, showing that they had once been confined in the troughs or ponds and that, after escaping, the hyperplasia involutes. (2) The 1913 distribution of the fish made another observation possible. In house II (text-figure 1) there are 3,000 nineteen months old fish which have been fed with fish for the past ten months; all these fish have colloid glands. While above in house I and below in house III there are seven months old fry which have been fed only with liver and heart muscle and all have well marked active thyroid hyperplasia. There is also some evidence that liver when fed in excessive amounts is a more potent stimulus than when fed in small amounts, as the fish living in the runways between the houses also obtain small particles of liver which float through the screens but do not develop active hyperplasia. Plehn (9) has reported greater variations in the occurrence and distribution of the disease in a fish hatchery than they could account for purely on the basis of external changes. They suggest that these variations point to infection. I have also seen wide variations in its occurrence in different hatcheries and even in the same hatchery, but feel that all the variations could be accounted for on the basis of one or more of the following factors: (1) food, (2) water supply, (3) age, and (4) species of fish. Some observers have applied the term epidemic goitre to this form of goitre in fish. This is wrong. There is nothing acute or localized in its occurrence or distribution. It appears wherever fish are overfed with liver or other incomplete foods. It extends over the entire time of such feeding and all fish are affected.

Goitre has been present in this hatchery for the past twenty-five

years and, in my opinion, it will remain as long as fish of any age are fed with liver.

Treatment and Prevention.—Trout living in their normal environment and partaking of their normal food do not develop goitre, hence in the treatment and prevention our efforts should be directed toward imitating natural conditions as far as possible. However, as with many other animals it has been found possible to alter these natural environmental conditions within extremely wide limits without seriously impairing their health. Goitre is one of the serious diseases that has developed in testing the range of adaptability. The infectious diseases of fish, as of mammals, are better known and methods for the cure and prevention have been studied longer. Goitre belongs to the group of diseases dependent upon nutritional disturbances, and our knowledge of the food requirements of animals generally and of fish in particular is as yet in its infancy.

It has been conclusively shown that the feeding of the highly artificial and incomplete diet of liver and heart muscle is the major factor in the causation of fish goitre, and the first essential in treatment is to provide some other food that meets the animal's requirements. A natural food of trout is fish and the experiments of the past two years show that when sea fish is fed to these trout existing goitre is cured and the development of goitre is wholly prevented.

The feeding of fish with hard fine bones or with large heavy scales is associated with risks mentioned above. The fish stomach is adapted for the ingestion of relatively large food boli, and food should be fed in as large masses as they will take since digestion is a continuous process in fish. This would probably solve the bone question and would tend to control overfeeding. Some sort of chopper should be devised instead of hashers, since hashers mince the food and allow of too rapid digestion and, therefore, too long intervals of stomach inactivity. Coarse fish, like sharks, rays, etc., might be utilized. Sea fish, therefore, makes a perfect food as far as the cure and prevention of goitre are concerned. Overfeeding must be guarded against. Definite amounts of food should be fed but once a day with a fast day each week comparable to the fast day maintained among the carnivores at Zoölogical Gardens. No obser-

vations have been made as to the minimum amounts of sea fish necessary to involute or prevent hyperplasia, but judging from the rapidity of the involution when the food is changed to fish only, it would appear that the daily feeding with fish was not necessary to cure or prevent the hyperplasia. It might be beneficial to alternate between fish and liver or between fish and other foods daily or weekly. Overcrowding is dependent on the water supply and the food. It is a highly important factor as regards the general health of the fish, the prevention of traumata and infectious diseases, the oxygen supply, etc., but is only a minor factor in the production of goitre.

Cleanliness likewise is a secondary factor in goitre, but is of great importance in the prevention of other diseases and as a general hygienic measure cannot be neglected. Modification of pond construction with this in view would greatly simplify the cleaning and sanitary problems. Iodin in minute traces has also been found to prevent and cure goitre. Indeed it is a specific therapy for goitre but does not relieve other untoward manifestations of an incomplete food. Gaylord (6) has reported that arsenic and mercuric chloride also effect similar changes in fish thyroid hyperplasia. Our observations with arsenic in canine goitre were negative and in any event the action of arsenic and mercuric chloride is not comparable to the action of iodin on the thyroid.

CONCLUSIONS.

1. Goitre in fish is a non-infectious, non-contagious, symptomatic manifestation of a fault of nutrition, the exact biochemical nature of which has not been determined.

2. Feeding the highly artificial and incomplete diet of liver is the major etiological factor in bringing about this fault of nutrition which is at once corrected by feeding whole sea fish.

3. Water plays no essential part in the etiology, transmission, or distribution of the disease in the fish of this hatchery.

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EXPLANATION OF PLATES.

Plate 13.

Fig. 1. Rough projection sketch of a transverse section through the thyroid area of a brook trout with a normal thyroid.

Fig. 2. Rough projection sketch of a transverse section through the thyroid area of a brook trout with a mild degree of active hyperplasia.

Fig. 3. Rough projection sketch of a transverse section through the thyroid area of a brook trout with a mild degree of colloid (goitre) gland.

Plate 14.

Fig. 4. Transverse section of the thyroid area of a five months old brook trout showing the extent of the thyroid overgrowth at this age in fry of the hatch of 1910.

Fig. 5. Higher magnification of figure 4, showing the filling up of the thyroid area, the extension to the cuticle, to the pharyngeal mucosa, and on the right the extension to the gill filaments. Note the relation of the follicles to the two terminal branches of the ventral aorta, the size of the follicles, the high columnar epithelium with infoldings and plications, and the absence of stainable colloid.

PLATE 15.

FIG. 6. Transverse section of the thyroid area of a seven months old brook trout of the hatch of 1913 showing the pharyngeal mucosa above and gill filaments laterally. Note the distribution of the hyperplastic follicles about the ventral aorta and their irregular distribution throughout the thyroid area.

FIG. 7. Transverse section of the thyroid area of a seventeen months old brook trout, showing the whole thyroid area uniformly filled with hyperplastic thyroid follicles.

PLATE 16.

FIG. 8. Higher magnification of an area from figure 7, showing the infoldings and plications, vascularity, high columnar epithelium, absence of stainable colloid, and the great distortions and variations in the size of rapidly growing thyroid follicles.

FIG. 9. Transverse section of the thyroid area of a nineteen months old brook trout which during the first nine months of life had active hyperplasia, and upon the introduction of fish as the food all the follicles involuted back to the colloid state. Note the distribution and numbers of follicles as those attained during the stage of active hyperplasia, while the individual follicles now resemble in all essentials normal follicles. Note also the extension into bone and muscle. This is the colloid, or resting, or cured stage of a mild degree of active hyperplasia.

PLATE 17.

FIG. 10. Higher magnification of a portion of figure 9, showing part of the ventral aorta and the large venous space to the left. Compare the numbers and distribution of the follicles, their colloid contents, and their epithelial investments with those of figure 12.

FIG. 11. Transverse section through the thyroid area of a nineteen months old brook trout, showing the pharyngeal mucosa above, gill filaments laterally, and scattered thyroid follicles of different sizes widely distributed about the ventral aorta. Normal thyroid.

FIG. 12. Higher magnification of an area from figure 11, showing the size and arrangements of the follicles together with the colloid contents and epithelial investments.

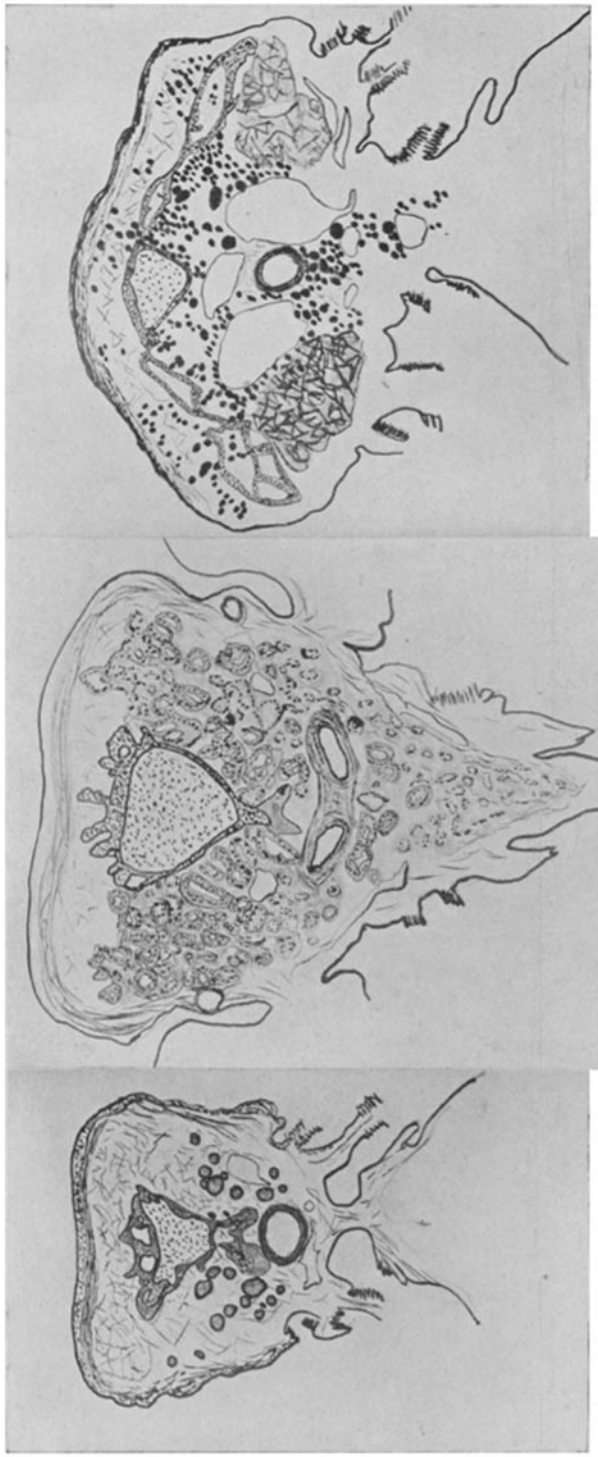

FIG. 3.
(Marine: Goitre in Brook Trout.)

FIG. 2.

FIG. 1.

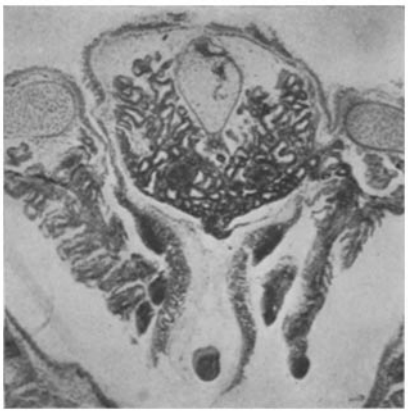

FIG. 4.

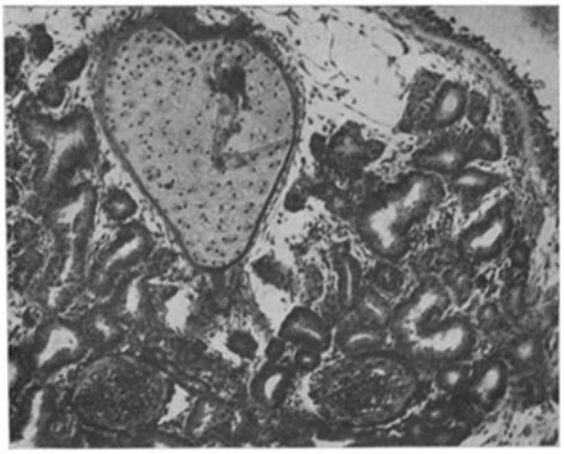

FIG. 5.

(Marine: Goitre in Brook Trout.)

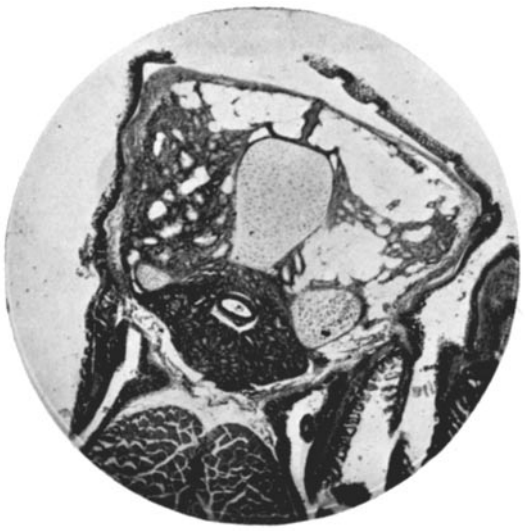

FIG. 6.

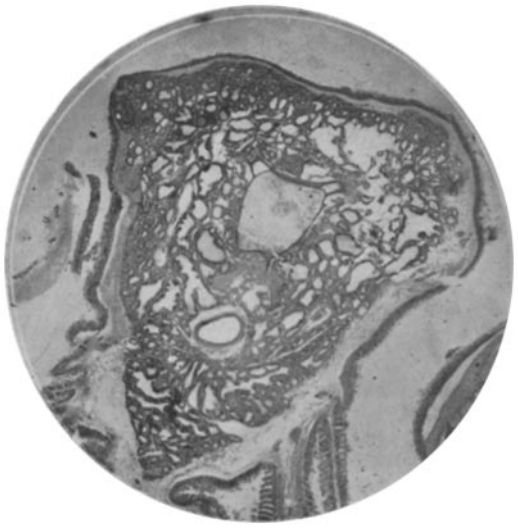

FIG. 7.

(Marine: Goitre in Brook Trout.)

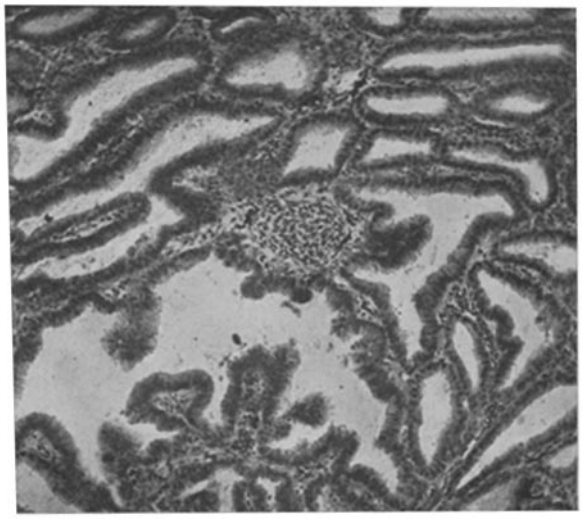

FIG. 8.

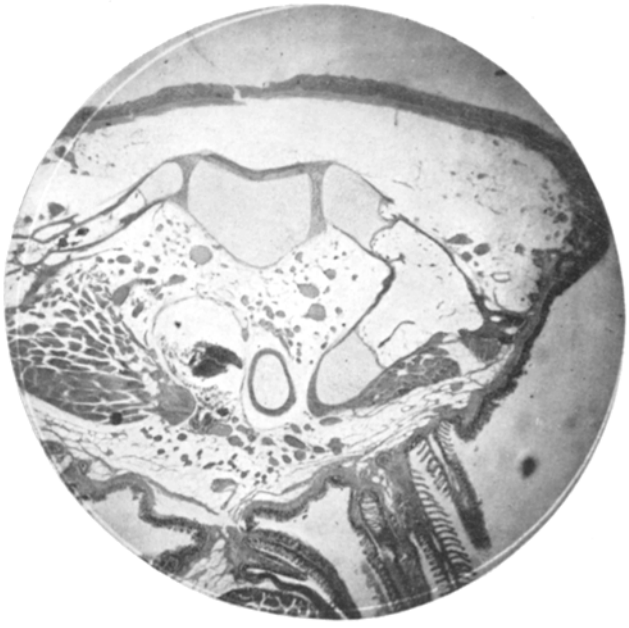

FIG. 9.

(Marine: Goitre in Brook Trout.

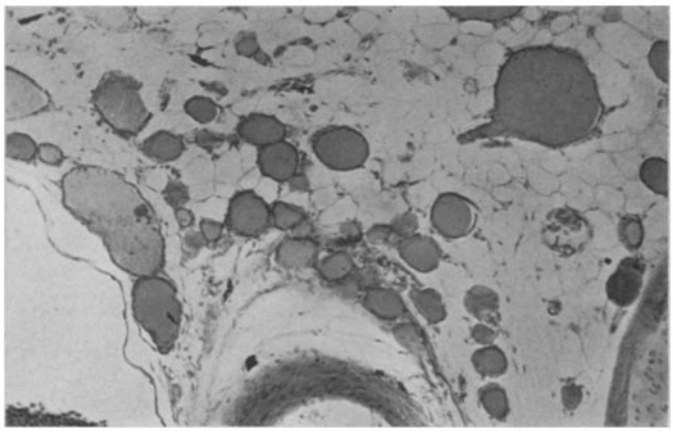

FIG. 10.

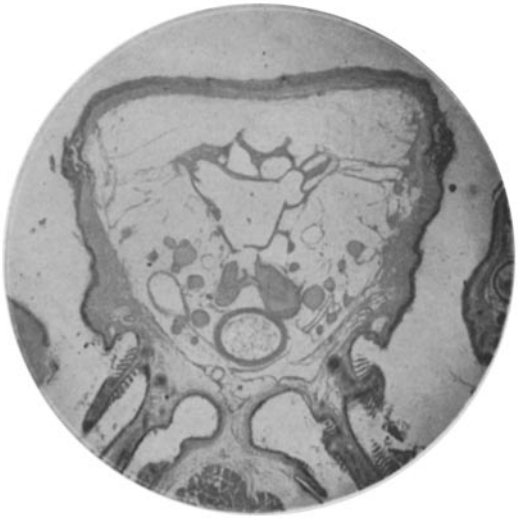

FIG. 11.

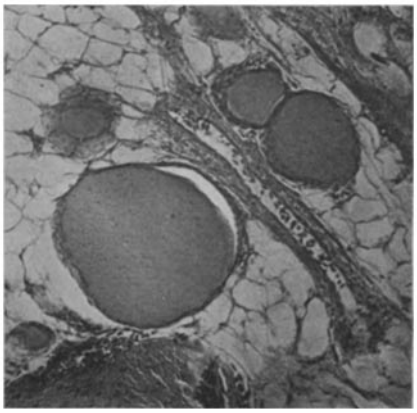

FIG. 12.

(Marine: Goitre in Brook Trout.)