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STUDIES ON IODINE METABOLISM IN CHRONIC THYROIDITIS

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In 1912, HASHIMOTO described four patients with a chronic disorder of the thyroid, which he termed struma lymphomatosa. The thyroid glands of these patients were characterized by diffuse lymphocytic infiltration, fibrosis, parenchymal atrophy, and an eosinophilic change in some of the acinar cells. This disease has been called as "Hashimoto's disease", "chronic thyroditis", "lymphocytic thyroiditis", and recently "autoimmune thyroiditis". The disease was thought to be uncommon for many years, and the diagnosis was usually made by the surgeon at the time of operation or by the pathologist after thyroidectomy. However, the increasing use of the needle biopsy has led to its more frequent recognition. Patients with chronic thyroiditis have various symptoms and signs. Most patients are in a euthyroid state, and few are hyperthyroid or hypothyroid.

The present report describes studies on iodine metabolism in animals with experimentally induced allergic thyroiditis and in patients with chronic thyroiditis. The mechanism of development of chronic thyroiditis will also be discussed.

Iodine metabolism in experimental allergic thyroiditis

The relationship between the pattern of incorporation of ^{125}I in the thyroid and serum and the pathological changes in the gland was studied in guinea pigs with experimental thyroiditis 3–6 weeks after a single immunizing dose of homologous thyroid extract in Freund's adjuvant. At 3–4 weeks, reduced thyroid ^{125}I uptake and low or normal serum ^{125}I-iodothyronine level were found. The pathological changes at this time were intense mononuclear infiltration with acinar invasion and disruption and focal hyperplasia, while the residual uninvolved acini appeared inactive. At 5–6 weeks after immunization, thyroid ^{125}I uptake and serum ^{125}I-iodothyronine level were elevated. The pathological appearance continued to

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be one of extensive inflammatory infiltration, but all acini showed hyperplasia. These findings indicate a good correlation between metabolic activity and pathological findings. In particular, metabolic hyperactivity and generalized hyperplasia were associated with each other. The iodine metabolism in TSH–treated guinea pigs was studied, and increased serum ^{125}I-iodothyronine level and increased thyroid ^{125}I uptake were observed.

These findings suggest that hypofunction of the thyroid in the early stage of thyroiditis stimulated TSH secretion, which later led to generalized hyperplasia.

Iodine metabolism in patients with chronic thyroiditis

A study was next made of the relationship among the histological findings of thyroid tissue, the immunopathological finding and the iodine metabolism in 161 patients with chronic thyroiditis, in whom open biopsies or needle biopsies were performed.

On a morphologic basis, chronic thyroiditis was divided into diffuse thyroiditis and focal thyroiditis according to Woolner's classification. The fully developed or advanced stage of the disease was characterized by change in follicular epithelium accompanied by a marked interfollicular infiltrate of plasma cells and lymphocytes. When these changes were apparently complete in all areas sampled, the disease was referred to as diffuse thyroiditis. On the other hand, the term focal thyroiditis was used to refer to a similar change that was spotty or focal, with larger or smaller islands of parenchyma composed of the characteristic infiltrate.

Diffuse thyroiditis was present in 53 cases, and was seen frequently in the 5th decade, while focal thyroiditis was present in 108 cases, and was most often seen in the 3rd and 5th decades.

Diffuse thyroiditis was subdivided histologically into 5 types: hyperplastic epithelial type, varied epithelial change type, oxyphilic epithelial type, lymphoid type and pronounced epithelial destruction type, according to Woolner's classification. The hyperplastic epithelial type was seen most frequently in the younger age group. The pronounced epithelial destruction type was seen most frequently in the older age group, and this type was the most severe type of chronic thyroiditis. Focal thyroiditis was subdivided histologically into 8 types: Types I-VI, and hyperplastic Types I and II. Type I was the mildest form of chronic thyroiditis, and Type VI was the most severe type of focal thyroiditis. In hyperplastic Type I, hyperplastic epithelium of thyroid follicles surrounded the lymph follicles, and both hyperplastic Types I and II were seen frequently in the younger age group.

Table 1 shows the incidence of thyroid autoantibodies in the sera of patients with chronic thyroiditis as determined by various immunological techniques. Circulating antithyroglobulin was demonstrated by the tanned red cell hemagglu-

Table 1. *Incidence of Thyroid Autoantibodies in Patients with Chronic Thyroiditis*

	Diffuse Thyroiditis	Focal Thyroiditis	Total
Precipitating Antibody (PT)	13/47 27.7%	1/102 0.9%	12/149 9.4%
Tanned Red Cell Hemagglutinating Antibody (TRC)	32/47 68.1	62/103 60.2	94/150 62.7
Antibody to Second Colloid Antigen (CA_2)	45/45 100.0	99/ 99 100.0	144/144 100.0
Complement Fixing Antibody (CF)	30/46 65.2	44/101 43.6	74/148 50.0
Cytotoxic Factor	18/35 51.4	44/ 73 54.8	58/108 53.7
Cytoplasmic (Immuno-fluorescent) Antibody	45/45 100.0	99/ 99 100.0	144/144 100.0
Antinuclear Antibody (ANF)	2/15 13.3	9/ 40 22.5	11/ 55 20.0
Prausnitz-Küstner Reaction (PKR)	15/31 48.4	29/ 62 46.8	44/ 93 47.3
Passive Cutaneous Anaphylaxis (PCA)	16/31 51.6	28/ 63 44.4	44/ 94 46.8

tination test. In higher titers, these antibodies may be shown by agar gel precipitation. Antithyroglobulin was also demonstrated by skin tests; i.e., passive cutaneous anaphylaxis (PCA) and Prausnitz-Küstner reaction (PKR). Antibody to a second colloid antigen was demonstrated by the immunofluorescence technique. Serum antibody to a cytoplasmic component of thyroid epithelial cells was demonstrated by complement fixation test and immunofluorescence technique. A cytotoxic factor was demonstrated by DONIACH and ROITT, and this factor has now been identified with a microsomal complement-fixing antibody. Anti-nuclear factor was demonstrated by immunofluorescence technique. The incidences and levels of thyroid antibodies in diffuse thyroiditis were higher than those in focal thyroiditis. Elevated gamma globulin levels were found in most cases, and these thyroid antibodies were indicated as IgG by immunoelectrophoresis.

In diffuse thyroiditis, thyroid ^{131}I uptake, basal metabolic rate and ^{131}I-T_3 resin uptake were higher in the hyperplastic type, and lower in the lymphoid type and the pronounced destruction type. The weight of the thyroid was lower in the varied epithelial change type, and higher in the lymphoid type and the pronounced destruction type. PBI values were higher in the hyperplastic type,

and lower in the lymphoid type and pronounced destruction type. Serum TSH levels were determined by Bakkes' method. These were lower in the hyperplastic type and the type with varied epithelial changes, and higher in the lymphoid type and pronounced epithelial destruction type. A negative correlation was noted between serum TSH levels and PBI values in diffuse thyroiditis.

In focal thyroiditis, in the majority of cases, thyroid ^{131}I uptake and ^{131}I-T_3 resin uptake were within normal range, but in some cases of Types I and III they were lower than normal. The thyroid weight in Type I was about 20 g, increasing to the size of a large goiter in Type VI. The PBI values in some cases of Types I and III were higher, and in some of Types V and VI lower than normal. The serum TSH levels were higher in Types III, V and VI, and lower in Types II and IV. In Types I, II and III, the PBI correlated roughly with serum TSH level, while in Types V and VI, there was a significant negative correlation between the PBI and the serum TSH level.

In cases of diffuse thyroiditis, the PBI alteration pattern after TSH administration showed a normal response in the hyperplastic type and the type with varied epithelial changes, a delayed response in the type with oxyphilic epithelial changes and in the lymphoid type, and no response in the type with pronounced epithelial destruction. In cases of focal thyroiditis, the response was normal in Types I-V, and delayed in Type VI. These results were apparently due to the greater reserve capacity of the gland in focal thyroiditis than in diffuse thyroiditis.

From the above-mentioned results, in chronic thyroiditis TSH may play a major role in the production of goiter, and it may be speculated that chronic thyroiditis starts as Type I or hyperplastic Type I of focal thyroiditis, and develops into Type

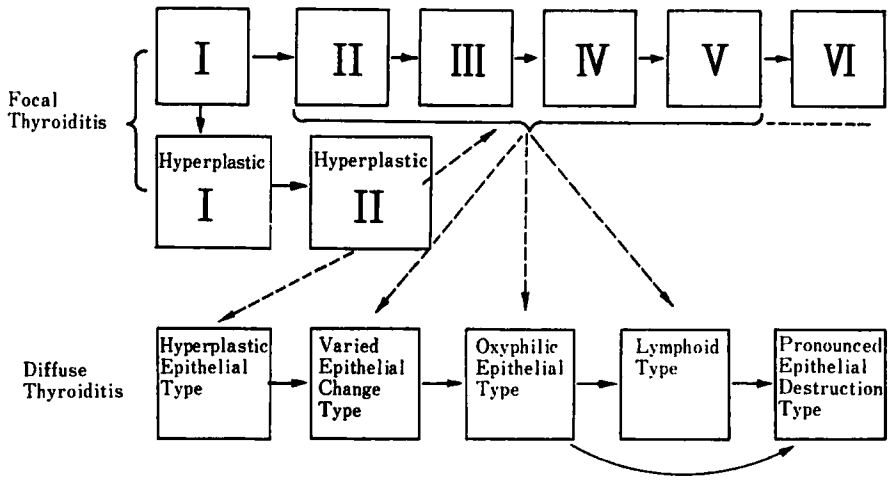

Fig. 1. Speculation of Development of Chronic Thyroiditis

VI with repeated episodes of overactivity and underactivity, or changes into diffuse thyroiditis and finally into hypothyroidism, as demonstrated in Fig. 1.

The patients with chronic thyroiditis were treated with desiccated thyroid powder or prednisolone. The antibody level tended to become lower as the size of the goiter decreased, especially during steroid treatment. Needle biopsies were performed at various intervals in 29 patients with chronic thyroiditis. Table 2 shows the histological changes in thyroid tissues before and after treatment. In 10 cases with diffuse thyroiditis, 4 cases were unchanged, 3 cases of the oxyphilic epithelial type developed into the pronounced epithelial destruction type, 2 cases of the hyperplastic epithelial type developed into the varied epithelial change type, and one case of the oxyphilic epithelial type treated for 1 month with steroids moved to the varied epithelial change type. Of 19 cases with focal thyroiditis, 17 remained unchanged, one Type IV case developed into Type V, and one Type V case of focal thyroiditis developed into the oxyphilic epithelial type of diffuse thyroiditis. These results confirm our speculation on the development of chronic thyroiditis.

Table 2. *Followed-up Cases of Chronic Thyroiditis*

DIFFUSE THYROIDITIS

			Before Treatment						After Treatment				
Name	Sex	Age	Type	PT	TRC	CF	Treatment	Period	Type after Treat.	Size of Goiter	PT	TRC	CF
F.H.	F	43	Oxy.	+	10^6	640	Glucocorticoid Thyroid P.	34M	Dest.	↓	+	10^5	80
H.H.	M	40	Oxy.	−	10^4	320	Thyroid P.	14M	Dest.	↓	−	10^3	20
M.M.	F	53	Oxy.	−	−	−	Thyroid P.	11M	Dest.	↓	−	10^3	20
T.A.	F	26	Hyper.	−	−	−	Thyroid P.	14M	Varied	↓	−	10^3	10
H.S.	F	17	Hyper.	−	−	−	Thyroid P.	33M	Varied	↓	−	10	80
T.H.	F	29	Oxy.	−	−	−	Glucocorticoid	1M	Varied	↓	−	−	−
H.A.	F	56	Oxy.	+	10^6	40	Glucocorticoid	10M	Oxy.	↓	+	10^6	320
K.S.	F	52	Oxy.	−	10^6	320	Thyroid P.	4M	Oxy.	↓	+	10^6	320
K.W.	F	51	Oxy.	−	10^3	80	Thyroid P.	6M	Oxy.	↓	−	10^3	80
K.S.	F	48	Varied	−	10^5	40	Thyroid P.	11M	Varied	↓	−	10^4	−

FOCAL THYROIDITIS

			Before Treament						After Treatment				
Name	Sex	Age	Type	PT	TRC	CF	Treatment	Period	Type after Treat.	Size of Goiter	PT	TRC	CF
T.I.	F	19	III	–	10	80	Thyroid P.	14M	V	→	–	–	–
N.K.	F	39	V	–	10^6	–	Thyroid P.	6M	Varied	↘	–	10^6	–
S.F.	F	40	II	–	10	80	Thyroid P.	24M	II	↓	–	10^3	–
T.M.	F	52	I	–	10^2	–	Thyroid P.	20M	I	↓	–	10	–
S.S.	F	42	III	–	10^3	10	Thyroid P.	6M	III	↓	–	10^2	–
S.K.	F	27	IV	–	10^2	–	Thyroid P.	15M	IV	↓	–	10	–
T.T.	F	51	IV	–	10^5	–	Glucocorticoid Thyroid P.	12M	IV	↓	–	10^3	–
M.M.	F	59	VI	+	10^2	–	Glucocorticoid Thyroid P.	21M	VI	→	–	10^2	20
							Thyroid P.	14M	VI	→	–	10^2	20
K.Y.	F	48	V	–	10^6	320	Thyroid P.	6M	V	↘	–	10^6	320
							Glucocorticoid Thyroid P.	3M	V	↘	–	10^6	20
M.T.	F	40	V	–	10^3	640	Glucocorticoid Thyroid P.	15M	V	↘	–	10^3	320
K.K.	F	35	I	–	10	–	Thyroid P.	3M	I	↓	–	10	–
M.K.	F	37	II	–	–		Glucocorticoid Thyroid P.	10M	II	↓	–	–	80
M.K.	F	40	II	–	10^3	–	Thyroid P.	11M	II	↓	–	10^3	–
							Thyroid P.	8M	II	↓	–	10^3	–
F.M.	F	22	III	–	10	–	Thyroid P.	19M	III	↓	–	10	40
K.E.	F	46	IV	–	–		Thyroid P.	13M	IV	↓	–	–	
K.S.	F	38	IV	–	–	–	Thyroid P.	12M	IV	↓	–	–	–
T.N.	F	58	II	–	–	–	Thyroid P.	6M	II	→	–	–	
							Thyroid P.	6M	II	→			
S.T.	F	58	IV	–	–		Thyroid P.	11M	IV	→	–	–	–
S.H.	F	22	III	–	–	–	Thyroid P.	21M	II	→	–	–	–