The Syndrome of Sporadic Goitre and Congenital Deafness

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Abstract

A study was conducted on 44 sibs with congenital deafness and goitre, belonging to 26 families. 1-131 uptake test was done in 38 patients and it showed that the percent increase between two successive readings was lower than in euthyroids and those with simple goitre. Perchlorate discharge test was done in 29 cases and it was established that the percentage of discharge was related to the severity of the disease. The size and nodularity of the goitres was found to be directly proportional to the age of the patient. By genetic studies the simple autosomal recessive inheritance of the syndrome was reconfirmed. Treatment with thyroxine was found to be effective in controlling the thyroid related problems by compensating for the hormonal deficiency (JPMA 32:240, 1982).

Introduction

In 1896 Vaughan Pendred presented two cases belonging to a large family, living in an area where goitre was not endemic. He first brought to notice the curious association of deaf-mutism and goitre by recording these two cases (Vaughan Pendred, 1896).

Brain in 1927 studied this syndrome in greater detail and described 12 members of five families, all deaf-mute from birth and with goitres dating from middle childhood. None of his cases presented with either goitre or congenital deafness alone. Because the physical and mental development of the affected persons was quite normal and because the deafness antedated the onset of goitre, it could not be due to hypothyroidism. Brain further established that the goitre and the deafness were the independent manifestations of the same recessive gene defect (Brain, 1927).

Since then, single families with two or more members apparently of the same syndrome have been described by Deraemaeker (1956), Elman (1958) and Morgans and Trotter (1958). In addition, Johnson (1957) described two families who may well belong to the same syndrome, though many of his affected cases were hypothyroid.

In 1960, Fraser, Morgans and Trotter described 28 subjects belonging to 18 families. They observed that labelled iodine could be partially discharged from the thyroid by the administration of potassium perchlorate. The finding was taken to indicate a partial block in the iodination of thyroid proteins due to an inability to form organic iodine compounds at a normal rate. Most of the subjects were found to be euthyroid though some were hypothyroid. The deafness was found to be perceptive in type and in some cases was accompanied by defective vestibular function. The audiograms showed high tone deafness in all cases with a positive perchlorate discharge test. Genetic studies showed that the goitre-deafness syndrome was inherited as a simple recessive with the frequency of the defective gene between 1:150 and 1:500 (Fraser et al., 1960).

In the endemic goitre regions of Gilgit in Pakistan a 10% incidence of deaf-mutism has been reported as against 0.57% in the whole country. It included all types of acquired deafness and partially deaf individuals without mutism. The deaf-mute individuals seen in the Gilgit area were without any clinical evidence of thyroid deficiency though they had very low total serum iodine levels (mean; 3.2 uGm/100 ml). A sizeable portion of these individuals may well belong to the goitre-deafness syndrome. In the non-endemic regions, cases of deaf-mutism associated with thyroid enlargement have been reported by a number of workers (Chapman et al., 1972).

A number of different types of disease entities may partially or completely mimic a classical picture of

the Pendred Syndrome. Deafness of varying degrees is often associated with hypothyroidism, both congenital and acquired, though it shows remarkable improvement with thyroid medications.
A congenitally deaf individual may develop goitre which may or may not be due to an enzymatic defect but which in fact is not related to the deafness genetically and is an isolated occurrence. Conversely a goitrous individual with or without the peroxidase defect may become deaf at some stage in his life. Though such occurrences are comparatively rare but they nonetheless give rise to complications in diagnosis. Therefore in addition to the perchlorate discharge test, which by itself is quite invaluable, it is necessary to study the syndrome in greater detail and establish and define more clinical parameters for it's differ-rentiation.
The present study gives information on a number of patients labelled as belonging to the "Pendred Syndrome", examined and investigated at the Atomic Energy Medical Centre, Mayo Hospital, Lahore.

Material and Methods

A total number of 44 siblings belonging to 26 families were examined and investigated during the period of 16 years from 1965 to 1980.
Past and present family history was explored for a history of the syndrome in the patient's family and near relatives. Other relevant data such as consanguinity in parents was also recorded.
Though the family history was noted, the normal sibs in these families were neither examined clinically nor subjected to laboratory analysis. Initially on clinical examination an opinion regarding the thyroid status was made in each individual and ether relevant clinical data such as the age of onset of goitre and that of deafness was also collected. The 1-131 uptake test was performed on 38 patients and 29 patients were subjected to the perchlorate discharge test.
Information regarding the history of treatment was collected with particular attention to the recurrence of goitre after thyroidectomy and the response to thyroid medication.

I-131 Uptake Tests

Care was taken to screen out patients who had received Iodine in any form other than the tracer doses, because previous Iodine medication taken by the patients invalidates the uptake results making then spurious.
To ensure better absorption the I-131 dose was given to the patients in a fasting state. This was done by advising the patients to report to the laboratory in the morning with empty stomach. The radioiodine (I-131) used for the test was caliberated and given in liquid form.
The dose was adjusted according to the age of the patient and the size of the goitre. The usual dose regimen was as follows:-
2 uCi for patients below 2 years of age.
5 uCi for patients between 2 to 5 years of age.
10 uCi for patients between 5 to 15 years of age.
20 uCi for patients above 15 years of age.\
The uptake readings were taken at one, three and twenty four hours after the administration of the dose. The equipment used, included a ratemeter with a scintillation detector and a NaI crystal of 1.5" diameter with an IAEA flat field thyroid uptake collimator, and a neck phantom for the measurement of standard.
At the fixed intervals as mentioned above, total thyroid activity was measured at a 30 cm crystal-thyroid distance, and background taken with a 2 cm "B" filter (lead). Measurements of "standard" were done in the same manner and net thyroid and standard counts were calculated. The results were expressed as percent-uptake (Gomez Vetter, 1966).

Perchlorate Discharge Test

The method is essentially the same as that for the uptake studies. An uptake reading was taken three

hours after a tracer dose of radioactive iodine, administered in fasting state. Then potassium perchlorate was given orally to the patient still with empty stomach. The dose was 200-600 mg depending upon the age of the patient. It was taken dissolved in 50 ml of water. One hour later, counts were again taken and the percentage of discharge was calculated.
As many of the subjects had undergone a routine I-131 uptake study, necessary correction for the residual thyroid radioactivity was done while making calculations for the perchlorate test.

Results and Discussion

Clinical Features

Some of the clinical findings of the subjects investigated are given in Table I.

Table I

Clinical Features of the Subjects Investigated

Family No.	*Subject No.*	*Sex*	*Age (Years)*	*Age at Onset of Goitre (Yrs)*	*Age at Onset of Deafness (Yrs)*	*Goitre — Est. Wt. & Nodularity*		*Clinical Thyroid Status*	*Physical & Mental Development*
	1 (a)	F	12.5	5	2	250 (h)	N (b)	E (d)	— (f)
I	2	M	10	5	2	40	N	E	—
	3	F	4.5	—	3	20	—	E	—
II	1	F	22	0	—	150	N	E	—
III	1	M	32	12	Infancy	300	N	E	—
	1	F	17	2	Infancy	55	D (c)	E	—
IV	2	M	11	1	,,	30	D	E	—
	3	M	3	2	,,	25	D	E	—
V	1	F	12	7	Infancy	30	D	E	—
VI	1	M	22	10	Infancy	200	N	E	—
	2	M	30	10	,,	200	N	E	—
	1	M	16	0	Infancy	200	N	E	—
	2	M	8	0	,,	40	D	E	—
	3	F	9	0	,,	40	D	E	—
VII	4	M	12	0	,,	45	D	E	—
	5	F	11	0	,,	70	D	E	—
	6	F	19	0	,,	60	N	E	—
	7	F	22	0	,,	60	D	E	—
	8	F	5	0	—	15	—	E	—
VIII	1	M	8	0.5	Infancy	50	D	E	—
	2	M	11	0.5	—	50	D	H (e)	↓ (g)
IX	1	M	18	12	12	200	N	E	—
X	1	F	12	11	Infancy	100	N	E	—
	2	M	10	3	,,	30	D	E	—
XI	1	F	15	0	Infancy	80	D	E	—
XII	1	F	15	10	—	45	D	H	↓
	2	F	9	7	—	45	D	E	—
XIII	1	F	20	14	—	200	N	H	—
XIV	1	F	20	10	Infancy	50	N	E	—
XV	1	F	17	16	Infancy	160	N	E	—
XVI	1	F	23	18	3	70	N	E	—
XVII	1	F	18	17.5	—	45	N	E	—
	2	F	10	9.5	4	30	D	E	—
XVIII	1	M	30	10	Infancy	220	D	H	—
XIX	1	M	15	14	Infancy	70	N	H	↓
XX	1	M	22	15	4	35	N	E	—
XXI	1	F	20	19	Infancy	100	N	H	—
	2	M	16	8	,,	80	N	E	—
XXII	1	F	20	19	Infancy	200	N	E	—
XXIII	1	F	11	10	Infancy	50	D	E	—
XXIV	1	F	7	6.5	—	35	D	E	—
	2	F	5	4	—	25	D	H	↓
XXV	1	M	25	20	Infancy	45	D	E	—
XXVI	1	M	40	10	Infancy	80	N	E	—

(a) The first subject in each family is the propositus.
(b) N=Nodular Goitre.
(c) D=Diffuse Goitre.
(d) E=Euthyroid.
(e) H=Hypothyroid.
(f) —=Normal Development.
(g) ↓ =Mentally retarded with delayed physical development.
(h) WT. in Grams.

With only four exceptions, all the affected persons showed with normal physical and mental development. These four patients were all obviously hypothyroid, their physical development was delayed and they had varying degrees of mental retardation. Only 7 pateints out of a total of 44 were clinically hypothyroid whereas the rest were clinically euthyroid (84%).

In nearly all the cases the onset of deafness preceded the onset of goitre. Most of the affected persons must have been deaf from a very early age since they had not learned to talk intelligibly. The degree of deafness varied from person to person and in a few the deafness was only partial.
The goitre usually dated from middle childhood and the average age of onset of goitre was 7.5±6 years. The size of the thyroid glands varied from hardly detectable enlargements to goitres of about 300 grams estimated weight. A direct relation was found between the thyroid size and the age of the patient. Goitres arising in older patients tended to be larger than in younger patients i.e. the later the age of it's onset the larger the goitre tended to be, notwithstanding the age of the goitre itself (Fig. 1).

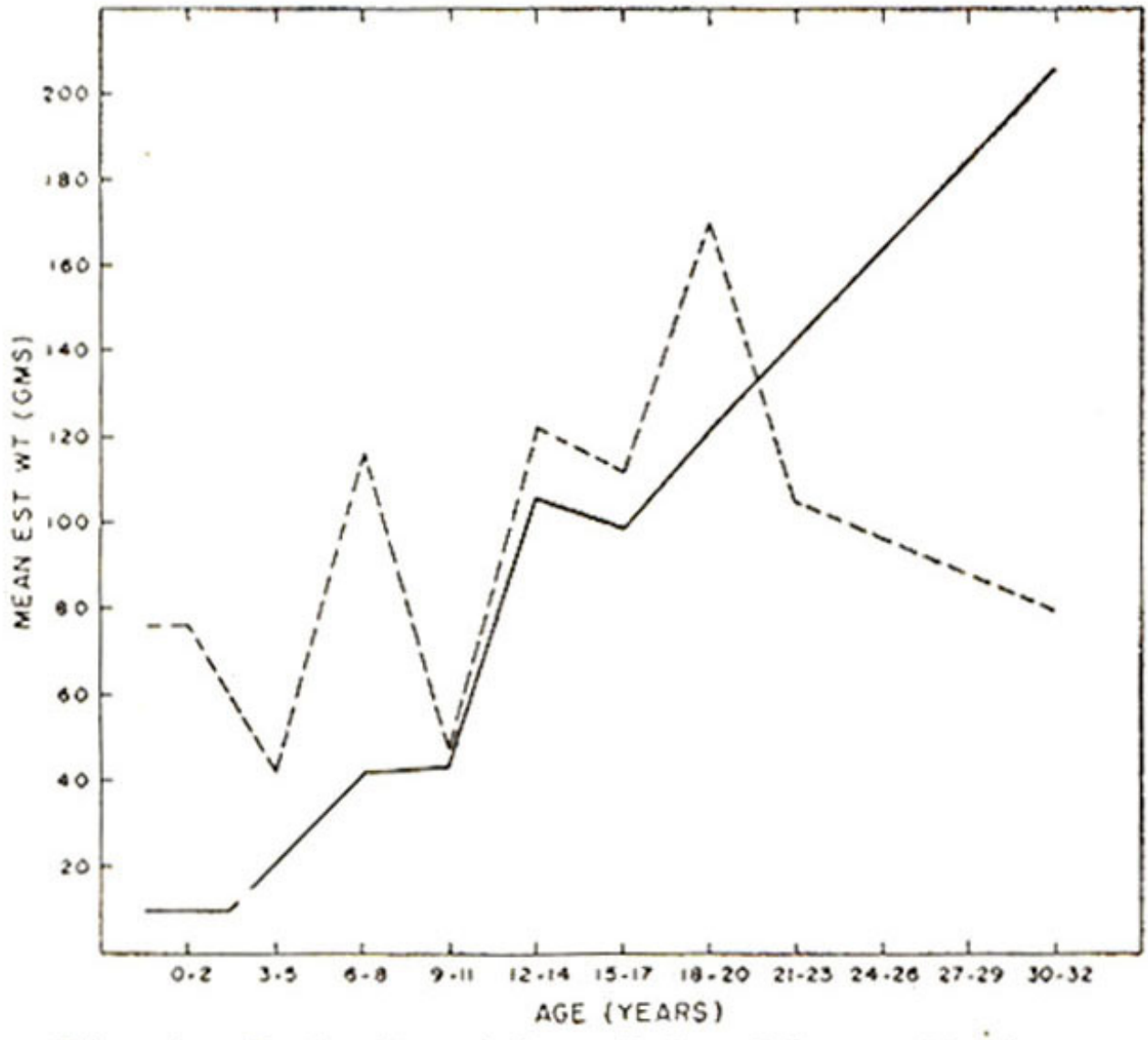

Fig. 1: Relationship of the Mean Estimated Wt. of the Thyroid with the Age of the Goitre (Dotted Line) and with the Age of the Patient (Cont. Line).

The goitres in younger patients appeared soft and diffuse on palpation whereas in older age groups they

tended to be more firm and nodular (Table II).

Table II

The Percentage of Nodular Goitres in Different Age Groups.

Age Group	*Percentage of Nodularity*
0-10 years	17%
10-20 years	50%
above 20 years	78%

These goitres have shown a marked tendency to recur.

Growth of the organs normally occurs at par with the growth of a person, and any moderate stimulus to the growth of a particular organ during this period will result in its enlargement as a whole. But afterwards, when the person's growth has slowed down or he has stopped growing, a strong stimulus to a particular organ will cause it's parenchyma to grow, whereas the connective tissue element fails to respond in a like manner. The above hypothesis may explain the increased nodularity of goitres in older patients.

The patient's thyroid because of it's inherent enzymatic defect cannot meet the increased physiologic demands of the growing child and responds by a compensatory hypertrophy under increased TSH stimulation.

Investigations

The results of the investigations done on the subjects are shown in Table III.

Table III

Results of Investigations of Subjects in Table—I

Family No	Subject No	I—131 Uptake 1Hr	3Hr	% 24Hr	Perchlorate 3Hr	4Hr	Disch %	Test Discharged
	1	48	53	72	—	—		—
I	2	29	45	71	—	—		—
	3	25	27	37	—	—		—
II	1	48	55	63	57.3	30.6		46.60
III	1	33	49	65	—	—		—
	1	2	6	40	—	—		48.0
IV	2	8	19	34	—	—		11.7
	3	2	6	40	—	—		43.0
V	1	37	65	81	—	—		—
VI	1	17	27	59	24	16		33.3
	2	16	17	39	15	11		26.6
	1	40	49	45	23	9		60.8
	—	—	—	—	—	—		—
	3	—	—	—	—	—		—
VII	4	—	—	—	—	—		—
	5	—	—	—	—	—		—
	6	—	—	—	—	—		—
	7	31	45	52	47.5	29.4		38.1
	8	—	—	—	—	—		—
VIII	1	70	80	80	54.6	45.1		17.4
	2	31	46	51	38.1	27.6		27.5
IX	1	10	30	45	100	89.7		10.3
X	1	46	59	72	36.9	10.7		71.0
	2	17	20	32	—	—		—
XI	1	4	5	6	4.5	2.4		46.6
XII	1	27	35	45	30.3	25.4		16.1
	2	34	44	58	41.2	32.7		20.6
XIII	1	28	46	56	26.7	14.1		47.2
XIV	1	5	28	56	—	—		—
XV	1	29	41	64	—	—		—
XVI	1	18	32	48	48.1	38.9		19.1
XVII	1	36	46	63	55.3	42.2		23.7
	2	60	65	74	81.3	61.5		24.3
XVIII	1	28	—	48	32.5	22		32.3
XIX	1	23	29	48	37.2	22.2		40.3
XX	1	23	36	55	—	—		
XXI	1	37	44	51	53.7	30.5		43.2
	2	22	41	64	42.5	36.7		13.6
XXII	1	31	38	56	43.8	27.7		36.7
XXIII	1	53	64	55	61.0	40.3		33.9
XXIV	1	39	64	83	64.7	68.6		—
	2	35	46	60	37.6	28.7		23.7
XXV	1	10	18	53	24.6	17.2		30.0
XXVI	1	26	31	47	32.6	22.3		31.6

I-131 Uptake Studies

I-131 uptake tests were done in 38 cases. The results were very varied. Unlike the perchlorate discharge test there was no uptake pattern characteristic of the syndrome. The uptake values were generally much

higher than in normals and 79% of the patients showed more than 45% twenty four hours uptake. The mean 1 hr, 3 hrs and 24 hrs uptake of • cases of Pendred Syndrome as compared with euthyroids without goitre and those with simple goitre are shown in Table IV and Fig. 2.

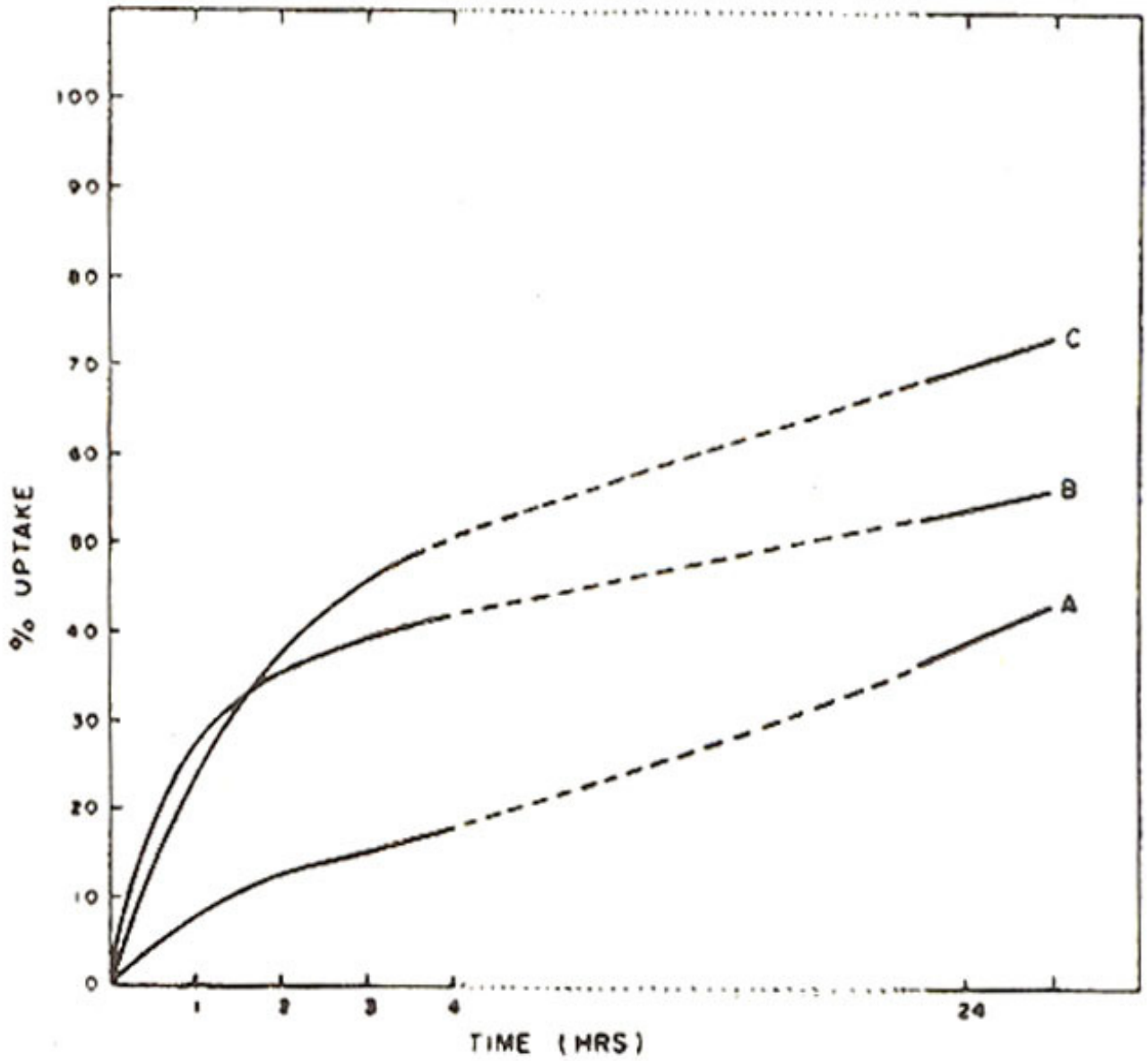

Fig. 2: The Mean Thyroid Uptake Curves of Euthyroids (A), Patients with Goitre-Deafness Syndrome (B) and Those with Simple Goitre (C).

Table IV

The Mean 1 Hr., 3 Hrs. and 24 Hrs. Uptake of Cases of Pendred Syndrome as Compared with Euthyroids without Goitre.

Class & No. of Subjects	*I—131 Uptake %*			*% Increase b/w Readings*	
	1 Hr	*3 Hrs*	*24 Hrs*	*1-2 Read.*	*2-3 Read.*
Euthyroid (12)	09±03	15±03	39±07	40%	61%
S. Goitre (12)	26±10	47±16	70±13	46%	33%
P. Syndrome (38)	28±16	39±18	54±15	28%	28%

Also shown in Table IV is the percentage increase in uptake between the three readings. It was observed that the percent increase of uptake in successive readings is considerably less in cases of Pendred's Syndrome as compared to that in patients with simple goitre and in normals.

This is obviously due to congenital peroxidase deficiency which results in slow organification of Iodide and hence the leakage of trapped iodide back into the extrathyroidal iodine pool.

Perchlorate Discharge Test

This test was done in 29 patients. In only one case the result was negative. This may well be due to some technical error or human omission. Also this may indicate the possibility of the preser.ce of some other type(s) of genetically determined goitre and deafness. In this case the patient (XXIV-1) was only partially deaf and could speak a little and his goitre too was comparatively small.

The percentage of I-131 discharged may be related to the severity of the patient's condition, the rough judgement of which can be made by the size of his goitre and the degree of his deafness.

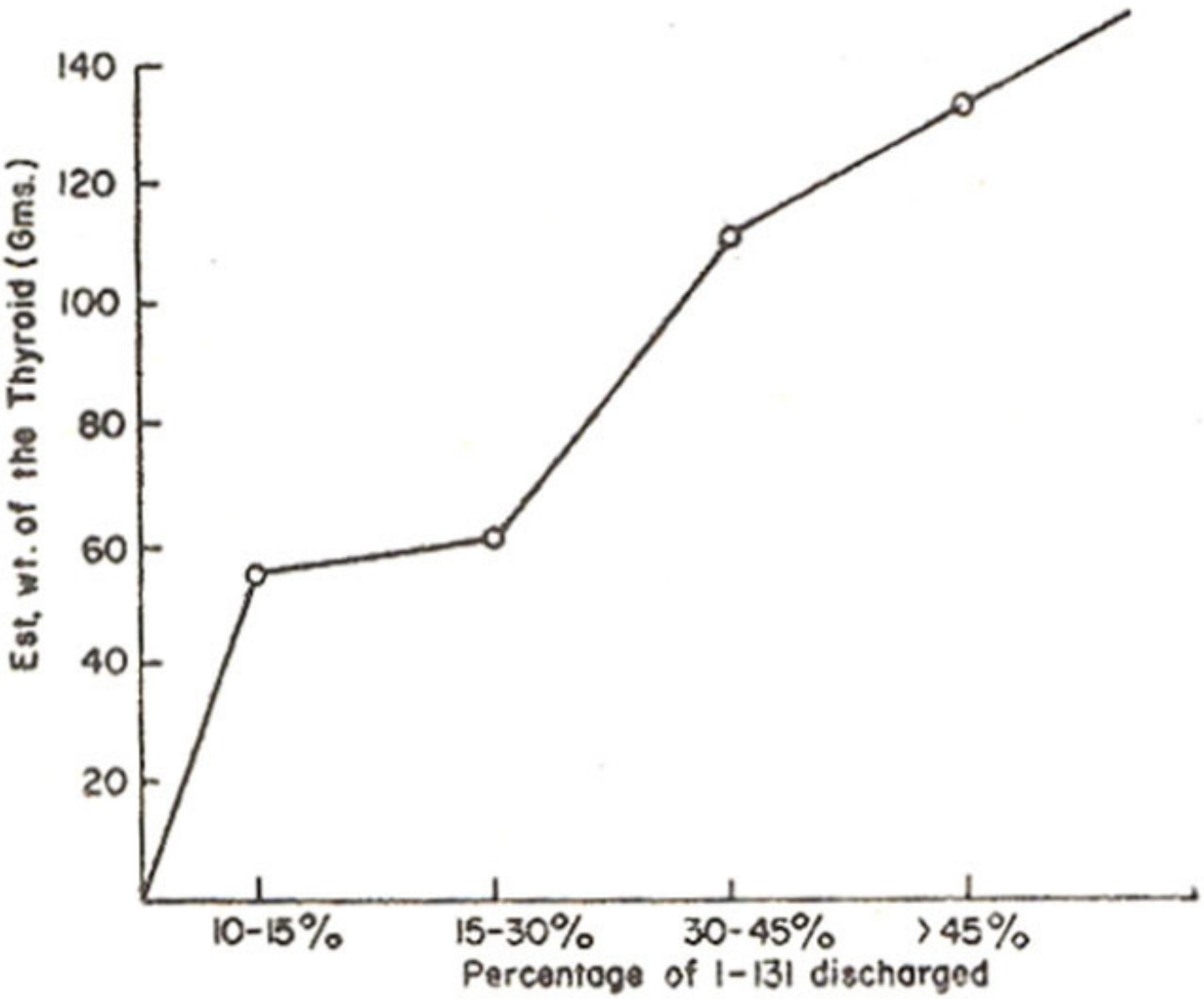

Fig. 3: Relationship Between the Dischare Percentage and the Mean estimated Wt. of Thyroid Gland.

In Fig. 3 a graph has been plotted between the increasing levels of discharge percentage and the mean of the estimated weights of the patients' thyroids in that group. It can be seen that the patients showing more discharge have larger thyroids.

Out of 29 cases, except for the one where the perchlorate discharge test was negative, all the cases showed more than 10% discharge.

We also compared the mean discharge percentages of two other groups of patients. The cases in the first group were only partially deaf and could speak a few words, whereas in the second group the degree of deafness was quite severe and the patients were completely mute. We found the mean discharge in the first group to be 24+11, compared with 36+-14 in the second group. This indicates that the percentage of the I-131 discharged by the KC104 may be related to the severity of the disease.

Out of 29 cases, except for the one where the perchlorate discharge test was negative, all the cases showed more than 10% discharge.

There were six patients each having 10-20% and 20-30% discharge whereas 16 patients had more than

30% discharge.
No significant difference was found in the discharge levels between the euthyroids and the hypothyroids. Examples of the discharge patterns in five cases are shown in Fig. 4.

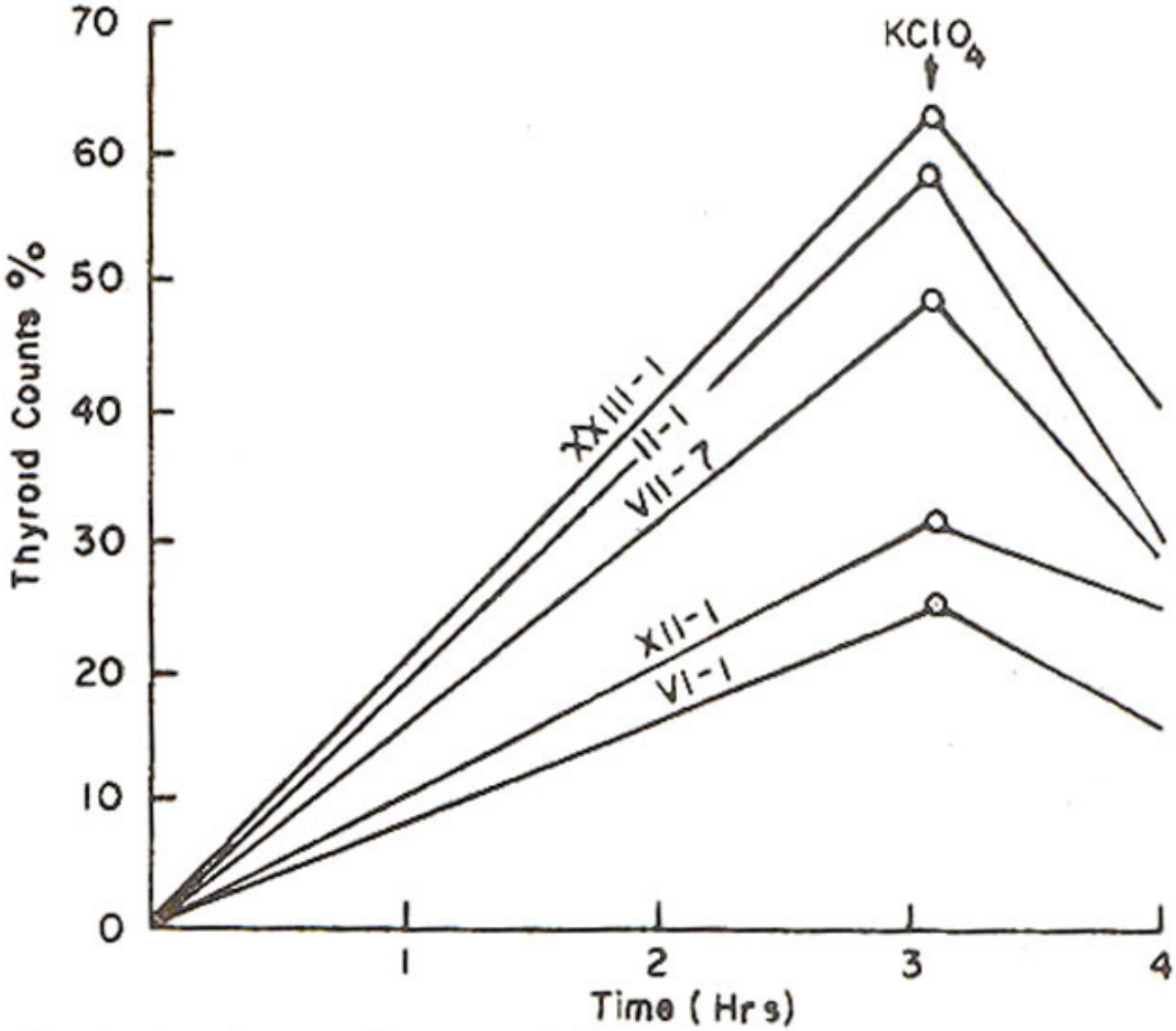

Fig. 4: Perchlorate Discharge Test Patterns in five Subjects.

The first reading is a measure of the total thyroid avidity for the radioactive iodine 3 hrs after administration. The second reading taken at 4 hours gives the percentage of administered I-131 that has been organically bound, because the unbound iodide has been discharged by the perchlorate.

The Nature of the Thyroid Defect

After the Iodide is trapped by the special receptors in thyroid cells, it is oxidised into free iodide ions by the action of peroxidase enzyme system, which is a pre-requisite for its binding with the tyrosine to make mono and diiodotyrosines (MIT & DIT), for further T3 and T4 synthesis. This process is well illustrated in Fig. 5.

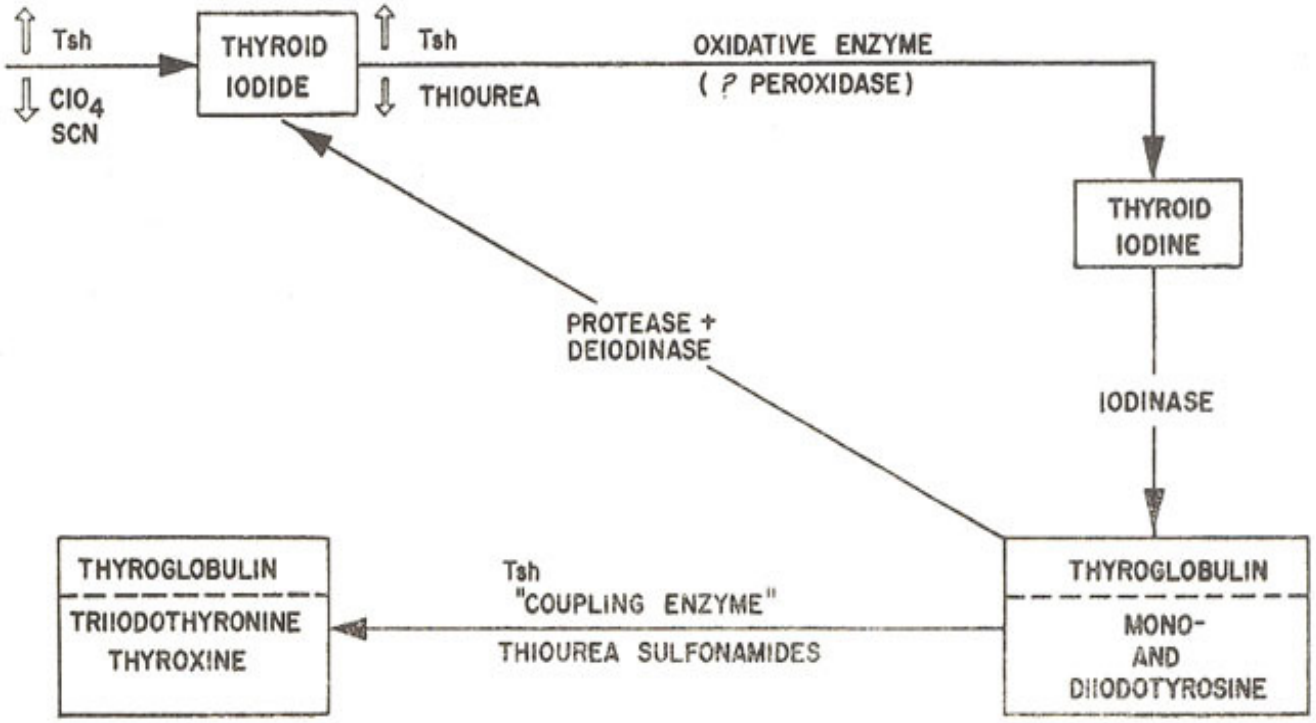

Fig. 5: Intrathyroidal Iodine Metabolism[8]

Trotter (1960) suggested that in this syndrome the organic binding of iodide with tyrosine may be proceeding at an abnormally slow rate, leading to an accumulation of unutilized iodide within the thyroid. Further there might be an additional defect of coupling of jodotyrosincs to form T3 and T4 either primarily or as a secondary consequence of the inadequacy of the enzyme responsible for oxidising iodide which may also assist in the coupling reaction.

In most of the cases of peroxidase defect, the iodine trapping exceeds the leakage of unbound iodide and thus this leakage remains obscure. In the perchlorate discharge test, by giving an appropriate dose of KC104 we only block the further trapping of Iodide, with the result that the leakage of unbound iodide into the extrathyroidal iodine pool becomes "visible".

This perchlorate discharge response in our subjects was similar to that in cases of Hashimoto's thyroiditis. But former workers have not been able to find any antithyroid antibodies in the serum of the patients of this syndrome and also no histological evidence of Hashimoto's disease has been found. Thus it rules out the possibility of the biochemical defect being related to an immunological reaction.

Genetic Studies

The genetic data is presented in table V.

Table V

Genetic Data

Family No	Total No of Sibs	♂	♀	Affected	Normal	Consanguinity in Parents
I	7	$3M^1$	$2F^{2*}$	3	4	—
II	1	0M	$1F^1$	1	0	+
III	8	$4M^2$	$4F^0$	2	5	+
IV	10	$4M^2$	$6F^1$	3	7	—
V	1	0M	$1F^1$	1	0	+
VI	7	$3M^2$	$4F^0$	2	5	+
VII	8	$3M^3$	$5F^4$	7	1	+
VIII	5	$4M^2$	$1F^0$	2	3	+
IX	7	$4M^3$	$3F^0$	3	4	—
X	5	$2M^1$	$3F^1$	2	3	+
XI	4	$2M^0$	$2F^1$	1	3	+
XII	2	OM	$2F^2$	2	0	+
XIII	2	0M	$2F^1$	1	1	+
XIV	4	$2M^1$	$2F^1$	2	2	+
XV	...	...	...	...	...	+
XVI	5	$1M^1$	$4F^1$	2	3	+
XVII	7	$5M^0$	$2F^2$	2	5	—
XVIII	3	$3M^3$	0F	3	0	...
XIX	5	...	...	/	4	+
XX	...	...	...	...	...	—
XXI	6	$3M^1$	$3F^2$	3	3	+
XXII	5	...	...	2	3	...
XXIII	5	0M	$5F^5$	5	0	+
XXIV	4	$1M^0$	$3F^3$	3	1	—
XXV	8	$5M^3$	$3F^1$	4	4	+
XXVI	6	$3M^1$	$3F^1$	2	4	+

* The exponent indicates the no. of affected in each sex.

Genetic history of 24 families, containing a total of 125 siblings was available to us. Perchlorate discharge test was not performed on all of them but most were examined clinically and a detailed family history was taken. It was ascertained that all the subjects recorded were identical in that they all had goitres associated with deaf-mutism.

The ratio of affected to normals was approximately 11:10, with 59 normals and 66 affected. Out of a total of 52 males in 22 families for which data was available, 28 (50%) were found to be affected whereas 30 (48%) females out of 63 were affected. The ratio of the affected males and females was found to be 13:15.

In none of the cases studied there was goitre without deafness or the reverse. A history of consanguinity of parents in the involved families was taken and in 18 families (78%) a positive history was present whereas only in 5 families the parents were not related by blood.

In 6 families the parents were first cousins. The mothers in family III and family XX both were deaf-mute and goitrous and each was married to her first cousin. The subjects in family XX had two first

cousins who were both deaf-mute and goitrous and whose parents had consanguinity (first cousins).

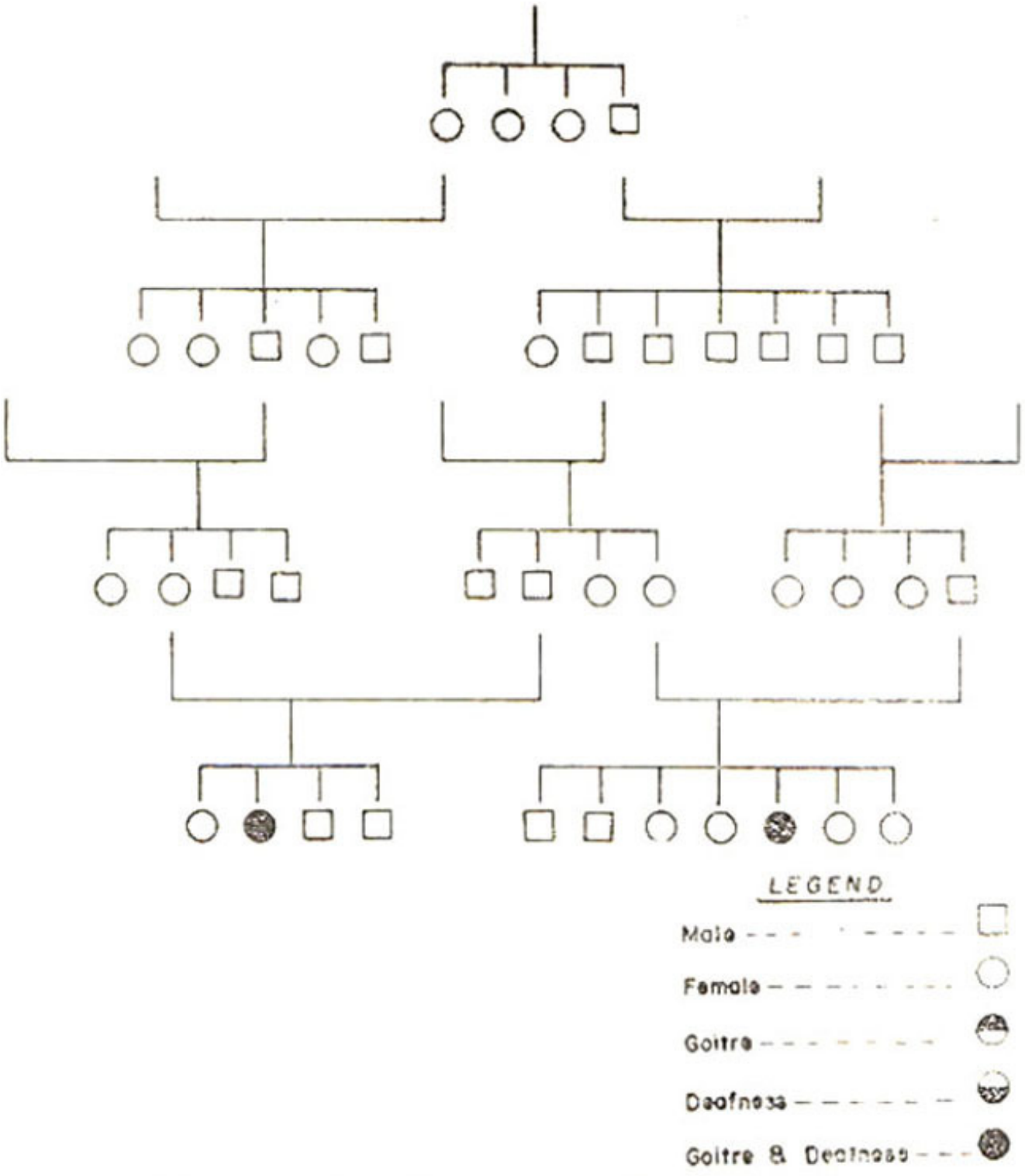

Fig. 6: Pedigree of Family XI.

A cousin of family XI (Fig. 6) was deaf-mute and goitrous and his parents too were first cousins. In family X the cousins of the patient's parents were deaf-mute and goitrous. In family XXVI two cousins of the propositus in addition to her own two daughters were found to be deaf-mute, with goitre.

With the exception of the families referred to above the syndrome of goitre and deafness was found to appear in successive generations only. This substantiates Brain's (1927) conclusion that the syndrome is probably inherited in a recessive manner.

If we apply Fisher's (1934) correction for inadequate ascertainment to our proportion of affected to total sibs by excluding the 8 male and 16 female propositi, then our ratio of affected to non-affected is very nearly 1:3, and this in addition to the very high consanguinity rate (78%) in our families very strongly supports the hypothesis for autosomal recessive inheritance.

The apparent excess of the females over the males involved disappears when the propositi are removed, because more of the females than the males present as propositi. The sex distribution then becomes nearly equal.

The reason as to why the thyroid and the VIII nerve are both involved is not clear. It may be either due to the close linkage of the relevant genes or due to the pleiotropic action of a single abnormal gene as is suggested by the consistent association of goitre and deafness.

Therapeutics

Fifteen patients with small to medium sized goitres were selected and treated with thyroxine. The response varied from moderate to good as far as reduction in the thyroid size was concerned. Partial thyroidectomy (sometimes more than once) was performed in 8 of our cases. Most of them showed a recurrence of the goitre. The tendency to recur after partial thyroidectomy is obviously due to the fact that the underlying cause has not been treated.

Our view is that the patients with small to medium sized goitres should be treated with thyroxine medication and that the patients with large goitres should be advised surgery, followed by thyroxine medication. By following the above treatment plan we have achieved satisfactory results in most of the cases.

Summary

1. A total of 44 sibs with congenital deafness and goitre belonging to 26 families were studied. The perchlorate discharge test was done in 29 cases. In 28 subjects the labelled iodine was partially discharged by the perchlorate ion, with more than 10% discharge in all of them. The percentage of discharge was found to be related to the severity of the disease.

2. I-131 uptake studies in 38 affected patients showed that the percent increase in successive readings was lower than in normals and those with simple goitre.

3. It was found that the goitres arising in older patients tended to be larger in size, notwithstanding the age of the goitre itself. It was also observed that the nodularity in goitres increases with the increasing age of the patient.

4. Genetic studies showed that this syndrome is inherited as a simple autosomal recessive.

5. The main feature of the thyroid defect seems to be a deficiency in the peroxidase-iodinase enzyme system resulting in a partial block in the synthesis of thyroid hormones. This dyshormonogenesis is responsible for the goitre.

6. Treatment with thyroxine was found to be effective in controlling the thyroid related problems by compensating for the hormonal deficiency.

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