

THYROID FUNCTION IN ENDEMIC HYDROFLUOROSIS IN SICILY

by

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As a follow-up of previous observations on hydrofluorosis, a disease endemic in several areas of Sicily, and supplementing research started in 1953, we investigated the function of the thyroid gland in subjects with hydrofluorosis.

The existence of a goiter in dogs, sheep and cattle, affected by fluorosis of industrial origin and of thyroid hypertrophy often encountered in laboratory animals which are treated with fluoride compounds, has given rise to the goitrogenic theory of fluoride and to the conclusion that iodine and fluoride are antagonistic.

The literature on this question is contradictory: Goldemberg (1) had given to rats daily doses of 2-3 mg of sodium fluoride. In all animals he encountered hyperplasia and hypertrophy of the gland, degenerative lesions of blood vessels, emaciation, developmental and mental retardation, which he defined as "Fluoride Cretinism."

Christiani (2) treated calves with sodium fluoride in the same manner as Goldemberg. The thyroid gland exhibited more extensive anatomical lesions than those encountered by Goldemberg who treated only a small number of animals.

Slaviero (3) encountered an increase of colloidal substance of the thyroid in dogs to which sodium fluoride had been administered.

Goldemberg (4) also demonstrated a consistent decrease in basal metabolism in rats treated with a single, large but non-fatal, dose of sodium fluoride. These results were much less evident in chronic intoxication of animals. On the basis of additional experiments on mice, Goldemberg produced evidence that fluorotic cachexia should be considered a manifestation of induced fluoride cretinism and that the changes in thyroid tissues represent experimental goiter.

Goldemberg considered the possibility that in goiter areas, fluoride in water, in soil and in certain foods constitutes the true cause of goiter and that iodine deficiency only accentuates the effect of fluoride, without being its sole cause.

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Phillips (5) noted an increase in metabolic rate in rats treated with sodium fluoride. This increase is more pronounced when dry thyroid substance is added to the animal ration. Goldemberg and May (6) reported satisfactory results upon administering sodium fluoride in hyperthyroidism.

On the assumption of a fluoride-iodine antagonism and considering the possible therapeutic use of fluoride in thyroid toxicosis, some have prepared fluorinated derivatives of tyrosine analogs of the same amino-acid (mono and di-iodotyrosine). May (6) obtained good therapeutic results in hyperthyroid subjects with 3-fluorotyrosine, and with the 3-fluorohydrobenzoic acid.

Roche (7) confirmed that substitution of one or two atoms of iodine by one or two atoms of fluorine (3-fluoro-3, 5, 5-tyrosine and 3 fluoro-3, 5, 5-tri-iodotyrosine and 3, 5-di-iodo-3', 5'-difluorotyrosine) attained a thyroxin effect whereas 3, 5-fluorotyrosine is completely ineffective.

Anbar (8) demonstrated that the accumulation of fluoroborate in the thyroid gland is superimposed upon iodide ions. Fluoroborate ions do not become organically fixed in the thyroid, and their presence in the gland establishes a specific index of the phase of thyroid uptake. The same author, utilizing fluoroborate ions labeled $^{18}\text{F}^-$, demonstrated that thyroid stimulating hormone (TSH) inhibits the accumulation of fluoroborate during the first hour after its administration whereas after 24 hours it increases fluoroborate accumulation.

In the U. S. A. and England endemic goiter, due to lack of iodine, occurs independently of fluoride content of water. Demole (9) asserts that in Switzerland administration of iodine alone eliminated goiter where the fluoride level in water ranged between 1 and 1.4 ppm and where the population was exposed to industrial pollution by F^- . Daily administration of 1 mg per day of sodium fluoride to students in an endemic goiter area failed to induce thyroid hypertrophy (10).

Present Study

Our investigation was conducted on the population of Acquaviva Platani, in the province of Caltanissetta, a town about 625 meters above sea-level with a rather humid climate. The area is somewhat depressed economically. The 2,500 inhabitants make their living from agriculture and from mining rock salt which abounds in the area. The nutrition is poor. Because of the scarcity of protein, especially animal protein, a vegetarian and cereal diet prevails. Drinking water is obtained from a public spring which contains 5.2 ppm fluoride.

We examined 400 subjects. They were free of diseases which could interfere with the results of our investigation. All adult subjects presented typical evidence of dental and skeletal fluorosis of various degrees.

Signs of early aging, features of hypoadrenalism and, not infrequently, evidence of precocious arteriosclerosis were noted. In children evidence of somatic underdevelopment with signs of rachitis was usual, presumably attributable to a deficiency in protein and vitamins. Infantile morbidity was not different from that of other communities of central Sicily. Most adults exhibited degenerative diseases of the joints and of digestive apparatus, namely dyspepsias due largely to chronic catarrhal gastritis and gastroduodenitis accompanied by spastic colitis and by signs of hepatic insufficiency. These conditions must in part be attributed to the action of fluoride. In women data concerning the menstrual cycle, fertility, the course of pregnancy were unremarkable. The incidence of intercurrent diseases was also insignificant. We frequently encountered hypochromic microcytic anemia with normal blood corpuscle-resistance and a deficiency of erythrocyte-forming activity of the bone marrow. Histoplasmocytosis was of some importance. Frequently an increase of the alkaline phosphatase and of inorganic phosphates in the serum, hypocalcemia and hypercalcinuria were found.

In the subjects whom we examined the incidence of goiter was rare, namely about 2%. This percentage is close to the average in any nearby non-fluoride area. A former survey of another center of hydrofluorosis in Sicily disclosed an incidence of goiter between 2% and 2.7%.

Among the 400 subjects, natives of Acquaviva Platani, a group of 52 (Table 1) was selected, ranging in ages from 20 to 60 (39 males and 13 females) for investigation of the thyroid function with radioactive iodine. Two of the 52 were afflicted with a diffuse parenchymatous goiter of moderate size with clinical signs of a slight hyperfunction. In another case a clinically irrelevant increase of the thyroid function but no appreciable morphological changes of the gland were noted.

Our studies were carried out in our mobile unit. The apparatus used was manufactured by the Chicago Nuclear Corporation. It consisted of a group of scintillation probes, one scanner and a deep well counter with analyzer.

All subjects had been fasting since the preceding night. They were given a single oral dose of 50 microcuries of ^{131}I in the form of sodium iodide. The ^{131}I thyroid area was counted at 1, 2, 8 and 24 hours after administration of ^{131}I . Blood samples were taken from the brachial vein after 24 hours for determination of the conversion index (PBI). This was another approach in order to differentiate the high values of fixation due to actual hyperfunction of the thyroid from those that could be indicative of increased uptake without simultaneous hormone hypersecretion.

The results of our investigation as illustrated in the accompanying table can be summarized as follows:

TABLE 1

¹³¹I Data on 52 Selected Subjects

Number	Age	Sex	Occupation	¹³¹ I Uptake in % After				Conversion (PBI) in 24 hrs. in %
				1 hr.	2 hrs.	8 hrs.	24 hrs.	
1	54	M	Miner	12	16	24	39	28
2	27	M	Farmer	8	13	22	32	25
3	27	F	Housewife	13	18	29	50	33
4	30	F	Housewife	35	42	78	92	84
5	60	M	Miner	10	12	20	31	26
6	45	M	Farmer	15	35	50	58	32
7	37	M	Farmer	15	40	55	60	40
8	38	M	Farmer	12	16	38	50	38
9	29	M	Farmer	12	15	22	39	40
10	23	M	Farmer	14	18	28	40	28
11	50	M	Miner	10	13	24	32	32
12	57	M	Sailor	13	25	50	60	39
13	41	M	Miner	16	30	55	60	43
14	53	M	Miner	20	30	60	70	38
15	46	M	Miner	13	18	22	39	25
16	60	M	Miner	12	14	22	29	25
17	60	F	Housewife	12	15	26	40	35
18	46	M	Farmer	19	22	25	30	32
19	31	M	Farmer	11	12	20	31	28
20	48	M	Farmer	14	18	28	48	40
21	57	M	Farmer	15	18	26	42	42
22	21	M	Farmer	12	15	28	38	33
23	48	M	Farmer	16	18	31	41	34
24	47	M	Farmer	14	18	31	36	33
25	44	M	Farmer	30	41	75	89	78
26	44	F	Housewife	18	21	36	41	39
27	51	F	Housewife	10	13	24	30	33
28	40	F	Housewife	13	16	30	37	31
29	27	M	Miner	16	20	36	46	39
30	27	F	Housewife	15	20	36	43	39
31	32	F	Housewife	11	18	26	31	35
32	55	F	Housewife	13	25	34	40	42
33	59	F	Farmer	10	14	28	40	32
34	58	M	Miner	19	22	39	43	38
35	26	F	Housewife	12	13	22	32	38
36	37	F	Housewife	12	16	31	45	40
37	36	M	Farmer	10	12	21	26	31
38	30	F	Farmer	15	16	25	36	40
39	60	M	Miner	15	18	29	40	39
40	28	M	Miner	16	20	31	46	40
41	52	M	Farmer	14	17	25	38	31
42	60	M	Miner	10	13	21	31	36
43	24	M	Farmer	14	18	25	39	36
44	28	M	Miner	14	20	30	39	30
45	40	M	Farmer	18	23	33	41	40
46	20	M	Farmer	10	12	18	30	36
47	52	M	Farmer	15	21	33	45	39
48	60	M	Miner	13	18	29	39	42
49	45	M	Farmer	13	19	33	40	34
50	40	M	Farmer	16	19	28	38	36
51	58	M	Miner	35	48	90	90	80
52	49	M	Miner	18	22	31	43	36

1. In 44 individuals or 84.6% of the cases examined, the percentage of uptake and the value of reported conversion (PBI) in 24 hours was maintained within normal limits from 15 to 50%.

2. In five cases or 10.4% of our cases (6, 7, 12, 13 and 14), the uptake was slightly above normal limits. In one case there was an uptake up to 70%. The reported conversion was within normal limits, varying between 32 and 43%. In these persons there was no clinical evidence of impairment of thyroid function and their PBI levels were within normal limits. In spite of the increased uptake, they could be considered euthyroid.

3. In only 3 cases (4, 25 and 51) or 4.99%, which included two patients with a goitre and one with signs of hyperthyroidism without appreciable morphological alteration of the gland, the percentage of external uptake was above normal. In one case an increase up to 92% was noted. This value was found to correspond with the reported index of conversion (PBI) which amounted to about 80% in 24 hours.

The clinical-statistical and laboratory observations reported here, revealed that the incidence of goiter in the hydrofluorotic area which we investigated was not higher than that encountered in a neighboring non-fluorotic zone. No evidence of hyperfunction was observed in patients with goiter.

The high percentage of euthyroid cases in our hydrofluorotic subjects (up to 95%) indicates that fluoride has no apparent effect on the thyroid function or on the size of the thyroid gland.

Summary

In pursuit of former observations on hydrofluorosis the authors conducted an investigation concerning the incidence of goiter and the function of the thyroid gland in subjects with hydrofluorosis from Aquaviva Platani, a large endemic center of Sicily. To evaluate thyroid function, radio-iodine uptake and the conversion index (PBI) with ^{131}I were adopted. The incidence of goiter was not higher in endemic centers of hydrofluorosis than in nonfluorotic areas. Endemic goiter in hydrofluorotic areas is not attributable to the action of fluoride

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INCIDENCE OF SIMPLE GOITER IN AREAS OF ENDEMIC FLUOROSIS
IN NALGONDA DISTRICT, ANDHRA PRADESH, INDIA

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For many years, considerable interest has centered upon the metabolic interrelationship of two halogens, fluorine and iodine, and their effect on the thyroid gland. Several studies have been reported concerning the influence of fluorine compounds on the size of the thyroid gland. The reports are conflicting (1-9). It was therefore considered desirable to examine in detail the possible relationship between simple goiter and fluorosis as found in an endemic fluorosis belt in India.

Investigation

The villages of Kamaguda, Yedvelli and Yellareddyguda in Nalgonda District, Andhra Pradesh were selected for the investigation. These villages lie close to each other and are known areas of endemic fluorosis, as indicated in a detailed account published earlier (10). The climate is hot and the temperature in the shade reaches 115° F (46.1°C) in summer. The inhabitants are manual laborers working on tobacco plantations.

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