

J. med. Genet. (1964). **I**, 82.

Endemic Goitre in Greece: Family Studies*

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The evidence implicating iodine deficiency in the aetiology of endemic goitre is overwhelming, and a deficiency of iodine in the diet has been accepted as the main cause of this condition (Kelly and Snedden, 1960; Greer, 1962; Wayne, Koutras, and Alexander, 1964).

Considerations of the quantitative aspects of iodine metabolism leave little doubt that in the presence of a sufficiently severe and prolonged iodine deficiency the development of goitre is an obligatory response if the individual is to remain euthyroid (Riggs, 1952). Nevertheless, it is an old observation that in most endemic areas all the inhabitants are not similarly affected, and that villages with and without endemic goitre may be situated the one near the other, sharing presumably similar food supplies. It is, therefore, probable that when the environmental iodine deficiency is not unusually severe, only certain predisposed individuals may develop a goitre, whereas others similarly exposed do not do so. It has been suggested that in certain cases endemic goitre might be the result of a mild environmental iodine deficiency playing upon a genetic abnormality commonly present in the inhabitants of the community concerned (Stanbury, 1960a). Even Curtis and Fertman (1949) noted that residence for 6 months in the Yunnan district sufficed to induce goitre in 'susceptible' persons, thus distinguishing between more and less susceptible subjects.

The familial factor in simple goitre is obvious in the rare cases of sporadic goitre due to a clearly defined inborn error of iodine metabolism (Stanbury, 1960b), whereas in the endemic goitre areas of Switzerland monozygotic twins did not show any more concordance with respect to goitre than did dizygotic ones (Eugster, 1934). Obviously when the environmental factor is very potent a possible familial predisposition is overshadowed.

In London, however, 134 patients with non-toxic nodular goitre showed a proportion of 41% of non-tasters for phenylthiourea compared to a value of 31.2% derived from normal controls (Harris, Kalmus, and Trotter, 1949), and these results have been confirmed by Kitchin, Howel-Evans, Clarke, McConnell, and Sheppard (1959). In a goitre survey in the Vale of Glamorgan (South Wales), relatives of goitrous patients showed a higher prevalence of goitre than relatives of a control group matched for age and sex (Trotter, Cochrane, Benjamin, Miall, and Exley, 1962). In the same study, goitrous patients appeared to consume less fish than the controls, thus supporting the view that dietary and familial factors may both be important.

In many areas of Greece simple goitre is endemic (Hadjidakis, 1959). In these areas many families are obviously more affected than other ones in the same village, and this has prompted the present study, involving the physical examination and the construction of family trees of all the inhabitants of seven villages in the goitre area.

General Description of the Endemic Area

A field survey on endemic goitre has been conducted during the past few years by mobile units of the Child Welfare Organization, PIKPA, as part of a long-term project in co-operation with UNICEF and WHO. The survey comprises the district of Thessalia with the adjacent portions of the districts of Macedonia and Epirus (Fig. 1); a preliminary report has been published previously (Hadjidakis, 1959). So far endemic goitre has been recognized in 320 villages, some of them on frankly mountainous ground, some of them in valleys or low-lying districts. The villages with a high goitre prevalence do not always form a continuous area, but it is not uncommon to find two severely affected villages separated by a third one where goitre is scarcely detectable. On the whole, a relatively homogeneous goitre prevalence is found

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FIG. 1. Map of the region studied in Thessalia, Central Greece. This shows the four main cities and the seven villages studied.

direct estimate of the iodine content of the diet, but the urinary excretion of iodine* seems to be extremely low, being below 10.0 $\mu\text{g.}$ a day in 9 out of 13 goitrous patients. This is evidence for the presence of a frank iodine deficiency in the majority of the population concerned.

In these endemic areas simple goitre seems to spare newborn infants and to be rare in children below the age of 4. From the age of 5 it appears rather suddenly in both sexes, with a prevalence rate, which is relatively uniform, till the age of 13 years. Children between 10 and 12 seem to have the largest goitres. From the age of 13 and onwards the prevalence drops sharply in boys; however, it remains more or less constant in girls, with the end result that after the age of 17 years the affected persons are almost exclusively women. Fig. 2 shows these results in graph form. The data are based on a survey of 70 villages, where 18,534 children have been examined. Some of these data have been previously published by Hadjidakis (1959).

only in small villages in the mountainous districts, whereas in the lowlands goitrous villages are scattered among non-goitrous ones. Endemic cretinism is not observed.

The food consumed is derived chiefly from local sources, and consists mainly of milk, cheese, bread (usually from wheat, but some also from corn), potatoes, beans, and locally produced fruits and vegetables. In these regions cabbages and related vegetables are not cultivated. Sea fish is practically never eaten, with the occasional exception of small quantities of salted fish. It is difficult to obtain a

TABLE I
GENERAL CHARACTERISTICS OF THE
VILLAGES STUDIED

Village	Location	Altitude in metres	Total Population	Percentage with Goitre
Zarko	Trikkala	100	1693	11
Philia	Karditsa	145	789	22
Kotroni	Trikkala	680	619	11
Kallipefki	Olympus	1050	1604	53
Mikro Perivoli	Magnesia	200	423	42
Gonni	Larissa	110	2584	39
Ossa	Larissa	130	846	37

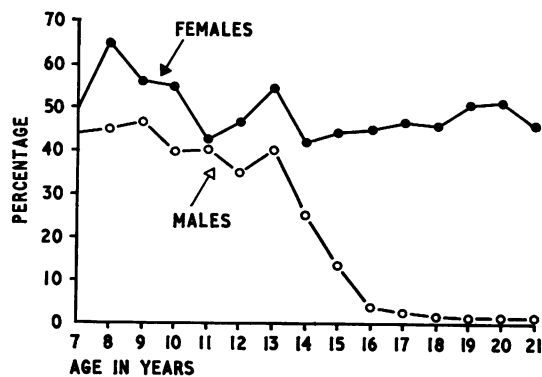


FIG. 2. Goitre prevalence according to age and sex. Results obtained from 70 villages with endemic goitre.

Methods of Family Studies

Since goitre prevalence differs strikingly from village to village, a comparison has been made of the families living within the same village, and this has been repeated in 7 villages, the general characteristics of which are shown in Table I. For this purpose complete family trees have been constructed for all the inhabitants of these villages by studying the birth and marriage registers of the communities concerned. For each person living a card was made, and then one of us (S.G.H.) examined the person concerned to check whether goitre was present or not. Repeated visits to these villages were required, but this ensured a uniform criterion. Persons dead or having permanently left the village were not taken into consideration. A goitre

* Determined through the courtesy of Dr W. D. Alexander, Western Infirmary, Glasgow.

was considered to be present if there was a visible enlargement of the thyroid gland under standard conditions of observation, that is with the observer standing directly in front of the subject who extended his head upwards, so that the manubrium sterni and the hair-line were equally distant from a line connecting the two earlobes (Fig. 3). The goitre, if present, was visible below

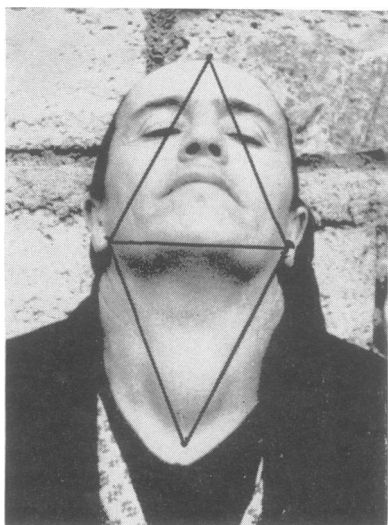


FIG. 3. Position in which the person is examined for the presence of goitre. The head is extended upwards, so that the hair-line and the manubrium sterni are equally distant from the line connecting the earlobes.

this line. In every case where a goitre was visible this was subsequently confirmed by palpation and by instructing the person to swallow.

The family trees constructed were analysed in the following way. For each couple and their offspring the mother was classified as goitrous or non-goitrous and the prevalence of goitre in all her living children was calculated. Similarly, the first child of each family

was classified as goitrous or non-goitrous and the prevalence of goitre in his younger brothers or sisters was calculated. The same procedure was repeated for girls only. Mothers with a goitre had on an average the same number of children as those without a goitre, and this suggests that they were of about the same average age and that their children also had a similar age distribution.

Results

Presence of Goitre in the Mother. Table II shows that when the mother is goitrous there is an increased prevalence of goitre in her children, usually 2-3 times more than when the mother has no goitre, but in the village Gonni 68% of the children from goitrous mothers also had a goitre, compared with a prevalence of 8.5% in those whose mother was not affected. In each village studied the difference is highly significant statistically ($p < 0.001$).

Mother-daughter Studies. From Table III it is evident that similar considerations apply when only the daughters of goitrous mothers are examined. The prevalence of goitre in the daughters is much increased when the mother also has a goitre, i.e. about 2-4 times the prevalence found in the daughters of mothers without goitre. The difference is highly significant ($p < 0.001$), except for the village Ossa, where it is just significant ($p < 0.05$). On the whole the prevalence of goitre in daughters is higher than that in children in general, especially in villages like Zarko and Philia, where the over-all goitre prevalence is below 25%. The ratio, however, of the goitre prevalence in children of affected mothers over that of unaffected ones is not very different from a similar ratio derived from the study of the daughters only.

TABLE II
PREVALENCE RATES IN CHILDREN ACCORDING TO WHETHER THEIR MOTHER HAS A GOITRE OR NOT

Villages	Mother with Goitre					Mother without Goitre					p Value of Difference
	No. of Families	Children				No. of Families	Children				
		Total	With Goitre	Without Goitre	Percentage with Goitre		Total	With Goitre	Without Goitre	Percentage with Goitre	
Zarko	66	165	51	114	30.9	500	1318	192	1126	14.6	< 0.001
Philia	67	272	51	221	18.7	316	937	93	844	9.9	< 0.001
Kotroni	9	28	12	16	42.9	170	488	66	422	13.5	< 0.001
Kallipefki	147	458	284	174	62.0	104	329	145	184	44.1	< 0.100
Mikro Perivoli	40	121	89	32	73.6	28	80	23	57	28.7	< 0.001
Gonni	166	528	357	171	67.6	142	377	32	345	8.5	< 0.001
Ossa	68	149	86	63	57.7	74	186	63	123	33.9	< 0.001

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TABLE III

PREVALENCE RATES IN DAUGHTERS ACCORDING TO WHETHER THEIR MOTHER HAS A GOITRE OR NOT

Village	Mother with Goitre					Mother without Goitre					p Value of Difference
	No. of Families	Daughter				No. of Families	Daughter				
		Total	With Goitre	Without Goitre	Percentage with Goitre		Total	With Goitre	Without Goitre	Percentage with Goitre	
Zarko	43	67	34	33	50.7	353	606	137	469	22.6	< 0.001
Philia	51	87	34	53	39.1	207	403	71	332	17.6	< 0.001
Kotroni	9	17	10	7	58.8	127	279	39	240	14.0	< 0.001
Kallipefki	104	200	160	40	80.0	104	207	123	84	59.4	< 0.001
Mikro Perivoli	39	71	60	11	84.5	24	35	14	21	40.0	< 0.001
Gonni	147	258	198	60	76.7	117	195	25	170	12.8	< 0.001
Ossa	57	77	63	14	81.8	56	82	54	28	65.9	< 0.05

TABLE IV

PREVALENCE RATES IN YOUNGER SIBS, ACCORDING TO WHETHER FIRST SIB HAS A GOITRE OR NOT

Village	First Child with Goitre					First Child without Goitre					p Value of Difference
	No. of Families	Sibs Other Than First				No. of Families	Sibs Other Than First				
		Total	With Goitre	Without Goitre	Percentage with Goitre		Total	With Goitre	Without Goitre	Percentage with Goitre	
Zarko	70	128	36	92	28.1	418	900	128	772	14.2	< 0.001
Philia	43	102	35	67	34.3	244	595	59	536	9.9	< 0.001
Kotroni	20	41	14	27	34.1	145	374	50	324	13.4	< 0.001
Kallipefki	158	430	267	163	62.1	159	377	146	231	38.7	< 0.001
Mikro Perivoli	26	62	51	11	82.3	39	91	33	58	36.3	< 0.001
Gonni	98	220	164	56	74.5	231	535	123	412	23.0	< 0.001
Ossa	50	72	47	25	65.3	85	139	45	94	32.4	< 0.001

Presence or Not of Goitre in First Sib.

Table IV shows that in sibships where the first sib is goitrous, there is an increased prevalence of goitre in the younger sibs, about two to three times the goitre prevalence found in other sibships living in the same village. In each village the difference is highly significant statistically ($p < 0.001$).

Presence of Goitre in First Sister.

When the first daughter in a sibship has a goitre, her younger sisters are more heavily affected than when the first daughter is not affected (Table V). The difference is statistically significant with $p < 0.001$ for Zarko, Philia, Kotroni, and Kallipefki, $p < 0.005$ for Mikro Perivoli, with $p < 0.05$ for Ossa. The genetical predisposition seems to be more

TABLE V

PREVALENCE RATES IN YOUNGER SISTERS, ACCORDING TO WHETHER FIRST SISTER HAS A GOITRE OR NOT

Village	First Sister with Goitre					First Sister without Goitre					p Value of Difference
	No. of Families	Sisters Other Than First				No. of Families	Sisters Other Than First				
		Total	With Goitre	Without Goitre	Percentage with Goitre		Total	With Goitre	Without Goitre	Percentage with Goitre	
Zarko	37	52	27	25	51.9	113	191	22	169	11.5	< 0.001
Philia	24	50	23	27	46.0	54	97	12	85	12.4	< 0.001
Kotroni	17	30	15	15	50.0	70	117	16	101	13.7	< 0.001
Kallipefki	95	170	125	45	73.5	34	61	26	35	42.6	< 0.001
Mikro Perivoli	14	38	28	10	73.7	8	25	8	17	32.0	< 0.005
Gonni	58					63					
Ossa	27	29	25	4	86.2	5	8	3	5	37.5	< 0.05

prominent here than for sibs in general, because in villages like Zarko, Philia, and Kotroni with only a moderate over-all prevalence of goitre, sisters of affected first daughters show a four-fold increase in goitre prevalence.

Presence of Goitre in the Father. Few adult men are affected with goitre, and thus an adequate study of the paternal genetical predisposition cannot be done. Nevertheless, in Zarko 6 fathers had a goitre, whereas their wives had not. Of their 11 offspring, 4 were goitrous, i.e. a prevalence of 36%, which is not very different from the figure of 31% found for the offspring of goitrous mothers. In Kallipefki, 2 fathers had a goitre and 2 of their 6 children were also goitrous. In a third family both parents were affected, yet neither of their 2 children had a goitre. In 2 similar families in Mikro Perivoli, 1 of the 2 children had a goitre.

Presence of Goitre in the Paternal Grandmother. In 12 families in Ossa a goitre was present both in the paternal grandmother and the mother. Of the 23 children of these families, 13 had a goitre, a prevalence rate of 61%, compared with 58% for the children of goitrous mothers at large. These two prevalence rates do not seem very different, but the small number of cases preclude an adequate statistical comparison. Of these 23 children, 8 were girls, and of these, 5 had a goitre.

Discussion

The results presented above leave no doubt that, in the regions studied, endemic goitre affects some families more than others. This could be due either to similar environmental conditions to which members of the same family are exposed, or to a true genetic factor, i.e. an inherited susceptibility to develop a goitre in the presence of a relatively mild iodine deficiency.

The first of these possibilities cannot be dismissed off-hand. Ligdas (1953) has suggested that in some regions goitrous patients seem to eat less fish than normal persons living in the same region, and repeated studies in Glasgow (Koutras, Alexander, Buchanan, Crooks, and Wayne, 1960; Alexander, Koutras, Crooks, Buchanan, Macdonald, Richmond, and Wayne, 1962; Wayne *et al.*, 1964) have consistently shown that goitrous patients, as a group, have a lower mean dietary iodine intake than controls from the same region, and that this difference is even greater if only

goitrous cases with a high radioiodine uptake are considered. It is, therefore, possible that in the endemic regions here reported some families may supplement their usual diet by salted fish from time to time, whereas others do not. Nevertheless, though this factor is probably operating in a few individuals, it seems unlikely that it could be the whole explanation, since the regular consumption of salted fish is too infrequent to protect more than a few exceptional families. Questionnaires did not reveal an obvious systematic dietary difference in the various families. Even in Glasgow (Wayne *et al.*, 1964), if individual figures are considered, the impression is that the dietary iodine intake of the goitrous patients seems to lie at the lower end of the normal distribution curve rather than below it.

We are, therefore, inclined to conclude, though very tentatively, that a true genetic factor is indeed implicated in the endemic goitre studied. From the data available this genetic factor does not seem to be inherited in a clear Mendelian fashion, nor can this problem be easily solved for two reasons. First, a goitre, especially in males, may disappear after puberty, and so the person concerned may be classified as non-goitrous, whereas in fact he may have the same genetic make-up as his goitrous young son, and, secondly, environmental factors have a big influence on the expression of the genotype. Trotter and his associates (1962) point out that sibs of goitrous persons do not seem to be more affected than parents, and this points against a recessive mode of inheritance. From the present study it is evident that adult males have less goitre than young boys, and so the comparison of the prevalence rates in fathers and brothers respectively is not a satisfactory one. In any case, the theory that the susceptibility to goitre is transmitted as a dominant character, and that this susceptibility takes the form of a disease only in the presence of a suitable environment (iodine deficiency) seems compatible with the present findings.

If a genetic factor is indeed implicated in the development of endemic goitre in Greece, one might speculate about its mode of action. None of the known inborn defects responsible for some cases of sporadic familial goitre and cretinism has been detected in endemic goitre (Murray and Stanbury, 1962).

On the other hand, an increased renal clearance of iodide has been suggested as a cause of iodine loss and goitre (Cassano, Baschieri, and Andreani, 1957, 1959). More recent studies in Glasgow have confirmed that goitrous patients have a higher mean renal iodide clearance than matched controls

(Wayne *et al.*, 1964). Furthermore, an excessive iodine loss with the faeces has also been suggested as a cause of goitre (Van Middlesworth, 1960).

It is thus possible that a genetic factor may increase the rate of elimination of iodine from the body, and in this way lower the concentration of the plasma inorganic iodine (PII). If exogenous iodine supply is limited, goitre will ensue.

Alternatively, the thyroid itself may be genetically more prone to develop iodine-deficiency goitre. Studies in rodents have shown that some strains have a lower thyroid/serum (T/S) ratio but a larger gland than others (Silverstein, Sokoloff, Mickelson, and Jay, 1960; Silverstein and Lee, 1961), and it is possible that these may more readily develop thyroid enlargement when a marginal drop in the plasma inorganic iodine level occurs. This trait, if shown in humans, could be considered as a partial form of the congenital absence of an iodide-concentrating mechanism described in a case of sporadic goitrous cretinism (Stanbury and Chapman, 1960).

The present data do not permit a clearer appreciation of the nature of the familial factor involved in endemic goitre, but a large-scale study has now started, which, it is hoped, will shed some light on this perplexing problem.

Summary

The entire population of 7 villages in the endemic goitre district of Central Greece has been examined. It was found that when the mother was goitrous, her children showed goitre in a greater proportion than the children of non-goitrous mothers; and that when the first sib in a sibship was goitrous, the younger sibs also had a higher prevalence of goitre. Few adult men are affected, and so the influence of the presence of goitre in the father cannot be tested statistically. It is concluded that the results obtained are best explained by the presence of an inherited factor, predisposing to goitre development in the presence of a relatively mild environmental iodine deficiency.

We wish to thank Professor B. Malamos for his helpful advice and comments.

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J Med Genet 1964 1: 82-87
doi: 10.1136/jmg.1.2.82

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