MIDDLES

For debate: Drifting continents and endemic goitre in northern Pakistan

Alex G Stewart

Abstract

Although Baltistan, north east Pakistan, is in a region of iodine deficiency disorders, the distribution of goitre within the district, according to age and sex, has not been clearly defined. To establish the prevalence of the condition and to measure the reported difference in prevalence in the north and south of the district thyroid size was assessed in new patients attending the Aman clinic, Khapalu, and outlying areas between April and September from 1981 to 1986. Samples of potable water collected from villages were analysed for iodine (as iodide) concentrations in Britain. Population weighted prevalences were: in the north in males 20·4%, in females 28·1% and in the south in males 13·9%, in females 21·2%. There was an overall deficiency of iodine in the water (mean iodine (as iodide) concentrations (north) 11·0 nmol/l (1·4 μg/l), (south) 11·8 nmol/l (1·5 μg/l) (95% confidence interval −0·7 to 0·9). The differences followed the Main Karakoram Thrust, suggesting a geological goitrogen in the north, which might be minerals containing ions such as BF_4^- and SO_3F^-, and molybdenite and calcium, which are present in rocks in Baltistan.

A new hypothesis for the genesis of endemic goitre is proposed—that is, that continents on crustal plates drift across the earth and collide, one plate sliding under the other and melting, giving rise to characteristic mineral assemblages in the overlying rocks. As the minerals weather out they enter the diet of the local population, where in the presence of iodine deficiency they produce or enhance iodine deficiency disorders.

Despite the current iodised oil campaign by the Pakistani government with Unicef a long term working iodisation programme is still urgently needed.

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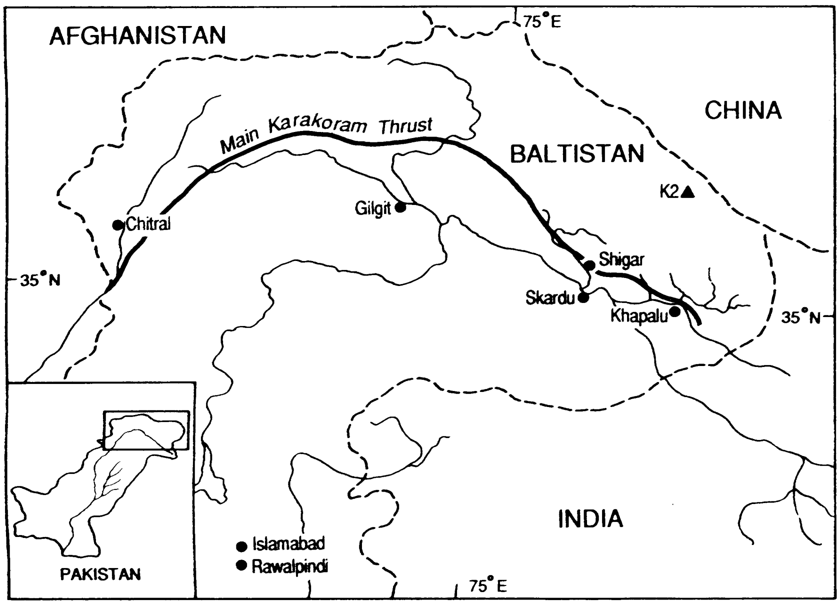

FIG 1—*Northern Pakistan, showing Main Karakoram Thrust, the suture between Asia and the Indian subcontinent*

Introduction

The bare but beautiful valleys of Baltistan in the north east of Pakistan lie within the belt of iodine deficiency disorders spreading from Bukhara and Samarkand in southern Soviet Union along the Himalayas and down through South East Asia to Papua New Guinea and New Britain.[1] Although McCarrison did his early work on goitre and cretinism in the neighbouring valleys of Gilgit and Chitral over 80 years ago,[2] it is only in the past decade that goitre has been studied in Baltistan. An overall prevalence of goitre of 68% was found in schoolchildren in Shigar,[3] and a further study in the general population of the Shigar valley found a prevalence of 77%, with a prevalence of cretinism of 11%.[4] Unfortunately, neither of the studies specified clearly the age and sex breakdown of the samples studied, and as prevalence of goitre can vary appreciably with age and sex the importance of these results is not clear. The first aim of this study was to provide a clear picture of the distribution of goitre within the community in the standard age and sex groups.[5]

The Shigar valley has long been known to be associated with goitre. Filipo de Filippi, reporting on a year spent exploring in and around Baltistan with the Duke of Abruzzi,[6] noted many goitres and some rachitic deformity (cretinism?) in Shigar. He wrote of the Shigaris that they are "neither so good looking nor so healthy" as the people in Skardu. The Baltis themselves reckon that in the Shigar valley one person in 10 is goitrous whereas in the other main centres of population, Skardu and Khapalu, the rate is only one in 100 (fig 1). They also point out that the Thale valley, which backs on to Shigar, and the neighbouring Hushe valley are centres of goitre. The differences between the northern and southern Baltis in goitre and cretinism are indeed striking even to casual observers; the only reason that no previous work has been done on this problem must simply be the isolation of the whole area. The second aim of this study was to measure this difference in prevalence of goitre.

If it is true that there is a startling difference in local prevalences of goitre then it is likely that the reason would be something equally divergent between the two areas. Culturally, linguistically, and socially the Baltis are a compact whole. Though there is some ethnic difference, it follows an east-west course, not a north-south one. The major known disconformity is in the structural geology of the area. The Main Karakoram Thrust is a continuation in Pakistan of the Indus-Tsangpo line in Tibet and Ladakh (India). It forms part of the suture between Eurasia to the north and India to the south, formed by the Indian plate smashing into the Eurasian plate. In Baltistan it is known on the north (right) bank of the Shyok river across from Khapalu, and in the Shigar valley. The third aim of this study was to investigate the possible connection between the suture and the difference in prevalence of goitre.

Patients and methods

Patients in Baltistan do not attend clinics for goitre, having enough other medical problems to contend with, nor does a goitre affect their way of life or mobility. It is seen as a simple fact of life, like eye colour. Thus I thought that it was sufficient to assess new patients presenting at the clinic according to the World Health Organisation 1979 classification.[5] More women than men, however, tend to be ill and so a greater number of women were seen. Patients seen in clinics held in outlying areas were also assessed after excluding any already seen in the clinic in Khapalu. As the clinic operates only in summer all observations were made between April and September from 1981 to 1986, except for a small group of patients seen in February 1985 near Shigar. Village totals were calculated by age and sex. Various area totals were then obtained for comparison, including all villages north and south of the suture line. A total prevalence weighted by population was also calculated.[5] Statistical comparison was by logistic regression and calculating confidence intervals.[7,8] Logistic regression is useful when several factors such as age, sex, and geographical distribution may affect the variable under study.

Water samples from potable sources were taken in 10 ml glass bottles with inert plastic lids without wadding. The bottles were rinsed three times in the water to be sampled, and the fourth filling was retained. Water from springs and rivers were sampled, according to the source of the village drinking water.

TABLE I—*Prevalence of goitre in Baltistan across Main Karakoram Thrust. Figures are numbers (percentages)*

	North				South*			
Age (years)	No of subjects	No with goitre	No with visible goitre†	No with adenoma	No of subjects	No with goitre	No with visible goitre†	No with adenoma
				Females				
≥19	902	705 (78)	470 (52)	193 (21)	1871	1134 (61)	650 (35)	191 (10)
13-18	85	55 (65)	23 (27)	8 (9)	210	104 (50)	42 (20)	5 (2)
6-12	55	27 (49)	8 (15)	3 (5)	254	80 (31)	22 (9)	11 (4)
0-5	35	3 (9)	1 (3)	0	121	4 (3)	0	0
				Males				
≥19	560	203 (36)	113 (20)	63 (11)	1113	239 (21)	114 (10)	48 (4)
13-18	136	57 (42)	18 (13)	5 (4)	211	79 (37)	21 (10)	10 (5)
6-12	94	45 (48)	8 (9)	1 (1)	365	136 (37)	31 (8)	6 (2)
0-5	29	2 (7)	0	0	176	16 (9)	2 (1)	0

*p<0·01 (95% confidence interval for odds ratio 45 to 55%).
†Visible goitre=goitre size ≥2.[4]

TABLE II—*Population weighted* prevalence of goitre in Baltistan across Main Karakoram Thrust by age and sex*

		North		South	
Age (years)	Total population (%)	Unweighted prevalence (%)	Weighted prevalence	Unweighted prevalence (%)	Weighted prevalence
0-5:					
Male	4·9	7	0·3	9	0·4
Female	4·7	9	0·4	3	0·1
6-12:					
Male	8·8	48	4·2	37	3·3
Female	7·1	49	3·5	31	2·2
13-18:					
Male	7·9	42	3·3	37	2·9
Female	3·6	65	2·3	50	1·8
≥19:					
Male	34·9	36	12·6	21	7·3
Female	28·1	78	21·9	61	17·1
Total:					
Male	56·5		20·4		13·9
Female	43·5		28·1		21·2
All	100·0		48·5		35·1

*Total population×relevant prevalence of goitre/100.

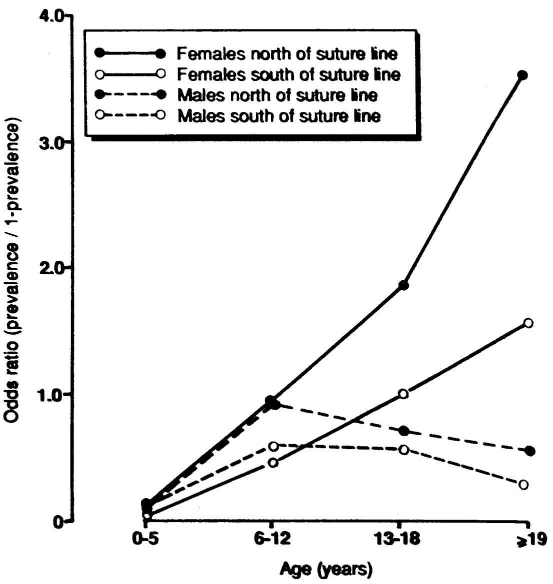

FIG 2—*Odds ratios for goitre in Baltistan north and south of Main Karakoram Thrust taking into account age, sex, and region (the shapes of the graphs are very similar to graphs of prevalence v age)*

Samples were sent to the Hydrological Institute, Wallingford, Oxfordshire, for analysis after filtration through filter paper and an 0·45 μm microfilter to remove sediment and bacteria respectively. Clear samples were rendered bacteriologically safe by more than two hours' exposure to sunlight to protect laboratory staff from exotic diseases.

Iodine in the samples was determined as iodide by an automated colorimetric procedure utilising the catalytic effect of iodine on the reactions between cerium (IV) and arsenic (III).[9] Spatial statistical analysis was by *t* test, and confidence intervals were calculated. The Mann-Whitney U test was used for the non-parametric temporal analysis. Intramuscular iodised oil (Lipoidal) was given to any goitrous woman of childbearing age, any goitrous infertile man (both 2 ml), any goitrous child, and to any non-goitrous infertile man or woman (all 1 ml) as supplies of oil allowed.

Results

A total of 6217 persons were screened, of whom 2684 (43%) were male and 3533 (57%) female; 1896 (30%) lived to the north of the suture line and 4321 (70%) lived to the south. The comparable proportions for the population of Baltistan are 54% (male), 46% (female); 26% (total north of the suture), and 74% (south of suture). The sample covered 3·4% of the northern population and 2·7% of the southern.

Table I shows the results of screening for goitre by age, sex, and region. Logistic regression showed that these variables were all important factors in the various prevalences of goitre. As expected, age and sex showed a statistical interaction, but the regional differences were independent (all at p<0·01). The only consistent difference when age and sex groups were totalled according to village distribution was across the suture line (fig 2). An approximate 95% confidence interval for the decrease in odds ratio for the south over the north was 44% to 55%. This was borne out in the figure, in which the regression line for females in the south was about half the height of that for females in the north at all points. The population weighted prevalence (table II) gave the best total figures for comparing with other areas, while bearing out the north-south difference in prevalence of goitre. It also emphasised that almost half the prevalence of goitre was among the adult women.

The prevalence of visible goitre was high, being found even in the 0-5 age group. Adenomas (table I) were a common finding from puberty onwards, but such is the severity of the endemia that some adenomas were found before the age of 12. Though I did not make a formal survey of cretinism, my general impressions were consistent with the differences in prevalence of goitre, in that many cretins were easily seen in the northern villages whereas in the south few were to be found and their disability was also less severe. Most, if not all, were neurological cretins.

Spatial analysis of the water samples gave the following results: mean (SD) iodine as iodide concentrations in the north (n=17) 11·0 (10·2) nmol/l (1·4 (1·3) μg/l) and in the south (n=20) 11·8 (8·7) nmol/l (1·5 (1·1) μg/l) (t=0·1631, df=35, p>0·5, 95% confidence interval −0·7 to 0·9) and for all samples (n=44), including streams not usually used as a water supply and four samples from villages whose relation to the suture is unclear, 11·8 (8·7) nmol/l (1·5 (1·1) μg/l) (standard error of mean 0·165, 95% confidence interval 1·2 to 1·9). No sample had an iodide concentration >31·5 nmol/l (>4·0 μg/l).

Temporal analysis showed mean (SD) iodine as iodide concentrations as follows: April (n=14) 6·3 (3·15) nmol/l (0·8 (0·4) μg/l)); June (n=8) 15·75 (6·3) nmol/l (2·0 (0·8) μg/l); and September (n=9) 22·8 (4·7) nmol/l (2·9 (0·6) μg/l); Mann-Whitney one sided U test April-June=7·5, p<0·005; June-September=12, 0·24>p>0·005.

Discussion

The prevalences of goitre in this survey are in keeping with the general severity of iodine deficiency disorders across the whole Himalayan range. The highest rates of iodine deficiency disorders are found in Bhutan and Nepal[10] on the southern and opposite side of the Himalayan watershed, but Ramalingaswami *et al* found a prevalence of almost 100% in schoolchildren in Bihar,[11] well to the south of the Himalayas. Adenomas are notoriously difficult to observe accurately and are easier to find in large thyroids.[12] Prevalences of adenomas must therefore be treated with caution, but a measure of the size of the problem in the Baltis is that adenomas were found not only in adults but also in 21 children (3·2%) aged 6-12 (table I). As a percentage of goitres in this age group 17% were adenomatous. Given that in smaller goitres the rate of perception of adenomas is low, this prevalence is a serious problem and would lead to a suspicion of a wide range of iodine deficiency disorders. Skin disorders, deafness, infertility, abortions, and cretinism in the human population and poor wool from the goats and sheep are well known in the area. Nevertheless, there was no frank abnormality of thyroid stimulating hormone in 135 adult patients (unpublished results), and almost no clinical hypothyroidism was seen during the study. This accords with McCarrison's observation that most of the cretins he saw were deaf,[2] indicating that neurological cretinism is the normal local form, as is also the case in Nepal.[13] A similar situation exists in other endemias in young mountain ranges in New Guinea[14] and South America.[15] In pronounced contrast is the situation in Zaire, where hypothyroidism is common.[16]

With an average water iodine content of 11·8 nmol/l (1·5 μg/l) the area may be considered to be iodine deficient. The average concentration of iodine in surface water is usually taken as 40 nmol/l (5 μg/l),[17,18] but there is not sufficient knowledge to delineate a minimum desirable concentration. There have been few studies of iodine content in water in the Himalayas and Karakoram, but all indicate iodine deficiency. The results of Tulpule[19] in India are considerably higher than any others, but in his two northern states with endemic goitre water iodine concentrations were a third of those of the rest of the country. Also Karmarkar *et al* found the lowest iodine concentrations in water in the area of highest goitre.[20] Day and Powell-Jackson found low iodine concentrations in Nepal,[21] as did Chapman *et al* in Gilgit.[22] Studies of urinary iodide concentration in Nepal showed that in people untouched by iodisation 85% had iodine deficiency and a third had severe deficiency.[23] It is, therefore, consistent that iodine deficiency is the basic cause of the endemia among Baltis.

There is, however, appreciable seasonal variation in iodine concentration in Baltistan from 6·3 nmol/l (0·8 μg/l) in April to 22·8 nmol/l (2·9 μg/l) in September. With the increasing temperatures in the spring the snow cover melts and the rivers increase in volume and speed to an August maximum. The minimum flow in February is a tenth of this. The carrying capacity of a river varies exponentially with the flow rate. The threefold increase in water iodine concentration from April to September thus requires only a small increase in flow rate. This seasonal swing in available iodine could explain adenomas being so common, as a cyclical change in iodine supply will result in a cyclical change in size of the thyroid. It is worth noting that even the maximum iodine concentrations are still well below average.

Women had nearly half of all the goitres present (table II). Most of the resulting morbidity from iodine deficiency disorders is focused in pregnancy, fetal life, and infancy.[24] A salt iodisation plant established in Skardu, the main town of Baltistan, in the late 1950s has not been functioning for at least the past 15 years. Iodised salt is manufactured in Rawalpindi and Peshawar but not yet in sufficient quantity to cope with all the needs of Baltistan, let alone the whole goitrous belt in northern Pakistan. So far the salt iodisation programme has had little effect in the hills; with 98% of hill families using non-iodised rock salt and only 1% using iodised salt[25] there is a long way to go. The current iodised oil campaign by the government with Unicef faces difficulties of isolation and the seclusion of women, but it could be completed successfully given enough staff and encouragement. A long term working iodisation programme remains an urgent necessity.

NORTH-SOUTH DIFFERENCES

For the long term control of iodine deficiency disorders in Baltistan and possibly the whole of the north of Pakistan, however, an understanding of the spatial difference in prevalences of goitre in the Balti valleys is needed. Tables I and II confirm the empirical observations by the Baltis of a difference in the prevalence of goitre between northern and southern valleys. Although the 10-fold difference the Baltis described was not substantiated there was a twofold rise in the prevalence of visible goitre in men aged 19 or over in the northern villages compared with those in the southern villages and a 1·5-fold increase in women aged 19 or over. The difference extended to girls aged 6-12 and males aged 13-18 in the total rates, and the trend was present in boys aged 6-12. Differences in rates are well known in areas of endemic goitre. They are often minor, but if they are major the changes progress across large areas.[26] In few other situations, if any, is such a large difference so pronounced, so close, and so abrupt in its occurrence. The north-south difference follows the suture line; no other possible distribution gave such a clear result. The suture line as boundary also fits with the local observations of the prevalence of goitre and occurrence of cretinism. Tahirkheli located the Main Karakoram Thrust at Muchlu, north of Khapalu, and at Shigar, north of Skardu, and projected a line between them.[27] This projection has been shown to be wrong; for at least 20 km west of Muchlu the thrust runs along the northern side of the Shyok valley before turning northwards up the Thale valley towards the main Shigar valley (M Searle, A Barnicoat, personal communication). This allows a much more accurate analysis of the distribution of goitre. The villages on the northern side of the Shyok river west of Khapalu are situated to the south of the suture, but all receive their irrigation and drinking water from the north of the line and were treated as northern villages. The suture has not been defined east of Khapalu, but it is likely to run along the Shyok valley as it is known at the Shyok-Nubra confluence some 80 km upstream from Khapalu. Also the Tsaltaro valley north east of Khapalu has a high prevalence of goitre consistent with being on the northern side.

The prevalences of goitre in the north in this survey are at first glance lower than in the two previous surveys in Baltistan. The report by the Nutrition Cell Planning Division of the Pakistan government on schoolchildren in the Shigar valley reported a prevalence of 72% in 6-12 year olds and 61% in 13-18 year olds[3] whereas in 1980 an overall prevalence of 77% was given for the same valley.[4] This 1980 report has no age and sex breakdown and is thus impossible to compare with any other survey, as it is not known which group is dominant. This is where the population weighted prevalence (table II) comes into its own[5] as it compensates for different sizes of different age groups and allows only the truly dominant group to dominate. The government report is also vague as to whether any girls are included or not. But if the prevalences of visible goitre in this study are compared there is no difference. In boys aged 6-12 years the prevalence of visible goitre is quoted in the report as 4% (difference 5%, 95% confidence interval −2% to 12%, $\chi^2=1\cdot671$, $p>0\cdot10$) and in males aged 13-18 it is 13% (difference 0%, −18% to 18%, $\chi^2=0\cdot0058$, $p>0\cdot50$); the differences lie in the 1a and 1b classes, which are notoriously prone to interobserver variation.

When the northern and southern prevalences are compared in the same age and sex groups a reasonably consistent picture emerges of the strength of the difference: 15-18% is added on to the southern rates. This consistency implies a northern goitrogen that is widely distributed in the community. The excess of goitre in puberty in an otherwise non-goitrous community is usually about 10% so the northern goitrogen exerts an effect of about 1·5 times this.

SUTURE ZONE

In considering the spatial difference in prevalence racial and dietary differences cannot be ruled out completely. Racially the Baltis are of Tibetan origin, with a small addition of more Western Asian blood through the ruling families. There is a gradation from east to west in the amount of this mixture, but any differences in prevalence of goitre are north-south, not east-west differences. Diet is also uniform across the area, and though fresh or dried apricots are an important food, only the sweeter strains give kernels that are eaten. Even the oil of the more bitter strains, which are richer in thiocyanate, is not used in cooking. It remains a possibility that some of the goitre on both sides is caused by ingestion of apricot kernels. Nevertheless, considering the uniformity of the community and the close statistical link between the line of the suture and the distribution of goitre, it is highly unlikely that dietary or racial factors account for the spatial differences in prevalence of goitre. The iodine concentration in potable waters on both sides of the suture line is nearly identical. This is not surprising as the main source of iodine is the atmosphere[17 18] and the weather pattern across the area is uniform. The whole of Baltistan lies in the trans Himalayan rain shadow and is a moderate to high altitude desert.

The suture line itself is a narrow zone of a few hundred metres width, which can often be seen as a pale stripe along the hills on the north of the Indus and Shyok rivers. To the north lies the Asian continental plate, to the south an arc of offshore islands, turned on their side as they were caught between Asia and the northward driving India. Such an island arc is found where two plates of the earth's crust collide, one subducting under the other.[28] The arc can be formed of material from either plate. The origin of the Kohistan and Deosai islands in the south of Baltisan are as yet unclear, but the island arc remnants east and west are believed to be Asian rather than Indian. Modern examples of island arcs in situ are the Indonesian and Japanese island chains. The Kohistan and Deosai islands consist of a vertical slice of material from deep within the earth's crust up to the surface, turned so that the deep material is found at the southern edge of the arc against India and the surface abuts Asia. The Asian plate at this point is made up of an elongated block of granite edged by a metamorphic zone and termed the main Karakoram batholith. The metamorphism was a result of the pressures and temperatures generated by the collision.[27] It is becoming clearer that certain assemblages of elements are associated with subduction zones. Molybdenum, lithium, boron, and fluorine are all recognised as being concentrated in these areas. This is due to the common factors in subduction zones of crustal melting, rising heat, and rising water vapour, causing characteristic mineral changes within even widely ranging structural geological facies (fig 3).

In Baltistan tourmaline, containing BF_4^- ions, graphite schists (fool's gold), containing SO_3F^- ions, molbdenite (MoS_2), and calcium are known. In the contiguous rocks in Afghanistan lithium mica has been found in pegmatites and granites and, though expected in Pakistan, has not yet been reported (Qasim Jan, personal communication); BF_4^- ions, SO_3F^- ions, molybdate, calcium, and lithium are all known goitrogens.[29-33] Any one of them, either alone or in combination, might be the cause of the northern excess of goitre. So many possibilities, though making the discovery of the northern goitrogen more difficult, add weight to the idea that it is geological in origin.

It remains possible that the goitrogen is as yet unsuspected. Gaitan *et al* found a large molecule in Colombian water acting as a goitrogen,[34] but such a possibility is unlikely here because of the intense heat the rocks have been subjected to. The goitrogen in Baltistan may, like thiocyanate, depend for its action on a ratio of iodine to goitrogen. Studies in Sicily[35] and Zaire[36] have shown that a urinary iodine to thiocyanate ratio of two or less leads to goitre. This may also be an important principle in the genesis of goitre elsewhere.

OTHER AREAS

The suture line extends west from Baltistan through the Gilgit and Chitral districts into Afghanistan. When the study of Sardar-ul-Mulk *et al*[37] in Maroi (24 km north of Chitral town and north of the suture) was compared with that of Chapman *et al*,[22] retesting McCarrison's theory of bacterial pollution in Dainyor (a village near Gilgit town and south of the suture) similar results to those of this study were obtained. In Maroi the prevalence of visible goitre in females aged ≥21 was 85% and in those aged 11-20, 73%, and 0-10, 28%; the prevalence in males aged ≥21 was 55% and in those aged 11-20, 63%, and 0-10, 31%. In Dainyor the prevalence in females was 65%, 40%, and 20% respectively and in males was 39%, 44%, and 13% respectively. Logistic regression showed that the difference was affected by age and sex interactively and by region independently ($p<0\cdot01$, approximate

95% confidence interval of odds ratio 33% to 55%). The prevalences of visible goitre were compared as being less subjective, but all authors of the Maroi study had participated in the Dainyor study four years earlier. This supports the idea that the local geology has a real effect on the genesis of goitre.

It would be interesting to check the wider situation to the west and east. Though it may not be easy to do so in the Afghan, many older refugees reside in Pakistan, and older people, particularly those with large adenomatous goitres, reflect earlier influences even though better iodine supplies recently will cloud the picture. Further east it has not been possible to check any surveys across the suture, but it is noteworthy that the trend of the Himalayan goitre belt as it extends east and south is along the Indo-Asian plate boundary. Burma has areas in the north where iodine concentration and prevalence of goitre are not correlated,[38] which lie on the Asian side of the suture. Indonesia also lies to the north and is notorious for goitre. There is a report from Java of a lack of correlation between water iodine concentration and goitre[38]; cretinism is also high, as it is in northern Baltistan. New Guinea is well known for its iodine deficiency diseases. Like Baltistan it is formed by the collision of the Indo-Australian plate in the south with another to the north, though here the northern plate has subducted under New Guinea. Leaching of iodine from the soil is an often quoted cause of goitre in New Guinea, but this seems to be merely unsubstantiated speculation. Is it not possible that the plate boundary has some part to play in this continuous goitre belt?

The Alps are a similar mountain chain to the Himalayas, raised by continental collision, and southern Europe is a hotchpotch of little plates ground between Europe and Africa. Western Central and South America have a subduction zone offshore, as has some of North America. Indeed, the Cascade mountains are thought to be an old island arc welded on to the northern continent. North Island, New Zealand, and Japan and the Philippines are all close to subduction zones. Endemic goitre exists throughout these areas, all of which lie on the same side of the subduction zone suture (fig 3). Iodine deficiency is well recognised as the cause of endemic goitre. In several places, however, goitrogens are recognised as playing a part also. Thiocyanate is known to be goitrogenic only in the presence of a certain degree of iodine deficiency. It seems likely that iodine deficiency is only a permissive factor and not an absolute cause in many cases. Because iodine supplies are often borderline or low the cause of the endemia seems to be iodine deficiency and is accepted as such without further inquiry.

The main cause of the worldwide distribution of goitre is therefore proposed as follows: as the crustal plates move around the globe they collide, with one plate being subducted beneath the other; as a result certain characteristic mineral assemblages occur in the rocks above, and one or more of these minerals released by weathering enters the diet of the local population, where in the presence of iodine deficiency it produces or enhances endemic goitre. One final point of interest in this hypothesis is that of cretinism. Of the two types of cretinism known, the nervous type, described by McCarrison in these same mountains, is by far the commonest in the mountain ranges around the world. Hypothyroid cretinism is extremely common in Zaire, which is far from any active subduction zone. The pathogenesis of cretinism is obscure with at least three different mechanisms having been suggested. It is possible that whatever causes goitre near the subduction zone also causes nervous cretinism. In other words, the global movements and collisions of crustal plates are the cause not only of goitre but all the iodine deficiency disorders.

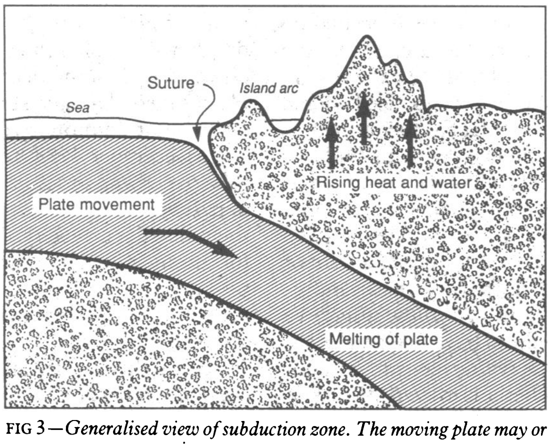

FIG 3—*Generalised view of subduction zone. The moving plate may or may not support a continent*

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Hammersmith Staff Rounds

An independent diagnosis

A treatable metabolic disorder is diagnosed by molecular analysis of human genes

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A young man referred himself after reading an article in a national newspaper that described two patients with an inherited disorder whose symptoms he had recognised. He had a 10 year history of grand mal seizures. Investigations had previously shown nothing, and he had been obliged to surrender his driving licence and modify his work. After self referral hereditary fructose intolerance was diagnosed by analysis of epithelial cell DNA recovered from mouthwash samples. Since following a strict exclusion diet free from fructose and related sugars he has reported an improvement in wellbeing and has been free from seizures. This case history illustrates the usefulness of genetic analysis in diagnosing this treatable genetic disorder and detecting symptomless carriers of the disease.

Case history

The patient was an environmental health officer who had been well until the age of 20 in 1979, when he had had an episode of generalised convulsions and loss of consciousness. He was examined by a neurologist shortly after the attack and sodium valproate was prescribed. By 1984 he had had no further seizures while taking regular anticonvulsant. An electroencephalogram was found to be normal and the valproate was stopped.

In February 1988, when he was 29, he had a second generalised seizure attack. This occurred at 11 am after a late breakfast of cereal. The attack was preceded by a distant sensation and impaired awareness of the surroundings; witnesses reported that the patient sank to the ground and then showed generalised clonic movements rapidly thereafter. He had no incontinence. The night before the attack he had consumed a large quantity of home brewed beer, which he described as "unfinished." He had also drunk half a bottle of wine. Investigations immediately after the episode included repeat encephalography, blood count, measurement of blood glucose concentrations, and an automated multiple biochemical analysis of serum. All these tests gave normal results. He was thought to have had an alcohol induced fit and for a time thereafter consumed nonalcoholic beers and lagers. These, however, provoked attacks of sweating that were relieved only by eating starchy foods such as bread.

Later in 1988 he applied for a year's leave of absence to travel abroad with his wife. In August they visited Pakistan, where ambient temperatures exceeded 28°C. After a day's sightseeing he purchased and drank a bottle (0·3 litres) of a local brand of carbonated sweet drink but immediately became nauseous. After 20 minutes he noticed epigastric discomfort, dizziness, and profuse sweating. These sensations worsened over the next hour and his speech became incoherent. Finally, he lost consciousness and had generalised convulsions. On this occasion he bruised his back and was incontinent of urine. After a series of seizures that were witnessed by his wife he remained unconscious for about an hour, after which he remained disoriented and drowsy for several hours. The symptoms improved in the evening after he had eaten a light meal. He returned home immediately and was further investigated. An electroencephalogram was normal, as were the results of a two hour glucose tolerance test. Blood sugar determinations after a prolonged fast remained normal and nothing was clearly diagnosed, although attacks of hypoglycaemia were considered to be possible. He was advised to discontinue his travels abroad, and he surrendered his driving licence.

The patient has three siblings, who are all healthy, as are his parents, who are not known to be related by blood. He had been healthy throughout childhood, but unlike all other members of his family he had avoided fruit, sugar, and confectionary for as long as he could remember because he did not enjoy the taste. On his return from abroad the patient noted that when he drank drinks containing sugar he became lightheaded, especially when the drinks were followed by exercise. He recalled that this sensation resembled closely the premonitory symptoms of his last two seizures.

In December 1988 he read an article in a national newspaper that described two young doctors who had hereditary fructose intolerance and had diagnosed their disorder correctly.[1] The genetic defect responsible for this disorder had been characterised, and on noting the resemblance to his complaint and with his general practitioner's consent the patient sought further advice on the nature of his dietary preferences and their relation to his seizure attacks. Later, on review at this hospital, he was found to have no other important past illness or injury and was not taking drugs regularly. Physical examination showed no abnormality.