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Preliminary Report of an Experiment in the Kangra Valley for the Prevention of Himalayan Endemic Goitre with Iodized Salt*,†

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This report incorporates the results of an investigation designed to test the effectiveness of potassium iodide and potassium iodate in the control of Himalayan endemic goitre when these compounds are added in small physiological doses to the domestic salt habitually consumed by the people in the endemic belt. In a prospective study lasting five years, a striking reduction in the prevalence of goitre was observed in areas receiving salt fortified with either potassium iodide or potassium iodate. During the same period, goitre prevalence remained unchanged in the control zone, which received plain, unfortified salt. The study has an important bearing on the problem of goitre control in developing countries that use moist, coarsely crystalline salt.

> "Simple goitre is the easiest and cheapest of all known diseases to prevent and its control may be accomplished by available methods as soon as organized society determines to make the effort."
>
> MARINE (1924)

In extensive tracts of Africa, Central and South America and Asia goitre is still endemic. A recent estimate by Kelly & Snedden (1960) indicates that the probable number of sufferers from goitre throughout the world today is not far short of two hundred million.

The existence of endemic goitre in an extensive belt along the southern slopes of the Himalayas has been known for a considerable time. This goitre belt covers a distance of over 2400 kilometres, comprising the northern parts of the States of Jammu and Kashmir, Punjab, Uttar Pradesh, Bihar, Bengal, Assam and the North-East Frontier Agency, and is one of the world's classical and most intense areas of endemic disease (Ramalingaswami, 1953).

Rational measures for the prevention of any disease depend upon the adequacy of knowledge about its etiology and pathogenesis. The etiology of Himalayan endemic goitre was the subject of intensive study by the late Sir Robert McCarrison for nearly three decades. McCarrison's pioneering work constitutes an important chapter in the history of this condition. He studied the disease both in the field and in the laboratory, and concluded that it was of complex derivation, being related to infection with the coliform group of intestinal organisms and to faulty and unbalanced diets (McCarrison, 1917; McCarrison & Madhava, 1932). Several years later Stott et al. (1931), working with endemic goitre in Uttar Pradesh, drew attention to the role of excessive consumption of calcium salts through drinking hard waters. Still later, Wilson (1941), on the basis of a study in the Punjab, thought that

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excessive intake of fluorine was probably important in the etiology of endemic goitre there.

In spite of this early interest in the study of Himalayan endemic goitre, and although neither McCarrison nor Stott ever denied the prophylactic value of iodine, very little has been accomplished over the years in the prevention of this condition in India. Isolated and sporadic measures were taken from time to time, but these have had no impact on the problem.

Recent developments in the use of radioactive iodine and of more refined methods of chemical assay of stable iodine and iodized compounds have brought about renewed interest in a re-evaluation of the etiology of endemic goitre in different parts of the world. The study made by Stanbury and his colleagues in Argentina was the first to provide conclusive evidence for iodine deficiency as a primary factor in the etiology of endemic goitre in the Andes (Stanbury et al., 1954). Soon afterwards, the Himalayan endemic was investigated in a similar manner and, contrary to earlier belief, all the responses observed in persons with the Himalayan endemic were entirely consistent with the iodine-deficiency hypothesis (Ramalingaswami, Subrahmanyan & Deo, 1961). The results of this study not only demonstrated the primary role of iodine-deficiency but also showed that the deficiency was extreme and severe. This study was made in two sub Himalayan goitre areas—one in the Punjab and the other in north Bihar—separated by a distance of nearly 600 miles (950 km). The results in both areas were identical, and there was reason to believe that they would be applicable to the entire Himalayan goitre belt. They provide an important background to the experiment in iodine prophylaxis to be described in this report.

OBJECTIVES OF THE EXPERIMENT

Faced with a goitre problem of great magnitude, the Government of India, in collaboration with the Government of Punjab and the Indian Council of Medical Research, decided in 1954 to undertake a systematic field experiment with the following objectives in mind:

(1) To demonstrate the effectiveness of iodine, when added in small physiological doses as a supplement to the common salt habitually consumed by the people in the endemic areas, in the prevention of goitre. The study was to be made over a period of five years and the results, after continuous iodine prophylaxis, evaluated at the end of this period.

(2) To test the relative effectiveness of potassium iodide and potassium iodate, when added in amounts that would supply equal amounts of iodine, in the prophylaxis of endemic goitre.

This part of the investigation was included in view of the fact that the salt generally consumed by the people of India is somewhat crude and coarsely crystalline. The salt habitually consumed in most parts of India is predominantly a solar salt. A small quantity of rock salt is also consumed. It was reported by Kelly (1953) that when potassium iodide was added to an impure and moist salt, considerable loss of iodine occurred. It was also reported by other workers in the Chilean Iodine Educational Bureau that such salts should be iodized by the addition of potassium iodate, which was more stable than iodide and which could replace iodide for the biochemical synthesis of thyroid hormone (Holman & McCartney, 1960).

There have been several reports in the past indicating the effectiveness of iodized salt in the control of goitre. The most impressive of these come from Switzerland and the United States of America (Wespi, 1942; Nicod, 1953; Brush & Altland, 1952). It has, however, been pointed out that the improvement in goitre prevalence in such studies occurred over several decades, during which time, in addition to the use of iodized salt, several other changes have taken place in the socio-economic and living condition of the population, and that it is not possible to say with certainty that the decline in the prevalence of goitre is entirely attributable to the iodized salt (Greenwald, 1950). Furthermore, most studies reported in the past were retrospective in nature and lacked adequate controls.

The main feature of the present study is that it is a prospective study in which the effect of the addition of small physiological doses of iodine to common salt has been evaluated over a period of five years. Built into it from the inception was the idea of using a control zone with similar goitre prevalence and comparable socio-economic and living conditions where no iodization of salt was made. The study was made as a prelude to large-scale operations against endemic goitre in the entire sub-Himalayan goitre belt.

SELECTION OF FIELD AREA

The following criteria were employed for the selection of the area of study:

1. The area should be a territory in the Himalayan goitre belt with a high prevalence of endemic goitre.

2. It should be divisible for experimental purposes into three zones, the population in one zone to receive salt fortified with potassium iodide, that in another to receive salt fortified with potassium iodate, and that in the third to serve as a control group with no addition of iodine compound to its salt.

3. The population in the three zones should be similar with regard to habits, customs, dietary practices, socio-economic status and ethnic origin. The climatological and geological features of the zones should also be similar.

4. The prevalence and severity of goitre should be similar in the three zones at the beginning of the experiment.

A field area fulfilling these criteria was selected in the Kangra and Palampur subdivisions of the Kangra district in the State of Punjab (Fig. 1 and 2). This area was divided into three zones; zone A lies entirely in the Kangra subdivision and has 37 villages with a total population of 33 391; zone C lies entirely

FIG. 1
AREA OF HIMALAYAN ENDEMIC GOITRE BELT AND OF THE PROJECT IN KANGRA DISTRICT, PUNJAB

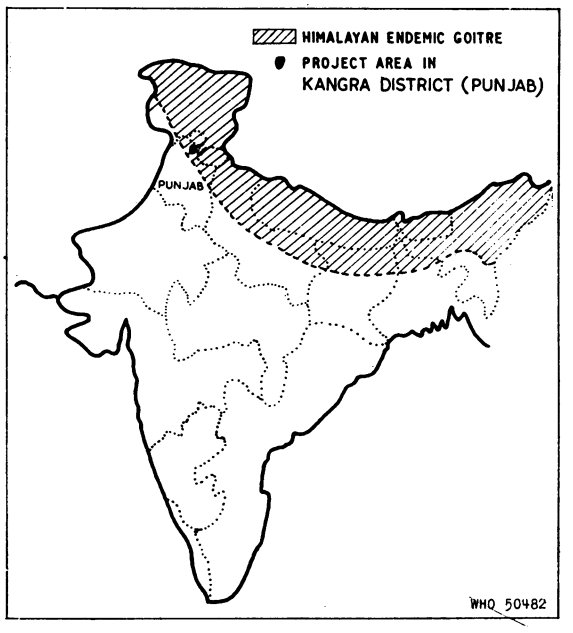


FIG. 2
DETAIL OF PROJECT AREA

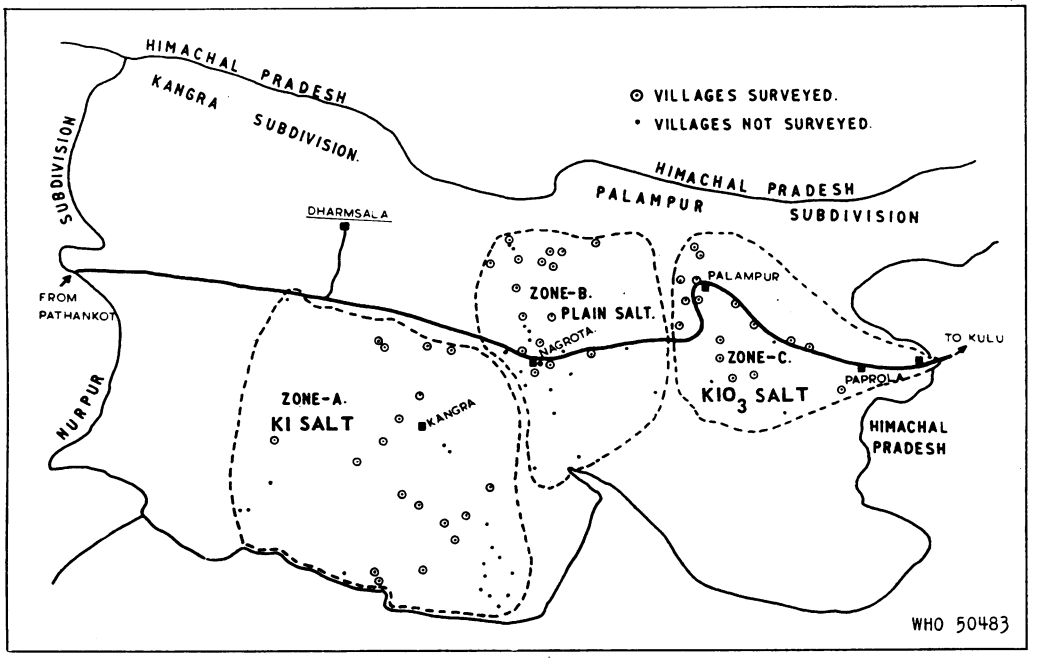


TABLE 1
DATA ON THE POPULATION SURVEYED

	Zone A	Zone B	Zone C
1956 survey			
Estimated total population in villages surveyed	24 314	22 602	35 696
Number examined	6 929	7 103	7 115
Children of school age	2 529	2 027	2 964
General population	4 400	5 076	4 151
1962 survey			
Estimated total population in villages surveyed	27 187	25 274	39 915
Number examined	6 785	8 590	6 241
Children of school age	3 495	4 544	3 420
General population	3 290	4 046	2 821

in the Palampur subdivision and comprises 20 villages with a population of 37 543; zone B lies partly in Kangra and partly in Palampur subdivisions and comprises 35 villages with a population of 37 609. These population figures were derived from the census figures of 1951. Zone A was supplied with salt fortified with KI (iodized salt), zone C with salt fortified with KIO_3 (iodated salt), and zone B, the control, was supplied with plain unfortified salt.

SAMPLING PROCEDURES

Since the primary objective of this study was to determine the effectiveness of iodization of salt in the control of goitre and not assessment of the precise prevalence of goitre in the community, sampling procedures were kept as simple as possible. Advantage was taken of the fact that children of school age constitute a vulnerable group for endemic goitre. As they form a readily accessible and convenient group in which to observe the effects of the iodization programme, all children of school age in all three zones were surveyed at the beginning, in the middle and at the end of the experiment. Because of the high endemicity of goitre in the area and the large number of children examined, any error involved in estimating the percentage of prevalence is likely to be relatively small. Table 1 shows the number of school-age children examined in each zone at the beginning and end of the study.

An attempt was also made to determine the effect of the iodization programme on goitre prevalence in the general population in various age-groups. A goitre survey of the general population was made at the beginning of the study. Approximately two-thirds of the villages in each zone were surveyed for this purpose, the remainder being left out because of inaccessibility and poor communications (Fig. 2). In the villages surveyed, all those present in the village at the time of the visit were examined. They constituted 18% of the population in zone A, 22% in zone B and 11% in zone C. The low percentages are due to the fact that, since agriculture is the main occupation of the people, a large number of them were out in the fields during the day. At the end of the five-year experimental period, the general population was resurveyed in an identical manner. A great deal of effort was spent in following up the same persons who were examined initially. Thus, approximately 53% of those examined in 1956 could be followed up and re-examined in 1962. This group, consisting of 7206 persons, constitutes a valuable one in which a longitudinal study of the effect of iodization could be made at an interval of five years. Failure to follow up the remainder was due to a number of factors such as movement to a neighbouring village, work elsewhere at the time of resurvey, marriage into a neighbouring village, death, etc. These factors are unrelated to goitre and appeared unlikely to influence the validity of the goitre response observed in the group that could be followed. Table 1 gives the number of persons examined in the general population in 1956 and 1962 in the three zones.

METHODS OF STUDY

The technique of goitre survey described by the late Professor Ryle and his colleagues (Murray et al., 1948) was essentially followed in the present study. The grading of the thyroid was made as follows:

(1) no thyroid swelling visible or palpable (normal)—designated in this study as stage *a*;

(2) a mild diffuse enlargement of the thyroid, may be just visible, but always palpable—designated as stage *b*;

(3) Rossetti neck with marked diffuse smooth enlargement of the gland—designated as stage *c*;

(4) abnormal enlargement showing irregularity, nodulation and distortion—designated as stage *d*.[1]

The surveys were made by physicians specially trained in the detection and grading of goitre. Inter-physician variation was reduced to a minimum by mutual agreement on a series of trial cases before the survey.

The iodine content of salt was estimated according to the method of Rogina & Dubravčić (1953) and that of drinking water according to Dubravčić (1955).

Measurement of ^{131}I uptakes by the thyroids of schoolchildren in the three zones was made according to standard methods (Ramalingaswami, Subrahmanyan & Deo, 1961) during the final survey in 1962. For this purpose, all schoolchildren between the ages of 14 and 16 in one school situated in the urban centre of each zone were examined. Each child received an oral dose of 30 μc of ^{131}I.

Ancillary measurements

A diet survey by the weighment method, extending over seven consecutive days, was made on 240 families in the three zones at the beginning of the experiment in order to get an idea of the pattern of diets of the population in the three zones. In addition to the goitre grading, height, weight and the presence of mottled enamel as an indication of fluorosis were recorded. Haemoglobin was estimated in each person on a standardized Sahli haemoglobinometer. The number of cretins, deaf-mutes and feeble-minded persons encountered in each zone during the survey was also recorded. These ancillary data will, however, not be discussed in detail in this report.

[1] This classification is more or less identical with that of WHO, except for the nomenclature; instead of letters the WHO classification uses numbers.

DURATION OF THE STUDY

The experiment began with the distribution of the different salts to the three zones in January 1957 and terminated in January 1962. The initial goitre survey was made in 1956 and the final survey in 1962. This report incorporates the results of surveys in 1956 and 1962 in the three zones.

LEVEL OF IODIZATION OF SALT

A major objective of this study was to evaluate the effectiveness in goitre prophylaxis of small physiological doses of iodine incorporated in common salt. There is a great deal of uncertainty about the optimum human requirements of iodine; it is probable that the requirement does not exceed 100 μg per day (Greenwald, 1955). The problem is further complicated by the fact that the requirement is influenced by a number of factors, including the presence in the diet of goitrogens whose importance may vary from area to area. It is therefore not surprising that there is considerable variation in the level of iodization of salt adopted by various countries. In the United States of America, the level of iodization is 1 part of potassium iodide in 10 000 parts of salt, whereas in Poland it is 1 part in 200 000 parts of salt (Matovinović & Ramalingaswami, 1960). Considering the severity of the Himalayan endemic and the lack of convincing evidence for detectable goitrogens, it was decided for the purposes of this study to provide approximately 200 μg of iodine per head per day. Diet surveys conducted in this area had shown that the daily consumption of salt per head was approximately 15 g. Accordingly, the level of iodization adopted was 1 part of potassium iodide in 50 000 parts of salt in zone A and 1 part of potassium iodate in 40 000 parts of salt in zone C, yielding an estimated supply of 229 μg and 223 μg of iodine per head per day in the respective zones.

MANUFACTURE AND DISTRIBUTION OF IODIZED SALTS

An iodization plant especially designed to fortify coarse, moist, crystalline salt, as advocated by the WHO Study Group on Endemic Goitre (1953), was set up at Sambhar Lake in the State of Rajasthan for the manufacture of the fortified salts for this experiment. In principle, the machine consists of a sieve through which the salt is passed in order to

screen the big lumps. The salt is then carried along on a belt on to which are allowed to fall regulated quantities of iodide or iodate mixed with 20 times the amount of calcium carbonate (by weight), and intimate mixing of the salt and the iodine compound is carried out by passing the mixture through a worm screw. Salt from the same source but not fortified with any iodine compound was used in the control zone B.

Distribution of the salts to the respective zones was ensured through governmental agencies and ordinances. The district food and supply departments of the Government were responsible for the distribution of the salt to the traders in the project area. The prices were fixed by the Government from time to time to ensure that the price of fortified salt was not higher than that of plain salt. In order to prevent the sale of any salt other than the prescribed one in a particular zone, a prohibitory order was issued by the District Magistrate under the Punjab Salt Control Order, 1956. Once the distribution of salt was well under way, periodical checks were made to ensure the regular sale of fortified salt and also to safeguard the entry of plain salt into the control zone.

In spite of all steps taken to ensure a continuous supply of the fortified salts, their supply did break down for a period of 15 months in zone A and for six months in zone C in the five-year period. This point will be discussed later, because of its bearing on the results obtained in the two zones.

RESULTS

The three zones at the beginning of the experiment

The great majority of people in the experimental area are agriculturists cultivating their own lands, nearly 85% being engaged in agricultural work. The cultivable area is divided into fields, generally open and unenclosed, and the principal crop is rice. The fields descend in successive terraces, levelled and embanked with ridges to retain the water. The area has a moderate rainfall varying from 80 to 110 inches (2.03 to 2.79 m) annually.

Diet. At the beginning of the experiment, the diet of 210 families in the three zones was studied by the weighment method for a period of seven days. The families belonged to low-income groups whose total monthly emoluments rarely exceeded Rs 200. In most of them the income was less than Rs 100 per month. The families selected from the three zones were broadly homogeneous and comprised agricultural labourers, petty Government officials, and artisans. The family size varied, with an average of 5.1 consumption units per family. In general, the diets in all three zones appeared to be fairly satisfactory in quantity, although qualitatively they were somewhat defective (Table 2).

Goitrogenic food factors, such as foods of the Brassica family, were consumed so irregularly and in such small quantities that they could not be held responsible for the widespread occurrence of goitre. There was no consistent relationship between the prevalence of goitre and inadequacy of various nutrients in the diet. The intake of nutrients did not differ significantly between goitrous and non-goitrous families whose age and sex distribution were similar. There was also no evidence that endemic fluorosis as revealed by dental mottling was a major contributory factor in the causation of goitre.

Iodine in water. Samples of drinking water from the three zones were analysed for their iodine

TABLE 2
DAILY INTAKE OF NUTRIENTS IN THE THREE ZONES

Zone	No. of families	No. of individuals	Intake of nutrients											
			Protein (g)	Fat (g)	Carbohydrate (g)	Calories	Minerals			Vitamins				
							Ca (g)	P (g)	Fe (mg)	Vit. A (IU)	Vit. B_1 (mg)	Vit. C (mg)	Riboflavin (mg)	Nicotinic acid (mg)
A	82	504	90	32	575	2 930	0.5	1.6	37	1 340	1.6	26	0.9	13
B	76	474	78	33	525	2 700	0.5	1.3	35	630	1.1	22	0.8	11
C	52	332	73	21	515	2 530	0.4	1.1	34	450	1.0	11	0.8	11
Total	210	1 310	81	30	540	2 750	0.5	1.4	36	860	1.3	21	0.8	12

TABLE 3
IODINE CONTENT OF WATER IN THE THREE ZONES

Zone	No. of samples	Iodine content (μg/litre)	
		Range	Mean ± SE
A	25	0.6- 6.4	2.481 ± 0.3005
B	30	0.6-11.0	2.653 ± 0.3422
C	20	1.2- 5.7	2.785 ± 0.2750

content. The data presented in Table 3 show clearly that the mean iodine content of drinking water in all three zones was low (less than 3 μg per litre), and the levels did not show significant heterogeneity between the three zones, indicating that the degree of iodine deficiency in the environment was similar.

Iodine content of salt

At intervals throughout the period of study, a number of samples of salt were collected from the open market in the three zones and analysed for iodine content. Samples at the source of manufacture were also analysed. The results presented in Table 4 show that there was some variation in the concentration of iodine between the samples collected at different times. This variation was more marked in zone A than in zone C. Significant losses of iodine occurred during transportation and storage in both zone A and zone C. The losses in the case of salt with potassium iodide in zone A were greater than in salt with potassium iodate in zone C, but this difference was not statistically significant. The time elapsing between manufacture and field distribution was usually two to three months.

Goitre survey

The population in the three zones was under continuous observation by the field team of the project throughout the duration of the study. No mass migration of people occurred from one zone to the other, although minor displacements of families had undoubtedly taken place. There was also no evidence to indicate that any substantial changes took place in the dietary pattern of the population in the three zones during the experimental period. Catastrophic events such as droughts and floods did not affect any zone.

Children of school age

Table 5 shows the over-all prevalence of goitre (stages *b*, *c* and *d* combined) in children of school age in the three zones at the beginning of the experiment in 1956 and at the end in 1962. It will be seen that the prevalence of goitre was comparable in all three zones during the baseline surveys in 1956. The calculated value of χ^2 was 0.38 with 2 degrees of freedom, indicating that the prevalence of goitre did not differ significantly between the three zones. At the end of the experiment in 1962, however,

TABLE 4
THE IODINE CONTENT OF SALT

Source of salt	No. of samples	Range	Mean value ± SE
Salt with addition of KI: [a]			
At place of manufacture	39	0.64-2.10	1.26 ±0.075 parts KI/50 000 parts salt
In the field (Zone A)	352	0.10-2.19	0.93 ±0.017 parts KI/50 000 parts salt
Salt with addition of KIO_3: [b]			
At place of manufacture	69	0.86-1.745	1.11±0.021 parts KIO_3/40 000 parts salt
In the field (Zone C)	323	0.08-1.75	0.89±0.017 parts KIO_3/40 000 parts salt
Plain salt:			
In the field (Zone B)	10	0.02-0.16 [c]	1.0 part of iodine/1.4×10^6 parts salt

[a] Difference of means (KI salt) = 0.3324 (highly significant: t = 5.87; P < 0.001).
[b] Difference of means (KIO_3 salt) = 0.2314 (highly significant: t = 6.06; P < 0.001).
[c] Mg of iodine in 100 g of salt.

TABLE 5
PREVALENCE OF GOITRE IN CHILDREN OF SCHOOL AGE IN THE THREE ZONES IN 1956 AND 1962

Zone	No. examined	No. with goitre	Prevalence of goitre (%)
	1956 survey		
A	2 529	951	37.6
B	2 027	767	37.8
C	2 964	1 138	38.4
Total	7 520	2 856	38.0
	1962 survey		
A	3 495	666	19.1
B	4 544	1 829	40.3
C	3 420	500	14.6
Total	11 459	2 995	26.1

highly significant differences appeared between the zones as indicated by a χ^2 value of 795. In zones A and C, receiving salt fortified with potassium iodide and potassium iodate respectively, there was a marked and highly significant reduction in the prevalence of goitre. In zone A, the prevalence fell from 37.6% in 1956 to 19.1% in 1962. Likewise, in zone C, it fell from 38.4% in 1956 to 14.6% in 1962. On the other hand, in the control zone B, receiving plain salt, no such reduction was observed. In fact, a slight increase was registered from 37.8% in 1956 to 40.3% in 1962, but this was not significant even when tested at 5% level.

The prevalence rates of goitre in zones A and C differed significantly from one another at the end of the experiment in 1962, the value of χ^2 being 24.3 with 1 degree of freedom. There was a greater reduction in prevalence in zone C than in zone A.

Further analysis of the results in terms of age and sex is shown in Tables 6 and 7 and in Fig. 3. In accordance with the usual picture, the prevalence of goitre was higher in girls than in boys and these differences became accentuated from the time of puberty onwards in 1956. The marked reduction in the prevalence of goitre in zones A and C between 1956 and 1962 was observable in both boys and girls in all age-groups. During this period in zone B, however, a slight rise among boys and a slight fall among girls was noticeable, but these changes were not significant.

It was apparent in this study that not all children of school age actually attended school. It was therefore considered desirable to compare, age for age, the pattern of goitre in schoolchildren and children not at school at the beginning and end of the experiment in the three zones. This comparison showed that the prevalence of goitre in the three zones in the children not attending school was similar to that in schoolchildren at the beginning in 1956, and the changes observed in goitre prevalence from 1956 to 1962 were also similar between the two groups in the three zones.

The reduction in the prevalence of goitre observed in zones A and C was attributable in the main to a reduction in the number showing mild enlargement graded as stage *b*. This effect could be the result of the operation of two factors: prevention of those graded as normal (stage *a*) at the time of the baseline survey from developing mild *b* stage goitre, and reversion to normal stage *a* of stage *b* goitre. In the absence of a longitudinal study of the same children during the experimental period, it is difficult to evaluate the extent to which each of these factors

TABLE 6
PREVALENCE OF GOITRE IN CHILDREN OF SCHOOL AGE BY SEX IN THE THREE ZONES IN 1956 AND 1962

Zone	Sex	No. examined [a]	Prevalence of goitre (%)
		1956 survey	
A	Male	2 019 (689)	34.1
	Female	510 (262)	51.4
B	Male	1 605 (549)	34.2
	Female	422 (218)	51.7
C	Male	2 338 (841)	36.0
	Female	626 (297)	47.4
		1962 survey	
A	Male	2 539 (490)	19.3
	Female	956 (176)	18.4
B	Male	3 262 (1 297)	39.8
	Female	1 282 (532)	41.5
C	Male	2 527 (367)	14.5
	Female	893 (133)	14.9

[a] Numbers in parentheses indicate numbers with goitre.

TABLE 7

PREVALENCE OF GOITRE IN CHILDREN OF SCHOOL AGE BY AGE IN THE THREE ZONES IN 1956 AND 1962

Age (years)	Number examined [a]			Prevalence of goitre (%)		
	Zone A	Zone B	Zone C	Zone A	Zone B	Zone C
			1956 survey			
5-7	390 (104)	392 (120)	488 (114)	26.7	30.6	23.4
8-10	766 (273)	701 (278)	847 (314)	35.6	39.7	37.1
11-13	633 (269)	554 (227)	879 (394)	42.5	41.0	44.8
14-16	740 (305)	380 (142)	750 (316)	41.2	37.4	42.1
Total	2 529 (951)	2 027 (767)	2 964 (1 138)	37.6	37.8	38.4
			1962 survey			
5-7	687 (56)	1 095 (378)	759 (31)	8.2	34.5	4.1
8-10	1 059 (199)	1 290 (527)	1 187 (161)	18.8	40.9	13.6
11-13	1 076 (283)	1 501 (687)	1 017 (234)	26.3	45.8	23.0
14-16	673 (128)	658 (237)	457 (74)	19.0	36.0	16.2
Total	3 495 (666)	4 544 (1 829)	3 420 (500)	19.1	40.3	14.6

[a] Numbers in parentheses indicate numbers with goitre.

contributed to the observed effect. The study on the general population described below elucidates this point.

^{131}I uptakes

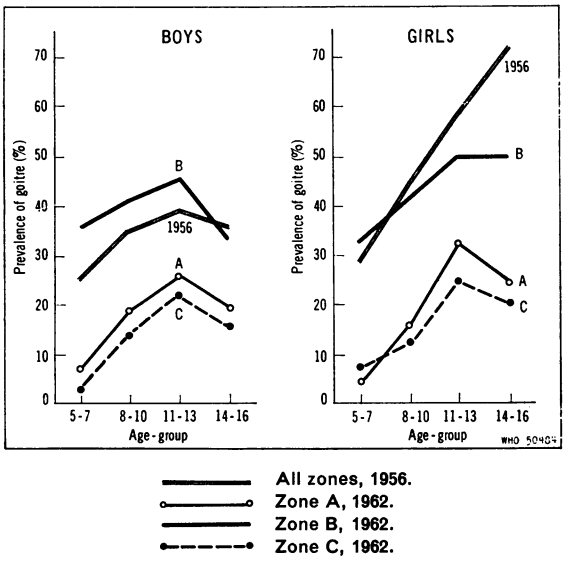
The results of 24-hour uptakes are presented in Fig. 4. They show quite clearly the differences between zones A and C on the one hand and zone B on the other. All children in zone B, the control zone, showed abnormally high uptakes similar to the uptakes found in other parts of the Himalayan endemic zone (Ramalingaswami, Subrahmanyan & Deo, 1961). In zones A and C the majority of the children had uptakes that fell within the limits of normal.

General population

Table 8 shows the over-all prevalence of goitre (stages *b*, *c* and *d* combined) in the general population of all ages in the three zones in 1956 and 1962. The goitre rate in the baseline survey in 1956, unlike that for children of school age, differed significantly between the zones, the value of χ^2 being 45.3 with 2 degrees of freedom. A marked and highly significant reduction in the prevalence of goitre took place in zones A and C between 1956 and 1962, while no significant change occurred in zone B during this period. In zone A, the prevalence fell from 42.4% in 1956 to 18.1% in 1962 and in zone C from 40.1% in 1956 to 16.8% in 1962. The greater reduction in goitre prevalence in children of school age

FIG. 3

PREVALENCE OF GOITRE AMONG CHILDREN OF SCHOOL AGE IN ZONES A, B AND C, BY AGE AND SEX, IN 1956 AND 1962



observed in zone C as compared with zone A was not demonstrable in the general population. The calculated value of χ^2 for zones A and C in 1962 was 1.83.

Further analysis of the results in terms of age and sex is shown in Tables 9 and 10 and in Fig. 5. In all zones and at both periods, the prevalence of goitre was higher in females than in males from the age of puberty onwards. The reduction in goitre prevalence in zones A and C was evident in all age-groups and in both sexes. It is of particular interest that while in 1956 5.5% of children under 5 years of age had goitre, no case of goitre was encountered in this age-group in 1962 in zones A and C. In other words, children born in these zones since the introduction of fortified salt were completely protected from acquiring goitre. In the control zone B, on the other hand, no such protection was observed; for children born between 1956 and 1962 in this zone the risk at birth of developing goitre was similar to that for children born in the preceding five-year period.

FIG. 4

24-HOUR UPTAKE AND URINARY EXCRETION OF ^{131}I BY CHILDREN IN ZONES A, B AND C

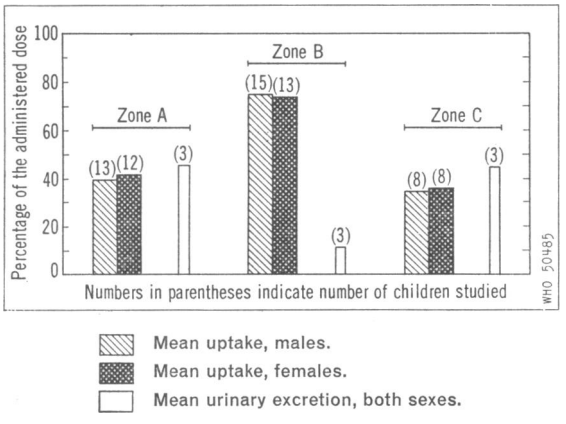


TABLE 8

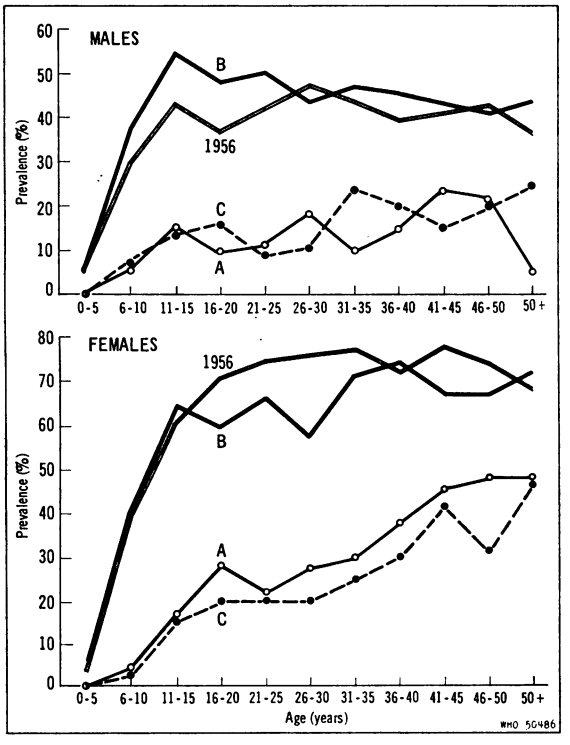
PREVALENCE OF GOITRE IN THE GENERAL POPULATION IN THE THREE ZONES IN 1956 AND 1962

Zone	No. examined	No. with goitre	Prevalence of goitre (%)
	1956 survey		
A	4 400	1 866	42.4
B	5 076	2 386	47.0
C	4 151	1 671	40.1
Total	13 627	5 923	43.5
	1962 survey		
A	3 290	594	18.1
B	4 046	1 850	45.7
C	2 821	473	16.8
Total	10 157	2 917	28.7

Follow-up study

Out of the 13 627 persons in the general population examined in 1956 in the three zones, 7206 persons were re-examined in 1962. Fig. 6 shows the change in the goitre status of this group in the three zones from 1956 to 1962, taking only the normal *a* stage gland and the mild *b* stage enlargements. The figure reveals that the reduction in goitre prevalence in zones A and C is brought about by the dual mechanism of (*a*) preventing goitre-free persons from developing goitre, and (*b*) reversion of mild established goitre to normality. Thus, in zone A, only 4.9% and in zone C only 4.1% of the females who

FIG. 5
PREVALENCE OF GOITRE AMONG GENERAL POPULATION IN ZONES A, B AND C, BY AGE AND SEX, IN 1956 AND 1962



were normal (stage *a*) in 1956 developed a mild enlargement (stage *b*) in 1962, while in zone B the corresponding figure was 22.9%. Furthermore, 33.1% of the females in zone A and 31.3% of the females in zone C with mild thyroid enlargement (stage *b* goitre) in 1956 were goitre-free in 1962, while the corresponding figure in zone B was only 14.1%.

The extent to which an established goitre can revert to normal depends on the degree of enlargement and the presence or absence of nodular distortion, which, in their turn, are a reflection of the intensity of the endemic condition and its duration. Fig. 7 shows in graphic form the pattern of change in the prevalence of various stages of goitre in the three zones between 1956 and 1962, according to age and sex. In zones A and C, where a marked reduction in the over-all prevalence of goitre took place, stage *b* goitre was the most responsive, while the *c* and *d* stages were generally resistant. In the individual follow-up studies, conversion of the *c* stage (Rossetti neck) to the *b* stage was registered in some cases, but no effect whatsoever was demonstrable on the nodular *d* stage. Fig. 8 depicts the pattern of change in the prevalence of goitre in children of school age and in the general population in the three zones from 1956 to 1962.

DISCUSSION

This is a prospective study which extended over a five-year period. It involved a population of approximately 90 000 persons comprising a predominantly rural population in the Himalayan goitre belt. The three zones into which the study area was divided were contiguous and broadly similar in geoclimatological conditions. The habits, customs, diet, socio-economic status and ethnic origin of the population were also alike. The similarity of the iodine content of water from the three zones indicated that the intensity of environmental iodide deficiency was essentially similar in

TABLE 9
PREVALENCE OF GOITRE IN GENERAL POPULATION BY SEX IN THE THREE ZONES IN 1956 AND 1962

Zone	Sex	No. examined [a]	Prevalence of goitre (%)
		1956 survey	
A	Male	2 023 (532)	26.3
	Female	2 377 (1 334)	56.1
B	Male	2 446 (892)	36.5
	Female	2 630 (1 494)	56.8
C	Male	1 942 (555)	28.6
	Female	2 209 (1 116)	50.5
		1962 survey	
A	Male	1 414 (165)	11.7
	Female	1 876 (429)	22.9
B	Male	1 775 (633)	35.7
	Female	2 271 (1 217)	53.6
C	Male	1 223 (149)	12.2
	Female	1 598 (324)	20.3

[a] Numbers in parentheses indicate numbers with goitre.

TABLE 10

PREVALENCE OF GOITRE IN GENERAL POPULATION BY AGE IN THE THREE ZONES IN 1956 AND 1962

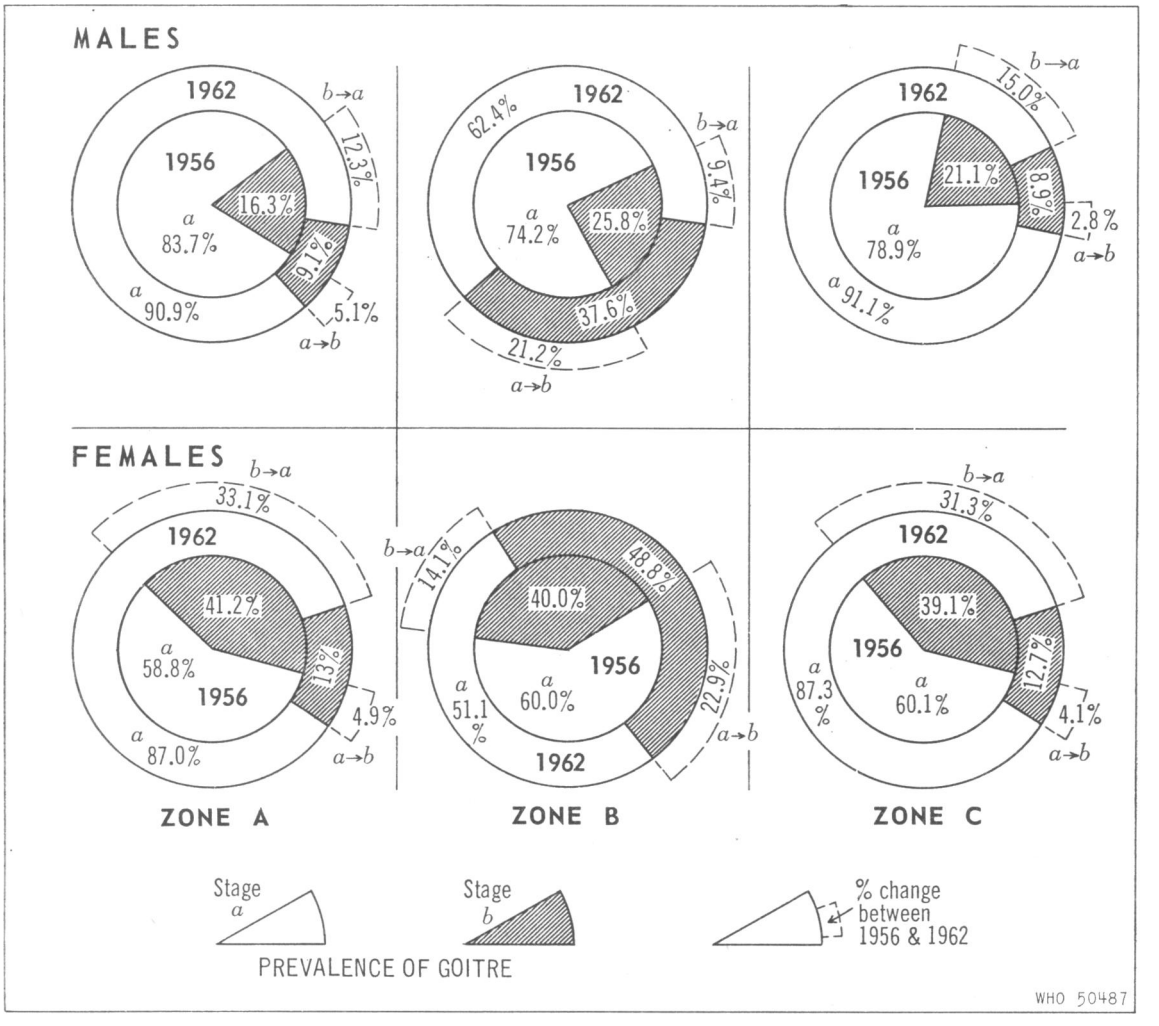
Age (years)	Prevalence of goitre (%) [a]			
	1956	1962		
	All zones	Zone A	Zone B	Zone C
		MALES		
0-5	5.2 (1 447)	— (347)	5.1 (370)	— (230)
6-10	29.6 (896)	4.9 (271)	35.9 (283)	7.3 (192)
11-15	42.4 (627)	13.6 (147)	53.2 (190)	12.6 (134)
16-20	36.7 (496)	9.5 (84)	47.8 (117)	13.1 (98)
21-25	40.9 (401)	10.2 (59)	41.7 (86)	8.9 (68)
26-30	45.5 (431)	18.3 (60)	43.6 (85)	10.0 (60)
31-35	43.3 (406)	9.0 (44)	46.0 (113)	22.6 (62)
36-40	39.9 (366)	14.0 (50)	44.9 (98)	19.6 (61)
41-45	40.7 (290)	22.8 (57)	42.6 (82)	14.7 (61)
46-50	41.5 (277)	21.5 (65)	41.6 (77)	20.0 (55)
Over 50	37.7 (774)	5.7 (230)	43.4 (274)	24.1 (202)
Total	30.9 (6 411)	11.7 (1 414)	35.7 (1 775)	12.2 (1 223)
		FEMALES		
0-5	5.7 (1 308)	— (301)	5.8 (345)	— (239)
6-10	37.3 (960)	3.7 (273)	39.6 (323)	3.4 (208)
11-15	60.2 (798)	15.6 (237)	63.4 (293)	15.1 (186)
16-20	70.3 (750)	27.3 (139)	59.3 (177)	20.4 (137)
21-25	74.7 (707)	22.1 (136)	66.3 (148)	20.6 (97)
26-30	75.6 (669)	27.6 (105)	58.6 (191)	20.2 (138)
31-35	76.0 (475)	29.9 (137)	71.2 (194)	24.5 (127)
36-40	73.1 (443)	37.6 (112)	74.1 (151)	30.3 (106)
41-45	77.2 (302)	43.5 (108)	67.1 (91)	41.2 (80)
46-50	73.2 (232)	47.6 (103)	67.7 (106)	31.7 (82)
Over 50	67.0 (572)	47.0 (225)	71.4 (252)	46.0 (198)
Total	54.7 (7 216)	22.9 (1 876)	53.6 (2 271)	20.3 (1 598)

[a] Numbers in parentheses indicate numbers examined.

the three zones. The prevalence of goitre in children of school age in the three zones was also similar at the beginning of the experiment. It was under these circumstances that the effectiveness of salt fortified with potassium iodide and potassium iodate in controlling the endemic goitre was clearly demonstrated in zones A and C respectively over a five-year period. During the same period, no significant change in the prevalence of goitre took place in the control zone, which received unfortified plain salt. The abnormally high ^{131}I uptakes of the thyroid in the control zone B demonstrated the continued iodine hunger of the gland, in marked contrast to the normal or near-normal uptakes in zones A and C.

FIG. 6

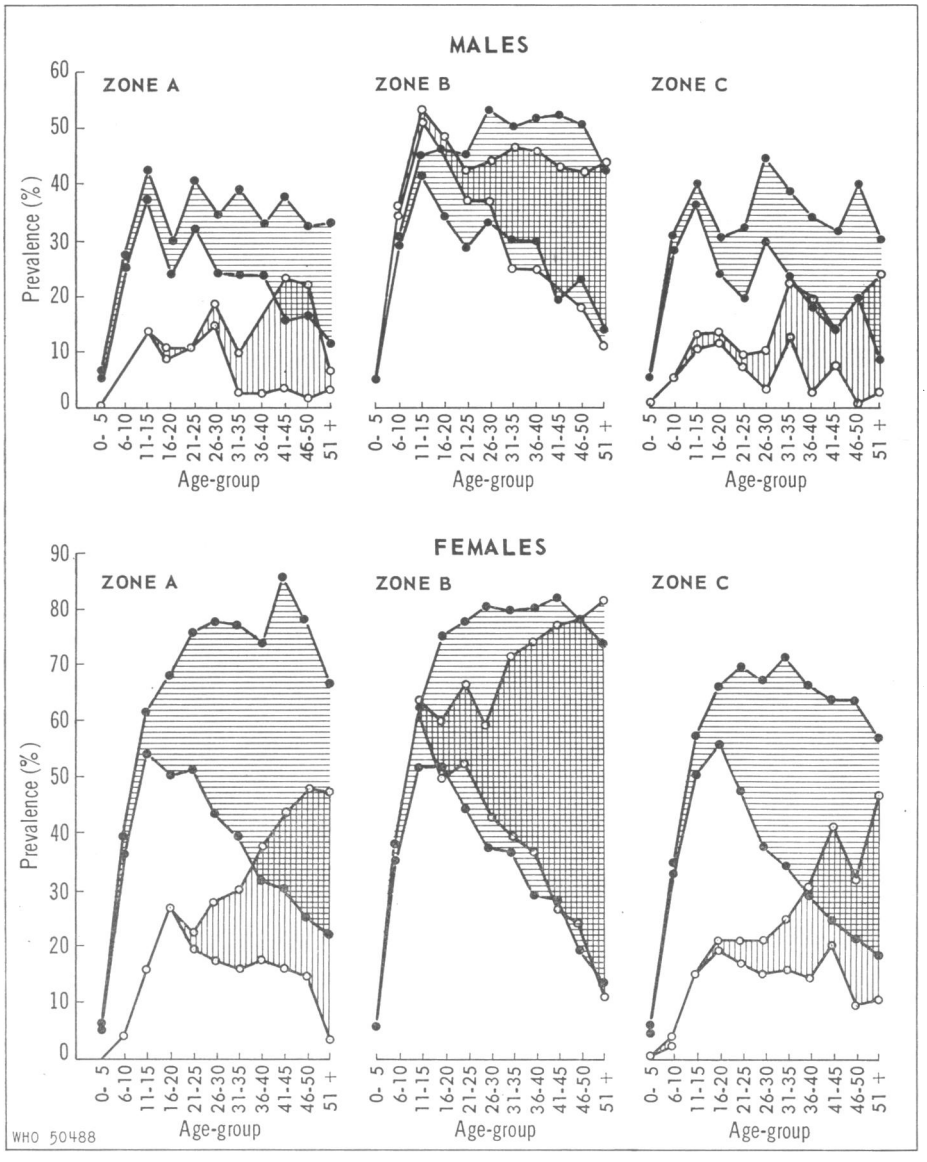
CHANGES IN GOITRE STATUS OF PERSONS FOLLOWED UP FROM 1956 TO 1962 IN ZONES A, B AND C



The results of the present experiment invalidate several of the criticisms made in the past about iodine prophylaxis of endemic goitre to which reference has been made earlier. In addition to the clear-cut results obtained in cross-sectional studies of school-age children and general population, the longitudinal follow-up data on 7209 persons leave no doubt that either KI or KIO_3, when added in physiological doses to domestic salt, effectively reduces the prevalence of goitre. These data also show that the reduction is brought about in several ways: (*a*) complete prevention of the development of goitre in all children born in the area after the introduction of fortified salt, (*b*) a substantially diminished risk of development of goitre in those who did not have demonstrable thyroid enlargement at the time fortified salt was introduced, and (*c*) reversion of a number of mild thyroid enlargements in the *b* stage to normality. Thus iodine supplementation could be regarded as a truly prophylactic measure, and a partially therapeutic measure in mild enlargement.

FIG. 7

CHANGES IN PREVALENCE OF GOITRE AMONG GENERAL POPULATION IN ZONES A, B AND C FROM 1956 TO 1962



Upper line indicates prevalence of all stages of goitre in 1956.

Upper line indicates prevalence of all stages of goitre in 1962.

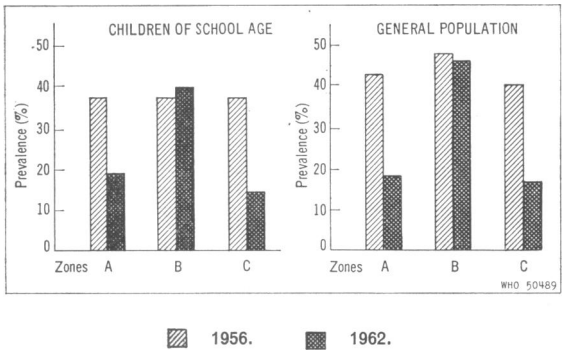
Lower line indicates prevalence of stage *b* goitre in 1956.

Lower line indicates prevalence of stage *b* goitre in 1962.

Area within lines indicates prevalence of stages *c* and *d* goitre in 1956.

Area within lines indicates prevalence of stages *c* and *d* goitre in 1962.

FIG. 8
PREVALENCE OF GOITRE AMONG CHILDREN OF SCHOOL AGE AND GENERAL POPULATION IN ZONES A, B AND C IN 1956 AND 1962



The study not only demonstrates the effectiveness of daily supplementation with 200 μg of iodine per head, but also shows that this level is effective even when the iodine compound is added to the coarsely crystalline moist salt habitually consumed in India. This is an encouraging feature, as similar salts are consumed in many developing nations that are faced with a significant goitre problem.

Scrimshaw et al. (1953) conducted a well-controlled study in the goitrous schoolchildren of Central America, who were given a weekly dose of tablets containing either potassium iodide or potassium iodate, with adequate controls receiving placebo tablets. In 15-20 weeks, a significant reduction in goitre rate was noted in those receiving either potassium iodide or potassium iodate, while no change occurred in the placebo group. This method of iodine supplementation is quite valuable as a temporary measure in selected groups, but as a permanent measure for the general population its usefulness would depend upon the efficacy of the distributing system and the co-operation of the people, both of which are difficult to ensure at all times (Matovinović & Ramalingaswami, 1960). Iodized salt does not suffer from these disadvantages.

A major objective of the present study was to test the relative effectiveness of iodide and iodate in the control of endemic goitre. A significantly greater reduction in goitre rate occurred with iodate than with iodide in school-age children, whereas in the general population no such difference was observed. It is possible that association with persons of higher age-groups with more advanced stages of goitre was responsible for the lack of detectable difference in the general population. The superior effect of iodate in children of school age may be due to the fact that iodate is more stable than iodide and hence larger quantities of iodine were available to the population in zone C than in zone A. However, the conditions of the present study do not permit one to draw such a conclusion. It has been stated earlier that the supply of fortified salt was interrupted to zones A and C for some time, and that it was interrupted for a much longer period to zone A than to zone C. The difference in the period of breakdown is so striking that this alone could explain the observed differences in goitre rate between zones A and C. This possibility derives further support from the data on the iodine content of market samples of salt as compared with the iodine content of salt at the source. There is no indication that salt fortified with potassium iodide suffered more significant losses than salt fortified with potassium iodate. The satisfactory responses observed in zone A to iodide supplementation show that potassium iodide can be used effectively in India, and perhaps even in other developing countries where coarsely crystalline moist salt is habitually consumed.

Throughout the study no toxic effects have been observed that could be attributed to the use of iodized salt. Jod-Basedow, so characteristically observed in association with iodine treatment of goitre, was never encountered in the present study.

The number of cases of cretinism, deaf-mutism, and other forms of mental and physical retardation, was recorded during the baseline and final surveys. There is a great deal of uncertainty about the precise relationship of these developmental disorders to endemic goitre and to iodine deficiency (Trotter, 1960). The data collected in the study, however, do indicate that these disorders occur with significant frequency in the study area, approximately 1% of the population surveyed showing mild or extreme forms of physical and mental retardation. No significant change in the prevalence of these sequelae, if indeed they can be regarded as such, was observed between 1956 and 1962 in any of the zones, nor would one expect any impact to be made on them by iodine prophylaxis in so short a period of time.

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This project is a joint endeavour between the Central Government, the Punjab State Government and the Indian Council of Medical Research, each of which contributed towards its cost.

RÉSUMÉ

Une enquête d'une durée de 5 ans a été menée dans une région de l'Himalaya à forte endémie goitreuse afin de déterminer l'efficacité de la prophylaxie par le sel iodé et de comparer les avantages respectifs de l'iodure et de l'iodate de potassium.

La région, habitée par une population rurale homogène d'environ 100 000 personnes, a été divisée en 3 zones où une étude préliminaire montra une incidence du goitre endémique et une teneur de l'eau en iode quasiment identiques. Les habitants de la zone A reçurent du sel additionné d'iodure de potassium (1 partie pour 50 000 parties de sel), ceux de la zone C, du sel iodé par l'iodate de potassium (1 partie pour 40 000 parties de sel), et ceux de la zone B, groupe témoin, du sel ordinaire non médicamenté.

Les résultats de la campagne d'iodation ont démontré de façon probante l'efficacité de la méthode pour la prévention du goitre endémique dans l'ensemble de la population et plus particulièrement chez les enfants d'âge scolaire. Pour ces derniers, la comparaison des fréquences globales de 1956 à 1962 donne, en zone A, des chiffres de 37,6% et 19,1% et en zone C, de 38,4% et 14,6%. Pour le même groupe d'âge, les pourcentages en zone B étaient de 37,8 en 1956 et de 40,3 en 1962. La mesure de la fixation de l'^{131}I par la thyroïde a permis de constater une accumulation anormalement élevée chez les enfants du groupe B et une fixation normale chez les enfants des groupes A et C. Une enquête subsidiaire portant sur 7206 personnes a révélé que l'effet prophylactique de l'iodation du sel se marque à la fois par l'absence de nouveaux cas de goitre parmi les sujets sains et par un retour à la normale chez les sujets présentant une légère augmentation de volume de la thyroïde. Aucun cas de goitre n'a été observé, de 1956 à 1962, chez les enfants nés dans les zones soumises à la prophylaxie par le sel iodé.

Bien que la diminution de la prévalence du goitre ait été significativement plus importante en zone C qu'en zone A, on ne peut conclure à une supériorité de l'iodate de potassium sur l'iodure, l'approvisionnement en ce dernier produit ayant été moins régulier.

Les auteurs considèrent que cette méthode, qui permet un apport journalier de 200 μg d'iode par habitant, assure efficacement la prophylaxie du goitre endémique.

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