REPORT OF THE PAHO SCIENTIFIC GROUP ON RESEARCH IN ENDEMIC GOITER

SECOND MEETING

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PAHO SCIENTIFIC GROUP ON RESEARCH IN ENDEMIC GOITER

Report of the Second Meeting

5-9 October 1965
Cuernavaca, Mexico

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PAHO SCIENTIFIC GROUP ON RESEARCH
IN ENDEMIC GOITER

Report of the Second Meeting

I. General Session

The PAHO Scientific Group on Research in Endemic Goiter which convened on 5-9 October 1965, and to which Dr. Jorge Maisterrena of the Hospital de Enfermedades de la Nutrición, Mexico City, was host, met in Cuernavaca, Mexico, for the purpose of reviewing progress made since the meeting in Caracas on 22-26 April 1963** and to explore needs and programs for future studies on endemic goiter in Latin America.

1.1 The meeting opened with a welcome from Dr. Maisterrena and Dr. John J. Kevany. Dr. John B. Stanbury discussed the general purpose of the meeting and pointed to the desirability of expanding the activities of the Latin American endemic goiter research centers to include teaching and additional research. He introduced the problem of continued financial support for the research which is underway or planned. A general discussion of this problem followed.

1.2 The first scientific paper of the program was that of Dr. Jacques Dumont. He reviewed the control of thyroid function with special emphasis on those processes which influence its growth. He discussed at length the various actions of the thyrotropic hormone on intermediary metabolism, and reviewed the hypothalamic-hypophyseal control of thyroid function and growth. Dr. Dumont's discussion served as an excellent

*Prepared for the Fifth Meeting of the PAHO Advisory Committee on Medical Research, 13-17 June 1966, by Dr. John B. Stanbury in his role as PAHO Consultant in Endemic Goiter Research.

introduction to the papers that followed, since control of thyroid growth is the central issue in the endemic goiter problem at fundamental levels.

1.3 Dr. Richard Follis reported field studies on endemic goiter as related to iodine deficiency which have been carried out as part of the program of the Interdepartmental Committee on Nutrition for National Development. He described his findings from Vietnam, Thailand, Taiwan, Bolivia, northeastern Brazil, Venezuela, and Guatemala. Excretion values were corrected by a creatinine coefficient factor which has been developed in close cooperation with the INCAP* staff.

1.4 During the past 2-3 years the International Atomic Energy Agency has sponsored calibrations of radioiodine uptake measurements in a large number of laboratories throughout the world. This has been done in many of the laboratories in Latin America. The results were described by Dr. Herbert Vetter. He presented the standard conditions for proper measurement as proposed by IAEA.

1.5 Dr. José Barzelatto gave an account of the development of the PAHO Reference Laboratory and Training Center for Iodine Determinations in Endemic Goiter which has been established in Chile under his direction. This laboratory, largely financed by a grant from the Williams-Waterman Fund, is to serve both as a reference laboratory and as a training center for scientists from various Latin American institutions. There was considerable discussion regarding qualifications of candidates for the training fellowships. It was agreed that well-trained biochemists should be in charge of measurements of iodine in individual laboratories and that the active working directors of these laboratories would be best suited for the kind of training to be provided.

*Institute of Nutrition of Central America and Panama
There was considerable discussion regarding the number of samples that the Reference Center could handle, the problems relating to the control of the Center by duplicate determinations done in the Boston Medical Laboratory and by activation analysis methods, and various other problems in establishing the Center. These have now been solved, and it is expected that the Center will be in operation early in January 1966. The first training fellow should be received by the middle of that year.

1.6 The final report of this part of the program was by Dr. Kevany on the recent meeting held in Salta, Argentina, from 21-25 June 1965, concerning salt iodization programs for endemic goiter prophylaxis. This meeting had been an earlier recommendation of the PAHO Scientific Group on Research in Endemic Goiter and the Group was gratified to learn that it had taken place.

Dr. Kevany reported in some detail on the agenda of the meeting, the nature of the discussions, and its final decisions and recommendations.

2. Laboratory Reports

2.1 Dr. L. C. Lobo reported the results of a genetic and clinical survey of 3,665 individuals in four villages of the western region of Brazil in which a higher relative prevalence of goiter was found in negroes and mestizos as compared to whites and in persons living in rural areas or at lower socio-economic conditions. The prevalence of goiter, cretinism, and congenital malformations in relation to type of water supply and to the inbreeding coefficient was also studied. The genetic characteristics of the population were analyzed (including sex ratio, fertility, prenatal mortality rate and the frequency of goiter in siblings per
inbreeding coefficient). There appeared to be no relation between goiter and perinatal mortality. Goiter incidence increased if the parents were goitrous. Thyroid function tests and kinetic studies were performed in 305 subjects. The results of these tests in goitrous and nongoitrous inhabitants were compared with those found in cretins.

2.2 The results of a clinical survey of almost 58,000 school children from 154 towns and villages of the State of São Paulo, Brazil, were reported by Dr. Y. Gandra. A goiter prevalence of around 20% was found. Two years after the first survey, a second study was performed in 19 cities in which more than 3,000 children were reexamined. The prevalence of goiter was practically the same. The salt used by this population was studied and an iodine content 50% lower than the amount of iodine established by law in Brazil (1/100,000) was found. Urinary iodine excretion confirmed these data. Furthermore, no statistically significant difference was found in the urinary iodine excretion (corrected by creatinine coefficient) of patients with and without goiter. However, radiiodide studies showed statistically different results in these two groups of children. Dr. Gandra stressed the importance of further studies in areas with mild endemicity of goiter.

2.3 Dr. José Barzelatto reported the studies of his group in the Pedregoso area of Chile. This is a genetic isolate of 600 Indians located in a valley of the Andes, in the south-central part of the country. Endemic goiter has a high prevalence in this community. A clinical, nutritional, genetic, and metabolic survey has been done and their principal characteristics were reported. Iodine deficiency seems to be the
principal etiological factor. Some metabolic abnormalities, such as the presence of endogenously labeled DIT, were demonstrated in a few. Preliminary data seem to suggest that the seed of the Araucaria tree, a dietary staple of these Indians, is goitrogenic in rats.

2.4 Dr. Rodrigo Fierro described the results of a survey carried out on the total population of small villages located at different altitudes in Ecuador. The goiter prevalence was highest in Tocachi (54.4%), Esperanza (51.0%), and in Penipe (49.3%). The survey also showed that Tocachi and Esperanza presented the most inadequate socio-economic conditions.

It was observed that the prevalence of goiter was lower at higher altitudes in spite of very low \( ^{127} \text{I} \) urinary excretion. The PBI in these places was lower than normal, and the thyroid \( ^{131} \text{I} \) uptake was similar to that in other villages with low iodine intake and located at lower altitudes.

A close correlation between nodular endemic goiter and the incidence of endemic cretinism \((r = 0.8)\) was observed in Tocachi. There were no clear relationships between severity of the endemic, as measured by prevalence of nodular goiter and endemic cretinism, and \( ^{127} \text{I} \) urinary excretion.

A salivary syndrome was described in cases of endemic goiter. The features were hyperplasia of the salivary glands, diminished salivary flow, diminished salivary clearance, increased number of serous elements in the submaxillary gland and an increased ratio of \( ^{131} \text{I} \) in parotid saliva to that in mixed saliva.
Dr. E. Gaitán reported on endemic goiter in the Department of Cali, Colombia. It is most prevalent in the agricultural and cattle raising area along the Cauca River. In Candelaria, a town located in the valley near the river, a heterogeneous distribution of goiter was encountered. The urinary iodine excretion was high in all areas studied, regardless of the prevalence of goiter (12 to 33%). These goiters presented functional characteristics similar to those of a normal thyroid. A slowing of thyroxine synthesis in the nodules of euthyroid goiters was noted in comparison with the normally functioning paranodular tissue of the same gland. Histologically two main types of goiter have been found in adults: these are parenchymatous nodular goiter (68%) and diffuse and nodular colloid goiter (26%). Hyperthyroidism was mostly associated with the former. In this area there seems to be an unusually high incidence of follicular and anaplastic carcinomas in association with parenchymatous goiter. There is a high mortality rate from carcinoma of the thyroid gland encountered in this valley.

Dr. Jorge Maisterrena, Adolfo Chavez and Enrique Tovar of Mexico City reported their studies carried out in Tepetlixpa, a Mexican village located in a mountainous area. Economic, social, and anthropological studies were done, as well as a nutrition survey. The prevalence of goiter was compared with that obtained three years before. The goiter prevalence of 1962 was close to 92% and in 1965 almost 68%. No specific prophylaxis has been instituted in the population but increasing access to the outside world and increased foods from elsewhere because of a new highway are thought to be the principal factors...
contributing to this change. Dr. Chavez has studied the relationships among goiter, bone maturation, and nutritional status. A positive relationship between under-nutrition and bone maturation was found, but not between goiter and bone maturation. Iodine balance studies were carried out in children from this area. The average iodine intake could be calculated from the urinary iodine excretion rate during fasting, plus a fraction of the hormonal iodine secretion represented by fecal excretion.

2.7 Dr. R. L. Vought of the National Institutes of Health, USPHS, summarized the results of a study of iodine metabolism and the epidemiology of goiter in a goiter area of eastern Kentucky, as well as a preliminary report of a similar survey in Warsaw, Virginia. In the Warsaw study the prevalence of goiter in school children was significantly higher among the population served by a shallow well as compared with those served by the protected public water supply. Dr. Vought and his colleagues have been unable to establish a clear relation between iodine supply and goiter, and are impressed with the possibility of fecal contamination of water as a cause of goiter.

3. Specific Topics

A large part of the meeting was devoted to the discussion of specific topics related to endemic goiter. Each topic was introduced by one of the participants and a free discussion followed.

3.1 Food Goitrogens - Dr. Gaitán reviewed the history and principal studies which have been done on food goitrogens. In addition, he reported results of his own from Cali where he has studied the influence of milk from local grazing cattle on MIT/DIT ratios in mice as compared
to mice fed on milk obtained from the United States. The local milk seemed to impair thyroid function. In the discussion which followed, it was pointed out that the role of a food goitrogen in the Australian endemic as reported by Clements is open to some doubt. The studies of Echapati in Nigeria on cassava as a goitrogen carrier were mentioned. It was the consensus that the possibility remains that food goitrogens may contribute toward the development of endemic goiter, but that iodide deficiency is probably the over-riding problem in most instances.

3.2 Altitude and Goiter - Dr. F. Moncloa reported studies concerning the relationships among goiter, thyroid metabolism, and altitude. The renal clearance of iodide is reduced at great altitudes. When natives were transferred from sea level to high altitudes, there was a decrease in their iodide urinary excretion and an increase in the uptake rate, together with a decrease in the PBI levels. The BMR remains the same. These studies are preliminary in nature.

3.3 Thyroxine Synthesis and Degradation - Dr. K. Gaede reported data related to the enzymology of the thyroid gland. The presence of an active Embden-Meyerhof pathway was demonstrated. Results of kinetic studies on lactic dehydrogenase were presented. These had been performed with the crystallized thyroid enzyme obtained by Dr. Gaede in highly purified form. The first step of the enzymatic synthesis of thyroid hormones was achieved by the Caracas group through the synthesis of $^{14}\text{-}\text{T}_4$, using thyroid slices and $^{14}\text{-L-tyrosine}$ (u.l.) as precursor. The systematic decomposition of this biosynthesized $^{14}\text{-}\text{T}_4$ will enable them to prove to what extent tyrosine contributes to the synthesis of the thyronine skeleton.
3.4 Pregnancy and Intrauterine Metabolism of Iodine in Relation to Goiter - A review of the literature on this subject was presented by Dr. Leslie DeGroot emphasizing recent findings such as the increase in renal clearance of iodine at the beginning of pregnancy. Knowledge of placental physiology and the transport and transfer of hormones through it were also reviewed. There was a lively discussion of the role of thyroid hormone in early fetal development and the role of the fetus in supplying its own thyroid hormone needs, as opposed to those deriving from the maternal circulation.

3.5 Endemic Cretinism in Ecuador - Dr. Rodrigo Fierro reported that endemic cretinism ranging from 0.2 to 0.8% of the population is frequent in those villages where goiter prevalence is above 50%, a good correlation between prevalence of goiter and cretinism being present. This demonstrates the importance of cretinism as an index of severity of the endemic as opposed to the prevalence of nodular goiter. Deaf-mutism was found only in villages where cretinism was present. No racial differences were detected. Retarded bone age and EEG abnormalities were demonstrated in most of the cretins. Their PBI\textsuperscript{127} did not differ from that of the other inhabitants and only one among them showed delayed reflex time. Radiiodide uptakes in these cases ranged from 77 to 87%, and these were increased by the administration of TSH. Six out of 10 had nodular goiters. Muscle biopsies showed minor abnormalities.

There was much discussion regarding the criteria for making a diagnosis of cretinism and for a definition of cretinism. In general, the definition of the First Meeting of the PAHO Scientific Group on Research in Endemic Goiter was accepted. It was generally held that
cretinism may take several forms and several degrees of severity depending on the precise timing of the critical hormonal deprivation during fetal and postnatal life. Again, the difficulty of making a diagnosis of the endemic cretin, in view of lack of precise methods of ascertainment, was accepted.

3.6 Endemic Cretinism in Brazil - The studies of the group from the Institute of Biophysics in Rio de Janeiro have been performed in the State of Mato Grosso, Brazil, in conjunction with representatives from the University of São Paulo. Drs. Doris Rosenthal and L. C. Lobo reported that sixteen cretins from Mato Grosso showed relatively low radioiodine uptakes and very low PBI, while in 24 cases from the State of Goiás these parameters were not significantly different from the rest of that population. All of them were responsive to TSH. Radioiodine disappearance curves were faster among cretins, while there was no difference in thyroxine degradation rates. Only two of the cretins were clinically hypothyroid. Seven cretins had a normal karyotype and only one showed an abnormal chromosome pattern; this last case had an abnormal DIT deiodinating mechanism.

There was further discussion regarding the nature of endemic cretinism. It was agreed that there is ample proof now that iodine prophylaxis eradicates most goiter, endemic deafmutism, and endemic cretinism. As to the pathogenesis involved, Dr. Querido suggested that deafmutism is the result of damage during early pregnancy due to some unknown mechanism, and that mental retardation results from low fetal thyroxine levels later in pregnancy. After birth, such subjects could develop with normal thyroid function or, for some unknown reason (genetic or environmental),
could suffer an anatomical loss of their thyroid tissue and become hypothyroid dwarfs.

3.7 Endemic Deafmutism - The literature regarding endemic deafmutism was reviewed by Dr. Andries Querido and the similarities between endemic deafmutism and the deafness of hypothyroidism were pointed out. Discussion centered upon the fact that neither normal maternal nor fetal thyroid functions seem to be necessary for the prevention of deafness, but a failure of both could not be discarded as the pathogenetic mechanism. It was pointed out that in the Pendred syndrome there is deafness without necessary loss of thyroid function, while sporadic goitrous cretins may be severely hypothyroid, but otherwise have normal hearing. The common denominator may be the lack of iodine unrelated to thyroid function, and the suggestion was made that deafness could be an extrathyroidal effect of iodine, which in the Pendred syndrome might be a transport defect in the placenta or in the developing ear. It was suggested that further studies on the possible extrathyroidal effects of iodine might be worth undertaking.

3.8 Genetics and Endemic Goiter - Dr. Rodrigo Fierro reported that extensive studies in the highlands of Ecuador have shown no racial difference in the frequency of goiter.

Phenylthiocarbamide testing ability among 763 school children showed, according to Dr. L. G. Lobo, no difference among goitrous and non-goitrous subjects when allowance was made for racial differences. Since the population is not genetically homogeneous it is not possible to define genetic influence with the number of cases studied. The prevalence of goiter was not different among patients where consan-
guinity was detected when compared with those where this was not the case.

3.9 Iodine Kinetics in Endemic Goiter - Drs. C. Beckers and J. Barzelatto lead the discussion dealing with investigations made in Chile in the Pedregoso endemic area. Dr. Barzelatto presented the general observations on these patients. The main finding obtained by the Chilean-Belgian team is that in these goitrous patients there is probably a huge iodine spillage from the thyroid gland. It is not known as yet if these disturbances are related to iodine deficiency per se or to some particular characteristic of this environment. Whatever the etiology, this misuse of iodine by the thyroid increases the effects of iodine deficiency, and starts the patients on a vicious cycle as far as thyroid hormone synthesis is concerned. It was pointed out that iodide wastage is also seen after thyrotropic stimulation and probably exists in thyrotoxicosis and may be an important factor also in the pathogenesis of certain types of sporadic goiter.

3.10 Fecal Loss of Iodine - Dr. Vought pointed out that the stools are an obligatory route for loss of iodine which can be important in people living in an iodine-deficient area. Nitrogen excretion may be used as a marker for iodine fecal loss, but this may not necessarily apply in areas of major impaired nitrogen intake.

3.11 Endemic Goiter in the Congo - Dr. A. Ermens presented a film on the preliminary survey and the investigations made in the Idjwi Island, in the Congo.

3.12 Iodine Balance Studies - Some of the difficulties involved in conducting iodine balance studies in the field were documented by Dr. Maisterrena. The discussor covered the relationships between
iodine intake, iodine excretion, and iodine balance. Seasonal fluctuations may be encountered depending on the source of foods available during various times of the year.

3.13 **Endemic Goiter and Cancer** - Dr. José Barzelatto reviewed the relationship between cancer and endemic goiter. Authorities differ diametrically in the interpretation of the available data and none seem to be entirely reliable. Dr. Gaitán's recent observations on the high incidence of thyroid cancer in Colombia were noted with interest. Dr. Gaitán mentioned in the discussion that it has been found that these thyroids seem to contain an excess of thorium and radium. The high incidence of thyroid cancer from the Malabar Coast region of India was mentioned, but there are no studies yet available on possible radio-trace metal contamination in these glands.

3.14 **Techniques of Goiter Surveys** - Dr. Follis reviewed some aspects of endemic goiter survey techniques. The definition of "endemic" as established by WHO was discussed with regard to the prevalence level (10%). The factors involved in selecting a statistically representative sample of the population in order to establish the presence of an endemic, as defined, were also reviewed. The usefulness of designating a specific evaluation group for the periodic appraisal of the population was discussed. It was generally agreed that the school age population (6-14 years) of both sexes provides a captive sector of the community which at the same time represents a sufficiently susceptible group in terms of disease prevalence. This sector would be of great use in carrying out initial reconnaissance studies prior to examining the whole population, if indicated, to establish the
presence of a 10% or greater prevalence. This same group would serve as a useful evaluation unit to study periodically any modification in the characteristics of the problem. Therefore, for the purpose of an initial public health survey, a problem could be said to exist if more than 10% of school children had "visible" goiters.

The classification of the size of goiter was discussed. It was the consensus that there is need for more exact information of the examiner variation involved in classifying different grades of goiter. It was suggested, on the basis of studies carried out by Hennessey in New Guinea, that examiner variation is much less if the criterion of visibility is used. According to this, only thyroids visible with the neck extended would be classified as goiters for the purpose of population studies. As noted in the WHO classification, virtually all thyroids enlarged more than 4-5 times are visible with the neck extended.

Drs. Lobo, Gaitán, and Barzelatto agreed to provide further precise data on observer variation in different degrees of thyroid enlargement.

4. General Recommendations

4.1 Prophylactic Programs - The Group recommended that all efforts be made to extend prophylaxis wherever endemic goiter continues as a problem. They further recommended that experiments be initiated, in particular localities where endemic goiter and cretinism are found, to study the feasibility of iodinated oil as a prophylactic measure. The Group is not of the opinion that prophylactic measures other than this and salt iodinization are presently feasible or desirable.

4.2 Foot Goitrogens - The Group recognized from the many studies
now available that goitrogenic agents present in food may contribute to the development of endemic goiter and that a further effort is desirable to identify these factors. The Group accepted the possibility of such factors in Colombia, Nigeria, Australia, and elsewhere, but is of the opinion that ample iodine prophylaxis would sharply reduce the incidence of goiter in these areas. The Group agreed with Dr. Gandra that iodide prophylaxis, by eliminating iodine deficiency, would spotlight residual patients who have specific metabolic disorders leading to the production of goiter. The Group recommended further studies of the type now in progress by Dr. Gaitán, in the Cauca Valley of Colombia, and by Dr. Barzelatto in Chile.

4.3 Iodine Standardization Laboratory - The Group expressed its pleasure at the establishment of this Laboratory and recommended that in due course, samples be sent to it for standardization and that the Laboratory in turn exert its own control through standard assays by sending spot samples to the Boston Medical Laboratory and to a laboratory of the IAEA for activation analysis.

The Group further recommended that, as rapidly as possible, highly competent biochemically trained personnel be sent to the standardization laboratory for thorough training in iodine analysis.

4.4 Epidemiological Data Gathering

The Group recommended that:

a. The incidence of endemic goiter should be monitored whenever possible.

b. A uniform method for assessing the incidence of endemic goiter should be employed and that observer reliability
should be tested.

c. Goiter surveys should be controlled insofar as possible with measurements of thyroid function in terms of iodine metabolism.

4.5 Thyroid Cancer - It was recommended that further studies of the pathogenesis of thyroid cancer in relation to endemic goiter should be pursued especially along the lines suggested by the findings of Dr. Gaitán in relation to radionucleide contamination.

5. Proposed Research by Participating Laboratories

5.1 Dr. Fierro

a. It is proposed to study the many parameters of physiological function already measured in endemic cretins before replacement therapy with thyroid hormone in order to assess the effect of such therapy in these subjects.

b. Measurements of protein-bound and butanol-extractable iodine in maternal and cord blood in Esperanza, a region of high goiter endemicity.

c. The effect of altitude on diet in soldiers. I\textsubscript{127}\textsuperscript{excretions will be measured in a group of soldiers in Guayaquil, and after they have moved to an iodine-deficient area at 3600 meters of altitude.

d. A study of iodized oil prophylaxis in Tocachi.

e. An x-ray survey of bone development in regions of iodide deficiency, and after iodide prophylaxis.
f. Triiodothyronine suppression tests in regions where there appears to be goiter without iodide deficiency.

5.2 Dr. Moncloa

a. Further studies on the effects of altitude on iodine in red cells and extracellular fluids, and on renal clearance. These findings are to be compared in patients with and without goiter.

b. Similar studies are to be conducted on domestic animals at normal and high altitudes.

c. A study of iodinated oil as a prophylactic measure using alternate patients.

5.3 Dr. Gaitán

a. Epidemiologic studies in Candelaria, by IBM card analysis. The data are to include goitrousness, familial nesting, the disease in domestic animals, the effects of migration, the effects of consanguinity, and the effects of economic status.

b. Further study of the possible presence of goitrogenic factor in milk.

c. Kinetic analysis of iodine metabolism in patients in a goitrous zone who appear to have normal iodine intake.

d. Repeated surveys to appraise the effect of goiter prophylaxis by iodine, with particular regard to season and to $^{127}$I excretion.

e. Further surveys of the incidence of goiter in the various districts in the environment of Cali.
f. A study of the appearance of goiter in cattle in the Cauca Valley.

g. Clinical-pathological correlations of nodular goiter with reference to TSH and IATS titers in goitrous patients.

h. The metabolism of labeled thyroxine by the liver of goitrous and normal subjects.

i. Spot mapping of the incidence of cancer in the region of Cali in an endeavor to gain some insight into the relationship of cancer to possible sources of radionuclide contamination.

5.4 Dr. Maisterrena

a. Further studies of $^{131}$I metabolism in Tepetlixpa with special reference to the effects of seasonal variations.

b. Estimation of $^{127}$I intakes in other regions of Mexico.

5.5 Dr. Lobo

a. Increase in sample size of patients studied in Mato Grosso for endemic goiter.

b. To confirm some findings in the urinary excretion of iodine in subjects in Mato Grosso.

c. Growth hormone and thyrotropic hormone assays in goitrous patients from the Mato Grosso region.

d. A study of the effect of iodized salt prophylaxis on the occurrence of deafness in regions of high incidence in central Brazil.

e. Further studies of the nervous system in endemic goiter in Mato Grosso.
5.6 Dr. Barzelatto

a. Detailed analysis of genetic data from Pedregoso with respect to clinical findings in thyroid disease.

b. Companion studies to (a.) on related isolates in Chile.

c. Extension of findings of mono- and diiodotyrosine in the sera of certain patients with endemic goiter in Pedregoso.

d. Detailed study of the goitrogenic effect of the araucaria nut in rats and its possible role as a goitrogenic agent in man.

5.7 Dr. Gandra

Continue the study of persons without goiter living in mildly endemic areas for other possible etiological factors. These studies include measurements of the absolute iodide uptake, radioactive PBI, estimation of thyroid binding globulin, serum electrophoresis, and perchlorate tests in a series of school children in a goitrous region.