Pan American Health Organization

ADVISORY COMMITTEE ON MEDICAL RESEARCH

Fifth Meeting

Washington, D.C., 13-17 June 1966

Item 8 of the Agenda

STUDIES ON ENDEMIC GOITER IN LATIN AMERICA

Ref: RES 5/13
25 May 1966
STUDIES ON ENDEMIC GOITER IN LATIN AMERICA *

Endemic goiter is prominent in the list of health problems chosen for primary consideration at the First Meeting of the PAHO Advisory Committee on Medical Research. This disease has been recognized for generations as a common affliction in many parts of Latin America. While earlier studies had indicated that iodine deficiency was the leading, if not the sole cause, many puzzling problems remained to be resolved, not the least of which were those relating to the difficulties involved in effective widespread iodide prophylaxis. The PAHO endemic goiter studies are now in their fifth year. It seems appropriate to review progress made to date, and to suggest directions to be taken in the future.

The first step taken early in 1962 was an identification of the investigators and laboratories in Latin America where appropriate research might be conducted. In the course of a survey trip, investigators in six institutes in six countries were selected. Choice was based on the competence of the investigator, his association with a laboratory appropriate for advanced studies, and proximity to a focus of the disease. These were Dr. Jorge Maisterrena at the Hospital de Enfermedades de la Nutrición in Mexico City, Dr. Rodrigo Fierro of the Polytechnic Institute in Quito, Dr. José Barzelatto at the Hospital del Salvador in Santiago, Dr. Yaro Gandra at the University of São Paulo, Dr. Luis Carlos Lobo at the Institute of Biophysics in Rio de Janeiro, and Drs. Marcel Roche and Karl Gaede at the Instituto Venezolano de Investigaciones Científicas (IVIC) in Caracas. All these investigators had already made contributions to the study of thyroid disease and all had

*Prepared for the Fifth Meeting of the PAHO/ACMR by Dr. John B. Stanbury, Department of Nutrition and Food Science, Massachusetts Institute of Technology, Cambridge, Massachusetts.
had training in advanced centers abroad. Each was equipped with an excellent laboratory, and each had a profound interest and enthusiasm for further research on the vexing problem of endemic goiter. Since the inception of the program, this group has been joined by Dr. Eduardo Gaitán, of the Universidad del Valle in Cali, Colombia, and Dr. Federico Moncloa of the Instituto de Investigaciones de la Altura in Lima, Perú.

At the inception of the program a number of problems were specified as in need of and open to attack. These were as follows:

1. There is inadequate information regarding the distribution of goiter in Latin America in terms of age, sex, and geography, and inadequate knowledge concerning the relationship of endemic goiter to cretinism, deaf-mutism, and mental and skeletal retardation.

2. There is inadequate information regarding thyroid function in endemic goiter as measured by modern techniques. Although isolated studies have been done, these need to be given more widespread application.

3. Far more knowledge is required concerning the nature of endemic cretinism in order that a workable definition of this disease may be formulated and its pathogenesis understood.

4. While iodine deficiency has been assumed to be the principal cause of endemic goiter, the possibility of ancillary or contributing or unrelated causative factors needs intensive study.

5. The genetic contribution to the occurrence of endemic goiter has not been defined.

6. Certain anomalies need further explanation, such as the high uptake of radioiodine among Venezuelan aborigines without goiter, and the appearance of endemic goiter without iodine deficiency.
(7) More information is needed regarding methods of iodine prophylaxis in endemic goiter.

(8) The nature of the autonomy of thyroid nodules in endemic goiter requires further study.

(9) Information is needed regarding techniques for suppressing radiiodine accumulation in order to prevent iodine uptake by the thyroids of the young at times of $^{131}\text{I}$ fallout.

(10) More information is required regarding the nature of the iodinated components of the thyroid in endemic goiter and the impact of iodine deficiency on the intermediary metabolism of the thyroid gland.

These and many other problems were discussed with the participating scientists, and studies were outlined with each group which were designed to provide answers to some of these problems. While there was overlap among the projects in various laboratories, there were also projects chosen by each which were unique to his own situation. Dr. Maisterrena, for example, undertook to set up a field research unit in the town of Tepetlixpa, not far from Mexico City, where it would be possible to do precise balance studies on selected children so that the presence of food goitrogens, the effect of variations in iodide intake, the net balance of iodine, and similar problems could be attacked. Dr. Fierro in Ecuador had unique access to subjects with extremely severe cretinism. He undertook to begin studies on the pathological physiology of these patients brought to his clinic and laboratory in Quito from the isolated villages. Dr. Barzelatto in Chile proposed to study the genetic contribution to endemic goiter in isolated villages in southern Chile where there was a high consanguinity rate. Dr. Gandra proposed large scale surveys of children with mild endemic
goiter, and measurements of the effect on thyroid function of prophylactic iodide in varying dose schedules. Dr. Lobo in Rio de Janeiro undertook a study of cretinism somewhat similar to that of Dr. Fierro, and in addition, proposed studies on the relationship of goiter to Chagas' disease and of the immunology of thyroid disease and endemic goiter, and the nature of the iodoproteins in thyroids removed from patients with endemic goiter. More recently he has undertaken extensive genetic surveys in endemic goiter regions. Drs. Roche and Gaede proposed studies on thyroid biochemistry on the one hand, and on the anomalous iodine metabolism of aborigenes who have no endemic goiter, on the other.

Through the help of local sources, the International Atomic Energy Agency, and the U. S. Public Health Service, it was possible to obtain early funding for these projects. The result was that by April, 1963 enough progress had been made to justify a meeting of the participating scientists. This was held at IVIC in Caracas. In addition to the participating senior members of each laboratory and their assistants, the group had the advantage of consultative assistance from Dr. Leslie J. DeGroot of the Massachusetts General Hospital in Boston, Dr. Andries Querido of the University of Leiden, who had just returned from studies on endemic goiter in New Guinea, and Dr. André Ermans of the Free University of Brussels and Dr. Christian Beckers of the University of Louvain, both of whom had recently studied endemic goiter in the Congo. Also assisting was Dr. Robert B. Vought of the National Institutes of Health, and Dr. Herbert Vetter of the International Atomic Energy Agency (IAEA) in Vienna. The meeting was entirely informal and enabled each of the investigators to present his own findings in detail and submit them to the scrutiny of
the consultants. As a result of these deliberations, conclusions, several proposals, and recommendations were made. It was possible to formulate a generally acceptable definition of endemic cretinism. This definition stressed the variability in the manifestations of the disease, and the fact that it is necessarily an epidemiological diagnosis. The group recommended that more attention be paid to goiter prevention by obtaining more information on the efficiency of utilization of prophylactic iodine under field conditions, by improved field methods for surveillance of prophylaxis programs, by intensive studies of the use of alternative methods, such as iodinated oil, and particularly by exploration with the governments of Latin America of ways and means by which iodination programs can be implemented. The group further recommended that measures be taken to promote uniformity of standards in the assessment of endemic goiter, both by physical examination and by laboratory methods. In particular, it recommended that measures be undertaken for the calibration of radiiodine measurements, and for measurements of $^{127}$I in a central control laboratory. The group then recommended that wherever possible more information be collected regarding the impact of endemic goiter on such things as growth, incidence of thyrotoxicosis, and hypothyroidism, thyroid cancer, fertility, complications of pregnancy and pregnancy wastage. A number of detailed studies primarily of a physiological nature were suggested, such as detailed iodide kinetics, the nature of thyroxine binding by the serum proteins of patients with endemic goiter, exploration of survey methods for iodine needs, such as the fecal iodine/nitrogen ratio, and the urine iodine/creatinine ratio as indices of iodine nutrition, assay of thyrotropic hormone concentration in patients with endemic goiter, and others. These studies are outlined in Pan American Health Organization document RES 2/20 of 15 May 1963.
By March, 1964, it seemed appropriate that several of the participating laboratories be visited by a consultant for purposes of discussion of results and outlining of further study. Dr. Leslie DeGroot visited the laboratories of Drs. Cortazar and Ucros in Bogotá, and Dr. Gaitán in Cali. He found Dr. Gaitán's situation particularly interesting and perhaps important because of the existence of mild endemic goiter without evidence of iodine deficiency. Protocols were developed attempting to relate this to dietary and water sources. Another interesting finding was the high incidence of anaplastic and small cell thyroid carcinoma in Dr. Gaitán's thyroid specimens. Dr. DeGroot then visited Dr. Fierro in Quito, where he spent five days going over the epidemiological data which Dr. Fierro had already obtained, and outlining further studies, particularly those related to pregnancy. In Chile he was able to review the early studies which had been done in the town of Pedregoso, where goiter has about an 85% incidence. Dr. Barzelatto and his group had already completed intensive initial physiological measurements on these patients. They proposed further investigations which have since been pursued with the consultative help of Dr. Christian Beckers of Louvain, and which are now being written up for publication. In Brazil, he consulted with Dr. Yaro Gandra of the School of Hygiene and Public Health and in Rio de Janeiro with Dr. Luis Carlos Lobo, where he had occasion to discuss in some detail Dr. Lobo's plans for surveys in the State of Mato Grosso. These are now under way.

In addition to his detailed recommendations regarding specific research, Dr. DeGroot made the important recommendation that the participating laboratories and scientists, now that they had their investigations well in progress, should spend more of their time and attention in broadening
the scope of their activities in their local universities in order to make
their influence as medical scientists more significant, and in order to
develop a cadre of young men who, by participating in their studies, can
learn the elements of medical science in order that medical science and
medical teaching can be strengthened in their respective countries.
Dr. DeGroot strongly recommended that more direct attention be given to
governmental iodide prophylactic programs.

Iodine Control Laboratory

It had been recommended at the meeting in Caracas in 1963
that it would be desirable to have a central laboratory for the measurement
of $^{127}$I in biological samples and in food and water, and where technical
persons from participating laboratories could be trained for making these
measurements. This laboratory is now becoming a reality. In 1964 the
Williams-Waterman Fund generously donated $32,000, and Dr. José Barzelatto
has agreed to establish this laboratory in Santiago. Full equipment has
now been purchased and installed and his own technical staff trained.
He is now ready to receive samples for standardization. His own results
will be controlled by the Boston Medical Laboratory and by activation
analysis at the International Atomic Energy Agency in Vienna through
Dr. Herbert Vetter. It will now be possible for Dr. Barzelatto to receive
several technical persons each year for intensive training in $^{127}$I
analysis, and also, to process control samples not only for the participating laboratories, but for others throughout Latin America who need this service for their own research and field studies.
The Salta Iodine Prophylaxis Meeting

As a result of recommendations made at the Caracas meeting (1963) and subsequently by Dr. DeGroot after his site visit, and because of the long interest of PAHO in the problem, a meeting of governmental representatives from throughout Latin America was held in June, 1965, in Salta, Argentina, for the purposes of discussing the need for iodine prophylaxis, the methods whereby it can be effected, the reasons why governmental programs so far have not uniformly been implemented, and ways and means whereby iodide prophylaxis can be extended in those areas where endemic goiter exists. As a result of this meeting, considerable enthusiasm was generated for programs in many of the participating countries, and there is now evidence that prophylactic programs are being extended.

The Cuernavaca Meeting

By the fall of 1965 a second meeting of the heads of the participating laboratories and consultants was convened. This was held at Cuernavaca, Mexico, in October, and was attended by the senior members of the eight participating laboratories, those in Mexico, Cali, Quito, Lima, Santiago, São Paulo, Rio de Janeiro, and Caracas, and by the consultants, Drs. Vought and Follis from Washington, Querido from Leiden, Beckers from Louvain, Ermans and Dumont from Brussels, Vetter from Vienna, and DeGroot from Boston, together with Dr. Stanbury as PAHO consultant. The meeting began with a discussion of recent advances in thyroid physiology by Dr. Dumont and was followed by an account of the ICNND surveys in Latin America by Dr. Follis. Dr. Vetter then described the success of the radio-iodine standardization program in laboratories throughout the world, and in particular, in Latin America. Dr. Barzelatto reported the progress made
in the establishment of the iodine reference laboratory, and Dr. John Kevany reported on the Salta salt iodization meeting. Research results from the participating laboratories were then recounted. Dr. Lobo described his survey program in the Mato Grosso, and Dr. Gandra discussed his studies on iodine supplementation in subjects with endemic goiter in São Paulo State. Doctor Barzelatto discussed his and Dr. Becker's measurements on thyroid physiology in the Indian isolate in Pedrogoso in southern Chile. The extensive surveys and physiological studies from several villages in Ecuador were described by Dr. Fierro, and comparable surveys on the mild endemic goiter of the valley of the Cauca River were discussed by Dr. Gaitán. He emphasized especially the high mortality rate from carcinoma of the thyroid in this region, and its possible relationship to ambient radioactive substances. Maisterrena and his colleagues discussed the declining incidence of goiter in rural Mexico as related to the intrusion of highways and changing nutrition. Finally, Dr. Vought from the NIH described his studies in Kentucky and Virginia and the apparent lack of a relationship between iodine and goiter. The meeting then turned to an exhaustive discussion of the specific problems related to endemic goiter, its pathogenesis, and its prevention. Among these topics were food goitrogens, the relationship of altitude to goiter, thyroid intermediary metabolism, the problem of iodine nutrition in pregnancy, the nature of endemic cretinism in Ecuador and Brazil, the relationship of endemic cretinism to endemic deafmutism, the problems of genetics in relation to endemic goiter, of iodine kinetics in endemic goiter, and of fecal loss of iodine in this disease. The group also discussed iodine balance and the relationship between endemic goiter and cancer. It was
able to come to a consensus on the grading of endemic goiter for purposes of goiter surveys.

As a result of its deliberations, the group recommended strongly that all measures possible be taken to extend iodine prophylaxis and advised that where salt prophylaxis is not feasible, iodinated oil programs be instituted, particularly if the possibility exists that this can be done in such a way as to provide detailed information as to the effectiveness of the prophylactic program on mental retardation, deafmutism, cretinism, growth, etc. The group also recommended that further studies be made of food goitrogens. This recommendation was made in view of the increasing evidence that other factors than iodine deficiency may be responsible or may aggravate endemic goiter. The group also recommended that full advantage be taken of the iodine standardization laboratory in Santiago, particularly insofar as training of technical personnel is concerned. In addition to these recommendations the group participated in outlining a large series of specific research projects for the participating individual laboratories. These are outlined in Pan American Health Organization document RES 5/2 of 29 December 1965.

The Ecuador Iodinated Oil Prophylaxis Program

As a result of the recommendations made at the Cuernavaca meeting, an initial iodinated oil prophylaxis program was instituted north of Quito in March, 1966, under the direction of Dr. Rodrigo Fierro. Participating as consultants were Professor Andries Querido of Leiden, Holland, and Drs. Kevany and Stanbury. Dr. Fierro had the assistance of a group of medical students, a radiologist, and several pediatricians, and had solid local and governmental backing. Thorough surveys were made of all the personnel
in the highly goitrous and adjoining towns of Tocachi and La Esperanza, and in the lowland town of Salinas, where endemic goiter does not exist. An astonishing intensity of endemic goiter, endemic cretinism, deafmutism, mental deficiency, and short stature were recorded, both in Esperanza and Tocachi. Bone age and dentition were recorded in a large number of sex- and age-matched children in all three towns. Ethiodol, and iodinated poppyseed oil containing 37% iodine, was administered to virtually all the inhabitants of the town of Tocachi, numbering something over 800.

Over the course of at least the next two years a physician will be provided to the towns of Esperanza and Tocachi. He will record the growth milestones of all newborns in these towns, and will obtain other data, such as are necessary for ascertaining the impact of the iodinated oil prophylactic program on this population group where endemic goiter is perhaps as severe as anywhere in the world. If the program meets with its anticipated success, positive information will be at hand for extending this form of prophylaxis to the entire Andean region, where iodide prophylaxis is difficult or impossible at the present time.

Summary of Accomplishments to Date

(1) Medical scientists with a primary interest in thyroid disease have been identified in eight well equipped laboratories in Latin America. Research projects into the nature and prevention of endemic goiter now have been instituted by these investigators in each of these laboratories. This research continues. Participating members have met on two occasions for consolidation of their research effort and hope to meet from time to time for this same purpose in the future.
(2) A large amount of information has been collected on the occurrence and incidence of endemic goiter, cretinism, and related disturbances in Mexico, Colombia, Ecuador, Peru, Chile, Brazil, and Venezuela.

(3) An iodine balance laboratory has been established in a village with endemic goiter near Mexico City. The annual variation in iodine intake and balance has been recorded. The slow decline in the severity of the endemic in this region has been recorded as a new highway has improved access to the rest of the country. An improved method for estimating iodine balance was devised as the result of the studies in this laboratory. No evidence for the participation of food goitrogens was found, but this search continues now by application of a new method. Estimations of the amount of iodine and of thyroxine needed to inhibit thyroid function and thus lessen the retention of ambient iodine, such as might be occasioned by $^{131}$I fallout, have been obtained and published.

(4) The usual relationship between thyroid activity as measured by radiiodine uptake and iodine availability in the diet has not been found in the Cauca Valley. There is evidence that there may be positive goitrogenic factors in food or in water. Evidence has also been obtained that anaplastic carcinoma is commonly associated with endemic goiter in this region, and may be a result of the appearance of high atomic weight radioactive substances.

(5) Evidence has been obtained of some relationship between altitude and endemic goiter in that the disease apparently does not appear above about 12,000 feet.

(6) The relationship between endemic goiter and iodine availability has been carefully documented in several isolated villages in Ecuador. Complete inventories have been made of the occurrence of endemic goiter,
cretinism, consanguinity, and other sociological features in these villages. Dr. Fierro has begun the first iodinated oil prophylaxis program in the Western Hemisphere, and has carefully documented background information which will enable him to prove for the first time whether the suspected relationship between endemic goiter on the one hand, and cretinism, endemic deaf-mutism, endemic mental retardation, and short stature on the other is, in fact, a reality. He has studied a group of severely retarded cretins in his laboratory in Quito from the anthropological and medical point of view. These studies are now being prepared for publication.

(7) The studies of Dr. Barzelatto and his IAEA consultant, Dr. Beckers, from the Pedrogoso region in southern Chile are now in preparation for publication. They have found little evidence for any genetic predisposing factors, but have evidence that a common dietary stable, a nut of the Araucaria tree, may be a contributing factor. Their kinetic studies have shown a large loss of inorganic iodide from the thyroid, which undoubtedly contributes to the development of the iodine deficiency state in these subjects.

(8) Wide-scale surveys for endemic goiter in the state of São Paulo have now been largely completed. These are being published at the present time. Dr. Gandra has obtained data regarding the amount of iodide needed for impairing the uptake of radioactive iodine and of the amount of thyroxine needed for accomplishing this, as well. He has found that in spite of iodide prophylaxis there is a residual group of patients who have endemic goiter. He intends to study this group now because of the possibility that they have some cause for their goiter not related to iodine deficiency.
(9) The studies of Dr. Lobo in Brazil have failed to disclose any relationship between endemic goiter and Chagas' disease. He has also found no evidence that endemic goiter is accompanied by any significant rise in antithyroglobulin antibodies. He has studied a series of cretins brought from western Brazil to Rio de Janeiro for neurological, osteological, and other abnormalities. These studies have now been published. He has surveyed several towns in the Mato Grosso for iodine deficiency, and for the relationship of iodine intake to the occurrence of goiter. The usual relationships have been found. He continues his genetic surveys in this region for the possibility of a genetic background for endemic goiter.

(10) The IVIC group had already observed the curious phenomenon of high $^{131}$I uptake without goiter in the aborigene population of Venezuela prior to the formulation of the PAHO endemic goiter research program. These studies were extended in the Alto Orinoco early in the inception of the PAHO program. Their laboratory efforts have recently been concerned with problems of labeled thyroxine synthesis and the study of thyroxine degradation using carbon-labeled thyroxine. This group has also been studying the intermediary metabolism of the thyroid.

Projections

The PAHO Scientific Group on Research in Endemic Goiter in its fifth year may be satisfied that it has become an active, cohesive scientific group, and happy in some of its accomplishments, especially in the establishment of the reference laboratory, the impetus given to iodide prophylaxis by the meeting in Salta, the Ecuador iodinated oil prophylaxis program, and many other research accomplishments. The participating
members and their consultants all share in the sense of frustration with many of the difficulties involved in the study of endemic goiter. While all agree that iodine deficiency is the principal cause of this disease, all have the suspicion that other factors are involved, and so far have been unable to devise valid experiments which will prove with certainty that genetic or environmental factors other than iodine deficiency actually play a role in the pathogenesis of this disease. This problem will yield only to continued thought and study and doubtless awaits the development of new methodologies. The group solicits the continued support of PAHO.