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PROGRESS REPORT ON PAHO-COORDINATED RESEARCH PROGRAM IN ENDEMIC GOITER:
BRAZIL, CHILE, PERU AND ECUADOR

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PAN AMERICAN HEALTH ORGANIZATION
Pan American Sanitary Bureau, Regional Office of the WORLD HEALTH ORGANIZATION
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I Brazilia, Brazil

Dr. Carlos Lobo was visited in Brazilia on February 26 - 28. Dr. Lobo became Dean of the new Medical School at the University of Brazilia in February 1966 and his first class of 80 students entered in August 1966. He has been deeply involved in the construction of the Medical School, installation of the teaching laboratories, development of a faculty and a teaching program, and building, staffing, and planning for a community and a university hospital. The new institution will be most unique in that all of its staff will be full time, the medical school curriculum will be fully integrated, and the community hospital will be designed to provide total health services for an entire designated city area. The development of this medical complex represents a very significant achievement and time devoted to it has necessarily interrupted Dr. Lobo's research program.

In the past two years two aspects of the studies on endemic goiter in Mato Grosso have continued. The original survey has been extended to include nearly 10,000 people, who have been examined for a number of genetic markers, goiter, and signs of physical or mental impairment. Information on ethnic, educational and socio-economic factors has been obtained. While the information has been put on I.B.M. cards and analyzed by a computer, the analysis is not complete. The initial

* Prepared by Leslie J. DeGroot, M.D., Department of Nutrition and Food Science, Massachusetts Institute of Technology, Cambridge, Massachusetts, following his visit 24 February - 11 March 1967, as PAHO Consultant to Brazil, Chile, Peru and Ecuador.
results are compatible with an increased familial incidence of goiter, but do not demonstrate the presence of a simple dominant or recessive gene inheritance pattern. No association between endemic goiter and mental retardation, still births, or deaths prior to age 21, has been developed. Endemic goiter is correlated with a Negro ethnic background, poverty, illiteracy, and rural habitat. It is possible that all of these factors are interrelated and an analysis for these relationships is being constructed at the present time.

Kinetic studies have been performed to substantiate the impression of a possible increased renal iodide excretion in the residents of the Mato Grosso area. Studies so far have suggested an accelerated iodide disappearance from blood and augmented renal iodide excretion rate, but further data are needed to establish or disprove this possible association. Residents of the area, who have a modest degree of iodide deficiency, also have been found to have P.B.I. values at the low range of normal. Initial studies using a resin uptake technique failed to demonstrate deficiency of binding proteins and studies on thyroxine binding capacity are now in progress.

It is Dr. Lobo's opinion that goiter in itself is a rather minor social and public health problem. He feels however, that an association between iodide deficiency, endemic goiter and mental and physical defects is still quite possible or even probable and that iodide deficiency could by this mechanism account for an important contribution to the load of defectives in the population. For this reason he believes further studies on the relationship of mental and physical defects to endemic goiter are needed, and supports the campaigns for the iodination of salt on a national basis.
São Paulo, Brazil

Dr. Geraldo Medeiros and Dr. Yaro Gandra were visited in São Paulo on March 1. Dr. Medeiros devotes mornings to the Hospital das Clínicas and afternoons to a private practice. His research is directed primarily toward study of the role of the particulate iodoprotein of the thyroid in overall iodide metabolism by the gland. He has collected a series of about 100 glands in which he has analyzed the content of iodoprotein, and has demonstrated through double label kinetic studies that the particulate protein turns over at a slower rate than does the soluble thyroglobulin. Presence of the iodoprotein was correlated with cellularity of the tissue. It contains less thyroxine per unit of iodine than does thyroglobulin. The quantity of iodoprotein in some tissues is estimated to be as high as 14 or more milligrams of iodine. From this, Dr. Medeiros estimates that it could represent, in areas of iodide deficiency a significant loss of iodide from the available iodide pool in diet or from thyroid endogenous iodide re-circulation. Since the quantity of iodine in the particulate iodoprotein increases as the gland grows in size, it is possible to estimate that five micrograms of iodide could be stored in this insoluble fraction of the gland per day over a period of two or three decades in some patients. Thus, one develops an analogy of endemic goiter as a storage disease in part, in some ways related conceptually to glycogen storage disease of liver or other storage diseases such as Gaucher's disease. Further studies on the particular iodoprotein will include solubilizing it by various techniques, attempting to identify its physical characteristics and origin.
Studies will include determination of the presence of a familiar protein in other tissues, and possibly study of immunologic relationships between this protein and other insoluble proteins in the liver or kidney. While Dr. Medeiros' studies have so far been directed toward the thyroid glands appearing in his surgical clinic at the hospital, the tissues do in fact represent the results of endemic goiter. His interest in the problem will now be expanded to a study of glands from an area of high endemicity to the west of São Paulo. Arrangements for study of surgical specimens in this area have been made.

Another study of considerable interest is being performed jointly by Dr. Medeiros and Drs. Klefer and Nicolau. Patients with hyperthyroidism are being treated with large doses of corticosteroids. To date, one patient in the third decade with long standing hyperthyroidism has failed to respond to large doses of steroid, but two teenage girls have responded dramatically to a short course of steroid therapy.

Dr. Yaro Gandra has spent the last two years deeply involved in the organization of his Department of Nutrition within the School of Hygiene and Public Health at the University of São Paulo. No studies relevant to endemic goiter have been performed. His past investigations have demonstrated that in the São Paulo area approximately 20 per cent of school children have goiter, although the salt was iodinated to an average level of around 1 to 100,000 - and urinary iodide excretion was approximately 80 micrograms per day. In looking carefully at large matched groups of people in this population where a minor endemic exists, it was found that goiter correlated with a very minimal elevation of the
radioactive iodide uptake (which was statistically significant), with a minimally lower urinary iodide excretion (which was not statistically significant), and with PBIs similar to patients in the same population matched in all respects who did not have goiter. Dr. Gandra plans eventually to return to the study of this group looking for possible genetic factors that select individuals within this population for development of goiter. He is interested in looking for alterations in such factors as absolute iodide uptake, thyroid iodide turnover, and may possibly pursue studies on salivary iodide clearance, and through the use of methimazole tests, on thyroid iodide leakage.

Both Drs. Medeiros and Gandra feel that goiter is a small problem in their area of Brazil and probably in most of Brazil but is nevertheless a real public health problem. People who have endemic goiter rarely have physical symptoms that can be directly attributed to it but nevertheless they wish to be rid of the disease. Drs. Medeiros and Gandra thus support iodinization of salt, but believe the problem is of less general importance than such problems as schistosomiasis, Chagas' disease, worm infestation, diarrheas, and malnutrition.

III Santiago, Chile

Dr. José Barzelatto was visited in Santiago on March 2 - 4. Through good fortune and considerable effort, Dr. Barzelatto has been able to move his entire laboratory area to a new basement laboratory in an institute originally devoted largely to cancer therapy, on the grounds of the Hospital del Salvador. Refurnishing the area was accomplished in part through assistance from the Pan American Health Organization and a very satisfactory laboratory area has been produced.
Within the area, he has established the Iodine Analysis Reference Laboratory supported by the Williams Waterman Fund, his own basic and clinical research laboratory, office and secretarial areas, and an area for clinical studies on all patients needing endocrine or isotope studies in the Hospital del Salvador. The Reference Laboratory has now been established and operating for several months and seems to be working smoothly. Iodine analyses are made on blood, urine, tissue, and food and salt. Reference is made frequently to a Hyland Laboratory standard and to a series of known specimens developed by Dr. Barzelatto. The first trainee is now in residence at the Laboratory, and a second trainee will presumably come from Dr. Lobo's laboratory in Brazilia.

Dr. Barzelatto has been busy in the past year in a number of projects that have taken him away from studies on thyroid disease. These include being on the Board of Trustees of the University of Santiago, on the Board of Trustees of the Chilean Atomic Energy Commission, and serving as a special advisor on health matters to the President of Chile. One result of these activities has been the development for the first time of a policy by the National Chilean Government to support medical research and it is anticipated that a mechanism for the study of research projects and allocation of funds will be developed in the coming year. Dr. Barzelatto's busy schedule includes running a training program in Nuclear Medicine sponsored by PAHO and the International Atomic Energy Agency, as well as running an endocrinological consultation and chemical laboratory for the Hospital del Salvador. Two publications done jointly with Dr. Christian Beckers, of Belgium, on the studies in the Pedregoso Indian Reservation will soon appear in Acta Endocrinológica. These indicate the
role of iodide deficiency in this endemic and the possible contribution of
a goitrogenic factor in the pine nut comprising a large fraction of the diet
of these people. Kinetic studies indicate a very large iodide secretion
from the thyroid despite a low normal PBI, suggesting an important iodide
leak, probably as iodotyrosine or iodopeptide material. Other evidence
for this iodide leakage is the presence of a small amount of iodotyrosines
in blood, and the presence of a 10 - 20% of blood iodine as iodoprotein.
DIT deiodination studies show that the population has on the average a
slightly increased excretion of iodotyrosine in urine, with values
ranging up to 20% of dose. Further studies on DIT metabolism in a
normal population show that loads of 30 milligrams of DIT augment
excretion of the labelled species. Barzelatto's hypothesis is that leakage
of iodotyrosines may overwhelm the body's iodotyrosine deiodinating
mechanisms and result in appearance of the iodotyrosines in blood.
Apparently, deiodination occurs largely in blood because little
iodotyrosine, if any, is found in urine. It is his belief that an
iodide leak plays a very important role on the genesis of the goiter
in this population, and he has found a correlation between thyroid size
and evidence of iodine leak.

Rats have been maintained on the pine nut, and using adequate dietary
controls, it has been demonstrated that the pine nut results in thyroid
hyperplasia and thyroid iodine depletion. These studies are continuing
and an effort will be made to determine whether the goitrogenic factor
acts primarily to inhibit binding of iodide, or possibly acts to augment
fecal excretion of iodine. Also, efforts will be made to extract a soluble goitrogenic factor so that it can be purified.

The interpretation of the genetic aspects of the study in Pedregoso were discussed with Dr. Barzelatto and his geneticist colleague. From the phenylthiocarbamide testing study, some rather dramatic correlations have developed. It appears that the ability to taste PTC is correlated with a lesser incidence of goiter, and with a lesser incidence of nodular rather than diffuse goiters. These data are compatible with an hypothesis that tasting of PTC correlates with aversion to a naturally occurring dietary goitrogen. People able to taste PTC, and perhaps the natural goitrogen, would tend to consume less of the goitrogen, have a smaller incidence of goiter, and more incidence of diffuse rather than nodular goiter. In support of this theory, the investigators have observed that the intake of the pine nut is higher in patients with diffuse goiter than in others.

Dr. Barzelatto had arranged through the International Atomic Energy Agency, for a visit by Professor William Schull of the University of Michigan Department of Human Genetics who contracted to spend two months as a consultant working on the interpretation of the studies from the Pedregoso area. It is essential at this point in the analysis of their data that the material be put on punch cards and be examined by appropriate programs on a computer which is available in the School of Engineering. It will otherwise be impossible to do the multifactorial analysis necessary to meaningfully interpret the mass of genetic data they have available. Unfortunately, the International Atomic Energy Agency has recently stated it is not willing to support Professor Schull's visit since it is not related to the use of radioactive
isotopes. Considering the availability of a completed genetic study, the strength of the genetic team in Santiago, and the availability of a computer, it seems essential that some way be found to support Professor Schull's visit. Perhaps it would be appropriate for the Pan American Health Organization to pay his expenses as a consultant for the period in question.

New studies projected by Dr. Barzelatto fall into three categories. The pine nut goitrogen will be assayed in laboratory animals. Studies will be made in Pedregoso of individuals who seem to have a large iodide leak and have iodotyrosine in their serum, to develop further evidence for spillage of iodotyrosines. Tyrosine load tests will be performed to see whether a consistently high pattern of plasma tyrosine emerges in the goitrous population, as seems to be evident so far. DIT deiodines tests will be performed to see whether release of iodotyrosines from the thyroid could alter the proportion of iodotyrosine excreted in the urine.

In cooperation with investigators in Bolivia, Dr. Barzelatto and his genetic team hope to pursue studies among four isolates of Indian ethnic groups in Bolivia. It is intended that the survey will include a clinical and socio-anthropologic study, and then a study of thyroid function, PTC tasting, anthropometric measurements, hemoglobin typing, leukocyte antigen typing, and haptoglobin typing. Dr. Barzelatto hopes to obtain support from the newly created Special Fund for Research in PAHO to initiate this research.
IV Lima, Peru

Dr. Eduardo Pretell was visited on March 2 - 4. Sixth months ago residents of three villages near Tarma were injected with iodized oil or a placebo. Dr. Pretell is in charge of the follow-up study of this program, in cooperation with Dr. Federico Moncloa. A major difficulty exists in finding funds to support the program. Little support is available presently at the High Altitude Research Institute, although it has been agreed that Pretell can spend one week per month on the goiter study. It is hoped that funds may become available from the Peruvian Public Health Service to support the study between May 1 and September 1, at which time a U. S. Public Health Service grant may be available to offer further support. Dr. Pretell visited the Tarma area in October to inject a larger group of patients, and in November to observe any possible reactions to the injection. None were found. Since that time he has been unable to return for follow-up studies because of lack of funds to support the cost of the trip, and because heavy rains and wind slides temporarily closed the roads. He anticipates returning in March for the follow-up visit, and in April for the six months' survey.

So far no information is available other than the original data showing high uptakes, normal to low PBI's, and low urinary iodide excretions. For follow-up purposes, Dr. Pretell will set up a serum thyroxine method on the basis of the Murphy and Pattee approach, thyroxine binding globulin determinations, T3 resin uptakes, and will continue to do PBI's, total iodide and butanol extractable iodides in his laboratory.
In the original survey, data on defectives in the population were not tabulated. It is anticipated that this will be done during the follow-up study. To study the newborns in the area it will be necessary to get a young physician to live in Tarma. So far arrangements have not been made because no funds have been in hand to support the physician. Further, arrangements must be made with the hospital in Tarma to provide free care for the villagers who come to it for the maternity period. It is anticipated that this collaboration can be obtained.

V Quito, Ecuador

Dr. Rodrigo Fierro was visited in Quito from March 6 - 10. After arriving we journeyed to Tocachi to participate in the one year follow-up study of the iodine injected villagers. Approximately 600 individuals were surveyed. It is now clear that there has been a reduction in size of many of the goiters although the data have not been formally tabulated. The original cases of possible thyrotoxicosis are still under observation, and no further cases have been discovered. Of the fifteen suspects, only three seem clearly to have hyperthyroidism. Two have required therapy with methimazole. All of these patients came to medical attention through the survey. None have come to the clinic requesting medical assistance.

Blood and urine samples were obtained from ten cretins in Esperanza and ten in Tocachi for determination of urinary amino acids and iodide, and plasma thyroid hormone blood levels. In addition, blood
samples were obtained from several normal subjects who have been
injected with oil, and several patients with suspected hyperthyroidism.

The maternity and prenatal clinic in Tocachi under Dr. Ramirez
seems to be going exceedingly well, as is the one in Esperanza under
the control of the midwife, Miss Aida Francis. Both of these
collaborators are excellent in all respects and are important contributors
to the project.

Dr. Fierro has published some of his results from the initial
survey in a local journal in Ecuador, and wishes now to translate the
paper for publication in English. He also hopes to publish data on
the follow-up study of the thyroxine treated cretins after they have
been re-studied, and possibly on the hyperthyroid patients when
further observations are available.
VI Summary and Suggestions

No special suggestions are offered relevant to activities in Brazilia and São Paulo other than it would be wise to invite Dr. Medeiros and Dr. Nicolaw to future meetings of the PAHO study group. In Santiago the chief problem is to arrange financing for the visit of Dr. William Schull as consultant for a two month period with Dr. Barzelatto. I believe this is an endeavor that PAHO should attempt to finance, as it certainly will lead to maximum utilization of the information already obtained in Dr. Barzelatto's study. Every effort should be made to support this consultant.

In Lima and Quito the fundamental problem seems to be the adequate long term funding of the investigations and if this is achieved both projects should move ahead. There can be no doubt that great strides have been made in Quito up to this time.

Several additional points came up during the visits. It is logical that some attention should be paid to obtaining annual information about the adequacy of iodine prophylaxis programs. Thus it might be appropriate for each member of the PAHO group to collect information on incidence of goiter in a small localized population isolate, such as a particular grade in a particular school class, to obtain urinary iodide samples from a similar specialized group, and to obtain salt iodine levels in a series of salt samples. This information could be obtained yearly, collated, and an interpretation published for newspaper distribution as a statement from the PAHO study group on the efficacy of government salt iodination programs.
Note is made also that no report of the Salta Iodine Prophylaxis Meeting has been distributed although all members of the study group are interested in receiving this information.

Each person would like to receive a complete set of the papers relevant to that Meeting, especially (for some of us) if they could be translated into English. A great deal of useful information on the history of salt iodination in South America and on the effectiveness of iodination campaigns is included in the proceedings of the Meeting.

Much interest was expressed in the proposed meeting of the PAHO goiter research group in March of 1968 and plans for this should be formulated.

An important additional project that can be formulated with Drs. Pretell and Pierro is the use of oral iodinated compounds for prophylaxis of endemic goiter. Discussions were held with them on appropriate methods and a trial will be carried out.