

PRNC 68

PUERTO RICO NUCLEAR CENTER

Clinical Radioisotope Program
Research Projects Information



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PUERTO RICO NUCLEAR CENTER

Clinical Applications Division

Clinical Radioisotope Program
Research Projects Information

July, 1965

PROJECTS CONCLUDED:

1. Evaluación Clínica de Pruebas Diagnósticas en la Función Tiroidea con I-131.

Aldo E. Lanaro, Clinical Applications Division, Puerto Rico Nuclear Center;
Sergio Irizarry, Clinical Applications Division, Puerto Rico Nuclear Center;
Lillian Haddock, Department of Medicine, University Hospital;
Manuel E. Paniagua, Department of Medicine, Río Piedras Municipal Hospital

2. The Effect of Cyclic Administration of Certain Progestin-Estrogen Combinations on the 24-hour radioiodine uptake (aided by research grants from Mrs. Stanley McCormick, the Andre and Bella Meyer Foundation and G.D. Searle and Co.)

Sergio Irizarry, Clinical Applications Division, Puerto Rico Nuclear Center;
Manuel E. Paniagua, Department of Medicine, Río Piedras Municipal Hospital;
Gregory Pincus, Worcester Foundation for Biology and Medicine;
José L. Janer, Biostatistic Division, School of Public Health, School of Medicine
Zenaida Frías, Radiotherapy and Cancer Division, Puerto Rico Nuclear Center;
Hada Livia R. de Colón, Clinical Applications Division, Puerto Rico Nuclear Center.

3. The Renogram as a Tool for Evaluating patients with Cancer of the Cervix Uteri.

Sergio Irizarry, Clinical Applications Division, Puerto Rico Nuclear Center;
A. L. Rodríguez Rosado, Formerly Clinical Applications Division, Puerto Rico Nuclear Center.

4. The Role of Calcium on the Intestinal Absorption of Vitamin B-12 in Tropical Sprue.

A. L. Rodríguez Rosado, Formerly Clinical Applications Division, Puerto Rico Nuclear Center;
T. W. Sheehy, Formerly Tropical Research Medical Army Laboratory.

5. Experimental Demonstration of Exudative Loss of Serum Albumen in Gastritis.

A. Rodríguez Olleros, School of Pharmacy, University of Puerto Rico;
Sergio Irizarry and M. Rivera, Clinical Applications Division, Puerto Rico Nuclear Center.

6. Uptake measurements: Determination of the probable maximum deviation of the uptake measurements at this laboratory.

Sergio Irizarry, Clinical Applications Division,
Puerto Rico Nuclear Center;
Hada L. Rodríguez de Colón, Clinical Applications
Division, Puerto Rico Nuclear
Center;
Zenaída Frías, Radiotherapy and Cancer Division, Puerto
Rico Nuclear Center.

7. The Effect of Radiation therapy in gastrointestinal absorption of I-131 Oleic Acid in humans.

Sergio Irizarry, Clinical Applications Division, Puerto
Rico Nuclear Center;
A. A. Cintrón Rivera, Department of Medicine, University
Hospital;
Victor Marcial, Radiotherapy and Cancer Division, Puerto
Rico Nuclear Center;
Myrna Rivera, Clinical Applications Division, Puerto
Rico Nuclear Center;
Zenaída Frías, Radiotherapy and Cancer Division, Puerto
Rico Nuclear Center;
Carmen C. Villodas, Clinical Applications Division, Puerto
Rico Nuclear Center.

8. Deposition of isotopically labelled antibodies in Trichinella Spiralis.

M. Bertholds, Formerly Clinical Applications Division,
Puerto Rico Nuclear Center;
J. O. González, Department of Parasitology, School of
Medicine;
J. B. Vilella, Formerly Clinical Applications Division,
Puerto Rico Nuclear Center;
Luz C. Reyes, Formerly Clinical Applications Division,
Puerto Rico Nuclear Center.

PROJECTS IN PROGRESS:

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1. Study of Thyroid Nodules.
A.E. Lanaro, Clinical Applications Division, Puerto Rico Nuclear Center;
S. Irizarry, Clinical Applications Division, Puerto Rico Nuclear Center;
L. Haddock, Department of Medicine, University Hospital.
2. The value of scanning in two projections in the evaluation of thyroid nodules.
Sergio Irizarry, Clinical Applications Division, Puerto Rico Nuclear Center.
A. E. Lanaro, Clinical Applications Division, Puerto Rico Nuclear Center;
Lillian Haddock, Department of Medicine, University Hospital;
O. Vázquez, Clinical Applications Division, Puerto Rico Nuclear Center.
3. Clinical Evaluation of 24 and 48 hour thyroid iodide accumulation and protein bound hormonal iodine 131 levels.
A. E. Lanaro, Clinical Applications Division, Puerto Rico Nuclear Center;
S. Irizarry, Clinical Applications Division, Puerto Rico Nuclear Center,
4. Evaluation of Thyroid Function in Sprue.
E. P. Santiago, Department of Medicine, University Hospital;
N. Maldonado, Department of Medicine, University Hospital;
S. Irizarry, Clinical Applications Division, Puerto Rico Nuclear Center.
5. Thyroid Gland as an Indicator of Gastro-Intestinal Absorption.
S. Irizarry, Clinical Applications Division, Puerto Rico Nuclear Center;
N. Maldonado, Department of Medicine, University Hospital;
M. Rivera, Clinical Applications Division, Puerto Rico Nuclear Center.
6. Iodine 131 Therapy of Carcinoma of the Thyroid.
S. Irizarry, Clinical Applications Division, Puerto Rico Nuclear Center.

7. Tapazole Inhibition of thyroid function in Hyperthyroid Patients.

Sergio Irizarry, Clinical Applications Division, Puerto Rico Nuclear Center.

8. Phase 2. Evaluation of long term effects of radiation on gastro-intestinal absorption of I-131 Oleic Acid in Humans.

Sergio Irizarry, Clinical Applications Division, Puerto Rico Nuclear Center;
Victor Marcial, Radiotherapy and Cancer Division, Puerto Rico Nuclear Center;
Myrna Rivera, Clinical Applications Division, Puerto Rico Nuclear Center.

9. Instrumentation- Modified Scanner.

Sergio Irizarry, Clinical Applications Division, Puerto Rico Nuclear Center;
William González, Clinical Applications Division, Puerto Rico Nuclear Center;
Pablo T. Collazo, Clinical Applications Division, Puerto Rico Nuclear Center.

10. Organ and Tumor Localization.

Sergio Irizarry, Clinical Applications Division, Puerto Rico Nuclear Center;
A.E. Lanaro, Clinical Applications Division, Puerto Rico Nuclear Center;
O. Vázquez, Clinical Applications Division, Puerto Rico Nuclear Center.

11. The Renogram in Patients with Carcinoma of the Cervix Uteri.

S. Irizarry, Clinical Applications Division, Puerto Rico Nuclear Center;
A. E. Lanaro, Clinical Applications Division, Puerto Rico Nuclear Center;
V. Marcial, Radiotherapy and Cancer Division, Puerto Rico Nuclear Center.

12. Correlation between isotopic renogram and other tests of renal function.

S. Irizarry, Clinical Applications Division, Puerto Rico Nuclear Center;
A.E. Lanaro, Clinical Applications Division, Puerto Rico Nuclear Center.

13. Evaluation of the renal function in diabetics patients
by the use of radioactive renogram.

A.E. Lanaro, Clinical Applications Division, Puerto
Rico Nuclear Center;
Mario Iturralde* Clinical Applications Division,
Puerto Rico Nuclear Center;
Sergio Irizarry, Clinical Applications Division,
Puerto Rico Nuclear Center.
M. Paniagua, Department of Medicine, Río Piedras
Municipal Hospital.

* Formerly trainee Clinical Applications Division, PRNC.

NEW PROJECTS:

1. The Cyclic Variation in the total body sodium, interchangeable sodium, the total body water and the Thyroxine binding protein (TBP) under the effect of periodical administration of ethinyl-estradiol-3-methylether-norethynodrel.

A.E.Lanaro, S. Irizarry, Clinical Applications Division,
Puerto Rico Nuclear Center;

B. Weinbren, Medical Sciences and Radiobiology, Division,
Puerto Rico Nuclear Center;

M. Paniagua, Department of Medicine, Río Piedras
Municipal Hospital.

2. Thyroid function studies in patients with so-called Hormonal Dependent Tumors.

A. E. Lanaro, S. Irizarry, Clinical Applications Division,
Puerto Rico Nuclear Center;

J. Ubiñas, V. Marcial, Z. Frías, Radiotherapy and Cancer
Division, Puerto Rico Nuclear
Center.

3. Thyroid Clearance

O. Vázquez, S. Irizarry, Clinical Applications Division,
Puerto Rico Nuclear Center.

4. Activation analysis - Evaluation of its routine use at this laboratory in selected patients with thyroid disorders in Puerto Rico.

S. Irizarry, J. Chiriboga, A.E. Lanaro, Clinical Applications
Division, Puerto Rico Nuclear
Center.

5. Brain Tumor Localization.

S. Irizarry, Clinical Applications Division, Puerto Rico
Nuclear Center;

J.V. Rivera, Radioisotope Laboratory, Veterans Administration
Hospital.

6. Radioimmunoassay of protein and peptide hormones.

Oscar N. Vázquez, Sergio Irizarry, Clinical Applications
Division, Puerto Rico Nuclear Center.

RESEARCH PROJECTS INFORMATION

Clinical Applications Division - PRNC

Project Director : SERGIO IRIZARRY, MD

Principal Investigation : CLINICAL APPLICATIONS OF RADIOISOTOPES

Source of Project Funds : AEC BUDGET ACTIVITY NO. 070102

Project Timetable : Several years

Title of Project : CLINICAL RADIOISOTOPE PROGRAM

Purpose : The main purpose of the program of this Division is teaching and training of Latin American physicians in the diagnostic and therapeutic uses of radioisotopes in humans. The scope is to offer varying types of training at different levels of interest or preparation of trainees. Our courses vary from those of general orientation given for information only to those of short term basic and advanced training in radioisotope techniques or a long course in clinical research. Research based on the clinical applications of radioisotopes is conducted as one of the basic activities underlying our teaching effort. Clinical material for research projects and teaching is obtained from the patient referral load to this Division from many sources in the Island providing a substantially large diagnostic and therapeutic load which is adequate for our program.

This report will first briefly describe all concluded projects following a special outline, in second term a progress report of projects under way, and in third term new projects.

The projects concluded at this Division are:

1. Evaluación clínica de pruebas diagnósticas en la función tiroidea con I-131.
2. The Effect of Cyclic Administration of certain progestin-estrogen combinations on the 24 hour radioiodine thyroid uptake.
3. The renogram as a tool for evaluating patients with cancer of the cervix uteri.

4. The role of calcium on the intestinal absorption of Vitamin B-12 in Tropical Sprue.
5. Experimental demonstration of exudative loss of serum albumen in gastritis.
6. Uptake measurements: Determination of the probable maximum deviation of the uptake measurement at this Laboratory.
7. The effect of radiation therapy on gastrointestinal absorption of I-131 Oleic acid in humans.
8. Deposition of isotopically labelled antibodies in *Trichinella Spiralis*.

PROJECTS CONCLUDED: Methods, findings, significance.

Thyroid Studies :

Project Title : Evaluación Clínica de pruebas diagnósticas en la Función Tiroidea con I-131.
Aldo Ernesto Lanaro, M.D.¹, Sergio Irizarry, M.D.²
Lillian Haddock, M.D.³, Manuel E. Paniagua, M.D.⁴

Method : Clinical appraisal of the 24 hour I-131 uptake test of thyroid function in patients with defined clinical pictures of euthyroid, hyperthyroid and hypothyroid states.

Findings : This study to evaluate the range of euthyroid, hyperthyroid and hypothyroid function in Puerto Rico patients was completed on 263 individuals with unequivocal clinical pictures of thyroid dysfunction or eufunction. The group was made up of ninety three (93) euthyroid individuals, eighty four (84) hyperthyroids, sixty two (62) patients with non toxic nodular goiter and twenty four (24) hypothyroid individuals. Results were as follows:

	<u>Number</u>	<u>24 hour I-131 uptake</u>		<u>Range</u>
		<u>Average</u>	<u>St. Deviation</u>	
Euthyroids	93	25.3 ±	8.4	13.2 - 67
Hyperthyroids	84	69.1 ±	13.9	31.6 - 97
Hypothyroids	24	6.6 ±	5.7	1.1 - 20.7
Non toxic Nodular Goiter	62	27.3 ±	12.9	7.7 - 81.9

Overlapping values between hyperthyroid and euthyroid patients occur in 5% of each group, while overlapping between hypothyroid and euthyroid values is dissimilar in that 30% of the hypothyroid patients overlap with euthyroid values, and 8% of euthyroid patients fall within the range of hypothyroid values.

Significance : The 24 hour I-131 thyroid uptake as performed in this laboratory can detect euthyroid and hyperthyroid states of the thyroid gland with a 95% confidence limit, and the hypothyroid state with a much lower precision of 70%. The procedure is useful to the clinician for the study of thyroid function in different pathological states. Reprint appended.

2. The Effect of cyclic administration of certain progestin-estrogen combinations on the 24 hour radioiodine thyroid uptake (aided by research grants from Mrs. Stanley McCormick, the Andre and Bella Meyer Foundation and G.D. Searle and Co.)

Sergio Irizarry, M.D., Manuel E. Paniagua, M.D., Gregory Pincus, Sc. D., José L. Janer, B.S. M. Sc., Zenaida Frías, M.P.H., Hada Livia R. de Colón, M.T.

Method

: The thyroid gland function was studied with I-131 by the method of Marshall Brucer, modified by us, in a group of 154 Puerto Rican women twice in a three month period to assess the magnitude of variation of the 24 hour thyroid iodine uptake in groups of women taking anticonceptive medications at short term (three months) or long term (three years) administration. The population studied included four groups: two on short term medication, one in long term medication and a control group on no medication.

Findings

: Uptake measurements repeated in all groups within a three months interval showed no significant variation other than that which can be ascribed to normal expected day to day variation as reported by other investigations.

Significance

: The result of this study indicates there is no evidence that the employment of a combination of estrogenic and progestational substances as anticonceptive measures at short or long intervals produce changes of clinical significance in the 24 hour I-131 uptake by the thyroid gland. Report appended.

3. The renogram as a tool for evaluating patients with cancer of the cervix uteri.

Sergio Irizarry, M.D., Angel L. Rodríguez Rosado, M.D.

Method

: Patients with carcinoma of the cervix uteri from the I. González Martínez Oncologic Hospital were selected for this study. The majority of patients studied were suffering from Stage III carcinoma. Renograms with the use of I-131 orthoiodohippuric acid were used to study renal function with particular interest in the study of the excretory phase. Correlations were made with other methods of assessing urinary tract function such as the phenolsulphophthalein chemistries, (blood urea nitrogen) and the intravenous pyelogram.

Findings

: In a group of 18 patients suffering from carcinoma of the cervix uteri stage III the renogram was able to detect signs of ureteral compression in 7 of them, the same proportion detected by intravenous pyelography.

Significance

: The renogram compares well with the intravenous pyelogram in detecting abnormalities of urinary flow in patients with carcinoma of the cervix uteri. (reprint appended)

4. The role of calcium on the intestinal absorption of Vitamin B-12 in Tropical Sprue.

A. L. Rodríguez Rosado, M.D., T. W. Sheehy, M.D.

Method : Puerto Rican patients with documented Tropical Sprue, 3 of which were untreated, were investigated twice in a week interval with the Schilling technique for measuring the absorption of labelled Vitamin B-12. The second Schilling test was accompanied with the addition of powdered calcium lactate 3.5 gm 30 minutes before and simultaneously with the administration of the radioactive vitamin.

Findings : In seventeen patients with Sprue abnormal Schilling test (normal range 10% to 35% administered dose in a 24 hour urine sample) were found both with and without the administration of calcium lactate.

Significance : This study appears to indicate that calcium does not improve the absorption of Vitamin B-12 in patients with Tropical Sprue. Reprint appended.

5. Experimental demonstration of exudative loss of serum albumen in gastritis.

A. Rodríguez Olleros, M.D., Sergio Irizarry, M.D., Myrna Rivera, R.T.

Method : Three groups of Mongrel dogs weighting approximately 30 pounds and in good healthy condition were subjected to three types of experimental gastritis induced by chemical means as follows:

I. Serous type of gastritis induced by exposure to Creosote - Diol solution.

II. Erosive gastritis induced by atophan.

III. Papillomatous gastritis induced by croton oil.

Three animals were studied prior to the experimental induction of the gastritis by following the blood disappearance activity curve of albumen I-131 (Biologic half life) and its detection in the gastric juice collected for a specified period of time, 25 minutes after histamine stimulation on the 4th day of the intravenous administration of labelled albumen.

The same study was repeated in these three animals and 7 others after the production of the gastritis.

- Findings : Blood albumen I-131 disappearance curves were more rapid and the detected level of exuded labelled protein into the gastric juice was higher than in control animals.
- Significance : Findings appear to add support to the hypothesis that in gastropathies of different types mucosal injury may contribute to protein malnutrition of the animal thru protein loss into the gastric lumen. (Report appended).
6. Uptake measurements: Determination of the probable maximum deviation of the uptake measurements at this Laboratory.
S. Irizarry, M.D., H.L. Rodríguez de Colón, T.M., Z. Frías
- Purpose : To determine the error of the measurement involving in the whole situation errors contributed by the patient, the technician and the instrument.
- Method : Eight patients were measured repeatedly 24 hours after the administration of an oral dose of I-131. Each measurement was performed as if it were a new procedure: the patient was moved out of the examining room and returned again for different repeated measurements. Phantom was measured each time, and the instrument was set out of the way and re-set in position for each new measurement. The technique of uptake measurement at this laboratory is based on that described by Marshall Brucer in 1959.
- Findings : In 72 measurements done on 8 patients the pooled standard deviation for the group was ± 0.77 units of the uptake measurement, whereas the maximum intraindividual variation was 1.72 units of uptake. The error of the uptake measurement is less than 5%. (Report included.)
7. The effect of radiation therapy in gastrointestinal absorption of I-131 oleic acid in humans.
S. Irizarry, M.D., A.A. Cintrón Rivera, M.D., V. Marcial, M.D., M. Rivera, Z Frías, C. Villodas.
- Purpose : Study the absorption of I-131 labelled oleic acid in patients undergoing radiation therapy to the abdomen to evaluate if the effects of such treatment on the intestine could affect its capacity for absorption for this material during the duration of exposure to radiation.
- Method : Twenty patients from the I. González Martínez Oncologic Hospital receiving radiation to the abdomen, composed mainly of women suffering from carcinoma of the cervix uteri, were selected as the experimental group. Two controls were used: Baseline determinations for individual control of each patient, and an external control consisting of a group of patients receiving extraabdominal radiation consisting mainly of patients with carcinoma of the head and neck region.

Baseline values for both groups were determined, and then serial determinations were performed at two week intervals during the duration of treatment. Intestinal transit was checked by barium meal. The test consisted in the oral administration of I-131 labelled oleic acid in the fasting state, and the collection of blood for radioactive assay 5 hours later. In some patients Vitamin A Tolerance curves were also determined. Blood absorption curves were evaluated against clinical changes in patients and progression of the radiotherapeutic treatment.

Findings : Normal baseline values for each group of patients were of a similar order: Patients with carcinoma of cervix absorbed 13.6 \pm 4.2% (per blood volume) of the oral dose of I-131 oleic acid. Patients with head and neck absorbed 12.8 \pm 3.4% (per blood volume) of the oral dose of I-131 oleic acid. Values below 13.6 - 2 standard deviations were considered abnormal. In the group of carcinoma of the cervix 14 out of 20 patients showed values that were considered abnormal. In the control group abnormal blood levels occurred in 3 out of 19 patients. Abnormal vitamin A Tolerance curves were observed in 7 out of 13 patients examined.

Significance : The evidence would appear to indicate that during a course of radiation therapy to the abdomen intestinal absorption may be significantly altered. In this study such alteration was observed in the two substances studied: I-131 oleic acid and Vitamin A. (Report included.)

8. Deposition of isotopically labelled antibodies - trichinella spiralis.

M. Bertholds, M.D., J.O. González, M.D., J.B. Villella, L.C. Reyes.

Purpose : To identify the sites of antigen-antibody reaction in the tissues of the larvae of Trichinella Spiralis by radio-autoradiography.

Method : Labelled antiserum against larvae of Trichinella spiralis was produced biosynthetically in rats receiving trichinella spiralis antigen and labelled aminoacids at the time of antibody build up for incorporation into the newly formed antibodies. Live Trichinella larvae were exposed to antiserum and then processed by the histologic and autoradiographic technique. The deposition of isotopic aggregates in the tissues of the larvae were studied. These were taken to represent the sites of antigen-antibody reaction. Radioelectrophoretic study of the immune protein fractions of blood from immunized animals was done for levels of radioactive tagging.

Findings

: The evidence obtained showed quantitative differences between larvae exposed to antiserum and their controls. Autographs did not possess sufficient resolution to permit quantitative estimates of the antigen antibody reaction and additional work is needed.

PROJECTS IN PROGRESS AT THIS DIVISION ARE:

Thyroid

- Project Title : Study of thyroid nodules.
A. E. Lanaro, M.D., Sergio Irizarry, M.D., L. Haddock, M.D.
- Purpose : To correlate clinical picture with histopathologic and radioisotopic visualization of the thyroid.
- Method : Scintigraphic localization of I-131 fixation by functioning thyroid tissue is visually compared with non functioning areas or nodules of decreased or absent activity. Scintigraphic signs are correlated with clinical and histopathologic findings.
- Findings : In 64 patients in which clinical, pathologic and scintigraphic correlation has been done, 22 nodules out of a group of 52 lesions turned out to be malignant on histopathologic examination, a rate approximately of 42%.
- Significance : The incidence of malignancy in nodules in this group of patients would indicate a relatively high incidence of neoplastic disease in thyroid nodules in Puerto Rico or else that the population under study was highly selected and does not reflect trends in the general population. Information on more cases needed. (Report appended).
2. The value of scanning in two plane projections in the evaluation of thyroid nodules.
Sergio Irizarry, M.D., A.E. Lanaro, M.D., Lillian Haddock, M.D., Dr. Oscar Vázquez
- Purpose : To determine the radioisotopic characterization of thyroid nodules which on antero-posterior views show isotopic images which may or may not arise in the nodule itself.
- Method : Scintigraphic method, either the plain paper dot graphic method or the combined gammaphoto-scan-radiography (gammagraphy) is used to obtain antero-posterior and true lateral isotopic images from which the spatial relation and isotopic characterization of thyroid nodules can be made with greater precision.
- Findings : Over a hundred thyroid studies have been made with this technique in patients referred to the Puerto Rico Nuclear Center with thyroid nodules. In these cases the vast majority of nodules examined by the combined antero-posterior and lateral approach appear devoid or with decreased activity when compared with the adjacent

thyroid tissue. This has been documented well with the additional help of simultaneous x-ray localization studies of the soft tissues of the neck in combination with isotopic mapping of thyroid lesions. An effort to correlate with findings at surgery is being made.

Significance : If present findings hold true then the scintigraphic evaluation of thyroid enlargements by antero-posterior examination will need re-appraisal. Our preliminary data suggest that findings by antero-posterior examination could be misleading in many instances.

3. Clinical evaluation of 24 and 48 hour thyroid iodide accumulation and protein bound hormonal iodine 131 levels.

A.E.Lanaro, Sergio Irizarry, Clinical Applications Division, Puerto Rico Nuclear Center

Purpose : To determine normal and abnormal values of the 24 and 48 hour thyroid I-131 uptake tests, and rates of production of thyroid hormone synthesis.

Method : Patients referred to the Puerto Rico Nuclear Center laboratory for the routine 24 hour uptake and tagged protein bound hormone blood levels are being studied also at 48 hours. Records will be reviewed for correlation of clinical data with the laboratory values obtained to gain necessary information to define the values for normal and abnormal function in Puerto Rican patients with well defined pictures of thyroid function.

Findings : More than 285 patients have entered the study. This material has not been analyzed yet.

Significance : Study might give additional useful information on parameters of thyroid function that have not been previously studied in Puerto Rico.

4. The evaluation of thyroid function in Sprue.

E.P. Santiago, M.D.; N. Maldonado, M.D.; S. Irizarry, M.D.

Purpose : No information is available about thyroid function in this well known disease in Puerto Rico. Low thyroid function is suspected in these patients; to our knowledge it has not been previously documented in P. R.

Method : Patients with well defined clinical pictures of Sprue and with additional supporting clinical and laboratory data for intestinal malabsorption and megaloblastic anemia are being selected and referred to the Puerto Rico Nuclear Center laboratory for study of thyroid function with radioactive iodine. The study will be done first following the usual procedure of the 24 hour

I-131 uptake in which iodine 131 is given orally; and then the test is repeated using the intravenous route regardless of the result obtained in the first procedure.

Findings : Project is now beginning and not enough data is available for a report.

Significance : Thyroid function is suspected to be altered in sprue. This information is needed since it might help to a better understanding of the disease.

5. Thyroid gland as an Indicator of gastro-intestinal absorption.

Sergio Irizarry, M.D., N. Maldonado, M.D., M. Rivera, R.T.

Purpose : To use the iodide trapping mechanism of the thyroid gland as a physiologic indicator of I-131 set free from metabolic breakdown after gastro-intestinal absorption of radioactive labelled food stuffs, mainly neutral fat. The function of iodine uptake by the thyroid gland is determined in all patients in this study.

Method : Triolein I-131 is administered orally to patients in fasting or in non fasting state. Peak activity in blood usually appears 4-6 hours later. Radioactivity levels of I-131 are assayed as total and lipid bound activity at 5 hours after oral administration of the labelled fat, and 24 hours later the iodine 131 accumulated in the thyroid gland is measured. Individuals with well known normal and abnormal gastrointestinal absorption states are studied. Thyroid levels of I-131 are correlated with the blood absorption levels and other parameters of intestinal absorption. The thyroid gland serves to indicate the extent of labelling of the iodide pool by I-131 liberated from the fat.

Findings : Twenty-one healthy individuals showed that the iodide pool contained about 66.4 ± 17.9% of the administered dose 24 hour after its oral administration. In 17 patients 4 showed abnormally low blood activity levels at 5 hours after oral administration of the labelled fat, but the thyroid showed a large amount of I-131 indicating good absorption.

Significance : This is a procedure which may prove useful in the determination of intestinal absorption of fat. Report appended.

6. Iodine - 131 Therapy of Carcinoma of the Thyroid.

- Purpose : To offer palliative therapy to patients with advanced thyroid carcinoma with pulmonary and skeletal metastasis.
- To ablate residual thyroid tissue following partial thyroidectomies for cancer of the thyroid.
- To learn appropriate dosage schedules of treatment and gain a better understanding of the management of the disease with the use of internal emitters.
- Method : Patients with carcinoma of the thyroid, some with residual thyroid tissue in the neck after surgical intervention and the majority with evidence of far advanced disease in lungs and bones are evaluated for this modality of therapy. Prime requisite is the detection of foci of metastatic thyroid tumors with ability to concentrate I-131.
- Findings : Seven patients from the I.G.M. Oncologic and University Hospitals have been treated. Four patients with far advanced disease who received a single dose of 25 mc I-131 died within a period of 2 years.
- Three patients were successfully treated as follows:
- 13 mc were given for ablation of residual thyroid tissue.
- 105 mc, in five doses in 2 years, with ablation of neck metastasis and partial resolution of pulmonary lesions.
- 125 mc in seven doses in one year with successful remission of a bone fracture and other foci of functioning tumors.
- Significance : Series is too small to comment upon. However, relatively small amounts of I-131 were necessary to produce a good clinical and objective response in the last three patients mentioned. (Report appended)

7. Tapazole inhibition of thyroid function in Hyperthyroid patients.

- Purpose : To study the degree of thyroid function inhibition by pharmacologic doses of tapazole in hyperthyroid patients.
- To determine how frequently the antithyroid effect of the medication is partial or unsuccessful.
- To learn whether so called "clinically resistant patients to antithyroid medication" are due to lack of adequate pharmacologic drug action on said patients.
- To gain personal experience with this radioisotopic technique in the anticipation of the clinical response of a patient to antithyroid medication. This has been demonstrated by Stanley and Astwood in 1948.

Method

: Phase I - Patients with documented hyperthyroidism are being studied by the technique using Potassium thyocyanate to discharge, from the thyroid gland, trapped iodide which has not yet been bound to thyroid hormone precursor due to the inhibitory effect of antithyroid medication.

In this phase enough patients are to be studied to determine the criteria of failure of the antithyroid drug to successfully inhibit hormone synthesis and its rate of incidence among a group of hyperthyroid patients.

Phase II - In this phase a search for hyperthyroid patients with "clinically resistant pictures to antithyroid management" will be done to test the hypothesis if the resistance is due to a pharmacologic failure of the drug in producing the necessary metabolic blockade of hormone synthesis or to other factors.

Findings

: A group of 21 patients in whom the diagnosis of hyperthyroidism was well established by clinical and laboratory criteria were initially studied by the Potassium Thyocyanate discharge test in which patient is medicated with 40 mg tapazole simultaneously with the diagnostic I-131 tracer dose. Three hours later a baseline uptake is performed followed immediately by the oral administration of 1 gm KCNS. Uptake measurements are subsequently done every 30 minutes for 3 times, to follow the release of free iodide from the thyroid gland into the blood causing a sharp fall in the activity in the thyroid region. The comparison of the last uptake taken 1 1/2 hour after KCNS administration with the 3 hour baseline uptake in the 21 patients yielded an average level of 15.9%. Three patients had exceptionally high residual thyroid values at the 1 1/2 hour post KCNS uptake measurement. These patients fall in the group that may be considered as demonstrative of failure of the antithyroid drug to effectively suppress thyroid hormone synthesis.

In the eighteen (18) remaining patients the 1 1/2 hour post KCNS uptake was 12.9% (average) of the baseline 3 hour uptake.

The residual activity the 3 patients with presumed resistance to antithyroid medication was 32.1% of the baseline value. Two out of 3 patients in whom refractoriness to antithyroid medication was clinically suspected gave values in the same range (34.8%). Additional observations in patients belonging to phase 2 of the study will continue.

- Fat Absorption : 8. Phase 2: Evaluation of long term effects of radiation on gastrointestinal absorption of I-131 oleic acid in humans.
- S. Irizarry, M.D., V. Marcial, M.D., M. Rivera
- Purpose : To evaluate if malabsorption defects found during the acute phase of radiation to the abdomen in a course of radiotherapy persist beyond the initial injury.
- To evaluate if patients not showing initial signs of malabsorption could later on develop this defect.
- Method : Patients with carcinoma of the cervix, treated with radiation whose gastrointestinal absorption has been determined prior to or shortly after the initiation of therapy enter this study provided they do not show clinical or laboratory evidence of an absorption defect. This group of patients is then followed up by blood absorption curves of I-131 oleic acid twice yearly.
- Findings : Patients of the control (head and neck tumors) and experimental (carcinoma of the cervix) groups have been examined one and one year and a half after radiotherapy. In the control group only one abnormality was detected in 13 patients examined one year after therapy, and no abnormality was observed in another group of 7 patients examined 1 1/2 year post radiation.
- In the experimental group one abnormality occurred in a group of 15 patients examined at 1 year post therapy, and one abnormality occurred in a group of 11 patients examined 1 1/2 year after radiation.
- Significance : The frequency of low fat blood levels observed in both groups of patients (controls and patients radiated to the abdomen) is very low and similar to that occurring in pre-irradiated patients. This information indicates that there is no significant occurrence of malabsorption defects in patients receiving direct irradiation to the abdomen as measured by this technique, at the 1 year and 1 1/2 year post radiation follow up examination in these patients.

Isotopic Localization

: 9. Instrumentation - Modified Scanner

S. Irizarry, M.D.; William González and Pablo T. Collazo, Clinical Applications Division, Puerto Rico Nuclear Center

Purpose : To introduce such modifications in our scanning equipment to enhance its capacity for localization studies in various organs for evaluation of parenchymal disease or tumor localization.

Method : The scanning equipment has been modified by the addition of an X-ray facility to permit collection of isotopic data in a radiographic film in combination with radiographic examination of the region under analysis. The isotopic localization of organs and tumors can be done by double successive exposure of the same film without moving the patient or the film.

Findings : With this adaptation it has been possible to obtain combined photo-scintigraphic and radiographic images. The study of an area by isotopic localization is enhanced when the final record of the data is presented with the anatomic background obtained by radiography. The method has been particularly useful in elucidating spatial relationships of clinically palpable masses in the neck (in the thyroid region) and the thyroid gland, in the differentiation of masses of vascular and non vascular origin in the mediastinum, brain tumor localization, etc.

Significance : Enhanced contrast is obtained with photoscan records and the advantage of radiography strengthens the image obtained from isotopic localization.

Isotopic localization

: 10. Organ and Tumor localization.

Sergio Irizarry, M.D.; A. E. Lanaro; O. Vázquez, M.D. Clinical Applications Division. Puerto Rico Nuclear Center

Purpose : To learn the normal and abnormal patterns of distribution of isotopic labelled substances, to correlate clinical findings with isotopic localization patterns, to seek information applicable to clinical diagnosis and therapy.

Method : Isotopic localization is performed by an automatic isotopic scanner with paper dot print out recorder and photoscanner. In some instances a paper dot registration and simple photoscan image or a combined

photoscan image with radiography is obtained. The following organs are currently being examined: thyroid, heart, kidneys, liver, brain, pancreas, parathyroid, spleen with a variety of labelled substances which include albumen I-131 and Hg 203 Chlormerodrin for brain neoplasms; I-131 for thyroid studies; albumen I-131 for visualization of the cardiac blood pool; I-131 Rose Bengal for liver and gall bladder, Se-75 methionine for pancreas and parathyroid, Hg 203 Chlormerodrin for kidneys and Cr.51 for the spleen.

Significance : Scanning of organs and tissues for isotopic localization is a very useful method for obtaining complementary information in the study of pathological states and localization of tumors in various organs. Thyroid nodularities - single or multiple are being evaluated with this technique. Our observations on non functioning and slightly functioning nodules of the thyroid gland show a high frequency rate of neoplastic involvement documented by histopathologic examination. Localization of liver tumors larger than 2 centimeters in size can be carried out quite well. Jaundice, regardless of the etiologic type, has produced images of isotopic distribution which are not dissimilar from those produced by space occupying lesions. The method has been useful in the study of renal disease, brain tumor localization, evaluation of abnormal cardiac silhouettes and splenomegaly. Other areas for its extended use are the study of skeletal disease, particularly neoplastic -(occult metastatic bone disease) and cardio-pulmonary pathology - mainly infarcts. Progress in this area is needed to extend this method to organs not yet easily localized by any method available such as the pituitary gland, the adrenal gland and the ovary.

Title of Project : 11. The renogram in patients with Carcinoma of the Cervix Uteri

Sergio Irizarry, M.D. A. Lanaro, Clinical Applications Division, Puerto Rico Nuclear Center, and Dr. Victor Marcial, M.D., Radiotherapy and Cancer Division, Puerto Rico Nuclear Center.

Purpose : To evaluate the function of the urinary tract in patients with carcinoma of the cervix uteri in the period of follow up subsequent to their definite treatment with radiotherapy to detect early changes of dysfunction of urinary drainage before the advent of irreversible drainage to the renal parenchyma, so that urological treatment may be obtained much sooner in these patients.

- Method : Patients with carcinoma of the cervix uteri treated at the Radiotherapy department of the I. González Martínez Oncologic Hospital and the Division of Cancer and Radiotherapy of the Puerto Rico Nuclear Center are selected for this study. Serial renograms using I-131 orthoiodohippuric acid are done at intervals, the length of which depends on the stage of the disease, thus Stage I carcinoma of the disease are followed up once every 6 months and Stage IV every four weeks.
- Significance : Information on the early onset of urinary difficulties during the post treatment follow up of patients with carcinoma of the cervix uteri is needed as an additional guide in the management of these patients. Results might be improved and some of the complications of urinary tract involvement may be prevented or managed having the advantage of an early diagnosis.
- Title of Project : 12. Correlation between isotopic renogram and other tests of renal function.
- Sergio Irizarry, M.D.; A. E. Lanaro, Clinical Applications Division, Puerto Rico Nuclear Center.
- Purpose : To relate the results obtained in renographic tracings obtained with Hippuric Acid I-131 and the classic tests of renal function: Creatinine and PSP (phenolsulfonphtalein).
- Method : Renogram is done in patient using hippuric acid labelled with I-131. This test is preceded by sampling the blood and having patient empty his bladder. At the end of the completion of the renogram (30 minutes) patient is asked to void. Complete urine sample is obtained again at 60 and 120 minutes in order to complete the Creatinine test. A similar procedure is followed for the PSP renal function test. In this case the dye (PSP) is injected simultaneously with the radioactive material and the first urine collection is obtained at 30 minutes after the injection and simultaneously with the determination of the renogram. It is not possible at this moment to render an analysis of data because the series is too small for evaluation.

Title of Project : 13. Evaluation of the renal function in diabetic patients by the use of the radioactive renogram.

A. E. Lanaro, M. Iturralde, Sergio Irizarry,
Clinical Applications Division, Puerto Rico
Nuclear Center.

M. Paniagua, Department of Medicine, Río
Piedras Municipal Hospital

Purpose : To study renal function in diabetics and take advantage of the radioisotopic renogram and to compare the results with other tests of renal function to assess the possibility whether it is feasible to uncover early renal lesions not easily discovered by routine clinical and laboratory methods.

Method : Diabetic patients were selected from the Río Piedras Municipal Hospital. A complete urinalysis is done on all patients and a renogram after hydration of the patient is carried out using hippuric acid I-131 and Neohydrin labelled with Hg 203. In all instances the renogram is performed using the standard position in which the renographic detector over the right kidney is placed 2" away from the midline and 1 1/2" below the right costal border. If the results are normal the test is repeated for confirmation, and at this time a Creatinine Clearance test is carried out. If the test is abnormal, the procedure is repeated improving the localization of the kidneys by the use of an upright plain radiographic film of the abdomen. At this time also, a Creatinine Clearance test is performed.

Findings : 63 patients of different ages and different stages of progression of the disease were evaluated. 52 patients had normal urinalysis, 31 of which were normal at the first examination and 11 which were read as abnormal in the first examination were found to be normal after repeating the test with the help of radiographic localization of the kidneys. A group of 6 patients with repeated normal urinalysis had persistently abnormal tracings. It was not possible to repeat all tests in the remaining patients. In another group of patients with documented abnormalities in the urine (proteinuria, cylindruria, etc.) 4 of them showed a normal renogram.

Significance : The results tend to indicate that 10% of patients in whom the radioisotopic test was abnormal were free of abnormality by other methods of clinical and laboratory evaluation. This suggests that the renogram may be helpful as a complementary test in uncovering renal abnormalities which may go undetected by other methods. It is not full proof because in some group of patients the renogram may fail to detect abnormalities already detected by other tests. The frequency of this occurrence is of the order of 7% in our experience.

NEW PROJECTS

Title of Project : 1. The cyclic variation in the total body sodium, interchangeable sodium, the total body water and the Thyroxine binding protein (TBP) under the effect of periodical administration of ethinyl-estradiol-3-methyl ether - norethynodrel.

A. E. Lanaro, Sergio Irizarry, Clinical Applications Division, Puerto Rico Nuclear Center;

B. Weinbren, Division of Medical Sciences and Radiobiology, Puerto Rico Nuclear Center;

M. Paniagua, Department of Medicine, Río Piedras Municipal Hospital

Purpose : The object of this investigation is to study the possible changes in total body water, total and interchangeable sodium and plasma thyroxine binding protein in different dates of the women during the cyclic administration of estrogenic and progestogenic substances (ENOVID).

Method : Patients to be studied must have regular cycles, must be 25 to 40 years old and must not have any pathological manifestations. A total of 50 patients will be divided into 5 groups (10 patients each) to be tested Group I on the first or second day of their menses. The Group II the fourth day, the Group III the 13 to 14th day, Group IV the 23 to 24th day and Group V the 26 to 27th day of the menses. All these patients must be tested before and two months after the treatment. This treatment consists to take one 5 mg pill of Enovid daily from the fifth till the twenty-fourth day of the cycle.

Upon approval of project proposal, patients will be admitted at the Multidisciplinary Clinic Research Center and the test to be performed are chemical measurement of the serum sodium, potassium, chloride, CO₂ and pH, total body and interchangeable sodium, total body water and Resin uptake of T₃ I-131. The results must be compared with the same patient to observe the possible changes.

Title of Project : 2. Thyroid Function Studies in Patients with So-Called Hormonal Dependent Tumors.

A. E. Lanaro, S. Irizarry, Clinical Applications Division, Puerto Rico Nuclear Center;
J. Ubiñas, V. A. Marcial, Z. Frías, Radiotherapy and Cancer Division, Puerto Rico Nuclear Center.

Purpose : The purpose of this study is to evaluate the thyroid function in groups of patients with different types of malignancies. The malignant tumors to be studied have all in common some hormonal response except for patients with thyroid malignancies that are not included for obvious reasons. Cancer of the cervix is also excluded because at present we are undergoing thyroid investigations in those patients.

Method : We have decided to study 20 patients of each of the malignancies subject to study and each subgroup will be compared with a control group of what we consider normal adults of the same age and sex. We will also compare our material with another group of patients with cancer who, up to our present knowledge, have not shown any hormonal relationship. We have then 3 groups:

a) Tumors with hormonal relationship: adenocarcinoma of the prostate, breast, endometrium, lung, ovaries, testis, adrenal glands, thymus, choriocarcinoma and carcinoids.

b) Will include patients with tumors in which no hormonal relation is known: carcinoma of the skin, oral cavity, hypopharynx, base of the tongue, esophagus, stomach, colon, rectum, sarcomas, etc.

c) Is a control group of non cancerous patients. The patients will have the following procedures done: physical examination, I-131 uptake at 24 hours, FBI 131 conversion ratio and plasma level at 24 hours and Resin Uptake of T-3 I-131.

These procedures will be run at the beginning of the treatment and if it is possible will be repeated at the end of the treatment and at a six month interval.

Title of Project : 3. Thyroid Clearance

O. Vázquez, S. Irizarry, Clinical Applications Division, Puerto Rico Nuclear Center

Purpose : To evaluate this method of thyroid function for incorporation of its routine use in the laboratory for the determination of thyroid function at the Puerto Rico Nuclear Center.

- Method : The technique is that described by Berson and Yalow. I-131 is injected intravenously, repeated net counts are obtained for 30 minutes, and the capacity of the thyroid to clear a unit volume of plasma per unit time is assayed.
- Significance : There is a great overlap of values of hypothyroid and hyperthyroid function in Puerto Rico. Since this test has a great sensitivity for the detection of thyroid function (Iodide phase) it is believed that it may be advantageous in separating hypothyroid patients from normal (euthyroid) patients whose value overlap.
- Title of Project : 4. Activation analysis--Evaluation of its routine use at this laboratory in selected patients with thyroid disorders in Puerto Rico.
- S. Irizarry, J. Chiriboga, A.E. Lanaro, Clinical Applications Division, Puerto Rico Nuclear Center
- Purpose : Activation analysis is a useful method to quantitate the levels of iodine circulating in the blood as thyroid hormone, and gives results which are comparable with protein bound iodine levels detected by chemical methods. Since we have a Reactor facility in which biological samples can be activated, it would be advisable to evaluate this technique for its application to the diagnosis of borderline disorders of the thyroid, specially in the group of patients whose thyroid function by laboratory measurements overlap. These patients are either hypo or euthyroid and there is great overlap by other laboratory methods currently in use in Puerto Rico.
- Method : Blood samples are obtained from patients coming to the laboratory for routine radioisotopic tests of thyroid function which include thyroid uptake and radioactive blood hormone levels. Blood collected is passed thru an ion-exchange resin column and then sent to Mayaguez for activation in the Reactor. Analysis of iodine is then done in these samples for the presence of I-131 in the protein fraction. Protein bound iodine activated iodine levels will then be correlated with the clinical condition of the patients and other radioisotopic measurements.
- Significance : This method has a potential which can be used with great advantage for it is comparable in sensitivity to the protein bound iodine chemical determination method.
- Title of Project : 5. Brain Tumor Localization
- Sergio Irizarry, Clinical Applications Division. Puerto Rico Nuclear Center, and

J. V. Rivera, Radioisotopes Laboratory, Veterans Administration Hospital

- Purpose** : To evaluate the efficacy of brain tumor localization by means of isotopic detection by the use of automatic gamma scintillation scanning and photoscanning.
- To compare the detectability of tumors by using different radioactive labelled substances.
- Method** : Patients suspected of having brain tumor referred to the Puerto Rico Nuclear Center for brain tumor localization are scanned after the injection of material suitable for this purpose. Two substances are currently being employed: Neohydrin labelled Hg 203 and Albumen I-131. After the injection of either substance, patient is scanned two to 4 or 6 hours the first day on 3 different positions: frontal and laterals. If the substance used is Albumen I-131, scans are repeated at daily intervals of 1, 2, 3 days after the injection of the substance, if findings in the previous tracings should indicate further work up. Whenever possible patient may undergo scans, first with one substance like Neohydrin 203 and then secondly with Albumen I-131. The findings in these patients will be compared to assess the quality and advantages of one substance over the other in the type of tracings obtained. Correlation of the brain scanning findings is to be obtained with surgery and other Neurosurgical and Neurologic techniques of evaluation.
- Significance** : Brain tumor localization by means of isotope is a painless method of examination which may provide valuable data before the patient is subjected to operation. It may also be of value in guiding radiotherapy treatment whenever this type of therapy is indicated. It may be the only in vivo method to document the disappearance of the lesion after therapy treatment or its recurrence after treatment.
- Title** : Radioimmunoassay of protein and peptide hormones.
- Oscar N. Vázquez, Sergio Irizarry, Clinical Applications Division, Puerto Rico Nuclear Center.
- Purpose** : The determination of hormone levels in blood, for the purpose of correctly assessing endocrine function in various clinical states, is often eminently desirable and mandatory at times.
- Because the large majority of the clinical material currently available to us lies in the range of thyroid function, we would be initially interested in determining metabolic activity with reference to TSH levels. At a later date, it may prove fruitful to extend the immunoassay to other substances and hormones of biologic interest.

Method : I-131 human thyrotroprin (HTSH) is prepared, and purified. HTSH anti-serum is obtained from guinea pigs. The extent of competitive inhibition of the labeled hormone-antibody reaction by unlabeled endogenous hormone, as shown on paper chromatoelectrophoresis, permits quantitation of endogenous hormone when compared to a standard.

Significance : The regulation of metabolic processes is, at present, imperfectly understood. The radioimmunoassay method has opened a whole new field which holds great promise for an increased understanding of the complex interrelationships between hormone function and distinct metabolic activities in specific tissues.

APPENDIX

1. Evaluación Clínica de Pruebas Diagnósticas en la función Tiroidea con I-131.
2. The Effect of Cyclic Administration of Certain Progestin-Estrogen Combinations on the 24-hour radioiodine thyroid uptake.
3. The Renogram as a tool for Evaluating patients with Cancer of the Cervix Uteri.
4. The Role of Calcium on the Intestinal Absorption of Vitamin B-12 in Tropical Sprue.
5. Demostración Experimental en la Excreción de Seroalbúmina en las Gastritis.
6. Uptake Measurements: Determination of the Probable Maximum Deviation of the Uptake Measurement at this Laboratory.
7. The Effect of Radiation Therapy on Gastrointestinal Absorption of I-131 Oleic Acid in Humans.
8. Patología Tiroidea: Correlación entre Gammagrama e Histopatología.
9. The use of Thyroid Trapping of Iodide as an Indicator for Absorption I-131 Labelled Fat.
10. Cancer of the Thyroid Gland - Review of Seven Patients Treated with I-131.

THE EFFECT OF CYCLIC ADMINISTRATION OF CERTAIN PROGESTIN-ESTROGEN COMBINATIONS ON THE 24-HOUR RADIOIODINE THYROID UPTAKE*,**

by: Sergio Irizarry, M.D.¹, Manuel Paniagua, M.D.²,
Gregory Pincus, Sc. D.³, José L. Janer, B.S. M. Sc.⁴
and Zenaida Frías, M.P.H.⁵

ABSTRACT

The effect of short and long term administration of a mixture of progestogen and estrogen in different doses on the 24-hour radioiodine uptake by the thyroid gland were studied in a group of 154 women. EE3ME (ethinyl estradiol-3-methyl ether) was the estrogen used in all cases while norethynodrel (17 α -ethinyl-estra-5,10-eneolone) and ethynodioldiacetate (17 α -ethinyl-4-estrene-3,17-diol-diacetate) were the progestogens. In all cases the compounds were administered daily, from the 5th through the 24th day of each cycle. The dosage schedule and duration of medication were as follows:

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** With the technical assistance of Mrs. Hada Livia R. de Colón.

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Norethynodrel 5 mg and EE3ME 0.075 mg for 3 months in short term users and for over 3 years in long term users; norethynodrel 2.5 mg and EE3ME 0.1 mg after 3 years of use; ethynodioldiacetate 1 mg with EE3ME 0.1 mg and 2 mg with EE3ME 0.1 mg both for 3 months.

Statistical analysis of the results showed no significant difference between the average of the long term users and those of the controls, or between the results of the tests before and after medication in the short-term users, with the exception of those taking ethynodioldiacetate 2 mg. The variation in this group, though significant by the "t" test, falls within the accepted day to day variation of radioiodine uptake and well within the limits of normal variation for euthyroid patients, so it is of no clinical importance.

THE EFFECT OF CYCLIC ADMINISTRATION OF CERTAIN
PROGESTIN-ESTROGEN COMBINATIONS ON THE 24-HOUR
RADIOIODINE THYROID UPTAKE

INTRODUCTION

The metabolic effects of estrogens on the binding capacity of human serum for thyroid hormone and the degradation fate of this substance have been the subject of numerous reports. The effect of estrogens on the iodide phase of thyroid function has not received great attention. There seems to be general agreement as to the increased thyroid hormone binding capacity of the plasma proteins (1,2,3,4,5,6,7) under the effect of exogenous estrogens but the available information on the effect of estrogens, exogenous or endogenous, on the thyroid uptake is controversial. Dowling et al (8,9) reported no effect on the thyroid uptake of euthyroid patients with the use of diethylstilbestrol, while Jensen (10) observed an increase of this function, and again Dowling et al (11) studying the effects of endogenous estrogens in hydatidiform moles and in choriocarcinoma found that the iodine uptake of the thyroid gland was elevated among other parameters of thyroid function in three women with hydatidiform mole. (12) Soliman and Reinecke demonstrated increase uptake of I-131 in adrenalectomized rats under the influence of estrogen therapy, but no effect in intact animals.

The evidence obtained from experimental animals through deprivation of gonadal function indicates that the lack of sex hormones may affect the I-131 thyroid uptake either way. Information on this point is controversial since Jovanovic et al (13) reported a profound depression of thyroid uptake maximal three weeks after castration in

(14)
either sex in the rat, while Tsuiguchi and Hatake found increased uptake maximal at 48 hours post-ovariectomy in adults white rats.

(15)
Becchini and Bianchi reported increased thyroid I-131 uptake by the administration of estrogens to rats, similar to that obtained with TSH but the effect was cancelled out by the simultaneous administration of the two drugs.

The influence of exogenous stimulation with female sex hormones assayed by histologic studies of the thyroid tissue shows unequivocally an opposing effect of estrogens and progestogens on the glandular epithelium. Barbazza et al (16) concluded that estrogens block the process of regeneration of epithelium in partially thyroidectomized rats, but on the contrary, Welch and collaborators (17) describe stimulation of epithelial growth (hypertrophy) similar to that of pregnancy in virgin rats treated with progesterone. The effect of progesterone on the I-131 thyroid uptake was measured in intact male rats by Andreoli (18) who found a depressing effect of this hormone on the iodine accumulation and renal iodine clearance. A similar result was found in adrenalectomized rats. The effect of anticonceptive therapy with combined estrogen-progestin type of medication at short or long intervals on the 24-hour radioiodine uptake by the thyroid gland in humans is not known. This study intends to evaluate this problem.

Materials and Methods-Selection of Patients and Sample Design:

Participants in this study were Puerto Rican women from the Puerto Rico Family Planning Association representing a sample selected from the lower socio-economic strata of the general population. The sample consisted of non medicated women to be examined before and after 3 months of therapy; a group medicated for over 3 years to be examined twice within a 3 month

interval, and a control group to be examined twice in 3 months.

The sample design is as follows:

- GROUP I Participants examined before and after at least three months of cyclic administration of 5 mg Enovid* (17 α -ethinylestra-5,10-eneolone plus 0.075 mg of ethinyl estradiol-3-methyl ether.)
- GROUP II Participants examined before and after at least three months administration of 1 mg of Ovulen* (17 α -ethinyl-4-estrene-3,17-diol-diacetate plus 0.1 mg of ethinyl-estradiol-3-methyl ether.)
- GROUP II-B Participants examined before and after 3 months administration of 2 mg Ovulen*.
- GROUP III-A Participants under continuous cyclic administration of 5 mg Enovid* for 3 years examined twice in 3 months.
- GROUP III-B Participants under continuous cyclic administration of 2.5 mg of Enovid* for 3 years examined twice in 3 months.
- GROUP IV Participants not taking contraceptive substances but who employed vaginal contraceptive devices.

All participants were taking their medication in cyclic form, starting the fifth day of the cycle and taking it daily for twenty consecutive days, waiting for withdrawal bleeding and re-starting on the fifth day of the following cycle. When withdrawal bleeding did not occur the subject would re-start medication eight days after their last pill. Groups I, II-A, II-B and III-A and III-B were compared with group IV, but in addition sub-groups III-A and III-B were considered as medicated controls at two dosage levels, while Group IV represented the non medicated control. Both medicated and non medicated controls served to monitor the magnitude of freely occurring spontaneous physiologic variations during the 3 months interval of the study.

PROCEDURES

Participants were instructed to come to the laboratory in the fasting state. A dose of 20 to 50 microcuries of Iodine-131 was administered early in the morning of the day prior to the uptake measurement. The technique is the usual twenty-four hour radioiodine uptake according to the method introduced by Marshall-Brucer⁽¹⁹⁾ with the following modifications: standard measurement are done in a plastic phantom using iodine-131 capsules as sources instead of mock iodine.

In our experience this technique shows a very low intraindividual variation (standard deviation) of 0.75 units of uptake; a working error of less than 5% of the measurement. Radioiodine thyroid uptake was determined twice within a period of at least three months in all patients in the four groups.

RESULTS

One hundred fifty-four healthy participants with no evidence of thyroid disease were selected for this study. The socio-economic characterization of the participants in the different groups showed an average age that varied from 21 to 30 years, average number of pregnancies 2-5; average education 6th to 9th grade; and average per capita weekly income of 6-10 dollars. Table I

The results of the 24 hour radioiodine uptake in 28 participants of group I and of 39 in group II, before and after medication, are shown in Table II. The average % thyroid uptake before medication was 18.9 (Group I), 20.6 (Group II-A), 18.1 (Group II-B) and after 3 months medication the average % uptake was 17.5 (Group I), 18.3 (Group II-A), and 16.6 (Group II-B). Differences in uptakes for group I and sub-group II-A were not significant to the "t" test. The difference in sub-group II-B is statistically significant to the "t" test at the 5% level.

Twenty-five long term users of 5 mg Enovid* had an average % uptake 18.2 and 17.5 three months apart; while 32 long term users of 2.5 mg Enovid* had 21.4 and 21.7 average % uptake in the same period. The control group showed 21.4 and 20.2 average % uptake in 3 months.

The difference in the means of the uptakes between sub-groups III-A, III-B and the control are not statistically significant at the 5% level. Table III.

The magnitude of the freely occurring spontaneous physiologic variation at 3 months interval was of the order of 4 units of uptake for the medicated (long term users) group III-A and III-B and for the control group IV: Graphs 1, 2, 3.

DISCUSSION

The data obtained uniformly appear to indicate no measurable significant change in the radiiodine thyroid uptake function in these groups of patients using Enovid* or Ovulen* on two different dosage schedules over a relatively short period of time (three months).

Similarly no appreciable or significant effect was seen on long term users of Enovid* when compared with the control group. The difference in the radiiodine uptake before and after 3 months of anticonceptive treatment in participants of sub-group III-B though statistically significant is within the expected range of normal physiological variation. The normal expected day to day variation has been reported to be plus or minus seven units of uptake in normal euthyroid individuals (20) and in a few instances it may even be over plus or minus ten units of uptake. Our patients were examined three months later and the degree of variation (average deviation) was of the order of \pm 4 units of uptake for the control groups of medicated and non medicated patients. Graphs 1,2,3. The average deviation for sub-group III-B was 4.8 units.

An incidental finding in this study is the observation of a low average value for the 24-hour radioiodine uptake tests in all the groups studied: lowest 16.6%, highest 21.7%. This is remarkable when compared with the average uptake of the order of 25% for euthyroid patients from clinical populations in Puerto Rico.⁽²¹⁾⁽²²⁾ No explanation can be offered at this time for this difference and additional investigations will be necessary to elucidate this problem.

CONCLUSION

This study was conducted in 154 healthy Puerto Rican women to evaluate the effect of Enovid (R) and Ovulen (R) on the 24 hour radioiodine uptake by the thyroid gland during a 3 months interval (short term users) and for 3 years or more (long term users).

Uptake measurements repeated in all groups within a 3 months interval showed no significant variation other than that which can be ascribed to normal expected day to day variation as reported elsewhere.

The results of this study indicate there is no evidence that the employment of a combination of estrogenic and progestational substances as anticonceptive measures at short or long intervals produce changes of clinical significance in the 24 hour I-131 uptake by the thyroid gland.

TABLE I

DISTRIBUTION AND CHARACTERISTICS OF 154 PARTICIPANTS
BY GROUP

GROUP	AVERAGE AGE	AVERAGE NUMBER PREGNANCIES (FERTILITY)	EDUCATION	PER CAPITA WEEKLY INCOME U.S. DOLLARS	NUMBER PARTICIPANTS
I	30	4.6	8.8	9.8	28
II-A	23	3.1	8.3	7.7	13
II-B	21	2.5	8.8	7.9	26
III-A	31	5.3	-	-	25
III-B	25	3.0	-	-	32
IV	31	5.5	6.6	6.0	30

TABLE II

COMPARISON OF AVERAGE THYROIDAL
UPTAKE BEFORE AND AFTER DRUG INTAKE

GROUP	I	II-A	II-B
Number of Subjects	28	13	26
Average Before Drug	19.5 (<u>+6.7</u>)	20.6 (<u>+3.7</u>)	18.1 (<u>+5.1</u>)
Average After Drug	17.2 (<u>+5.9</u>)	18.3 (<u>+3.9</u>)	16.6 (<u>+4.0</u>)

Standard Deviation in Parenthesis.

Statistical test performed:

"t" test for significance of difference between means before and after drug intake, for each group.

Group II-B - significant difference at 5% level.

TABLE III

COMPARISON OF AVERAGE THYROIDAL UPTAKE
IN LONG TERM USERS AND CONTROL GROUPS,
AT THE BEGINNING OF THE STUDY AND THREE MONTHS AFTER

GROUP	III-A	III-B	CONTROL
Number of Subjects	25	32	30
Baseline Average Uptake	18.2 (<u>+6.3</u>)	21.4 (<u>+9.6</u>)	21.4 (<u>+4.8</u>)
Average Uptake 3 Mo. After	17.5 (<u>+4.9</u>)	21.7 (<u>+10.2</u>)	20.2 (<u>+4.6</u>)

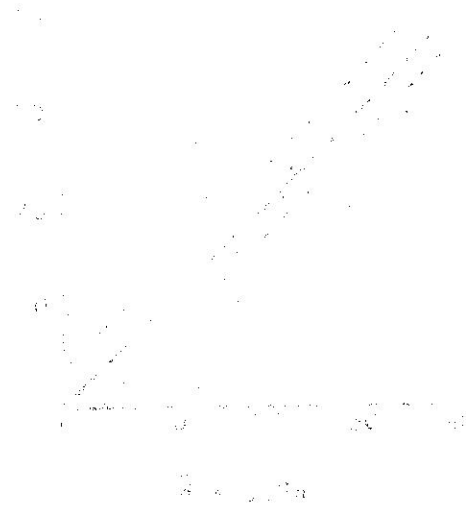
Statistical test performed:

"t" test for significance of difference between means of each group vs. control group.

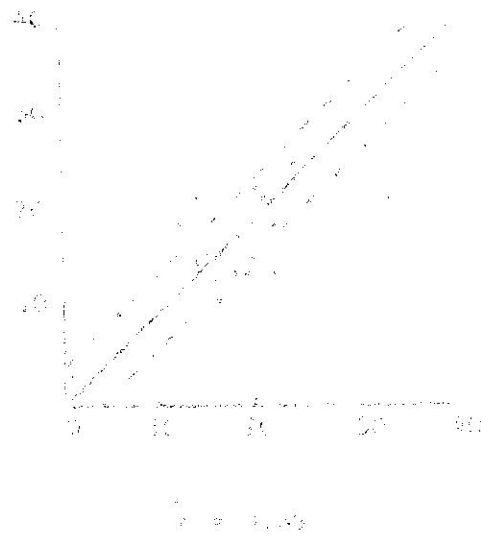
No significant difference at 5% level.

ANALYSIS OF VARIANCE FOR THE DATA OF THE EXPERIMENT

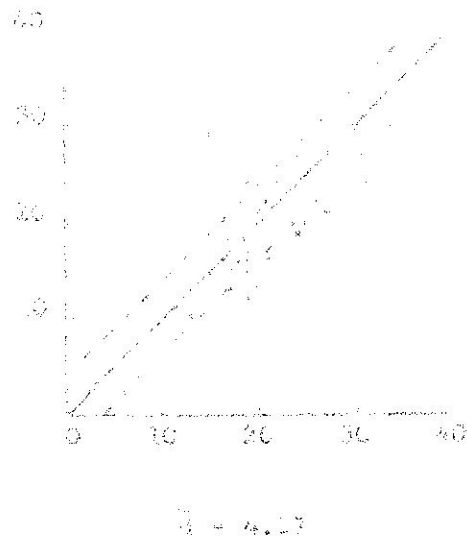
ANALYSIS OF VARIANCE FOR THE DATA OF THE EXPERIMENT



GROUP III-3



GROUP III-4



GROUP III-5

GROUP: I

APPENDIX A

<u>Patient Number</u>	<u>Baseline Uptake</u>	<u>Uptake 3 Mo. After</u>
1	13.8%	14.1%
2	30.5%	27.8%
3	18.2%	21.2%
4	4.9%	0.9%
5	18.1%	8.7%
6	14.1%	10.3%
7	17.8%	11.6%
8	21.8%	14.1%
9	26.5%	21.5%
10	21.1%	20.9%
11	21.9%	16.4%
12	24.0%	21.6%
13	27.3%	13.8%
14	18.8%	16.4%
15	17.6%	12.9%
16	25.4%	26.0%
17	12.8%	25.1%
18	27.6%	19.8%
19	18.2%	21.1%
20	28.8%	14.9%

<u>Patient Number</u>	<u>Baseline Uptake</u>	<u>Uptake 3 Mo. After</u>
21	17.0%	16.7%
22	19.0%	22.1%
23	17.2%	16.2%
24	13.1%	18.0%
25	10.8%	16.3%
26	16.6%	18.7%
27	33.0%	23.7%
28	9.2%	10.2%

GROUP: II-A

<u>Patient Number</u>	<u>Baseline Uptake</u>	<u>Uptake 3 Mo. After</u>
1	18.3%	27.3%
2	18.7%	14.5%
3	21.3%	18.8%
4	27.8%	16.6%
5	17.1%	14.0%
6	25.8%	21.7%
7	20.4%	18.3%
8	18.7%	18.0%
9	19.6%	23.9%
10	18.0%	14.7%
11	23.2%	15.4%
12	14.2%	17.7%
13	23.8%	17.3%

GROUP: II-B

<u>Patient Number</u>	<u>Baseline Uptake</u>	<u>Uptake 3 Mo. After</u>
1	17.0%	14.2%
2	16.6%	17.2%
3	22.5%	12.6%
4	19.2%	13.2%
5	21.1%	18.5%
6	18.4%	11.2%
7	16.9%	11.6%
8	15.1%	16.8%
9	23.0%	15.5%
10	14.1%	19.4%
11	22.8%	14.4%
12	15.7%	21.8%
13	12.6%	12.6%
14	11.3%	12.2%
15	16.9%	10.2%
16	13.8%	13.8%
17	22.8%	14.5%
18	16.1%	20.8%
19	26.4%	21.6%
20	32.2%	21.0%
21	23.6%	18.0%
22	9.8%	20.4%
23	21.7%	19.0%
24	22.4%	16.5%
25	15.7%	18.3%
26	24.3%	26.5%

GROUP: III-A

<u>Patient Number</u>	<u>Baseline Uptake</u>	<u>Uptake 3 Mo. After</u>
1	33.6%	21.7%
2	0.6%	2.8%
3	32.6%	21.3%
4	14.2%	22.0%
5	21.6%	14.2%
6	18.4%	18.1%
7	12.4%	19.3%
8	16.1%	20.9%
9	20.6%	21.7%
10	19.0%	14.4%
11	16.3%	11.0%
12	19.3%	17.5%
13	19.3%	18.2%
14	13.1%	12.7%
15	16.3%	13.3%
16	14.2%	14.8%
17	15.6%	17.5%
18	22.1%	18.7%
19	24.4%	25.0%
20	17.7%	19.0%
21	17.9%	13.9%
22	15.4%	15.6%
23	19.2%	25.4%
24	16.4%	15.7%
25	19.5%	23.0%

GROUP: III-B

<u>Patient Number</u>	<u>Baseline Uptake</u>	<u>Uptake 3 Mo. After</u>
	24.8%	20.4%
2	24.3%	18.6%
3	18.0%	16.3%
4	15.1%	29.1%
5	3.7%	21.2%
6	26.4%	18.7%
7	29.8%	30.5%
8	26.7%	21.2%
9	17.3%	14.9%
10	21.6%	23.5%
11	18.3%	18.2%
12	31.4%	24.3%
13	21.0%	21.6%
14	16.8%	13.1%
15	13.4%	10.4%
16	20.8%	16.2%
17	18.7%	12.1%
18	66.6%	69.6%
19	20.0%	21.2%
20	17.4%	18.1%
21	17.2%	18.0%
22	18.4%	22.4%
23	20.3%	21.3%

<u>Patient Number</u>	<u>Baseline Uptake</u>	<u>Uptake 3 Mo. After</u>
24	20.0%	13.3%
25	18.6%	17.2%
26	19.2%	16.3%
27	19.5%	20.6%
28	20.1%	32.5%
29	24.5%	27.4%
30	17.7%	25.8%
31	18.7%	23.5%
32	17.7%	16.0%

GROUP: IV

<u>Patient Number</u>	<u>Baseline Uptake</u>	<u>Uptake 3 Mo. After</u>
1	29.9%	20.7%
2	22.9%	21.9%
3	25.3%	20.1%
4	22.9%	17.7%
5	25.2%	16.9%
6	22.8%	21.5%
7	14.4%	28.1%
8	28.2%	27.9%
9	24.3%	25.0%
10	21.7%	18.4%
11	19.0%	20.1%
12	17.6%	15.8%
13	24.0%	20.9%
14	36.2%	31.4%
15	18.4%	10.8%
16	21.2%	20.7%
17	25.3%	22.3%
18	16.2%	19.6%
19	21.8%	21.9%
20	14.8%	16.5%
21	18.3%	18.0%
22	14.9%	21.0%
23	13.7%	13.9%

<u>Patient Number</u>	<u>Baseline Uptake</u>	<u>Uptake 3 Mo. After</u>
24	26.9%	26.1%
25	16.2%	18.8%
26	14.3%	2.5%
27	29.4%	22.7%
28	19.2%	21.8%
29	15.3%	23.1%
30	22.0%	17.9%

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