PRNC 33

PUERTO RICO NUCLEAR CENTER

The Renogram as a Tool for Evaluating Patients with Cancer of the Cervix Uteri

OPERATED BY UNIVERSITY OF PUERTO RICO UNDER CONTRACT NO. AT (40-1)-1833 FOR U. S. ATOMIC ENERGY COMMISSION

THE RENOGRAM AS A TOOL FOR EVALUATING PATIENTS WITH CANCER OF THE CERVIX UTERI

SERGIO IRIZARRY
CLINICAL APPLICATIONS DIVISION, PUERTO RICO NUCLEAR CENTER, UNIVERSITY OF PUERTO RICO AND THE DEPARTMENT OF MEDICINE OF THE I. GONZÁLEZ MARTÍNEZ ONCOLOGIC HOSPITAL,

AND

ANGEL LUIS RODRÍGUEZ ROSADO
RADIOISOTOPE LABORATORY AND DEPARTMENT OF MEDICINE OF THE SAN JUAN CITY HOSPITAL
San Juan, PUERTO RICO

Abstract

The renogram as a tool for evaluating patients with cancer of the cervix uteri. The purpose of this report is to assess the value of the isotope renogram in the evaluation of the patency of the urinary tract and renal function in patients with cancer of the cervix. This cancer is the first neoplastic problem in women in Puerto Rico, after the age of 40. Because in a large number of patients the disease is diagnosed late, the problem of ureteral compression by the tumor becomes critical for management. It is of importance for the surgeon to know the status of the patency of the urinary stream. The urologist wants to know the difference between a blocked kidney that is still functioning and a blocked kidney that is out of order, so that he can decide when to do decompressive surgery. The renogram differentiates a nonfunctioning kidney from a blocked kidney, which differentiation is not always possible with the excretory urogram.

In this study patients with advanced pelvic cancer, preferably cancer of the cervix, stage III, were selected from the I. Gonzáles Martínez Oncologic Hospital.

Hippotope I^{131} (Orthoiodohippuric acid I^{131}) was injected intravenously in a dose of 1 μc per 5 kilograms of body weight. The radioactivity levels were followed up over each renal area for half an hour using surface scintillation counters. The activity was measured with ratemeters connected to strip chart recorders. Twenty four patients were examined, of which 18 had carcinoma of the cervix, stage III; 15 had normal renal function and excretion of urine as reflected by both the isotope test and the intravenous pyelogram. Eight patients had abnormal function in both tests. In two patients the tests were at variance; one was normal by the renogram but was abnormal by the urogram, and the other showed the reverse. There are four cases in which the renogram gives more information as to the nature of the renal status: two cases showed irreversible kidney damage unilaterally with reversible damage in the contralateral kidneys, and both cases showed hydronephrosis by the X-ray tests. In two other cases the renogram shows absence of excretion and renal function whereas the pyelogram shows absence of renal function. There was complete correlation between the 15 renograms and pyelograms but one out of eight renograms failed to correlate with the intravenous pyelogram and vice versa. The lesions of the urinary systems may be of three types in these cases: excretory, secretory, or both. Comparison of the information given by the renogram with the intravenous pyelogram leads one to believe that the renogram may be of value in judging both the patency of the ureters and the integrity of function of the renal parenchyma. The frequency of ureteral compression was two fifths in the group of stage III carcinoma of the cervix uteri. In conclusion, the renogram appears as good as the intravenous pyelogram in demonstrating disturbances of renal excretion and superior for renal secretion. For the sick cancer patient this test seems to be more suitable as a screening procedure for abnormalities of the renal apparatus because it can be done more easily.

Resumen

Valor del renograma como instrumento evaluador de cáncer del cuello uterino. El propósito de esta memoria es analizar el valor del renograma de isótopos para evaluar el estado de patente del sistema urinario y la función renal en pacientes con cáncer cervical. Este tipo de cáncer constituye el problema principal neo-

plástico en las mujeres de Puerto Rico, pasados los 40 años de edad. Debido a que en un gran número de pacientes la enfermedad es diagnosticada tardíamente, el problema de la compresión ureteral por el tumor asume un carácter crítico. Es importante para el cirujano conocer el estado de abertura de las vías urinarias. El urólogo, por su parte, precisa conocer la diferencia entre un riñón bloqueado que todavía funciona y un riñón bloqueado que está estropeado, para decidir el momento oportuno de una intervención quirúrgica. El renograma establece la diferencia entre un riñón que no funciona y un riñón bloqueado, lo cual no es siempre posible con un urograma excretorio.

Para este estudio se eligieron pacientes con cáncer pélvico avanzado, de preferencia cáncer de la cerviz en el estadio III, del Hospital Oncológico I. González Martínez.

Se inyectó en forma intravenosa Hipputope ^{131}I (ácido hipúrico marcado con yodo-131) en una dosis de 1 μc por 5 kilogramos de peso de la paciente. Se observaron los niveles de la radiactividad sobre cada área renal durante media hora utilizando contadores de centelleo de superficie. Se midió la actividad con intensímetros conectados a registradores gráficos de banda. Se examinaron 24 pacientes, 18 de ellas con carcinoma de la cerviz en el estadio III; 15 presentaban la función renal y excreción de orina normales según fue determinado tanto por el examen isotópico como por el pielograma intravenoso. Ocho enfermas tuvieron, en ambas pruebas, funciones anormales. En dos pacientes los resultados de las pruebas presentaron discrepancias, una prueba resultó normal con el renograma y anormal con el urograma, y la otra dió resultados opuestos. Hubo cuatro casos en los que el renograma brindó mayor información acerca de la condición de los riñones: en dos casos indicó daños irreversibles en un riñón con daños reversibles en el riñón contralateral y, en ambos casos, el examen con rayos X presentó evidencia de hidronefrosis. En otros dos casos, el renograma indicó ausencia de excreción y función renal, mientras que el pielograma mostró ausencia de la función renal. Hubo completa correlación entre los 15 renogramas y pielogramas, pero uno de cada ocho renogramas no presentó correlación con el pielograma intravenoso y viceversa. En estos casos las lesiones del sistema urinario pueden ser de tres tipos: excretorias, secretorias, o ambas. La comparación de las informaciones dadas por el renograma y el pielograma intravenoso nos lleva a la creencia de que el renograma puede ser de valor para juzgar tanto el estado de patente de los uréteres como la integridad funcional del parénquima renal. La frecuencia de compresión ureteral en este grupo de pacientes con carcinoma de la cerviz del útero, en el estadio III, fue de dos quintos. En conclusión, el renograma parece ser tan efectivo como el pielograma intravenoso para revelar alteraciones de la excreción renal y superior aún para la secreción renal. Para el enfermo de cáncer esta prueba parece ser más adecuada como examen previo de anormalidades del aparato renal puesto que puede ser realizada con mayor facilidad.

Resumo

Valor do renograma na determinação do estado do câncer uterino cervical. O objetivo visado no presente estudo é analisar o valor do renograma isotópico para avaliar-se a desobstrução das vias urinárias e a função renal em enfermas acometidas de câncer cervical. Êste tipo de câncer constitui o primeiro problema neoplástico, em Pôrto Rico, entre mulheres maiores de 40 anos. Em razão de ser tardia a diagnose da doença, em largo número de casos, o problema da compressão uretérica, exercida pelo tumor, assume caráter crítico. É de grande importância que o cirurgião conheça o estado da desobstrução das vias urinárias. O urologista precisa conhecer a diferença entre o rim obstruído, porém ainda funcionando, e o rim obstruído a ponto de não funcionar mais, de modo a poder determinar o momento exato para a intervenção descompressiva. O renograma indica a diferença entre um rim que cessou de funcionar, e outro apenas obstruído, o que nem sempre é possível conseguir por meio do urograma de excreção.

Os casos, apresentados neste estudo, de câncer pélvico avançado, preferivelmente câncer cervical na fase III, foram selecionados no Hospital Oncológico I. González Martínez.

Fizeram-se injeções endovenosas de Hipputope ^{131}I (ácido hipúrico marçado com iôdo-131) na dose de 1 μc por 5 quilogramas de pêso da enferma. Os níveis de radioatividade foram observados em cada uma das áreas renais por meia hora, através de cintilômetros superficiais, medindo-se a radioatividade por meio de aparelhos ligados a registradores automáticos de fita. Vinte e quatro pacientes foram examinadas, das quais 18 apresentavam carcinoma cervical na fase III; 15 apresentavam função renal e exceção de urina normais, determinadas tanto através do exame isotópico como do pielograma endovenoso. Oito enfermas revelaram, em ambas as provas, função anormal. Em duas outras, os exames variaram, sendo o renograma normal, porém anormal

urograma, em um caso, dando-se o reverso com a outra paciente. Houve quatro casos em que o renograma rneceu mais informações acêrca da condição dos rins: em dois, indicou danos irreversíveis em um rim, com nos reversíveis no outro rim, evidenciando os raios-X a existência de hidronefrose, em ambos os casos. Em tros dois casos, o renograma mostrou existir ausência de excreção e de função renal, ao passo que o pielograma dica ausência de função renal. Verificou-se completa correlação entre 15 renogramas e pielogramas, porém de da oito renogramas um deixou de correlacionar-se com o respectivo pielograma endovenoso, e vice-versa. s lesões do sistema urinário podem ser de três tipos nos seguintes casos: excreção, secreção, ou ambos. A comaração das informações fornecidas pelo renograma com as do pielograma endovenoso leva a crer que o renoama é de valor tanto para apreciar-se a desobstrução dos ureteres, como a integridade funcional do parênquia renal. A freqüência da compressão uretérica, nesse grupo, corresponden a 40% entre pacientes com carcinoma crino cervical na fase III. O renograma, em conclusão, se afigura tão efetivo quanto o pielograma endovenoso ara revelar perturbações da excreção renal, e é superior para a secreção renal. Relativamente à cancerosa, êste ame, por ser mais fácil, se afigura mais conveniente do que o processo de eliminação de anomalias do aparelho nal.

In 1956, Taplin, Meredith and Kade [1,2] developed e isotope renogram. Winter,[3] in the same year 956) introduced it into clinical practice. In 1957 id 1959, Winter [4,5] described the value of the test a screening procedure in renal hypertension. Donberg [6] in 1959 found good correlation between the nogram and other clinical and radiological findings patients with obstruction of the upper urinary tract. drígnez Rosado [7] found complete correlation beeen abnormal pyelography and renograms in a oup of 24 patients. Zum Winkel [8] in 1961 studying e urinary tract and renal function reported 85% rrelation between the renogram and the radiographic amination in a group of 104 patients with abdominal mors.

The purpose of this work is to describe our experice with the isotope renogram in investigating the ficiency of the urinary outflow of patients with cancer the cervix uteri. This form of cancer is the most evalent form of malignancy in women above the e of 40 in Puerto Rico. A large proportion of paents unfortunately come in late for diagnosis when eir disease is moderately or severely advanced. At is stage the problem of ureteral compression by the mor, and hence, interference with the urinary outw, becomes critical for management. It is of prime iportance for the surgeon to know the status of the ficiency of the urinary stream. The urologist wants differentiate between a blocked kidney with good nction and a blocked kidney without function, so at he can decide when to attempt decompressive rgery. Before the advent of the renogram this was t possible in many instances with the use of the ual clinical procedures for evaluating the renal funcon. Nowadays, with the use of the renogram we may able to differentiate a nonfunctioning kidney from blocked but functioning kidney.[9]

Materials and methods

This study was done on 24 patients with documented pelvic malignancy undergoing radiotherapy at the I. González Martínez Oncologic Hospital. Diagnosis was established by biopsy, and local extension of the disease was determined according to accepted international criteria for classifying carcinoma of the cervix by stages. Additional information was obtained by routine laboratory examinations, blood chemistries, renal function tests, intravenous pyelograms, and cystoscopy.

The renographic studies were carried out at the Clinical Applications Division of the Puerto Rico Nuclear Center using iodine I^{131} labelled orthoiodohippuric acid obtained in calibrated form ready for injection from Squibb Radiopharmaceutical Division. The technique is the same as that described by Winter *et al.*[10] The patient is positioned in a high chair with low back support, his abdomen facing the hind part of the chair, his back remaining free for adequate placement of the detectors. The detectors are made up of 1" x 1" thallium-activated sodium iodide scintillation crystals collimated by a lead shield, with an opening aperture of one and ½ inches (1½") and depth distance crystal to aperture of one and ½ inches (1½") subtending an angle of 30°. The instrumentation system consists of scintillation detectors, ratemeters and strip chart recorders for simultaneous recording of activity over each renal area. Hippuric acid I^{131} is injected intravenously in a dose of 1 μc per 5 kg of body weight. The dose of radioactivity injected usually ranges 10 to 20 μc per person per test, which has been considered to give the patient less than 1% of the radioactivity produced by a single X-ray exposure.[11] Renograms were interpreted according to the criteria of G. V. Taplin *et al.*[12,13] When hippuric acid is injected there is an initial almost upstraight peak of activity

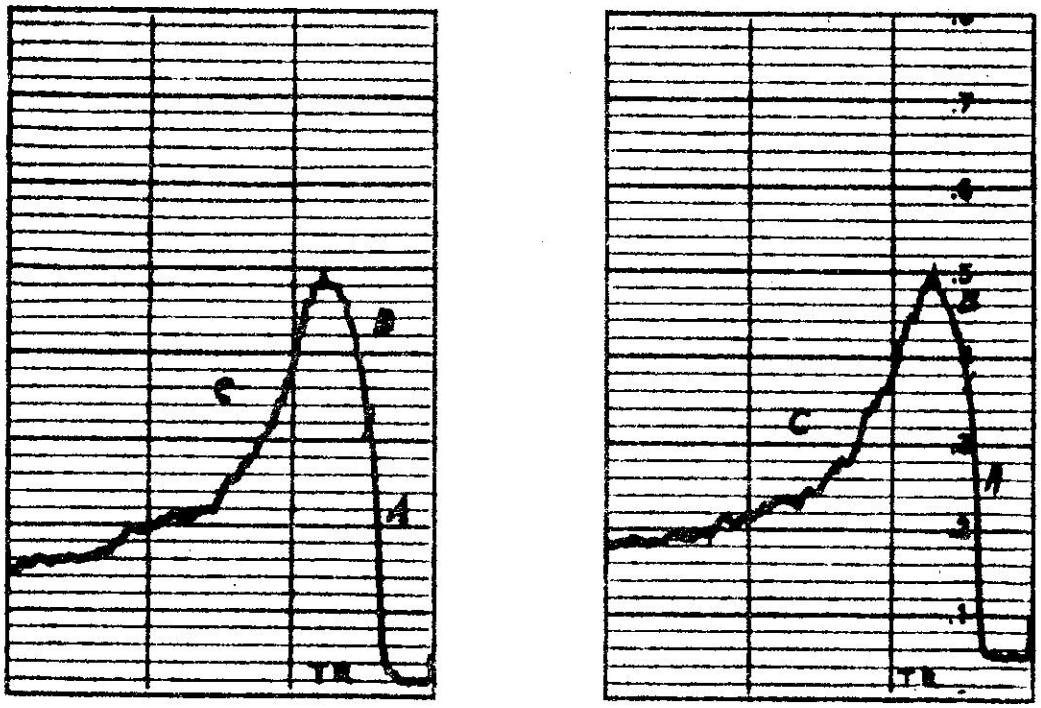


Fig. 1

Normal renogram.

that occurs in a few seconds and represents the vascularity of the kidneys, (Fig. 1, segment A) followed by a second less steep rise of the curve during the next 3-6 minutes. This is the interval of active tubular extraction of the labelled substance from the blood, (segment B or secretory phase). The last portion of the curve begins at the peak reached at B, and ends in a plateau near background 15-20 minutes later. This latter portion, called segment C represents the excretory function, which is delayed when there is difficulty with the urinary outflow.

Results

Twenty four patients were examined, of which 18 had carcinoma of the cervix uteri, stage III. Fifteen had normal renal function and excretion of urine as reflected by the renogram, the intravenous pyelogram and other clinical tests. All the abnormalities by either the renogram or the pyelogram were found in the stage III group. In seven instances both tests—the renogram and the pyelogram—were abnormal; there was one false negative and one false positive renogram when the renogram was evaluated in terms of the excretory urogram. The PSP (Table III) was done on 16 patients; 11 were normal and 5 abnormal; two of these were found abnormal by the X-ray or isotope examination, two had diastolic hypertension, and no explanation was found for the fifth case. In the group of 11 normal PSP, there were 3 abnormalities detected by the renogram and the intravenous pyelogram.

Lack of visualization of the dye contrast media occurred in 4 instances. This was associated with nonfunctioning kidneys. The renograms showed a pattern

TABLE I

DISTRIBUTION OF PATIENTS BY STAGES—CA CERVIX UTERI

Stage	Patients
I	2
II	4
III	18
Total	24

TABLE II

CORRELATION OF RENOGRAM WITH THE INTRAVENOUS PYELOGRAM BY STAGES

Renogram	IVP	Stage 1	2	3	Total
normal	normal	2	4	9	15
abnormal	abnormal	..	..	7	7
normal	abnormal	..	..	1	1
abnormal	normal	..	..	1	1
Total		2	4	18	24

TABLE III

CORRELATION BETWEEN THE PSP TEST (PHENOLSULPHONPHTHALEIN), THE RENOGRAM, AND THE INTRAVENOUS PYELOGRAM BY STAGES

PSP	IVP	Renogram	Stage 1	Stage 2	Stage 3	Patients
abnormal	normal	normal	1*	1*	1	3
abnormal	abnormal	abnormal	..	..	2	2
normal	normal	normal	..	3	5	8
normal	abnormal	abnormal	..	..	1	1
normal	abnormal	normal	..	..	1	1
normal	normal	abnormal	..	..	1	1
Total			1	4	11	16

* R.P. $\frac{140-150}{100}$

of absent kidney in these four cases. Hydronephrosis occurred in 4 instances. This was accompanied by unilateral lack of kidney function in two, and bilateral loss of function in the other two.

Discussion

The value of the isotope renogram to detect impairment of the excretory function in diseases affecting the upper urinary tract has been well established from the work of Taplin *et al.*,[14] Winter *et al.*,[15] and Donneberg.[16] The problem of ureteral compression by carcinoma of the cervix is well known by the clinician who treats these patients and the pathologist. Bockler and Prins [17] found ureteral blockage at autopsy in ⅓ of 150 women who had been treated with surgery and radiotherapy. A similar experience was reported by Marcial:[18] 71% ureteral obstruction in 169 necropsies in cases of cancer of the cervix. Zum Winkle [19] reported a high incidence of ureteral blockage due to abdominal tumors and carcinoma of the cervix uteri in 65% (90/138) of his patients. He also found 85% correlation between the renogram and the IVP.

In this group of patients the renogram and the IVP showed a high degree of correlation 15/15 normal, 7/7 abnormal, one false negative and one false positive. A false positive in most instances is probably due to positional factors; this can be checked by repeating the examination with better positioning of the patient. The incidence of urinary obstruction in 7 out of 18 is not as high as reported by other authors (ibid).[16-20] This may be related to the size of our sample.

Correlation between the PSP, renogram, and IVP was not good. The lesion of the urinary tract in cancer of the cervix is primarily an obstructive phe-

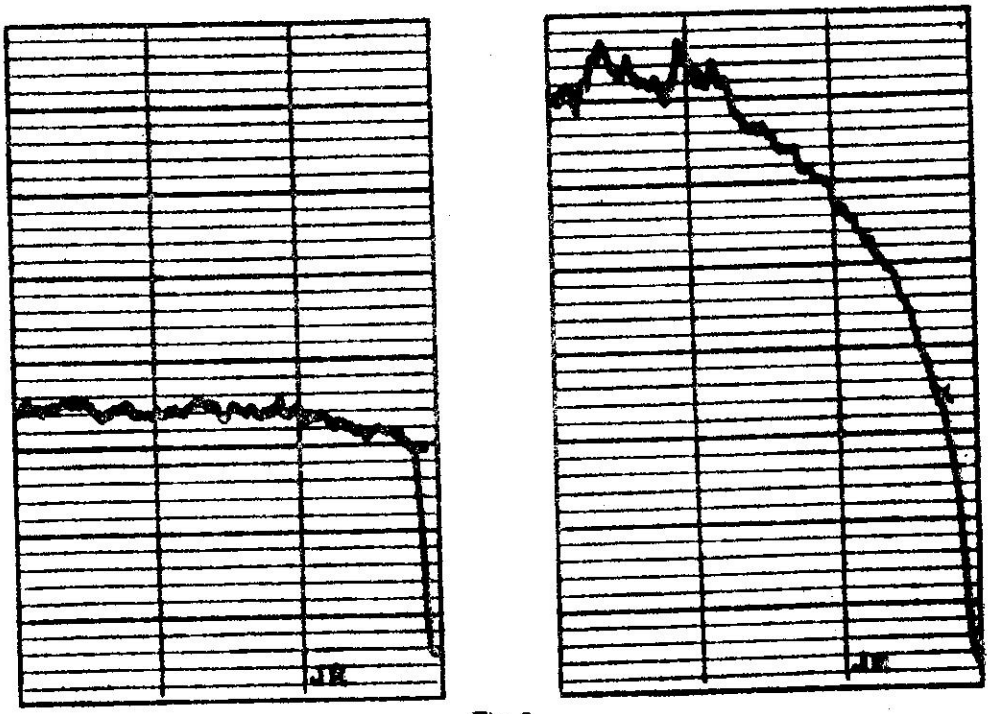


Fig. 2

Abnormal renogram. No function on right. Obstruction on left.

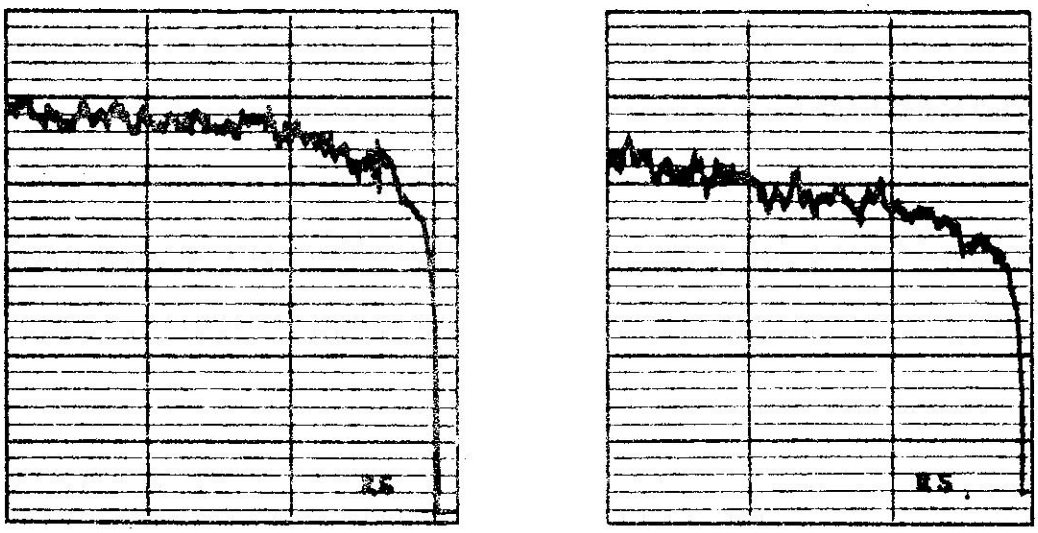


Fig. 3

Abnormal renogram. Bilateral obstruction. Impaired renal function.

nomenon, but sooner or later the secretory function of the renal parenchyma may be impaired, and ultimately the vascular flow will also be affected.

The renogram is a test that can be easily performed, can be done rapidly, is nontraumatic, can be done in all patients, and has shown a high degree of correlation with other clinical tests. At times it may even give information not obtainable by other means.

In two of this group of the four patients with hydronephrosis, the renogram added valuable information by showing unilateral and irreversible lack of kidney function with blocked but preserved contralateral kidneys (Fig. 2). This information cannot be obtained from the IVP alone. In another two cases (Fig. 3) the IVP showed no visualization, while the renogram showed this was due to lack of kidney function, a conclusion that cannot be reached on the basis of the IVP alone.

Summary

1. Twenty-four patients with cancer of the cervix were studied with the I^{131} hippuric acid renogram, intravenous pyelography, and other clinical tests.
2. Eighteen patients had carcinoma cervix uteri, stage III; all abnormalities detected by the renogram and IVP belong to this group of patients.
3. Approximately two fifths of the patients (7/18) had signs of ureteral compression as shown by the renograms or IVP.
4. Correlation between the renogram and the IVP was excellent.
5. The value of the renogram for detecting abnormalities of urinary excretion and renal function in patients with cancer of the cervix, particularly stage III, is discussed.

REFERENCES

(1) TAPLIN, G. V., *et al.* U.S. AEC Report UCLA-366.
(2) TAPLIN, G. V., *et al. J. Lab. Clin. Med.*, **48**, 886 (1956).
(3) WINTER, C. C. *J. Urol.*, **76**, 2, 182-196 (1956).
(4) WINTER, C. C. *J. Urol.*, **78**, 107 (1959).
(5) WINTER, C. C. *Amer. J. Roentgenol*, **82**, 862 (1959).
(6) DONNEBERG, T. *Acta Chir. Scandinava*, 118-231 (1960).
(7) RODRIGUEZ-ROSADO, A. L. Report to a Meeting of Puerto Rico Chapter of American College of Physicians at the Puerto Rico Medical Association, 1960.
(8) WINKEL ZUM, K. *Brit. J. Radiol.*, **34**, 241-245 (1961).
(9) WINKEL ZUM, K. *Ibid.*

(10) WINTER, C. C., *et al.* See references 3, 4, 5.
(11) WINKLE ZUM, K. See reference 8.
(12) TAPLIN, G. V., *et al.* Proc. 2nd UN Int. Conf. PUAE. A/Conf. 15/P/870 (1958).
(13) TAPLIN, G. V., *et al.* Exhibit 414 AMA Meeting. Miami, Fla. (1960).
(14) TAPLIN, G. V., *et al. Ibid.*
(15) WINTER, C. C., *et al.* See references 3, 4, 5.
(16) DONNEBERG, T. See reference 6.
(17) BOCKLER, H., *et al.* in WINKLE ZUM, K. See reference 8.
(18) MARCIAL ROJAS, RAUL, A., *et al. The Am. J. of Path.*, 31, 1077-1082 (1955).
(19) WINKLE ZUM, K., *et al.* See reference 8.
(20) WINKLE ZUM, K., *et al.* See reference 8.
(21) BOCKLER, H., *et al.* See reference 17.

Reprinted from the American Journal of the Medical Sciences, Vol. 242, No. 5, November, 1961

THE ROLE OF CALCIUM ON THE INTESTINAL ABSORPTION OF VITAMIN B_{12} IN TROPICAL SPRUE

By A. L. Rodriguez-Rosado, M.D.
RESIDENT IN MEDICINE AND RESEARCH ASSOCIATE

AND

T. W. Sheehy, Major, MC, USA
CONSULTANT HEMATOLOGIST

(From the Department of Medicine, San Juan City Hospital, the Clinical Applications Division, Puerto Rico Nuclear Center and the Army Medical Tropical Research Laboratories, San Juan, Puerto Rico)

Gräsbeck and Nyberg[5] observed that the urinary excretion of radioactive vitamin B_{12} obtained in the Schilling test was notably decreased in normal individuals given the calcium chelating agent ethylenediamine tetra-acetate (EDTA). This effect was avoided when calcium lactate was given orally with the EDTA and labeled vitamin B_{12}. In a series of experiments, Herbert[6,7] showed that calcium ions influence the ability of hog intrinsic factor concentrate to improve the uptake of vitamin B_{12} by everted sacs of rat small intestine and by liver slices *in vitro*. Later this observation was confirmed by Cooper and Castle[2]. Subsequently (Gräsbeck, Kantero and Siurala[4]) it was reported that calcium lactate improved the intestinal absorption of vitamin B_{12} in idiopathic steatorrhea but not in pernicious anemia. The similarity between tropical sprue and idiopathic steatorrhea prompted us to investigate the effect of calcium on the absorption of vitamin B_{12} in tropical sprue.

Materials and Methods. Seventeen Puerto Rican patients, age 17 to 90, with tropical sprue were studied. Three of the patients were untreated and 14 had been treated intermittently with liver extract, folic acid or vitamin B_{12} for periods ranging from 1 to 20 years. Criteria for diagnosis of tropical sprue consisted of macrocytic anemia, megaloblastic erythroid maturation, weight loss, steatorrhea and defective intestinal absorption of xylose and vitamin A. All treated patients had these findings initially, but were in clinical remission at the time of this study. Blood counts, vitamin A, and xylose absorption tests were done to determine the present hematologic and absorption status. Serum phosphorus and calcium determinations were performed according to the methods of Fiske-Subbarow and Clark-Collip respectively. Each patient was subjected to two Schilling tests, at an interval of one week. A tracer dose of 0.5 μc. of Co_{58}-labeled vitamin B_{12} was given orally. A 1 mg. flushing dose of vitamin B_{12} was injected 60 minutes after the oral dose and the urine collected for 24 hours. Intrinsic factor was given orally in the first test with the vitamin B_{12}. In the second test, 3.5 gm. of powdered calcium lactate was given orally 30 minutes before the radiovitamin and 3.5 gm. simultaneously.

Results. The results of the intestinal absorption tests are listed in Table 1. Vitamin A absorption was impaired in 13 of the 17 patients. Xylose absorption was impaired in all but one patient (Case 10). The Schilling test with intrinsic factor and with calcium lactate was abnormal in all 17 patients. Normally the 24-hour urinary excretion of labeled B_{12} ranges from 10 to 35% of the administered dose. In the present study, when intrinsic factor was administered, the 24-hour urinary excretion ranged from 0 to 6.5%, with a mean value of 2.2% of the oral dose. With calcium lactate it ranged from 0 to 9.5%, with mean value of 2.1%.

Discussion. The exact physiologic mechanism of the intestinal absorption

TABLE 1.

Case	Age	Sex	Race	Onset of Disease	Blood Values		Absorption Tests		Serum Ca (mg./100 ml.)	Serum P (mg./100 ml.)	Schilling's Tests	
					Hgb	MCV	Vitamin A*	Xylose†			With I.F.	With Co
1	74	F	W	1 yr.	8.6	91	46–108–130	0.34	9.9	2.7	0.0%	0.0%
2	62	F	W	9 yrs.	12.2	97	36–44–54	0.50	9.6	3.5	0.8%	3.0%
3	70	F	W	20 yrs.	13.0	91	35–45–75	0.51	10.4	3.8	0.8%	0.6%
4	83	F	W	2 yrs.	12.2	96	10–30–50	0.14	9.1	5.0	0.3%	0.5%
5	70	F	C	12 yrs.	11.9	92	68–110–136	0.55	9.0	3.6	1.0%	0.0%
6	65	M	W	4 yrs.	13.9	88	66–91–143	0.75	9.7	2.6	3.8%	3.0%
7	70	F	C	12 yrs.	12.2	72	86–143–246	1.30	9.9	3.9	4.1%	3.5%
8	50	F	W	8 yrs.	10.8	96	25–47–50	0.45	10.2	3.6	6.5%	7.5%
9	50	F	W	7 yrs.	12.7	95	86–155–261	1.30	9.9	4.1	1.0%	4.0%
10	46	M	W	7 yrs.	14.9	92	85–101–200	1.90	10.2	2.6	0.6%	0.8%
11	17	M	W	1 yr.	13.2	96	38–46–61	1.00	9.8	3.9	3.0%	0.2%
12	58	M	W	2 yrs.	13.8	96	52–105–155	0.82	10.4	3.6	0.2%	0.5%
13	48	F	W	3 yrs.	11.2	92	42–286–286	0.81	12.1	3.4	6.0%	9.5%
14	50	F	C	12 yrs.	11.0	78	85–146–171	1.40	11.2	3.3	0.0%	0.7%
15	80	M	W	onset	5.3	109	22–37–54	0.10	10.8	3.8	3.0%	0.2%
16	55	F	W	onset	6.0	110	57–98–159	0.41	9.9	3.4	1.4%	1.0%
17	80	F	W	onset	9.0	104	58–120–124	0.52	10.2	3.2	5.0%	1.5%

*Normal values, measured in μg./100 ml., are: 64 ± 25 for fasting specimen, 198 ± 50 for 5 hrs. and 297 ± 88 for 7 hrs. serum specimen.
†Normal values are 1.8 gm. ± 0.3 (Santini, Sheehy and Martinez, de Jésus[9]).
‡Repeated with B_{12} alone the result was 1.5%.

of vitamin B_{12} is still unknown. Recently evidence has been reported which implies calcium plays a role on the absorption of vitamin B_{12}. Glass, Boyd and Stephanson[3] observed that the percentage of vitamin B_{12} absorption decreased in man as the oral dose of the vitamin was increased. He postulated that vitamin B_{12} is absorbed in the distal ileum via an intramural receptor analogous to the apoferritin mechanism. Herbert suggested that the acceptors bound the vitamin B_{12}-intrinsic factor complex in the rat intestine and the presence of calcium ions is necessary for binding the complex.

Calcium, in defective fat digestion or absorption, forms insoluble soaps with fatty acids and is lost in the stools (Korelitz and Janowitz[8]). The amount of the ion available for the intestinal absorption is, therefore, reduced. The concomitant loss of the fat-soluble vitamin D further accentuates the inefficiency of calcium absorption. For reasons pending definite elucidation, derangements of calcium metabolism in tropical sprue are practically unknown in spite of steatorrhea.

The intestinal absorption of vitamin B_{12} is impaired in tropical sprue and the defect appears to be independent of intrinsic factor and calcium. Minor differences were observed in the two Schilling tests done on each patient. These differences were not significant and probably represent fluctuations inherent in the test itself. Analysis of Gräsbeck's cases of nontropical sprue shows only one person had a significant rise in the urinary excretion of the radiovitamin after the oral calcium load. In this instance, the urinary excretion rose from a very low value of 1% to 20% with calcium.

Malabsorption of vitamin B_{12} in patients with tropical sprue most likely results from damage to the receptor mechanism within the intestinal mucosa, as part of the histopathologic changes found in this disease (Butterworth and Perez-Santiago[1]). Moreover, the finding of patients asymptomatic for many years but with persistently abnormal vitamin B_{12} absorption, implies the damage to the receptor mechanism may be permanent and irreparable in many patients. This would explain the persistence of impaired vitamin B_{12} absorption and the failure of calcium or intrinsic factor to improve absorption.

Summary and Conclusions. The intestinal absorption of vitamin B_{12} was studied in 17 Puerto Rican patients with tropical sprue. Vitamin B_{12} absorption is markedly impaired in this disease and neither intrinsic factor nor calcium lactate improved absorption of the labelled vitamin.

ACKNOWLEDGMENT: The authors wish to express their appreciation to Dr. E. J. Marchand, Head of the Department of Medicine, San Juan City Hospital and to Dr. S. Irizarry, Head of the Clinical Applications Division of Puerto Rican Nuclear Center for their encouragement and advice in this study, and to Mr. Harold Santiago, M.T., and Sgt. Henry Higaki for their technical assistance.

REFERENCES

1. Butterworth, C. E., Jr., and Perez-Santiago, E.: Ann. Int. Med., 48, 8, 1958.
2. Cooper, B. A., and Castle, W. B.: J. Clin. Invest., 39, 199, 1960.
3. Glass, G. B., Boyd, L. J., and Stephanson, L.: Proc. Soc. Exper. Biol. & Med., 86, 522, 1954.
4. Gräsbeck, R., Kantero, I., and Siurala, M.: Lancet, 1, 234, 1959.
5. Gräsbeck, R., and Nyberg, W.: Scandinav. J. Clin. Lab. Invest., 10, 448, 1958.
6. Herbert, V.: J. Clin. Invest., 37, 646, 1958.
7. Idem: Ibid., 38, 102, 1959.
8. Korelitz, B. I., and Janowitz, H. D.: J. Mt. Sinai Hosp., 24, 181, 1957.
9. Santini, R., Sheehy, T. W., and Martinez de Jésus, J.: Gastroenterology, 40, 772, 1961.

Printed in the U.S.A.

DEMOSTRACION EXPERIMENTAL DE LA EXCRECION DE SEROALBUMINA EN LAS GASTRITIS

Por: Dr. A. Rodríguez Olleros, F.A.C.P., F.A.C.G*
Dr. S. Irizarry**
Miss M. Rivera***

Los estudios, ya clásicos de los autores alemanes, habían señalado la presencia de albúmina en cantidades anormales en el jugo gástrico de ciertas gastropatías. Katsch (1) estudia y demuestra contenido anormal de albúmina en el jugo gástrico de las gastritis de las infecciones y las gastritis "serosa". Este autor y Balker (2) habían desarrollado un método a base de la turbidez que produce el ácidosulfosalicílico en los líquidos albuminosos.

Citrin (3) describe el sindrome de "Hipoproteinemia hipercatabólica" consecuencia de la abundante excreción de seroalbúmina en los casos de gastritis hipertrófica gigante. Butz (4) lo confirma. Norpoth, Surman y Gloesges (5) usando la electroforesis sobre papel, demuestran en el jugo gástrico albúmina de origen "inflamatorio". Heinkel, Preisser y Henning (6) comprueban que los pacientes de gastritis atrófica tienen una baja de la cifra de albúmina sérica de valor estadístico. Glass e Ishimori (7) con la misma técnica de la electroforesis sobre papel demuestran que los jugos gástricos de pacientes de gastritis superficial y gastritis "hiperácida" contienen los productos de degradación de la seroalbúmina.

Material y Métodos:

Hemos usado perros mongroles de peso aproximado de 30 libras. Los dos días previos al experimento se les administró 1/2 cc. de Lugol dos veces al día.

Tres perros se usaron para los estudios de control. A cada uno se les inyectó intravenosamente en ayunas, Albúmina I-131 "RISA" en cantidad de 26 uc diluída con albúmina a razón de 2.6 uc x cc. Se obtuvo la sangre para contage a los diez minutos, estableciendo la distribución de actividad inicial en el plasma. Se volvió a obtener sangre para contage todos los días sucesivos durante 8-10 días, siempre en ayunas. El día cuarto después de la inyección de RISA se hace la prueba de obtención del contenido gástrico. Se inyecta a cada perro en ayunas 1/2 cc de Histalog (25 miligramos). A los 25 minutos se anestesia con Nembutal sódico intravenoso. Se intuba el estómago estando el perro en decúbito izquierdo y se extrae todo el contenido gástrico que se descarta.

---

*Profesor Asociado de la Escuela de Farmacia y Escuela de Medicina, Universidad de Puerto Rico.
**Director, División de Aplicaciones Clínicas, Centro Nuclear de Puerto Rico, Universidad de Puerto Rico.
***Técnico de Investigaciones, División de Aplicaciones Clínicas, Centro Nuclear de Puerto Rico, Universidad de Puerto Rico.

Desde entonces, durante 30 minutos exactos, se recoge con aspiración contínua la secreción gástrica que se mide y se envía al contage.

Se ha repetido la misma técnica en los siguientes tres grupos:

1) Dos perros a los que durante 64 días (9 semanas) se les administró por sonda 2 cc de Creoseta y 2 cc "Diol" diariamente excepto los domingos.

"Los perros desarrollaron la llamada gastritis serosa: congestión, dilatación capilar, edema y muy poco componente celular".

Terminado ese período se les inyectaba 26 uc "RISA" y se procede como hemos indicado en los controles.

2) A 2 perros se les administró por sonda gástrica dos gramos de cincophen (atofán) suspendidos en agua, dos veces una semana.

"Con este método (8) se produce una gastritis ulcerativa del cuerpo y del antro del estómago. Hay múltiples erosiones superficiales la mayordía de un milimetro de diámetro. La túnica propia está edematosa y moderadamente infiltrada con neutrófilos." (figuras 1 y 2).

El lunes de la semana siguiente se inició en ellos la prueba con "RISA" en idéntica forma que en los anteriores.

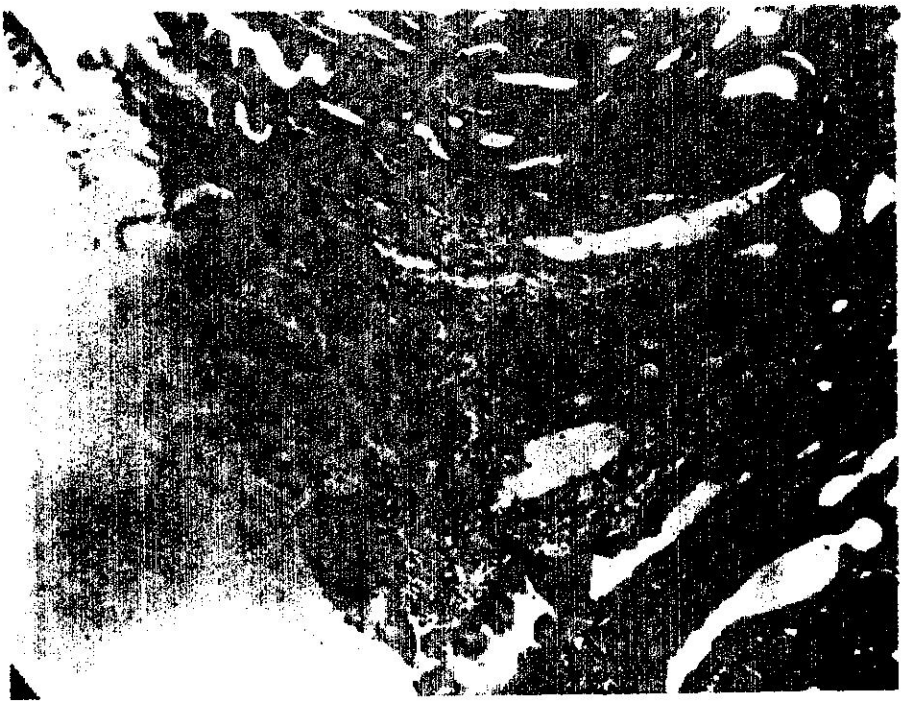
3) Tres perros a los que a través de un cáteter ureteral incluído y fijado en una sonda gástrica, se les instiló en la parte alta del estómago, dos veces por semana, durante cinco semanas 3 cc de la solución en alcohol-eter, de aceite de croton al 0.5%.

Se procedió con ellos inyectándoles 26 uc "RISA" en igual forma que la descrita. Estos perros desarrollaron gastritis papilomatosa (1) (Figuras 3, 4,5,6,7). Todos los animales de los tres grupos fueron sacrificados una vez terminado el experimento para el exámen histopatológico del estómago.

Resultados

Tres animales del grupo control y 7 animales del grupo experimental formaron la población estudiada. Se determinó el tiempo de semi-desaparición de la albúmina I-131 y el nivel de I-131 en el jugo gástrico antes y después de realizada la gastritis experimental. Como control de esta prueba se hizo un estudio de la fijación de iodo a la albúmina marcada y se determinó que en 10 días la presencia de I-131 inorgánico como resultado de liberación del yodo de la proteína era despreciable - gráfico 1. Las curvas de desaparición sanguínea de la albúmina I-131 se determinaron tomando valores de radioactividad total y radioactividad de la fracción proteíca encontrándose que el valor del yodo I-131 libre en plasma con relación de la radioactividad total el día que se tomó la muestra gástrica fué 4.9%, (Tabla 1 y gráfico II). Se asume que en el estado de equilibrio cuando se muestrea el jugo gástrico

(1) Esta gastritis será descrita en trabajo separado de los Drs. Rodríguez Olleros y L. Galindo.



Drs. A. Rodríguez Olleros, Sergio Irizarry

Figura #1 - Gastritis de Atofán en perro. Dilatación glandular, edema de la lámina propia, infiltración.

Drs. A. Rodríguez Olleros, Sergio Irizarry

Figura #2 - Gastritis de atofán en perro; úlcera superficial.

Figura #3 - Perro Normal - Gastritis papilomatosa con aceite de croton.

Drs. Rodríguez Olleros, Sergio Irizarry

Figura # 4 - Perro 8 instilaciones. Se ha perdido el paralelismo de las glándulas, comienza a dilatarse las glándulas superficiales. Gastritis papilomatosa con aceite de crotón.

Drs. A. Rodríguez Olleros, Sergio Irizarry

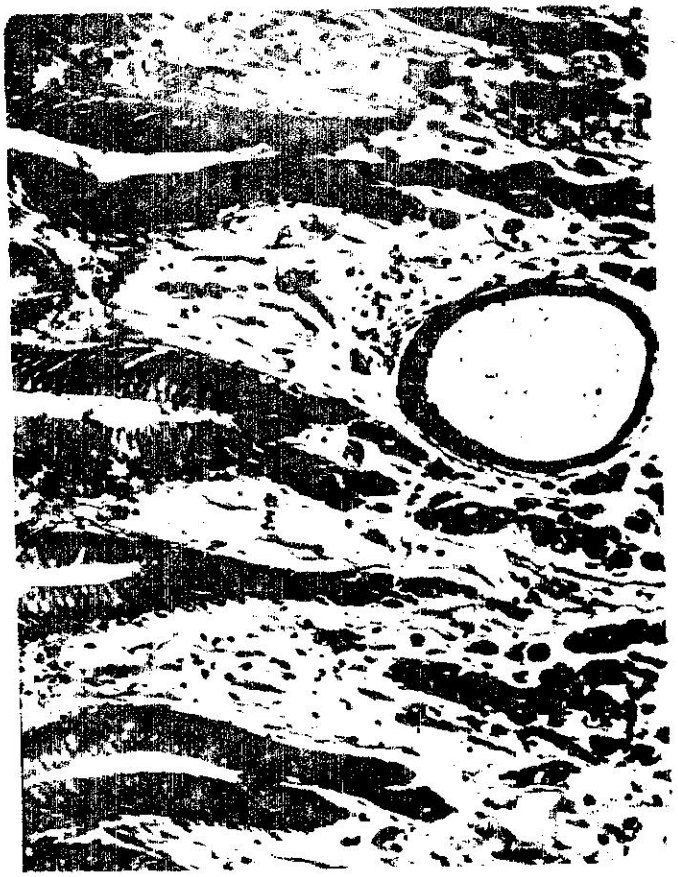


Figura #5 - 8 instilaciones; quiste, gran edema, infiltración célula redondas y algún cóxinófilo.
Gastritis papilomatosa con aceite de crotón.

Drs. A. Rodríguez Olleros, Sergio Irizarry

Drs. A. Rodríguez Olleros, Sergio Irizarry

Figura #6 - Zona pliegues epitelio superficial que está sufriendo transformación a papilona. Gastritis papilomatosa con aceite de crotón.

Figura # 7 - Contrastes zona hiperplasia con edema y zona estrecha. Gastritis papilomatosa con aceite de crotón.

GRAFICO I

CURVA CORREGIDA PARA DESINTEGRACION FISICA

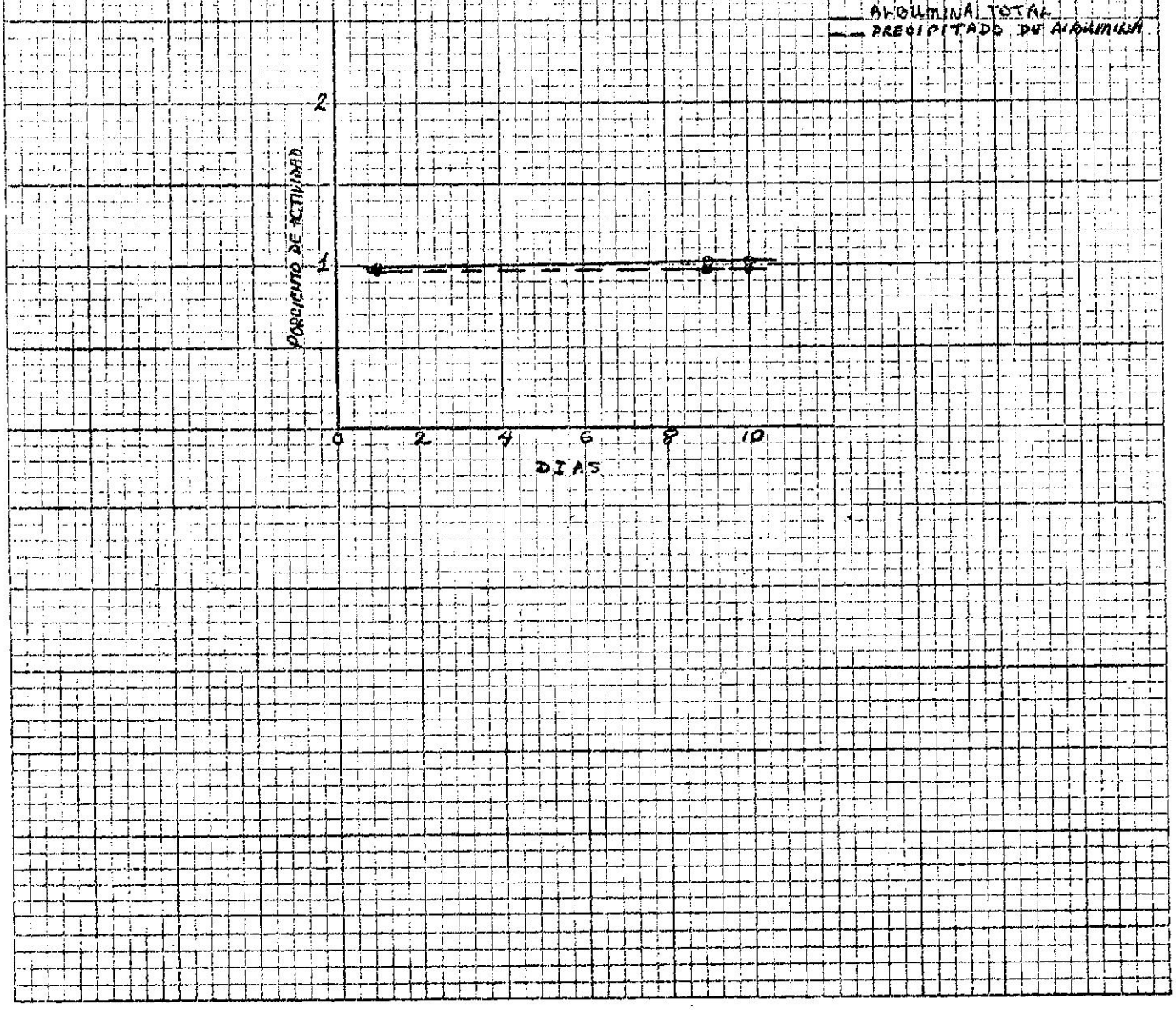


TABLA I

FRACCION (%) I-131 LIBRE EN SANGRE
AL TIEMPO DE MUESTREO DEL JUGO GASTRICO

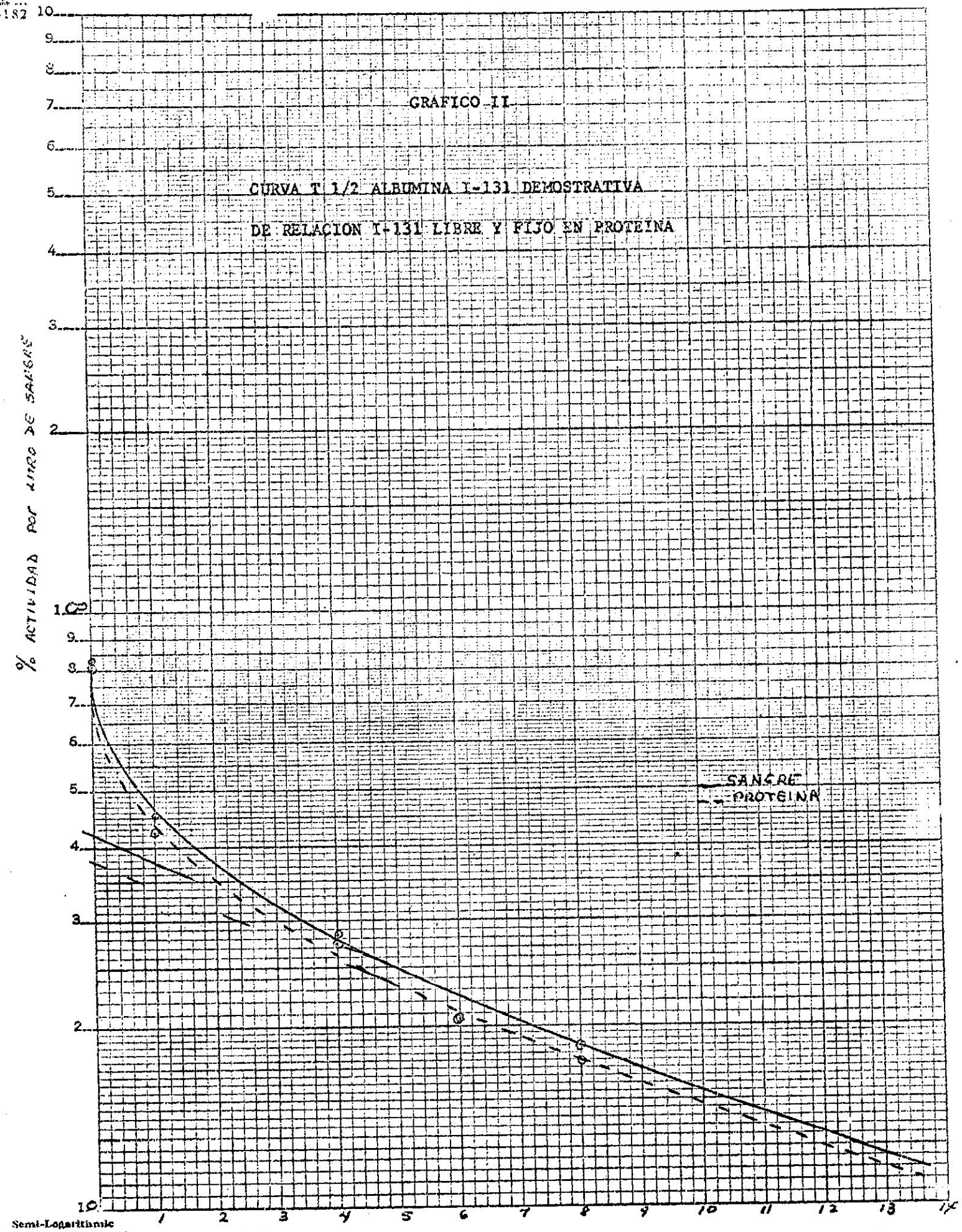
	PRE	POST
CANELA	2.7	6.1
BLANCA	4.2	7.9
DESENTIDO	6.7	5.7
CAFE		8.8
TABACO		5.4
BARQUILLA		0
PINTO		2.3

12-182

GRAFICO II

CURVA T 1/2 ALBUMINA I-131 DEMOSTRATIVA

DE RELACION I-131 LIBRE Y FIJO EN PROTEINA



Semi-Logarithmic
2 Cycles x 10 to the inch

la albúmina circulante está acompañada al pasar por un defecto en la pared gástrica al lúmen del estómago, de las fracciones de yodo libre y yodo proteíco correspondientes a las que existen en la circulación. El análisis del jugo gástrico no se hizo instantáneamente por lo que los valores del precipitado del jugo gástrico no son válidos para expresar el verdadero valor de radioactividad proteíca al momento de la trasudación. Por eso el valor del nivel de I-131 fijo en proteínas trasudadas se puede obtener aplicando una corrección que se obtiene tomando como factor de corrección el % de radioactividad proteíca presente en la albúmina circulante (Tabla I). Otra posibilidad es considerar la radioactividad total del jugo gástrico como indicadora de la actividad proteíca ya que ambos fluctúan en la misma dirección. Los valores de I-131 en el jugo gástrico se expresan como radioactividad total o como radioactividad corregida. Los resultados de 3 grupos de animales en los cuales se practicaron 3 tipos de gastritis aparecen en la siguiente tabla siendo los animales 1, 2, 3 tratados con Diolcreosota, el 4 y 5 con atofán y el 6 y 7 con aceite Croton.

TABLA II

Animal #	T 1/2 días alb.I-131		% dos I-131 jugo gástrico 1/2 hr.			
	Control - Experimental		Control		Experimental	
			Act.Tot.	-Correg.	Act.Tot.	-Correg.
1 (Canela)	9.0	6.2	0.16	0.16	2.41	2.29
2 (Blanco)	8.2	5.4	0.69	0.66	1.91	1.76
3 (Resentido)	6.0	4.2	0.57	0.53	0.60	0.56
4 (Barquilla)	-	6.0	-	-	1.03	-
5 (Pinto)	-	6.2	-	-	3.2	-
6 (Café)	-	6.6	-	-	1.3	-
7 (Tabaco)	-	4.1	-	-	1.2	-
PROMEDIO	7.7	5.5	0.47	-	1.66	-

La cantidad de jugo segregado en 1/2 hora en los animales experimentales antes y después de la gastritis se puede apreciar en la siguiente tabulación:

Tipo Gastritis	Animal #	Volúmen Jugo Gástrico de 1/2 hora Antes	1/2 hr. después
Diol Creosota	1	25 ml	72 ml
	2	50 ml	218 ml
	3	123 ml	160 ml
Atofán	4	-	60 ml
	5	-	144 ml
Crotón	6	-	34 ml
	7	-	111 ml
PROMEDIO		66 ml	114 ml

El promedio de la semidesaparición de la albúmina I-131 en los animales control fué 7.7 días y en los animales experimentales fué 5.5 días. El promedio de radioactividad total en jugo gástrico de animales control fué 0.47% dosis administrada y en los animales experimentales fué 1.66%. El promedio del volúmen segregado en 1/2 hora por los animales control fué de 66 ml y el volúmen segregado por los animales experimentales fué 114 ml. Los valores antes y después del experimento aparecen ilustrados en el gráfico III - curvas típicas T 1/2 albúmina-131 y gráfico IV T 1/2 albúmina 131 y actividad del jugo gástrico.

Hemos seleccionado el procedimiento de titulación del I-131 directamente en el jugo gástrico segregado durante un período de tiempo determinado, por considerar que es la prueba más evidente de que disponemos actualmente para demostrar la responsabilidad de la mucosa gástrica en la eliminación. Gordon (9) en 1959 usó con este propósito el Polivinil Pilorrido-Me (P.V.P.) señalado I-131 que si se elimina por el tubo digestivo no sería digerido ni reabsorbido y se recogería en la excreta. Pero el método ha sido descartado por objeciones tan serias, como la de que este preparado se fija en parte en el retículo endotelio; porque la desigualdad de sus moléculas que llevan el I-131 hace que se eliminen a diferente velocidad las de diferentes tamaños, y finalmente, siendo de estructura diferente a la seroalbúmina su comportamiento frente a la mucosa gastro-intestinal probablemente no sean idénticas.

La electroforesis sobre el papel ha sido el método utilizado por Norpoth (5) y Henning (10), Glass (7) y Gulberg (11).

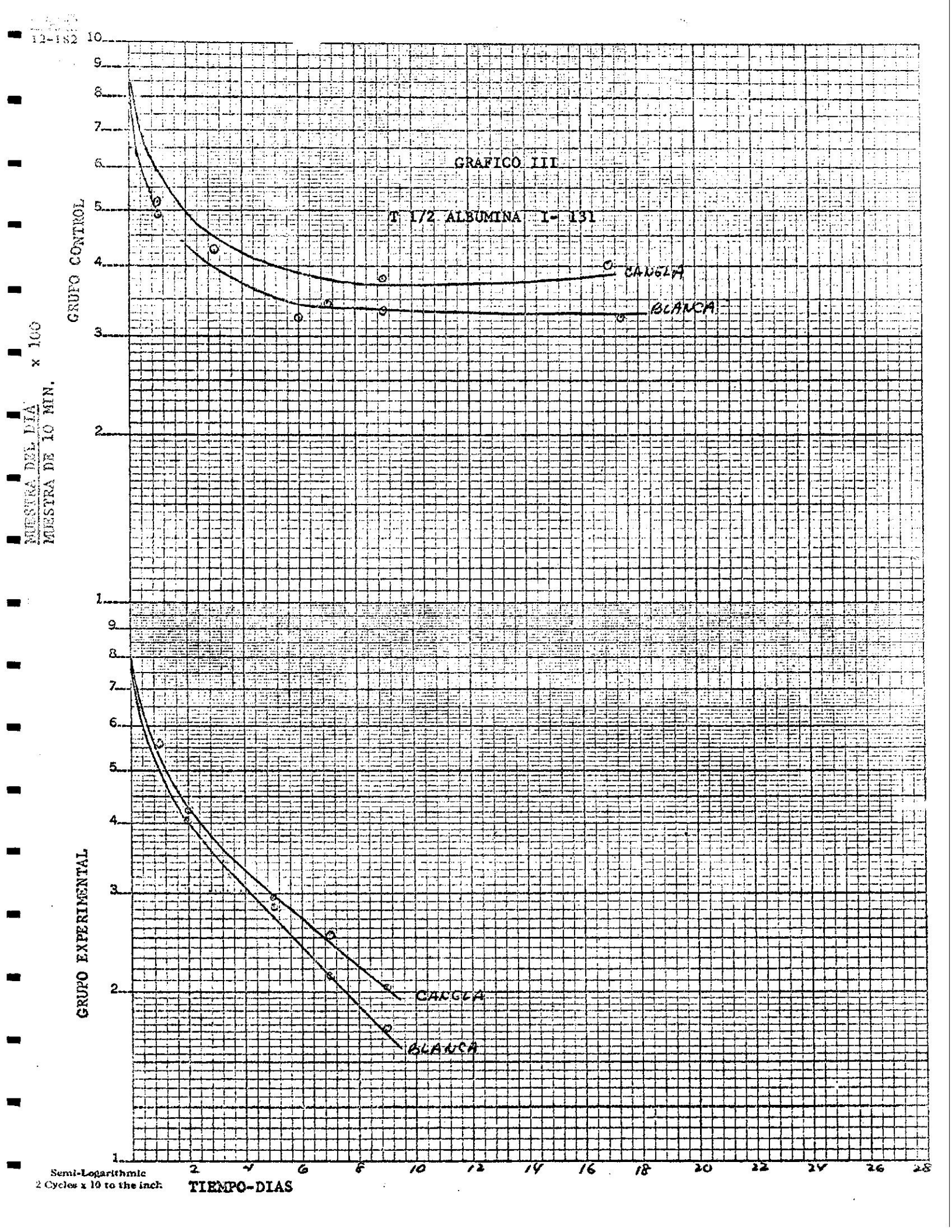
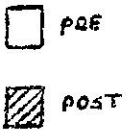


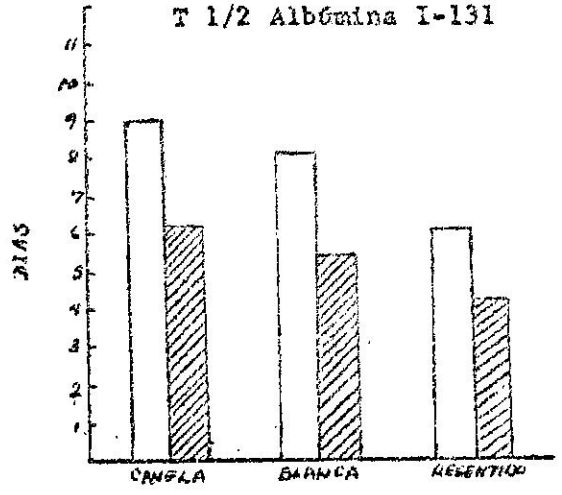
GRAFICO III
T 1/2 ALBUMINA I- 131
GRUPO CONTROL
GRUPO EXPERIMENTAL
MUESTRA DEL DIA
MUESTRA DE 10 MIN.
x 100
CANGLA
BLANCA
CANGLA
BLANCA
TIEMPO-DIAS
Semi-Logarithmic
2 Cycles x 10 to the inch

GRAFICO IV



GASTRITIS DIOL-CREOSOTA, y
ACEITE CROTON

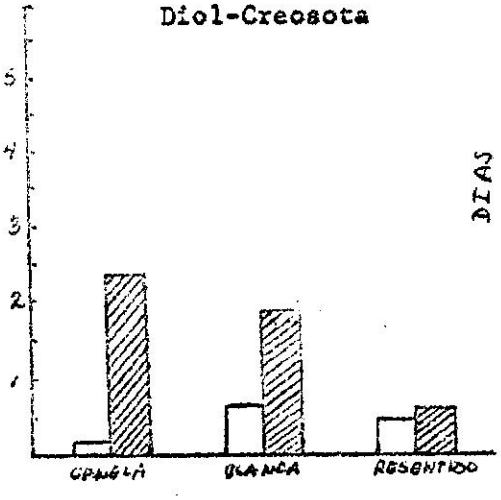
T 1/2 Albúmina I-131

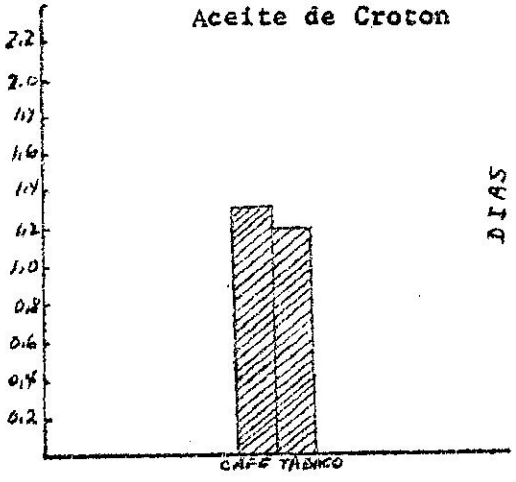


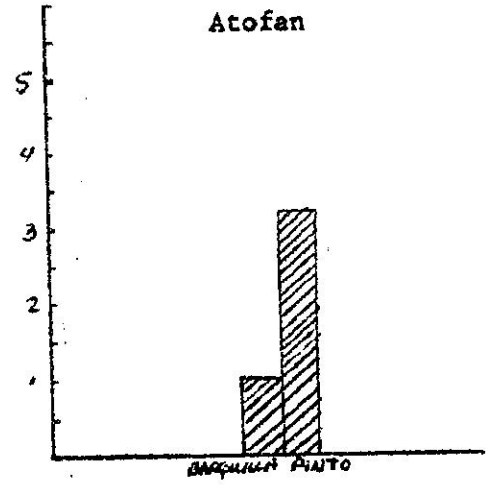
ANIMAL # 1 2 3

TRASUDACION ALBUMINA I-131

JUGO GASTRICO







ANIMAL# 1 2 3

Este método ha sido complementado con la técnica de inmunoelectroforesis por Oystese (12) y Hurliman (13). Estos autores han proporcionado excelentes datos sobre las vías de excreción y sobre las diferentes fracciones de las proteínas sanguíneas eliminadas. Hurliman ha demostrado que el estómago normal elimina muy pequeña cantidad de seroalbúmina y globulina. Solo en las gastritis anácidas y en los casos de anemia perniciosa la presencia de estas substancias puede evidenciarse tomando el jugo directamente. En los estómagos con normalidad clorhidro-pépsica es necesario neutralizar con una solución "buffer" el jugo gástrico según se va segregando. En el cáncer gástrico y en las gastritis, la cantidad de las mismas proteínas que se segregan en el estómago normal, aumentan considerablemente. Por eso en la "hipoproteinemia hipercatabólica" que se produce por éstas pérdidas el trazado electroferético tiene por característica el aumento proporcional que experimenta la onda de las globulinas.

Pero el método de la electroforesis es fundamentalmente cualitativo. Esta era la limitación para aplicarlo a nuestro proyecto.

En estos últimos años se ha aplicado al estudio de las pérdidas de proteínas a través de la mucosa gastrointestinal la combinación de "RISA" intravenosa y la resina Amberlite CL. por vía oral (5 gramos 4 veces al día).

Esta resina fija el I-131 y lo elimina en la excreta donde se dosifica. Han trabajado en este método Seejeebhoy (14), Jones, (15), Sum (16), Jiménez Diaz (17) y Lizoro (18). Con este método se recoge aproximadamente el 80% del I-131 que se elimina. Pero normalmente se elimina parte por la saliva y bilis y el resto por la mucosa gastrointestinal. La razón para no aplicar este método a nuestra investigación estriba en lo poco selectivo que es cuando se quiere determinar exclusivamente la eliminación gástrica.

Hemos practicado la recogida directa del jugo gástrico segregado durante un período de tiempo igual para los animales de control como para los del experimento.

Los autores antes citados (7) (10) (13) (14) han comprobado que el jugo gástrico activo disocia en pocos minutos la albúmina segregada en la cavidad gástrica.

El jugo gástrico de nuestros perros tanto controles como de experimento tenía un Ph 1-2. Por esto desistimos de precipitar la albúmina. El I-131 de la albúmina segregada y luego hidrolizada estaba en forma de polipeptidos I-131, tirosina I-131 y I-131 libre, ibid 7, 10, 13, 14. El contage de este I-131 en nuestros tres grupos de gastritis demuestra un aumento substancial en relación con los animales control. Las curvas del "turnover" del I-131 del suero evidencian un paralelismo sostenido entre la curva del I-131 total y la obtenida en la precipitación de las proteínas del suero. Por esto puede afirmarse que el aumento del I-131 del jugo gástrico procede de la albúmina excretada por la mucosa.

Simultáneamente el "turnover" del I-131 del suero de nuestros perros gastríticos está francamente acelerado en comparación con los controles.

La concordancia de estos dos datos, jugo gástrico y suero, nos lleva a la conclusión de que en nuestras gastritis experimentales está aumentada, la excreción de albúmina por el estómago.

Habiéndose comprobado por los autores citados la pérdida de albúmina en las gastritis humanas hiperplásicas, gigantes, atróficas e incluso en las agudizaciones de las gastritis superficiales, la demostración por nosotros de pérdidas anormales de albúmina en ciertas gastritis provocadas en los perros tiene valor para proyectarlo en la clínica.

Los perros son probablemente los animales de experimentación con estómago más resistente a la agresión.

Es muy probable que en los humanos gastríticos crónicos, que como cualquier humano que vive la medicina presente ingiere con relativa frecuencia medicamentos que contienen aspirina y antirreumáticos en general, balsámicos expectorantes, y minerales de Fe y Cu, sufran agudizaciones de su gastritis con mayores pérdidas de albúmina a través de su mucosa gástrica.

Este hipercatabolismo unido a las inadecuadas dietas en que se refugian estos pacientes para disminuír las molestias digestivas, son factores principales de la mala nutrición de gran parte de los gastríticos crónicos.

RESUMEN

Se han producido en 3 grupos de perros tres grupos de gastritis:

1) "Serosa" con creosota-Diol

2) "Erosiva" con atofán

3) Papilomatosa" con aceite de croton

En todos ellos se ha realizado la prueba de inyección intravenosa con albúmina I-131 RISA midiendo el"turnover"en suero y la eliminación por la mucosa gástrica.

Los resultados se han comparado con perros normales resultando que los perros gastríticos tiene un"turnover"más rápido y aumentan significativamente la excreción de albúmina I-131 por la mucosa gástrica por encima de lo que se podría explicar a base del aumento en el volúmen de jugo gástrico segregado.

1) Katsch, G.; Eiwaisagehalt des Magensaftes; Hanbuch der Inneren Medizin; III: 516, 1953.

2) Katsch, G and Baltzer Fs.; Eifaches verfahren zur Erkenncing der gastritis serosa;KLin. Woche.; 16: 554-561, 1936.

3) Citrin Y.; Sterling K. and Halsted S.A.: The mechanism of hypoproteinemia associated with giant hypertrophy of gastric mucosa: New England Med. 257: 906-912, 1957.

4) Butz, W.C.: Giant Hypertrophic Gastritis: Gastroenterology, 39, 183-190, 1960.

5) Norpoth, L., Surmann Th. and Cloeges J., Der Nachweis "enzundlicher" Eiweiss Korper in menschlichen Magensaft; Arztl. Wschr., 9: 389-391, 1954.

6) Heinkel K., Preisser F. und Henning N.:Histological findings in the gastric mucosa and the serum albunima level: Klin. Wschr., 39: 193-195, 1961.

7) Glass G.B.J. and Ishimori A.:Passage of serum albumen into the stomach: Amer. J. Dig. Dis., 6: 103-133, 1961.

8) Rodríguez Olleros, A. and Galindo L.: The action of cortisone and adreno-corticotrophic hormone on Experimental gastritis and gastric ulcer: Gastroenterology, 32: 675-688, 1957.

9) Gordon, R.S.: Exudative enteropathy: Lancet, I: 325-26, 1959.

10) Henning, N.; Kinylmeir, H. und Demling L.: Uber eleltroforetich dastellbaren Protein Normale and Pathologicher Magesafte: Much. Med. Wschr.: 95: 423-426, 1953.

11) Gulberg, R.: Electrophoresis fraction of B-12 binders in Gastric juice from patients with pernicious anemia and from controls. Proc. Soc. Exp. Biol.: 105: 62-66, 1960.

12) Oystese B and Torgensen O.: Excretion of Proteins from the human Gastric Mucosa. Act. Path. Microbial. Scand. 60: 93-98, 1964.

13) Hurliman, S.: The Protein of the Gastric Juice: Helv. Med. Acta. 30: 126-155, 1963.

14) Seejeebhoy, K. N. and Cophill, N. F.: The measurement of Gastro-intestinal protein loss by a new method: Gut. 2: 123-130, 1961.

15) Jones, S.H. and Morgan, D.B.: Measurement of Plasma Protein loss into gastro-intestinal tract using I-131 labelled protein and Amberlite resin: Lancet II: 626-629, 1963.

16) Sum, P.T., Hoffman, M.M. and Wester, D.R.: Protein losing gastro-enteropathy with Gastrointestinal Cancer: Cand. S. Surg. 7: 1-5, 1964.

17) Jimenez Diaz, C.; Linazoro, S.M. y Serrano Ríos, M.: Eliminación de seroalbúmina por las heces en la nefrosis. Rev. Clín. Española LXXXVIII: 302-4, 1963.

18) Linazoro, S.M.; Jimenez Diaz, C.: Ortíz Mallorens y Criado Ortiz, M.: Estudio experimental sobre la secreción intestinal de albúmina plasmática: Rev. Clín. Española LXXXVII: 362-367, 1962.

UPTAKE MEASUREMENTS: DETERMINATION OF THE PROBABLE MAXIMUM DEVIATION OF THE UPTAKE MEASUREMENT AT THIS LABORATORY

Dr. Sergio Irizarry, Clinical Applications Division, PRNC
Mrs. Hada Livia R. de Colón, Clinical Applications Division, PRNC
Miss Zenaida Frías, Radiotherapy and Cancer Division, PRNC

In order to determine the maximum deviation in our uptake measurements a study was conducted on eight cooperative patients who were measured repeatedly 24 hour after the administration of an oral dose of I-131. Each measurement was performed as if it were a new procedure; that is, the patient was moved out of the examining room and brought back in again for each measurement. Phantom measurements were similarly done anew each time and the instrument was changed from position and brought again to the measuring position for the phantom and patient each time as needed.

The technique used in this laboratory is based on the method published by Marshall Brucer, (1) 1959 which uses a combination of filters to measure the phantom and patient's thyroid gland. One of these filters, filter A, 1/16 inch lead thickness filter, is attached to the lower end of the detector; its purpose being to stop weak secondary radiations coming from the body of the patient, and to allow primary gamma rays from the source (the thyroid gland and phantom) to reach the detector. The other filter, filter B, is a 4 x 4 inch lead block which is applied over the source in the phantom and patient (thyroid gland) to cut off all primary radiations coming from the source to obtain background counts.

The measurement consists of 4 counting steps, two substractions and a division which are related in Marshall Brucers' (1) formula to obtain the final results as follows:

$$\% \text{ uptake by the thyroid gland} = \frac{\text{Counts in patient with filter A} - \text{Counts in patient with filter B}}{\text{Counts in phantom with filter A} - \text{Counts in phantom with filter B}} \times 100$$

The phantom we use is a phantocube (plastic phantom) and the source consists of I-131 capsules located at 3 cms depth in the phantom. The measuring distance is approximately 28 cms from the crystal and exactly 20 cms from the lower end of the detector to the skin of the patient or the outer surface of the phantom. The scintillation unit is a 2" D x 2" sodium iodide crystal housed 3 inches within the detector and the aperture of the detector is 3.25 inches in diameter. The counting efficiency of this system is of the order of 1000 counts per minute per microcurie at 20 cms from the lower end of the detector .

RESULTS

72 measurements were performed in 8 patients. Each patient was measured several times and the series of measurements were individually analyzed for the mean, standard deviation and the maximum deviation from the mean.

The following table shows the data obtained in the eight patients examined.

Patients No.	1	2	3	4	5	6	7	8
Uptakes % administered Dose	19.03	44.42	31.55	21.58	25.33	21.79	44.24	36.94
	18.55	43.85	30.61	21.80	24.70	22.73	45.27	38.09
	18.11	44.27	32.05	21.38	24.77	22.61	43.00	38.38
	18.48	44.28	30.55	20.92	23.35	21.46	42.98	38.56
	18.43	45.62	29.88	20.57	25.33	22.06	43.29	37.49
	18.82	45.12	28.91	20.61	25.08	23.28		38.64
	19.06	46.02	30.98	20.24	25.72	23.27		
	18.26	42.80	30.41	21.81	25.38	22.89		
	18.27	42.84	31.47	20.31	25.34	22.26		
MEAN	18.61	44.52	30.62	21.05	25.01	22.42	43.75	37.93
S.D. ±	0.36	1.16	0.94	0.60	0.65	0.69	0.99	0.65
Max. ± Dev. -	0.50	1.72	1.71	0.81	1.66	0.96	1.52	1.01

The pooled standard deviation for the group was ± 0.77 and the maximum deviation that occurred was ± 1.72 units of uptake. The pooled standard deviation may be considered as the probable standard variation that may occur in any one patient to be examined by this method.

---

(1) Thyroid Radioiodine Uptake measurements a Standard System for Universal Intercalibration. ORINS - 19, Biology and Medicine, 1959.

THE EFFECT OF RADIATION THERAPY ON GASTROINTESTINAL ABSORPTION OF I-131 OLEIC ACID IN HUMANS

Drs. Sergio Irizarry, Clinical Applications Division, PRNC
A.A.Cintrón Rivera, Department of Medicine, University Hospital
Víctor Marcial, Radiotherapy and Cancer Division, PRNC
Miss Myrna Rivera, Clinical Applications Division, PRNC
Miss Zenaida Frías, Radiotherapy and Cancer Division, PRNC
Mrs. Carmen C. Villodas, Clinical Applications Division, PRNC

There are many factors which may induce malabsorption difficulties of the gastrointestinal tract. Direct irradiation of the intestine has been considered as one of the many factors that can affect profoundly the wall of this organ and its function of absorption for a variety of foodstuffs. The alteration of gastrointestinal absorption by direct radiation of the intestine has been documented in experimental animals (1,2,3,4,5,6,7). This problem has not been studied in humans as extensively as in animals. There is evidence for and against radiation induced malabsorption to radioactive labelled fat in the works published by Reeves et al (8,9) and Goodrich and Hickman respectively (10).

This study was done in 20 patients of the Isaac González Martínez Oncologic Hospital with cancer of the cervix uteri undergoing radiation therapy with a Cobalt 60, gamma source. This group of patients did not show evidence of malabsorption of I-131 oleic acid in the baseline study done prior to the onset of the radiation treatment. Nineteen patients with carcinoma at extra abdominal sites who were going to receive radiation therapy were studied as an external control. None of these patients demonstrated malabsorption defects when examined with I-131 oleic acid. I-131 oleic acid was administered in capsule form to the patient in the fasting state and total blood and protein bound radioactivity per estimated circulating total blood volume was assayed three to five hours after the administration of the radioactive material. The higher percentage of the dose in the circulating blood volume three to five hours after the administration of the tagged oleic acid was taken as the absorption value.

The normal baseline value for the group of patients with cancer of the cervix uteri was 13.6 $\pm$ 4.2% total radioactivity and 4.2 $\pm$ 2.2% protein bound radioactivity. The control group of patients with extra abdominal cancer showed a baseline value of 12.8 $\pm$ 3.4% total radioactivity and 3.8 $\pm$ 2.1% protein bound radioactivity.

The criteria used to establish malabsorption for a patient during the study period of eight weeks following the initiation of radiation treatment was a value two standard deviations below the average value for normal 13.6 - 2 x 4.2 or 5.2% dose per blood volume. The protein bound values had a high degree of correlation (90% for abnormals and 100% for normals), with total blood radioactivity values..

In the group of twenty patients with cancer of the cervix uteri, fourteen patients developed profound alterations of intestinal absorption as determined by the I-131 oleic acid technique. These alterations occurred at different intervals: three occurred two weeks after the beginning of radiotherapy, eight in the fourth week, seven in the sixth week, and nine in the eighth week.

The frequency of alterations in the rates of absorption that could be judged abnormal by this technique was present one or more times: it occurred once in six patients; twice in four patients; three times in three patients and four times in one patient. In the external control group of patients the alteration in the rate of absorption that could be considered abnormal occurred only once on three patients.

A simultaneous Vitamin A absorption study was attempted in some of these patients in collaboration with Dr. A. A. Cintrón Rivera. Serial examinations were not done in enough numbers on these patients to permit satisfactory analysis. Thirteen patients were re-examined sometime during the study period; eight patients once; two patients twice; one patient three times and two patients four times. Abnormal vitamin A tolerance curves were observed on seven patients four of which were in the following six weeks. No good correlation was found between I-131 oleic acid and vitamin A since five abnormal vitamin A curves correlated with eleven abnormal oleic acid tests; and five abnormal oleic acid values correlated with nine abnormal vitamin levels. The following table shows the lack of correlation:

Abnormals for oleic acid and normal for vitamin A	6
Abnormals for vitamin A and normals for oleic acid	4
Abnormals for oleic acid and vitamin A	5
Normals for oleic acid and vitamin A	8

The evidence found in this study favors the conclusion of Reeves and co-workers (11,12) who claim that radiation alters gastrointestinal absorption of I-131 labelled fats and is at variance with the evidence given by Goodrich and Hickman (13) who found no evidence of malabsorption in patients radiated with a Cobalt 60 gamma source.

Preliminary data on vitamin A absorption in a limited number of observations on some of these patients is also suggestive of impairment of gastrointestinal function by radiation. Low correlation between vitamin A and oleic acid is not disturbing because it is probable that both substances are not necessarily absorbed in the same way (14, 15).

REFERENCES

1. Walsh, David: "Deep Tissue Traumatism from Roentgen Ray Exposure" Brit. M. J. 2: 272: 1897.

2. Warren, S.L. and Whipple, G.H.: "Roentgen Ray Intoxication - Bacterial Invasion of Blood Stream as Influenced by X-ray Destruction of Mucosal Epithelium of Small Intestine" J. Exper. Med. 38: 713-723, Dec. 1923.

3. Wallace, W. S.: "The Intestine in Radiation Sickness. Gross Effect on the Small Intestine of Protracted Deep Pelvic Irradiation." JAMA 116: 583-588, February 1941.

4. Conrad, R. A.: "Effect of X-Irradiation on Intestinal Motility." Am. J. Physiol. 165: 375-385, May 1951.

5. Greenfield, M.A.: "Gastrointestinal Transit" Am. J. of Physiol. 169: 236-241, April 1952.

6. Buchwald, K. W.: "Influence of X-ray lesion of Intestinal Mucosa on Absorption of Glucose and Other Sugars." J. Exper. Med. 53: 827-833, July 1931.

7. Mead, J. F.: "Effect of X-irradiation upon Fat Absorption in the Mouse." J. of Nutrition 43: 485-499, April 1951.

8. Reeves, R. J.:"Fat Absorption from the Human Gastrointestinal Tract in Patients Undergoing Radiation Therapy." Radiology Vol. 73: 398-401, September 1959.

9. Reeves, et al: "Fat Absorption from the Human Gastrointestinal Tract in Patients Undergoing Teletherapy." The American Journal of Roentgenology, Radium Therapy and Nuclear Therapy, Vol. 89, No. 1, 122, 1963.

10. Goodrich, J. K.: "Oleic Acid I-131 Intestinal Absorption in the Pelvic Cobalt 60 Irradiation." The Am. J. of Roentgenology, Radium Therapy and Nuclear Medicine. Vol. 87, No. 1, January 1962.

11. See 8 above

12. See 9 above

13. See 10 above

14. Harris, S. Robert: Vitamins and Hormones, Vol. 18, p. 388, Academic Press 1960, New York.

15. Seshadri, Sastry et al: Indian J. of Medical Res. 45, 263, 1957.

PATOLOGIA TIROIDEA: CORRELACION ENTRE GAMMAGRAMA E HISTOPATOLOGIA

Por los Drs. Sergio Irizarry y Aldo E. Lanaro
División de Aplicaciones Clínicas, Centro Nuclear
de Puerto Rico

Mucho se ha publicado ya sobre las características del gammagrama de tiroides y su significado en el diagnóstico del cáncer de esa glándula. La correspondencia entre la actividad de una zona, nodular o no, y la anatomía patológica de ella ha sido objeto de numerosos estudios estadísticos.

Ya en el año 48 Feitelberg y colaboradores hacían mediciones localizadas con un tubo de Geiger Muller blindado con plomo para dejarle un pequeño ángulo de abertura, tratando de comparar lo que llamaban perfil de actividad con las características anatomo-patológicas de las distintas zonas. Ellos describen ya, la causa que todavía actualmente consideramos como la más importante en la falta de correspondencia entre baja actividad y células indiferenciadas, que es la superposición de planos de distinta intensidad de función que puede simular función normal donde existe una zona fría. De cualquier manera ellos describieron el método como de utilidad para la sospecha de tejido neoplásico.

Este método se vió muy simplificado con la introducción de los "scanners" que realizan automáticamente la medición por zonas. En 1952 Baher y colaboradores describen la relación entre anomalidades morfológicas y la imagen del gammagrama.

A partir de entonces se han sucedido los trabajos donde cada Centro de aplicación de radioisótopos presenta su experiencia y los resultados estadísticos obtenidos.

Entre ellos podremos citar los de:

Perlmutter, Slater y Attie del año 1954 que en 85 nódulos solitarios de 24 calientes ninguno es maligno, en cambio entre los tibios lo es el 20% y entre los fríos el 32%.

Johnson y Beierwaltes en 1955 que hallaron 31% de carcinomas en nódulos fríos, 10% en los tibios y ninguno en los calientes sobre 44 casos en total.

Greene en 1947 acepta siendo, dice, muy conservador entre los fríos el 20% de cáncer y llamando la atención sobre la posibilidad de que el tejido funcionante cubriendo la neoplasia de un nódulo tibio o caliente para lo cual sugiere se haga inhibición con tiroxina para ver si son independientes.

Groesbeck que sobre 253 casos operados da entre los eufuncionantes 3,6 de malignidad, entre los hipofuncionantes 14,2 y 0% para los hiperfuncionantes.

Meadows en 1961 que haciendo diferencia entre nódulos no funcionantes e hipofuncionantes dice que entre los primeros la incidencia de cáncer es del 58% en 24 casos.

Hasta llegar hasta las más recientes publicaciones de Rose en 1963 y Dische en 1964, entre otros, que dan una correspondencia semejante entre hipofuncionante y carcinoma.

Esta comunicación, no trae ninguna novedad en este campo, tiene por objeto solamente presentar nuestra experiencia y los resultados obtenidos en este tema en la División de Aplicaciones Clínicas del Centro Nuclear de Puerto Rico.

Se han repasado 543 gammagramas de tiroides que se han realizado en esta División durante los años 1962, 63 y primera mitad del 64.

Tomando el total de los pacientes los diagnósticos semiológicos permiten agruparlos en la siguiente manera:

Diagnóstico	Núm. Casos	%
Nódulo único	247	45
Bocio difuso	74	13
Cáncer de Tiroides	66	12
Bocio polinodular	47	9,5
Tiroiditis	12	2,5
Restos de conducto tirogloso	9	2
Sin diagnóstico previo	88	16

El estudio de los gráficos obtenidos en ese grupo de enfermos lleva a hacer la siguiente clasificación.

Diagnóstico	Núm. Casos	%
Nódulos fríos	105	19
Nódulos tibios	114	21
Nódulos calientes	17	3
Captación uniforme	143	26
Captaciones irregulares no clasificables	164	31

Entre los de captación uniforme se comprenden bocios difusos y nódulos tibios que no habiendo sido marcados previamente no pueden diferenciarse por el gammagrama del resto del tejido glandular. El último grupo comprende de captaciones irregulares y en su mayor parte pacientes que habían sido operados previamente, que tenían algún problema de cuello que merecía investigarse desde el punto de vista tiroideo sin ser un proceso glandular, que tenían captación en general muy baja por diferentes motivos no siendo el "scanning" demostrativo, etc.

Para realizar estos estudios se dispone de dos aparatos Nuclear Chicago. Uno con un cristal de 2 x 2 pulgadas y un colimador en panal de abeja de 19 orificios con foco de 1 3/4". Y el otro con un dispositivo para "fotoscanning" al cual en la actualidad se le está agregando un tubo de rayos X para hacer placas de localización simultáneas, que tiene cristal de 3 x 3 pulgadas con foco de 2 3/4 pulgadas, con un gran blindaje y con colimador semejante al anterior de 19 orificios. Ambos con el analizador electrónico correspondiente.

Se coloca al paciente acostado con un almohadón bajo los hombros, habiéndose dado 24 horas antes una dosis de alrededor de 50 a 100 uc de I-131.

Se proyecta la imagen de la tiroides, con sus anormalidades, y el hioides y la horquilla esternal como puntos de referencia, sobre una hoja de pliofilm colocada horizontalmente sobre el cuello y esa imagen se transporta sobre el papel receptor del "scanning" para localizar.

De todos esos pacientes estudiados se han seleccionado 64, que habiendo realizado tratamiento quirúrgico tienen además efectuado el exámen anatomo-patológico de la pieza correspondiente.

Entre ellos por el gammagrama podemos citar:

Nódulos fríos	31
Nódulos tibios	21
Nódulos calientes	4
Captación general baja	5
Captación irregular	3

Por otra parte la anatomía patológica señala:

Procesos malignos	23	(36%)
Procesos benignos	32	(50%)
Tiroiditis de Hashimoto	4	
Diagnósticos varios	5	

Entre los benignos podemos diferenciar 26 adenomas y 6 quistes hemorrágicos.

La correspondencia entre estas dos agrupaciones es la siguiente:

Nódulos fríos (31) :	Procesos malignos	15	(49%)
	Procesos benignos	12	(39%)
	Procesos no tiroideos (Metástasis de cáncer no tiroideo)	3	
	Hashimoto's	1	
Nódulos tibios (21)	Procesos malignos	7	(33%)
	Procesos benignos	13	(62%)
	Hashimoto's	1	

Nódulos calientes (4)	:	Procesos malignos	0
		Procesos benignos	3
		Hashimoto's	1

Estos resultados que en realidad no son tan definidos en la diferenciación como los que relatan otros autores son los que hemos obtenido en nuestro medio y están acordes con el concepto aceptado de que las causas más comunes de los nódulos fríos son el carcinoma y el quiste hemorrágico.

The Use of Thyroid Trapping of Iodide as an Indicator for Absorption I-131 Labelled Fat

I-131 labelled fats - triolein or free oleic acid have been useful tools of examination of gastrointestinal digestion and absorption in patients suspected of having pancreatic steatorrhea or the malabsorption syndrome. Although blood absorption curves have been used extensively, in practice they may be difficult to follow on all patients since a substantial number of patients with good intestinal absorption may absorb rather late, and be misrepresented as malabsorbers if the blood curve is not followed long enough. For the hospitalized patients a test may be run for over 10 hours if necessary but repeated numerous venipuctures make the test less worthwhile. In the ambulatory patient it is not possible to obtain samples beyond the 6th. hour for obvious reasons.

In most laboratories the period of peak value of the curve is taken as sufficient for valid results. This period falls within 4-6 hours after oral administration of the tracer dose. It is estimated that the error for this determination within 4-6 hours may be as high as 20% for individuals with no malabsorption defects. Because of these difficulties and to avoid repeated blood samplings over a period of many hours, a new approach was sought by using a known physiologic function (iodide trapping by the thyroid gland) as an indicator of another physiologic function - (gastrointestinal absorption).

Rationale and Method - I-131 labelled fats once absorbed are metabolized and I-131 set free as iodide. This I-131 labels the iodide pool from which approximately 1/3 is trapped by the thyroid gland and 2/3 excreted via the kidneys in a person with normal thyroid gland function. Regardless of the iodide trapping capacity of the thyroid gland, the fraction of I-131 set free from absorbed fats and accumulated by the gland when related to the rate of thyroid uptake of I-131 at 24 hours will give information about the total I-131 absorbed from fats which labelled the iodide pool. Thus if the predetermined thyroid 24 hours uptake for I-131 is 50%, and a capsule of I-131 labelled fat containing 100 uc is administered, and the amount of I-131 set free from fat and trapped by the thyroid gland is 25% of the administered dose of labelled fat, it is evident that the iodide pool must have contained 50 uc of I-131 set free from fat, from which 25 uc accumulated in the thyroid gland.

By comparing the amount of I-131 set free from absorbed fat and entering into the iodide pool to the amount administered the fraction absorbed can then be calculated:

$$\frac{\text{Iodide I-131 in the iodide pool}}{\text{I-131 labelled fat administered}} \times 100 = \%\ \text{I-131 fat absorbed labelling the iodide pool.}$$

In this example 50 uc I-131 were present in iodide pool and 100 uc were administered, the % absorption is 50%.

Results: A group of 21 healthy Puerto Rico Nuclear Center employees were investigated. Thyroid gland uptake of I-131 at 24 hours was determined on all subjects. The next morning after noting residual activity in the thyroid gland, a dose of I-131 labelled fat was administered, blood samples were drawn 3 and 5 hours later for assay and a thyroid uptake of the I-131 set free from fat was determined 24 hours later. The assumption was made for practical purposes, that the peak of iodide trapping occurs at or about 24 hours and that the day to day variation is not great, (in this laboratory about $\pm$ 4 units of uptake).

- The 24 hour radioiodine uptake was 21% $\pm$ 1.6.
- The 24 hour radioiodine (set free from fat) uptake was 13.7 $\pm$ 3.9.
- The ratio* of I-131 from fat uptake to predetermined I-131 thyroid uptake is 66.4 $\pm$ 17.9.
- Fat absorption - Blood curve - % dose per blood volume 13.4% $\pm$ 6.7.

* This ratio times 100 reflects the same magnitude as that of the above formula.

Application to patients: A group of 17 patients have been examined by this technique and results correlated with blood levels at 5 hours. Four patients out of 17 showed low blood levels at 5 hours, but all of them showed normal thyroid iodide levels from the I-131 set free from the absorbed labelled fat.

The technique can dissect out the group of late absorbers from the group of early absorbers, when blood samples are collected. More patients will be examined and special application of this technique should prove helpful in malnourished children and adults with various gastrointestinal disorders of digestion and absorption here in the tropics.

CANCER OF THE THYROID GLAND - Review of Seven Patients Treated with I-131.

The clinical records of seven patients from the I.G.M. Oncologic and University Hospitals were reviewed to summarize past experience in the treatment of thryoid carcinoma with I-131 during the past three years.

Prior to treatment the patients had complete clinical evaluations to determine the presence of residual thyroid tissue in the neck and metastases in bones and soft tissues. This was followed by radioisotope studies of the neck and other tissues to localize the areas with avidity for I-131. The procedure was carried out initially in all patients without the benefit of the thyroid stimulating hormone which increases the capacity of thyroid carcinoma to take up I-131. When the first attempt failed to localize I-131 containing cancer deposits, the procedure was then repeated with the aid of the thyroid stimulating hormone.

The therapy plan consisted of the oral administration of approximately 25 mc of I-131 to ambulatory patients, followed by clinical and radioisotopic examinations at monthly or bimonthly intervals. Treatment was repeated as necessary until all radioisotopic evidence of active metastases disappeared. After completion of a full course of therapy, follow-up was continued every three to six months.

Six of the seven patients were adults whose average age was 53 years, the oldest being 83. The seventh patient was a girl 16 years old. One patient was male and six were female. A mass in the neck was present in six patients; the disease was confined to the neck in only one patient while it was widely disseminated in the other six patients. Two of them had pathologic fractures of bone; two showed lung metastases, and two had both lung and bone metastases.

Four patients received only one dose of I-131 for an average of 25 mc. All of these four patients died within two years.

Three patients who are surviving received a full therapeutic dose for the specific indication for which it was administered:

(1) 13 mc I-131 given April 1961 to produce ablation of residual thyroid tissue in a patient with localized disease in the neck, whose disease had been treated and controlled by surgery.

(2) 105 mc I-131 given in five doses (July 1962 to February 1964) to a 16 year old girl with bilateral clinical and pulmonary metastases caused remission of all neck manifestations and the pulmonary lesions are now diminishing.

(3) 125 mc I-131 in seven doses (November 1960 - November 1961) given to a 63 year old female with multiple bone and soft tissue metastases and a pathologic fracture of the femur was followed by remission of all radioisotopically demonstrable metastases and healing of the fracture. A recurrence in September 1963 was treated with a dose 25 MC I-131.