Glucose Intolerance in the Carcinoid Syndrome

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SUMMARY

We assayed glucose tolerance and insulin secretion in ten patients with metastatic carcinoid tumors and the carcinoid syndrome ("active tumors") and in seven patients with metastatic carcinoid tumors without the carcinoid syndrome ("inactive tumors"). The patients with "active tumors" had elevated serum serotonin levels while the patients with "inactive tumors" had normal serum serotonin levels. Of the ten patients with "active tumors," five had diabetic and three had borderline intravenous glucose disposal rate constants (K_G = 0.88 ± 0.07, M. ± S.E.M.). Their K_G was significantly lower ($p<0.01$) than a group of age-matched normals. All of the patients with "inactive tumors" had normal K_G values (K_G = 1.67 ± 0.24). Their K_G did not differ from that of age-matched normal subjects. Both groups of carcinoid patients had a comparable decrease in their insulinogenic index. Two days' administration of the serotonin antagonist cyproheptadine (Cypro) to eight of the patients with "active tumors" resulted in a significant increase in the "insulinogenic index" (50 per cent) but a nonsignificant increase in the K_G (12 per cent). Administration of p-chlorophenylalanine, a compound that blocks serotonin synthesis, resulted in an increase in both the K_G (60 per cent) and the "insulinogenic index" (55 per cent). The insulin half-life ($t_{1/2}$) of patients with "active tumors" (6.1 ± 0.4 min.) did not differ from the $t_{1/2}$ of normal subjects (6.6 ± 0.4 min.), suggesting that the decreased plasma insulin levels following intravenous glucose were due to impaired insulin secretion rather than accelerated insulin destruction. Seven of the patients received treatment with the antitumor agent streptozotocin (Strepto). The patients received cumulative doses of from 70 to 300 mg. of Strepto per kilogram body weight with no impairment in glucose tolerance or insulin secretion. We conclude that there is high incidence of glucose intolerance (80 per cent) and impaired insulin secretion in patients with the carcinoid syndrome and that serotonin plays a role in producing these alterations. DIABETES *24*:664-71, July, 1975.

Studies from our laboratory have shown that serotonin is a potent inhibitor of insulin secretion in golden hamsters, rabbits, and mice.[1,2] In 1972 we reported that two patients who had metastatic carcinoid tumors with the carcinoid syndrome had impaired insulin secretion and decreased glucose tolerance.[3] This was attributed to their hyperserotoninemic state, for their insulin secretion and glucose tolerance improved when serotonin production by the tumor was reduced with streptozotocin chemotherapy.[4,5] Our observations have now been extended to eighteen patients with metastatic carcinoid tumors. The purpose of this report is to further characterize the glucose intolerance associated with metastatic carcinoid tumors.

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MATERIALS AND METHODS

Experimental Subjects

Carcinoid patients. The study group consisted of eighteen patients with carcinoid tumors that had metastasized to the liver. In all patients the diagnosis of a carcinoid tumor was established by histologic examination of the tumor. The first group of patients was comprised of ten men (patients 1 to 10) and one woman (patient 11). The mean age of this group was sixty years (table 1). The carcinoid tumors of this first group of subjects were producing serotonin, and these patients had the carcinoid syndrome. Nine of the patients had primary tumors that originated in the ileum or jejunum. Patients 1 and 9 had primary tumors of bronchial origin. The second group of patients was comprised of six men (patients 12 and 14 through 18) and one woman (patient 13). The mean age of this group was forty-five years (table 2). The carcinoid tumors of the second group did not produce serotonin. Three of the patients had primary tumors of bronchial origin (patients 12, 15, and 18), three had

TABLE 1

Results of intravenous glucose tolerance tests in patients with carcinoid tumors and the carcinoid syndrome

Patient	Age (yr.)	Fasting Plasma Glucose (mg./dl.)	Fasting Plasma Insulin (μU./ml.)	KG	ΔI (μU.-min./ml.)	ΔG (mg.-min./dl.)	ΔI/ΔG	Serum Serotonin (μg./ml.)	Urinary 5-HIAA (mg./d.)
1	60	121	14	0.60	999	5,301	0.19	*	550
2	53	83	7	0.97	616	4,689	0.13	3.28	433
3	46	72	4	1.11	2,535	4,374	0.58	*	378
4†	49	78	4	0.86	1,178	4,277	0.28	1.49	185
5	69	95	16	0.85	1,066	5,989	0.18	2.60	84
6	54	144	29	0.54	762	4,596	0.17	0.39	80
7	65	83	12	0.70	1,355	5,433	0.13	0.60	70
8	65	78	<2	0.85	2,400	5,851	0.41	1.85	29
9	63	82	11	0.93	1,384	5,864	0.24	2.13	25
10	57	90	12	1.06	1,198	3,656	0.33	0.62	22
11	67	66	4	1.23	2,920	7,529	0.39	*	22
Patients									
Mean	60	90	10	0.88§	1,524	5,328‡	0.28§	1.64	169
±S.E.M.	±2.3	±6.9	±2	±0.07	±253	±342	±0.05	±0.42	±64
Normal Subjects								Normal Range	
Mean	61	79	13	1.90§	2,202	3,642‡	0.63§	0.05-0.32	2-9
±S.E.M.	±1.6	±2.9	±3	±0.35	±566	±508	±0.16		

*Not measured
†Not included in mean calculation because of dexamethasone therapy.
‡Means differ ($p<0.05$).
§Means differ ($p<0.01$).

primary tumors of rectal origin (patients 13, 16, and 17) and one had a primary tumor of unknown origin (patient 14). In addition to a metastatic carcinoid tumor, patient 15 also had a metastatic melanoma. The group with the carcinoid syndrome is referred to as having "active" carcinoid tumors and the group without the syndrome as having "inactive" carcinoid tumors.

With the exception of two patients, all the carcinoid patients were within 15 per cent of their ideal body weight.[6] Patient 4 was 25 per cent above his ideal body weight and patient 6 was 52 per cent over his ideal body weight. Patients 10 and 11 each had one parent with maturity-onset diabetes mellitus, while the remaining patients did not have a family history of the disease. None of the patients were azotemic, and only one patient was receiving a medication that could alter glucose tolerance. Patient 4 was

TABLE 2

Results of intravenous glucose tolerance tests in patients with carcinoid tumors without the carcinoid syndrome

Patient	Age (yr.)	Fasting Plasma Glucose (mg./dl.)	Fasting Plasma Insulin (μU./ml.)	KG	ΔI (μU.-min./ml.)	ΔG (mg.-min./dl.)	ΔI/ΔG	Serum Serotonin (μg./ml.)	Urinary 5-HIAA (mg./d)
12	57	90	6	1.34	1,332	3,495	0.38	0.26	3.6
13	59	71	<2	1.92	2,534	4,901	0.52	0.13	3.0
14	48	94	4	1.55	948	5,442	0.17	0.01	3.0
15	33	90	8	1.14	1,462	4,441	0.33	0.03	2.9
16	28	82	7	1.40	1,292	5,141	0.25	*	1.4
17	34	61	<2	1.32	24	3,729	0.04	0.0	1.1
18	54	56	<2	3.02	296	1,966	0.15	*	0.6
Patients									
Mean	45	78	4‡	1.67	1,126†	4,159	0.26†	0.11	2.2†
± S.E.M.	±5	±6	±1.0	±0.24	±312	±454	±0.06	±.05	±0.4
Normal Subjects								Normal Range	
Mean	42	86	10‡	1.93	2,700†	4,023	0.68†	0.05-0.32	2-9
±S.E.M.	±3.3	±3.1	±1.6	±0.24	±613	±207	±0.157		

*Not measured.
†Means differ ($p<0.05$).
‡Means differ ($p<0.01$).

receiving 0.75 mg. of dexamethasone three times a day for the five months prior to our studies for the treatment of pulmonary emphysema.

The patients were hospitalized during the study, the majority in the Duke University Medical Center Clinical Research Unit, although a small number were observed in the general medical wards of the Durham Veterans Administration Hospital. Some of the patients were hospitalized at monthly intervals in the Clinical Research Unit. After the tolerance tests and urine collections were completed some patients received a monthly intravenous infusion of streptozotocin for treatment of their carcinoid tumor.[5] Many had subjective and some had objective improvement in their condition (fall in serum alkaline phosphatase and urinary 5-hydroxyindoleacetic acid [5-HIAA]).

Normal volunteers. The normal volunteers, who underwent glucose tolerance tests, consisted of ten men and two women ranging in age from thirty-two to sixty-seven years. Two of these had one parent with maturity-onset diabetes mellitus. With the exception of one who was 18 per cent above his ideal body weight, all the volunteers were within 15 per cent of their ideal body weight. Six of the volunteers (mean age sixty-one years) were selected to match the patients with "active" carcinoid tumors, and the other six (mean age forty-one years) were selected to match the patients with "inactive" carcinoid tumors.

Test procedure. After their informed consent was obtained for the studies, the subjects were admitted to the Clinical Research Unit at the Duke University Medical Center. Hospital diets were matched as closely as possible to home diets, and a normal level of physical activity was encouraged. The patients consumed at least 200 gm. of carbohydrate for the three days preceding the tests. On the morning of the tolerance tests the patients remained at bedrest. The patients had been fasted overnight. A 19-gauge scalp vein needle was placed in an antecubital vein and irrigated with heparinized saline. After a forty-five-minute stabilization period, baseline blood samples were obtained. For the intravenous tolerance test (IVGTT) the subjects received 25 gm. of a 50 per cent dextrose solution over 2.5 min. Heparinized blood samples were drawn at 2.5, 5, 10, 15, 20, 25, 30, 35, 40, 50, 60, 90, and 120 min. For the insulin tolerance test, crystalline pork insulin was injected into an antecubital vein and heparinized blood samples collected at five-minute intervals for one hour through an indwelling needle in the opposite arm. The subjects received 0.1 U. of crystalline pork insulin per kilogram body weight.

After a control IVGTT was completed, eight of the patients with the carcinoid syndrome received a course of the serotonin antagonist cyproheptadine (Cypro). Cypro tablets were administered every six hours beginning at 12 noon of the day of the control tolerance test for a total of eight doses. Conventional doses of Cypro (4 mg. per dose) were employed. The last medication dose was given at 6 a.m. on the study day, and the tolerance test was started at 8 a.m.

After the control IVGTT was completed, five of the patients were treated with 1 to 2 gm. per day of the tryptophan hydroxylase inhibitor p-chlorophenylalanine (PCPA). The IVGTT was repeated after this medication had reduced serotonin production by the carcinoid tumor.

Analytic methods. Plasma insulin was determined by a double-antibody modification of a previously described radioimmunoassay method using ^{125}I-labeled pork insulin as tracer and human insulin as a standard.[7] Plasma glucose was measured by a glucose oxidase method.[8] 5-Hydroxyindoleacetic acid excretion (5-HIAA) was measured on twenty-four-hour urine samples by a colorimetric method.[9] Each value is the mean of two or more consecutive twenty-four-hour urine collections. Serum serotonin was measured with a fluorometric method.[10] The normality of the intravenous glucose tolerance tests was judged by previously published criteria that have been slightly modified in light of the experience of our laboratory.[11,13] The K_G ranges used are normal >1.1, borderline 0.9 to 1.1, and diabetic <0.9. Insulin secretion in response to intravenous glucose was expressed as the area under the plasma insulin curve above the fasting level from zero to sixty minutes, and plasma glucose elevation in response to intravenous glucose was expressed as the area under the plasma glucose curve above the fasting level from zero to sixty minutes. For each IVGTT, the cumulative insulin output per unit of secretory stimulus, "the insulinogenic index," ($\Delta I/\Delta G$) was calculated from zero to sixty minutes.[14] This was done by dividing the area circumscribed by the insulin curve, i.e. the increment above fasting level (ΔI), by the corresponding area circumscribed by the glucose curve (ΔG). The glucose disposal constants following intravenous glucose (K_G) or intravenous insulin (K_I) administration were calculated from the formula $K = -230.3\ b$, where b is the slope of the regression line for the log of the plasma glucose versus time. These rate constants were calculated from the linear segment of the curve by the method of least squares. The glucose disposal rate constants represent the rate of fall of the plasma glucose in per cent per

minute. To determine the plasma insulin half-life ($t\frac{1}{2}$), each plasma sample obtained after intravenous pork insulin was assayed for immunoreactive insulin by use of a crystalline pork insulin standard. When the plasma insulin is plotted on a log scale and the time after insulin injection on a linear scale the insulin disappearance is linear between five and twenty-five minutes.[15] The insulin $t\frac{1}{2}$ was determined by inspection of this phase of the curve.

Chemicals. Cyproheptadine (Periactin, Merck Sharpe and Dohme, West Point, Pennsylvania) was purchased from commercial sources. D, L-Parachlorophenylalanine (Fenclonine) was supplied by Dr. Mary Ghaly, of Charles Pfizer and Company (Groton, Connecticut). The streptozotocin was supplied by Dr. Milan Slavik, of the Cancer Therapy Evaluation Branch, National Cancer Institute (Bethesda, Maryland).

Statistical methods. The data were analyzed by standard statistical methods.[16] The difference between groups was established by Student's *t*-test or the paired *t*-test. The Pearson product correlation coefficient (r) was used for correlation analysis.

RESULTS

Glucose tolerance and insulin secretion in patients with carcinoid tumors. Table 1 shows the relationship between glucose tolerance, insulin secretion, and tumor serotonin production in eleven patients with the carcinoid syndrome. The patients are arranged in the order of decreasing 5-HIAA excretion. With the exception of patients 1 and 6, all of the carcinoid subjects have a normal fasting plasma glucose and plasma insulin levels. These two subjects, who have the most marked impairment of intravenous glucose tolerance, have elevated fasting plasma glucose concentrations. Subject 6, who was the only significantly overweight patient in the study, also had an elevated fasting plasma insulin concentration. Six patients had diabetic K_G values (<0.9), three patients had borderline K_G values (0.9-1.1), and only two patients had normal K_G values (>1.1). The correlation between K_G and serum serotonin ($r = -0.48$) and K_G and urinary 5-HIAA excretion ($r = -0.16$) was not statistically significant.

At the bottom of table 1, the mean data of the patients with the carcinoid syndrome are compared with the mean data of a group of age-matched normal volunteer subjects. There is no significant difference in the mean age, fasting plasma glucose concentration, fasting plasma insulin concentration, or ΔI of the two groups. The mean K_G and the $\Delta I/\Delta G$ of the carcinoid patients are lower than those of the normal volunteers, while the mean ΔG of the carcinoid patients is greater than that of the normal volunteers.

Table 2 shows the relationship between glucose tolerance, insulin secretion, and serotonin production in seven patients with metastatic carcinoid tumors without the carcinoid syndrome ("inactive tumors"). Although these subjects are also arranged in order of decreasing 5-HIAA excretion, they all had normal 5-HIAA excretion and normal serotonin levels. With the exception of patients 17 and 18, all the patients with "inactive" carcinoid tumors had fasting plasma glucose, fasting plasma insulin, K_G, and ΔI values that were in the normal range. Patients 17 and 18 had decreased fasting plasma glucose and plasma insulin concentrations and the lowest ΔI values in the "inactive tumor" group. However, the K_G values of patients 17 and 18 were within the normal range. It is of interest that these two subjects had the largest mass of metastatic tumor of any patients in this study.

At the bottom of table 2, the mean data of the patients with "inactive" carcinoid tumors are compared with the mean data of a group of age-matched normal volunteer subjects. There is no significant difference in the mean age, fasting plasma glucose, K_G, and ΔG of the two groups. The mean fasting plasma insulin concentration, ΔI, and $\Delta I/\Delta G$ of the carcinoid patients are lower than those of the normal subjects.

It is of interest to compare the mean values of the patients with the carcinoid syndrome (table 1) with the mean values of the patients with "inactive" carcinoid tumors (table 2). The carcinoid-syndrome patients were older and had lower K_G values, higher 5-HIAA excretion, and higher serum serotonin concentrations than the patients with "inactive" tumors. The two groups did not differ in mean fasting plasma glucose concentration, fasting plasma insulin concentration, ΔI, ΔG, or $\Delta I/\Delta G$.

To rule out the possibility that the decrease in plasma insulin concentration after glucose stimulation in patients with carcinoid tumors is due to accelerated plasma insulin disappearance rather than to impaired insulin secretion, we measured the disappearance of exogenous insulin as described in Methods. The plasma insulin half-life ($t\frac{1}{2}$) of seven patients with the carcinoid syndrome (6.1 ± 0.4 min., M. $\pm$S.E.M.) did not differ from the insulin $t\frac{1}{2}$ of normal subjects (6.6 ± 0.4 min.). Two patients with inactive carcinoid tumors who were studied also had normal insulin $t\frac{1}{2}$.

Effect of Cypro on glucose tolerance and insulin secretion. Table 3 shows the effect of two days of administration

of the serotonin antagonist Cypro on insulin secretion and intravenous glucose tolerance in patients with the carcinoid syndrome.[17] Although five of the eight subjects studied had an increase in KG following Cypro, the mean increase of 12 ± 11.6 per cent (M. ±S.E.M.) was not significant. Although six of the eight subjects had an increase in ΔI following Cypro administration, the mean increase of 33 ± 14.6 per cent failed to achieve statistical significance. Six of the eight subjects had an increase in ΔI/ΔG, and the 50 ± 13.8 per cent mean increase in ΔI/ΔG was significant ($p<.05$).

Effect of PCPA on glucose tolerance and insulin secretion. Figure 1 depicts the results of administration of the tryptophan hydroxylase inhibitor PCPA on glucose tolerance and insulin secretion of five patients with the carcinoid syndrome.[18] Prior to the second IVGTT the patients were receiving PCPA for the following durations: patient 4—thirty-two weeks; patients 8,9, and 10—ten weeks; and patient 5—two days. PCPA administration resulted in a 47 ± 9.6 per cent decrease in 5-HIAA excretion ($p<.01$), a 60 ± 20.7 per cent increase in KG ($p<.05$), and a 47 ± 9.6 per cent increase in ΔI/ΔG ($p<.05$).

Effect of streptozotocin (Strepto) on insulin secretion and glucose tolerance. Table 4 depicts the results of chronic streptozotocin (Strepto) therapy on glucose utilization and insulin secretion following an intravenous glucose injection in seven patients with the carcinoid syndrome. The tolerance tests were done prior to the monthly Strepto infusion (2 gm.); the last previous streptozotocin infusion was at least one month prior to the IVGTT. Despite therapy with 6 to 18 gm. of streptozotocin, none of the seven patients had a systematic alteration in KG, ΔI, or ΔI/ΔG.

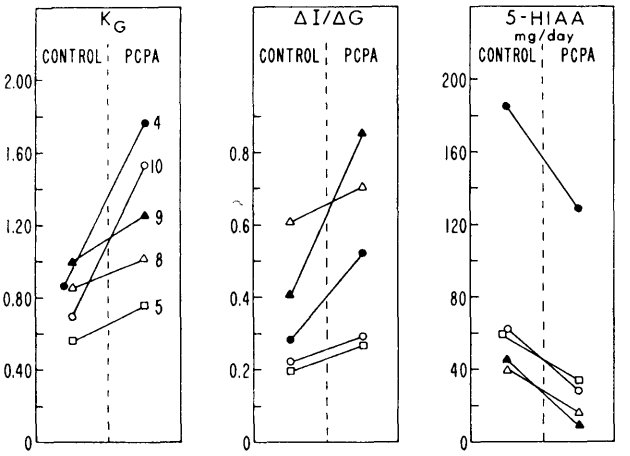

FIG. 1. Effect of PCPA on KG, ΔI/ΔG, and urinary 5-HIAA excretion of five patients with the carcinoid syndrome.

DISCUSSION

Glucose intolerance is frequently associated with pheochromocytoma, and this carbohydrate intolerance is in part due to inhibition of pancreatic insulin secretion by the catecholamines released from the pheochromocytoma.[19] The characteristics of the inhibition of insulin secretion by serotonin and catecholamines are quite similar.[20] One might predict that a hyperserotoninemic state, such as the carcinoid syndrome, may be associated with decreased insulin secretion and impaired glucose tolerance. A number of investigators have suggested that there may be an association between the carcinoid syndrome and diabetes mellitus.[21,22] Because diabetes mellitus is a common disease, Keen suggested that its concomitant presence in patients with the carcinoid syndrome may be a chance association.[23] In 1972 we reported that the impaired insulin secretion and glucose tolerance of two patients with the carcinoid syndrome was improved when serotonin production by the tumor was reduced with Strepto therapy.[3] This improvement in glucose tolerance might also be due to a decrease in the tumor mass.

TABLE 3

Effect of the serotonin antagonist Cypro on intravenous glucose tolerance tests in patients with the carcinoid syndrome

	KG			ΔI (μU.-min./ml.)			ΔI/ΔG		
Patient	Control	Cypro	Change (%)	Control	Cypro	Change (%)	Control	Cypro	Change (%)
1	0.66	0.91	38	1,090	818	−25	0.18	0.16	−11
2	0.97	0.99	2	616	823	34	0.13	0.21	62
3	0.98	0.75	−23	1,096	996	−9	0.26	0.26	0
4	0.86	1.06	23	1,178	2,529	115	0.28	0.54	93
6	0.54	0.74	37	762	1,089	43	0.17	0.22	29
9	0.93	0.72	−29	1,384	1,939	40	0.24	0.41	71
10	1.06	1.71	61	1,198	1,569	31	0.33	0.60	82
11	1.23	1.05	−15	2,920	3,966	36	0.39	0.68	74
Mean	0.90	0.99	12	1,281	1,641	33	0.25	0.39	50*
±S.E.M.	±0.08	±0.11	±11.6	±250	±409	±14.6	±0.03	±0.07	±13.8

*Cypro significantly different from control ($p<0.05$)

TABLE 4

Effect of streptozotocin therapy on intravenous glucose tolerance in patients with carcinoid tumors

Patient	Cumulative Dose Strepto-zotocin (gm.)	KG	ΔI	ΔI/ΔG	5-HIAA mg./d.
1	0	0.60	999	0.19	551
	2	0.78	932	0.21	270
	4	0.89	1,147	0.22	197
	6	0.75	1,218	0.29	387
	8	0.83	1,436	0.35	297
	10	0.97	1,788	0.44	385
2	0	0.97	616	0.13	433
	2	1.37	1,288	0.27	434
	8	0.85	927	0.19	445
3	0	1.11	2,535	0.58	378
	2	1.41	4,995	1.48	312
	6	1.22	2,554	0.64	385
	8	1.74	3,580	0.81	260
6	0	0.54	762	0.17	80
	12	0.60	868	0.17	80
8	0	0.85	2,400	0.41	29
	12	0.85	3,246	0.62	34
9	0	0.93	1,384	0.24	25
	2	1.02	938	0.20	22
	12	1.14	1,689	0.31	34
	18	0.99	2,135	0.41	45
10	0	1.06	1,198	0.33	22
	6	1.58	880	0.30	41

In the present study we have determined glucose tolerance in eleven patients with metastatic carcinoid tumors and the carcinoid syndrome. Although ten of the patients were not taking medications known to interfere with glucose tolerance and the group did not have a striking family history of diabetes, 80 per cent of these patients had borderline or diabetic tolerance to intravenous glucose with an impairment in insulin secretion. This could not be attributed to the patients' mean age of sixty, for their glucose utilization and insulin secretion were significantly impaired when compared with those of a group of healthy volunteers with a comparable age and sex distribution.

To determine if the impaired glucose utilization of patients with the carcinoid syndrome was due to hyperserotoninemia or to some other metabolic alteration produced by metastatic tumor, we studied seven patients with metastatic carcinoid tumors that were not producing serotonin. The glucose utilization of the patients with "inactive" tumors did not differ from the KG of a group of healthy volunteers with a comparable age and sex distribution. The KG of patients with the carcinoid syndrome was significantly lower than the KG of patients with "inactive" carcinoid tumors.

To determine if the alterations in insulin secretion and glucose utilization in patients with carcinoid syndrome are due to serotonin, we repeated the IVGTT after blocking the serotonin receptors with the serotonin antagonist Cypro.[17] This resulted in a significant increase in ΔI/ΔG and a modest but not statistically significant increase in KG. The increase in KG might have achieved statistical significance if we gave a more prolonged course of Cypro. In normal subjects, Cypro administration for two days does not alter ΔI/ΔG, ΔI, or KG.[24] We also repeated the IVGTT after decreasing the synthesis of serotonin with PCPA. In the doses used in this study PCPA is a specific inhibitor of tryptophan hydroxylase.[18] Decreased serotonin production resulted in a significant increase in KG and ΔI/ΔG. Neither Cypro nor PCPA has an antineoplastic effect, and thus the changes produced by these drugs suggests that serotonin contributes to the impaired insulin secretion and glucose utilization in the carcinoid syndrome.

If serotonin is responsible for the impaired glucose utilization and insulin secretion in the carcinoid syndrome, one might expect to see a significant negative correlation between serum serotonin concentration (or 5-HIAA excretion) and KG, ΔI, and ΔI/ΔG. However, the majority of serum serotonin is bound to circulating platelets and only a small amount of serotonin is "free" in the plasma. This small and variable amount of free plasma serotonin may be the physiologically active serotonin fraction.[25] It is technically difficult to measure free plasma serotonin, and we, like most investigators, measured total serum serotonin and total 5-HIAA excretion. The fact that the negative correlation did not achieve statistical significance in a small series of eleven patients is not totally unexpected.

The patients with "inactive" carcinoid tumors had normal KG values, but, surprisingly, they had decreased ΔI and ΔI/ΔG. This might occur if they had increased sensitivity to endogenous insulin, for Thorell has demonstrated a feedback system that calibrates the beta-cell response to correspond to the sensitivity of the peripheral tissues.[26] These findings differ from some previous studies on glucose utilization in patients with cancer. Rhodenberg noted essentially normal oral glucose tolerance in patients with cancer,[27] Glicksman and Rawson reported that patients with cancer had an impaired response to oral glucose,[28] and Marks and Bishop noted that cancer patients had a diabetic response to intravenous glucose.[29] The latter investigators also noted that patients with cancer have impaired sensitivity to in-

travenous insulin as manifested by decreased K_I values.[30] The present results differ from those of Marks and Bishop, for our patients with "inactive" metastatic carcinoid tumors had K_G values in the normal range. This difference is best explained by the fact that our patients had substantial amounts of metastatic tumor while the patients of Marks and Bishop had localized carcinoma amenable to curative therapy, lymphoma, or chronic leukemia. These patients thus had a smaller mass of neoplastic tissue than our patients. Large masses of tumor tissue can consume glucose[31,32] and inhibit gluconeogenesis.[32] Such patients can have normal intravenous glucose tolerance with a marked decrease in glucose-stimulated insulin secretion.[31] Patients 17 and 18 had the largest tumor masses in the "inactive" carcinoid group, and both had normal intravenous glucose tolerance, with markedly decreased insulin secretion (table 2). A larger mass of tumor tissue might thus improve glucose tolerance. This does not explain the differences between the "active" and "inactive" carcinoid patients that we noted, for the majority of the patients in the two groups had comparable masses of tumor tissue.

The carcinoid patients in the present study were treated with Strepto, and this allowed us to make some detailed observations on the effect of this drug on insulin secretion and glucose tolerance. Strepto, a broad-spectrum antibiotic with antitumor properties, causes selective pancreatic beta-cell destruction and diabetes in rats, mice, hamsters, dogs, monkeys, guinea pigs, and rabbits.[33,34] The drug has been used in the treatment of human islet-cell tumor[35] and in the treatment of metastatic carcinoid tumors.[4,5]

Our patients received monthly Strepto infusions ranging from 25 to 32 mg. of drug per kilogram of body weight. The cumulative dose during six to sixteen months of therapy ranged from 70 mg. to 300 mg. per kilogram of body weight. None of the patients that have received Strepto have developed impairment in insulin secretion or in glucose tolerance beyond the impairment they had prior to therapy.

There is considerable variability in species sensitivity to the diabetogenic effect of Strepto. In rats, a dose of 25 mg./kg. produces mild "chemical" diabetes, while a dose of 100 mg./kg. produces severe diabetes with ketonuria and insulin dependence.[36] The effect of Strepto in rats appears to be cumulative, for two injections of 25 mg./kg. three days apart produce severe diabetes.[36] Rhesus monkeys require 50 mg./kg. to produce diabetes,[37] while rabbits require 300 mg./kg. to produce consistent beta-cell lesions and diabetes.[34]

The present observations suggest that man is one of the more resistant species to the diabetogenic effects of Strepto. In general, our study is in agreement with other studies employing different dose schedules of Strepto.[4,38] Moertel et al. administered Strepto to patients with advanced gastrointestinal cancer.[4] They used doses of 500 mg./m.^{2}/day for five days or 1,000 mg./m.^{2}/week for four weeks. Eighteen of twenty patients treated with the daily regimen had transitory impairment of glucose tolerance, but only one patient of the twelve studied had a persistent diabetogenic effect at eight weeks. Eleven of sixteen patients treated on the weekly schedule had a transitory impairment of glucose tolerance, and only one of the six patients studied had a persistent diabetogenic effect at eight weeks. Two patients treated with three five-day courses had continued diabetic glucose tolerance, but neither exhibited symptomatic diabetes. Sadoff administered 50 to 600 mg./kg. of Strepto to fifteen patients with a variety of advanced neoplasms.[38] The patients were given 2,000 mg./m.^{2} at weekly intervals for from two to six weeks. One patient received repeated courses of therapy for a cumulative dose of 600 mg./kg. with no impairment in glucose tolerance. Minor to moderate impairment of glucose tolerance developed in nine patients after treatment, but insulin was required in none. Three patients showed improved glucose tolerance and three patients showed no change in tolerance. It is of interest that the monthly dose schedule of Strepto used in our study produced no impairment of insulin secretion or glucose tolerance. It is also of interest that we were able to administer Strepto to patients with pre-existing glucose intolerance without further impairing their glucose tolerance.

In conclusion, patients with metastatic carcinoid tumors and the carcinoid syndrome have a high incidence of glucose intolerance and impaired insulin secretion. This glucose intolerance is not explained solely by the presence of cancer or by the patients' age. Studies using Cypro and PCPA suggest that increased serotonin levels may play a role in the impaired carbohydrate tolerance. Finally, Strepto therapy for carcinoid tumors does not further impair the patients' glucose tolerance and insulin secretion.

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