carcinoma of the cervix, the amount of radiation delivered to the gonads makes preservation of ovarian function a near impossibility. The older literature affirms that even after radium therapy alone for cervical cancer continued ovarian activity as evidenced by regular menstruation was infrequent. Successful pregnancy after radium treatment for a malignant growth on the cervix is an extremely rare occurrence.

In the majority of cases reported before 1942 it was the omission of external radiation which permitted maintenance of genital function in these patients. In the case presented here, and also in the cases recently reported by Ivey (1963) and Whelton and McSweeney (1964), no external x-ray treatment was given.

One of the most critical physical laws which govern the amount of radiation delivered to a given point from a radio-active source is the inverse square law. The intensity of radiation decreases by the square of the distance from the source to the selected point. In the cases reported in the literature the preservation of ovarian function can be attributed in great measure to the increased distance from the radium sources at which the gonads were located because of intrauterine gestation, recent parturition or abortion, or a large exophytic growth. In the case reported by Whelton and McSweeney the radium application was made about eight weeks post-partum, and in Ivey's case there was a large exophytic growth. However, in the case presented here the growth was of an ulcerative type, and the radium application was made 18 months after the birth of the last child. The existence of amenorrhoea—for nine months in Ivey's case, 12 months in Whelton and McSweeney's case, and only two episodes of bleeding in about four years in our case—indicates the action of radiation on the gonads. In Ivey's and Whelton and McSweeney's cases the patients were young, being aged 21 and 26 years respectively, while our patient was about 31 years old when the radium was applied. For patients over 40, 1,000 r delivered at the ovaries is sufficient to induce the menopause. This dose is quite inadequate for a young woman, and 2,000 r delivered at the ovaries may well permit future ovulation.

The inverse square law also explains the presence of a functioning endometrium in these cases. The doses at the fundus may drop to 10% of that delivered at the cervix.

Patency of the cervix is rare, though obviously patency should have been there for the sperm to ascend in those cases where pregnancy has occurred. In Ivey's cases and the case reported by Whelton and McSweeney dilatation of the cervix had been carried out before the pregnancy. In the case reported here it was not possible to pass a uterine sound at any stage. Intense irradiation of the cervix destroys its inherent ability to dilate during parturition, but moderate radiation can be tolerated without apparent loss of this function. Stricture of the endocervical canal and possible scarring in the adjacent paracervical tissues would almost certainly result in deep tears in most of the cases if spontaneous delivery were attempted. Hence caesarean section is the treatment of choice.

Of the two cases referred to from the literature one has had since two more children born by caesarean section, and both the mothers have re-established regular periods. The case reported here has to be further followed up.

Among children born to mothers whose ovaries had received a subliminal castration dose of radiation no gross congenital defect, abnormal development, or behaviour problem has been observed. However, the follow-up on all of the children is not complete, and the possibility of a genetic defect in a future generation cannot be ruled out if children should be born to any of these individuals.

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Tolbutamide Test: A Misleading Response

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The blood-glucose response following intravenous administration of sodium tolbutamide has been reported to be useful for distinguishing insulinoma from other causes of hypoglycaemia (Fajans *et al.*, 1961). Since experience with this test has been limited to a relatively small number of patients, the circumstances in which misleading results may occur have not yet been clearly defined. This has prompted the report of the following case in which a positive response—that is, a rapid and marked decline in blood glucose—occurred but no insulinoma was found.

CASE REPORT

A 50-year-old white woman was studied because of hypoglycaemia (blood glucose 32 mg./100 ml.) manifested by diaphoresis and confusion during a glucose-tolerance (GT) test. Weakness, mental confusion, diaphoresis, and blurred vision had occurred between meals with increasing frequency for several years and were exacerbated by

exercise and relieved by eating. Despite irregular and sometimes poor food intake her weight had remained stable (about 112 lb.—50.8 kg.) for several years. Consumption of alcoholic beverages was negligible.

In 1954 excision of the left adrenal gland containing a cortical adenoma was performed after Cushing's syndrome was diagnosed. In 1958 Cushing's syndrome recurred and progressed despite pituitary irradiation. After a hyperplastic right adrenal gland had been removed, the stigmata of Cushing's syndrome disappeared, and she remained well while taking 12.5 mg. cortisone three times daily.

Physical examination was normal except for abdominal surgical scars, dorsal kyphosis from previous vertebral compression fractures, and generalized brownish pigmentation. Height was 5 ft. 1 in. (1.5 m.), weight 113 lb. (51.2 kg.).

The following investigations were carried out: Serum Na 132–139, K 4.5–5.2, Cl 92–93, HCO₃ 22–30.5 mEq/l. Routine blood and urine examination, serum calcium, phosphorus, alkaline phosphatase, bilirubin, glutamic-oxalic transaminase, amylase, thymol turbidity, cholesterol, creatinine, and protein-bound iodine were normal. Triiodothyronine red blood cell uptake, thyroid ¹³¹I uptake, electrocardiogram, and prothrombin time were normal. Cephalin-flocculation negative 24 hours, 2+48 hours; bromsulphthalein retention <1% (45 min.). Radiographs of the skull, chest, and gastrointestinal and urinary tracts were unremarkable except for compression fractures of several thoracic vertebrae and osteoporosis of the spine and pelvis.

Restricted carbohydrate intake before the GT test on 13 April may be responsible for the post-absorptive hyperglycaemia. The GT test on 24 April and the intravenous tolbutamide-tolerance (ITT) test on 5 May were performed after an intake of 2,100 calories, and 300 g. carbohydrate for three days. The GT test peak blood-glucose value was normal (<160 mg./100 ml.), but the fasting, three, four, and five-hour values were subnormal (<60 mg./100 ml.). For five days before and on the ITT test day 17.5 mg. cortisone acetate was administered intramuscularly every eight hours and 0.05 mg. 9 α -fluoro-hydrocortisone orally twice daily. One gramme sodium tolbutamide was administered in 10 ml. 0.9% saline intravenously over a two-minute period and two hours later hypoglycaemic symptoms culminating in virtual unresponsiveness occurred. The blood-glucose level after 36 hours of fasting was comparable to the lowest value occurring after tolbutamide administration, and hypoglycaemic symptoms were less intense (see Table).

The evidence was interpreted as indicating organic hyperinsulinism, but abdominal exploration did not reveal pancreatic nodules or aberrant pancreatic tissue. Splenectomy and distal hemipancreatectomy were performed. Microscopic examination of serial sections of pancreas by Dr. S. R. Wellings showed normal structure except for minimal focal atrophy and fibrosis of exocrine tissue. There was no evidence of neoplasia. The spleen was normal and no ectopic pancreatic tissue was found. The patient's poor condition precluded adequate investigation of carbohydrate metabolism during the post-operative period, but some subnormal fasting glucose values were obtained several months later when she had improved. Death occurred suddenly at home in February 1963.

Laboratory Studies Concerned with Carbohydrate Metabolism*

Fasting Blood Glucose		Oral Glucose Tolerance Test†				Intravenous Tolbutamide Tolerance Test	
		13.4.62 ^{1, 2, 5}		24.4.62 ^{1, 2, 6}		5.5.62 ^{1, 2, 6}	
Date	(mg./100 ml.)	(hr.)	(mg./100 ml.)	(mg./100 ml.)	(min.)	(mg./100 ml.)	
7.4.62	50 ^{1, 2}	Fasting	66	59	Fasting	56	
18.4.62	22 ^{1, 2}	½	180	157	15	51	
27.4.62	24 ^{1, 2, 3}	1	165	85	30	38	
4.6.62	78 ^{3, 4}	2	162	68	45	32	
31.10.62	10 ^{2, 4}	3	32	48	60	26	
28.11.62	56 ^{2, 4}	4	—	51	75	26	
23.1.63	96 ^{2, 4}	5	—	52	90	23	
		6	—	59	120	22	

* All values represent true blood glucose; normal fasting value 60–100 mg.

† Test dose: 100 g. glucose.

¹ Before hemipancreatectomy. ² Patient taking steroid replacement therapy. ³ After fasting 36 hr.; patient diaphoretic and lethargic. ⁴ Post-operative (hemipancreatectomy). ⁵ Previous diet consisted of high protein, restricted carbohydrate intake. ⁶ High carbohydrate intake for the preceding three days.

The necropsy findings were bilateral bronchopneumonia, chronic duodenal peptic ulceration, generalized arteriosclerosis, microscopic chromophobe adenoma of the pituitary, and leiomyoma (1 cm. in diameter) of the distal ileum. Serial pancreatic sections (1–2 mm. intervals) were similar to previously described pancreatic tissue and showed no adenomata. Careful examination of duodenal and stomach walls also failed to reveal any pancreatic adenomata. Brain sections were grossly normal; microscopic study was not performed. Dr. W. E. Toreson, University of California Medical School, kindly studied all pancreatic tissue and was able to differentiate only a few alpha cells. This was attributed to difficulty in staining formalin-fixed tissue.

DISCUSSION

Fajans and co-workers reported that the decline in blood glucose after the administration of intravenous tolbutamide was greater and more prolonged in patients with insulinomas than in normal subjects, patients with functional hyperinsulinism, patients with mild diabetes associated with hypoglycaemia, patients with adrenal insufficiency not treated with glucocorticoids, or many patients with liver disease. The rate of decline of blood glucose in our patient does not appear to differ from that reported thus far for patients with insulinomas (Fajans *et al.*, 1961, 1963; Samols and Marks, 1963). The need to terminate the test after two hours does not permit comparison of the duration of hypoglycaemia.

Several factors served to complicate this case. Corticosteroid deficiency as an explanation of hypoglycaemia and the response to tolbutamide can be excluded because of the lack of clinical evidence and the administration of adequate parenteral replacement therapy. Hypopituitarism cannot be definitely excluded, though tests of thyroid function were normal, hyperpigmentation existed, pubic and axillary hair were present, and the morphology of the gland was not grossly distorted. A single case of panhypopituitarism was reported (Fajans *et al.*, 1961) in which the blood glucose did not fall as markedly as did our patient's after the administration of tolbutamide. The evidence does not support the diagnosis of functional hyperinsulinism, and measures were taken to eliminate the possibility of surreptitious administration of hypoglycaemic agents. Despite careful examination at necropsy it is conceivable that a small insulinoma or hyperfunctioning ectopic pancreatic tissue was overlooked.

There is evidence that the measurement of plasma insulin after intravenous tolbutamide administration may be helpful in the diagnosis of patients with insulinomas (Pfeiffer *et al.*, 1959; Yalow and Berson, 1961; Samols and Marks, 1963; Floyd *et al.*, 1964). Since blood-insulin assays were not performed in our case no information can be offered concerning this point.

Three patients with hypoglycaemia were recently reported to have decreased numbers of pancreatic alpha cells (Grollman *et al.*, 1964). The failure to visualize more than a few alpha cells in our case was interpreted as due to technical difficulties, but it is possible alpha cells were decreased. Since glucagon was not measured in our patient or in those cases reported by Grollman *et al.*, it is conjectural whether the patients had a similar disorder and whether glucagon deficiency actually existed.

Some patients with large non-pancreatic neoplasia, liver disease, idiopathic hypoglycaemia of infancy, severe under-nutrition, or azotaemia may also have a blood-glucose response similar to that obtained in patients with insulinoma (Fajans *et al.*, 1963). Though our patient had none of these conditions the blood-glucose response following tolbutamide was distinctly abnormal. Since the ITT test as conducted at present does not provide a specific diagnostic test for insulinoma, caution should be exercised in attaching undue significance to a positive result, especially in the presence of complicating factors. Unless the specificity of the test can be improved, its greatest usefulness may be as an aid in excluding rather than establishing the diagnosis of insulinoma.

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