

METABOLIC STUDIES IN CHRONIC PANCREATITIS

Barry Isaac Joffe

A thesis submitted to the Faculty of Medicine, University of the Witwatersrand, Johannesburg, for the Degree of Doctor of Medicine

Johannesburg 1973

The
R.C
857
JoF



66662

DECLARATION

(a) This is to certify that this thesis is my own work and has not been presented for any degree to another University.

(b) Although the published work contained herein has appeared under the names of multiple authors, the candidate is the senior author in all publications and has performed the bulk of the clinical studies, laboratory investigations, statistical analysis of data and drafting of manuscripts himself. This has already been formally attested to by Professor W.P.U. Jackson, Director of the Endocrine Research Unit of Cape Town University Medical School, where the research work was carried out. (See original application to Senate for acceptance of title of proposed thesis on 8th June, 1973. Reference HD 405).

B. J. Joffe.

ABSTRACT

Chronic pancreatic disease has been extensively studied from an exocrine functional aspect, with relatively little attention being devoted to the assessment of endocrine function. This thesis deals primarily with aberrations of islet cell activity and lipid metabolism occurring in chronic pancreatitis.

Insulin reserve was firstly investigated in sixteen such patients by the technique of intensive beta-cell stimulation. It was found to be significantly reduced when compared to the response of normal controls, and the degree of insulinopaenia seemed to be proportional to the severity of glucose intolerance. Even nondiabetic pancreatitis patients, however, showed diminished insulin output. In an attempt to unmask the "latent" diabetic state of these nondiabetic cases, triamcinolone-augmented glucose tolerance tests were performed in seven of them. Although their steroid-augmented glucose tolerance deteriorated markedly, normal control subjects reacted in a similar (though less striking) fashion, implying a lack of specificity of the triamcinolone glucose tolerance test in this regard.

The pathogenesis of "pancreatic diabetes" (ie. diabetes secondary to chronic pancreatitis) was elucidated further in seven patients by administering the acute insulinogenic stimulus, intravenous tolbutamide, alone. Insulinopaenia

was florid and reflected in the subnormal plasma glucose fall observed after the tolbutamide injection. Arising from this study was the therapeutic implication that pancreatic diabetics would probably respond poorly to oral sulphonylurea drugs, and this was confirmed in six severe diabetics. Milder pancreatic diabetics, on the other hand, showed a partial improvement in glucose tolerance after two weeks of chlorpropamide therapy - in keeping with their greater, although still subnormal, insulin secretory capacity.

Sensitivity to exogenous insulin was documented in eight pancreatic diabetics after a standard intravenous insulin tolerance test. In a subsequent communication, this was shown to be due, at least in part, to significantly impaired growth hormone output in response to the hypoglycaemia. The explanation of this finding is speculative, but could be related to the lack of a pancreatic stimulus necessary to augment growth hormone secretion.

Turning to aspects of lipid metabolism in chronic pancreatitis, the mean fasting level of serum cholesterol and phospholipids in twenty pancreatic diabetics was significantly lower than levels found in matched groups of essential diabetics and normal controls. Mean fasting triglyceride values showed no significant difference between the three groups, although lowest in the pancreatitis patients. As a follow up study, oral fat tolerance tests were performed in nine of the pancreatitis patients and five healthy controls. After ingesting a meal containing seventy grams of butter fat, the pancreatitis group responded with significantly re-

duced serum chylomicron triglyceride values throughout the ensuing seven-hour test period. There was some indirect evidence to suggest impaired removal of chylomicron triglyceride from the plasma as well, consequent upon coexistent diabetes with insulinopaenia. In view of the dissociation between hyperglycaemia and serum lipid levels in pancreatic diabetics, it was of interest to assess their propensity to develop ischaemic heart disease. Resting and post-exercise electrocardiographs were performed in thirty nine cases and thirty matched essential diabetics. Electrocardiographic evidence of ischaemia was found only half as frequently in the pancreatic diabetics as in the essential diabetics. Furthermore, pancreatic diabetics with ischaemic electrocardiographs had significantly higher serum lipid levels than patients without these changes.

In conclusion, chronic pancreatitis has been shown to be associated with: 1) impaired beta-cell functional activity after a variety of insulinogenic stimuli, most marked in patients with impaired carbohydrate tolerance but also seen in nondiabetic subjects; 2) evidence of insulin sensitivity, which may be partly related to subnormal growth hormone output; and 3) reduced serum lipid levels, associated with a decreased absorption of dietary fat.

This thesis is dedicated to my four sources of
inspiration, my wife Rebecca and Harry, Daniel and
Gideon, our three sons.

ACKNOWLEDGEMENTS

Research work leading to the publication of articles included in this thesis was performed during the tenure of a Council for Scientific and Industrial Research Fellowship at the Endocrine Research Unit of Cape Town University Medical School. Particular gratitude is due to the following:

Professor W.P.U. Jackson, Director of the Endocrine Research Unit of Cape Town University Medical School, for his continued encouragement and free use of departmental facilities.

Professor S. Bank, Head of the Gastrointestinal Clinic at Groote Schuur Hospital, for access to cases under his care and enthusiastic co-operation in all research projects.

Dr. A.I. Vinik, for originally directing my attention to this field, and laboratory facilities in the Chemical Pathology Subdepartment, University of Natal.

Dr. Paul Keller, for instruction in the technique of insulin radioimmunoassay.

Dr. L. Krut, for laboratory facilities in connection with the lipid measurements.

Professor H.C. Seftel, for his everready assistance.

Mr. M.G. Toyer, Mr. K. Samsodien, Mr. S. Hendriks and Mrs. L. Schatz of the laboratory staff at the Endocrine Research Unit, Cape Town University Medical School.

Mrs. R.E. Joffe, for her loyal support and help in preparing this thesis for presentation.

The patients themselves, many of whom I got to know extremely well during the course of repeated investigations. Their co-operation was freely given at all times.

LIST OF PUBLICATIONS

1. Insulin reserve in patients with chronic pancreatitis.
Joffe, B.I., Bank, S., Jackson, W.P.U., Keller, P., O'Reilly, I., and Vinik, A.I.
Lancet, 2:890-892, 1968.
2. Triamcinolone-augmented glucose tolerance in non-diabetic patients with chronic pancreatitis.
Joffe, B.I., Jackson, W.P.U., and Bank, S.
Postgraduate Medical Journal, 1973 (in the press).
3. Effect of intravenous tolbutamide on serum insulin levels in pancreatic diabetes.
Joffe, B.I., Bank, S., Jackson, W.P.U., Vinik, A.I., and Keller, P.
Diabetes, 18:499-501, 1969.
4. Effect of oral hypoglycaemic agents on glucose tolerance in pancreatic diabetes.
Joffe, B.I., Jackson, W.P.U., Bank, S., and Vinik, A.I.
Gut, 13:285-288, 1972.
5. Hypoglycaemia in pancreatitis.
Joffe, B.I., Bank, S., and Marks, I.N.
Lancet, 2:1038, 1968.
6. Growth hormone response to insulin induced hypoglycaemia in diabetes secondary to chronic calcific pancreatitis.
Vinik, A.I., Joffe, B.I., Joubert, S.M., and Jackson, W.P.U.
Journal of Clinical Endocrinology and Metabolism, 31:86-88, 1970.

7. Serum lipid levels in diabetes secondary to chronic pancreatitis.
Joffe, B.I., Krut, L., Bank, S., Marks, I.N., and Keller, P.
Metabolism, 19:87-90, 1970.
8. Oral fat tolerance studies in chronic pancreatitis.
Joffe, B.I., Krut, L., Mendelsohn, D., and Seftel, H.C.
American Journal of Gastroenterology, 59:522-527, 1973.
9. Ischaemic heart-disease and pancreatic diabetes.
Joffe, B.I., Novis, B., Seftel, H.C., Krut, L., and Bank, S.
Lancet, 2:269, 1971.

INTRODUCTION

Chronic pancreatitis is a well recognised, if comparatively uncommon, clinical disorder. In certain areas, however, the disease appears to be unusually prevalent. One of these is the Western Cape region of South Africa; more than one thousand patients with pancreatitis have been studied at the Groote Schuur Hospital, Cape Town, over a ten year period (Bank, Marks, Lurie, Novis and Barbezat, 1972). Excessive alcohol intake is an important aetiological factor and the presence of pancreatic calcification a highly suggestive radiological sign (Marks, 1968).

Impairment of exocrine pancreatic function has been extensively documented in chronic pancreatitis, by a variety of techniques. One of the most specific investigations is the pancreatic function test, where the volume, bicarbonate content and enzyme level of pancreatic secretions is measured after secretin/pancreozymin stimulation (Bank, Marks, Moshal, Efron, and Silber, 1963; Hanscom, 1968). Tests involving radioselenium administration have also achieved prominence (Youngs, Agnew, Levin and Bouchier, 1973). Until recently, relatively little attention has been given to the assessment of endocrine function in chronic pancreatic disease - beyond estimation of glucose tolerance, which admittedly, is often abnormal (Chey, Shay, Nielsen and Lorber, 1967).

The development of sensitive radioimmunoassay methods for the analysis of polypeptide hormones, notably insulin (Yalow and Berson, 1960), has added a new dimension to this area of research. Preliminary reports of glucose-stimulated insulin release in chronic pancreatitis, however, disagree as to whether insulin secretion is inconsistently, usually or invariably impaired (Bank, Jackson, Keller and Marks, 1968; Anderson, Davison, Dick, Hales and Owens, 1970; Rogers, Howard and Pairent, 1970). Other hormonal relationships have not been studied at all.

In the ensuing publications, islet-cell activity has been explored in patients with chronic pancreatitis by a variety of provocative stimuli. Particular attention has been directed at characterising the diabetic "syndrome" complicating chronic pancreatitis, since it provides a valuable clinical model for observing some of the effects of acquired diabetes in man. Aspects of lipid metabolism have also been investigated, in order to complement the hormonal profile.

References

- Anderson, M.F., Davison, S.H.H., Dick, A.P., Hales, C.N., and Owens, J. 'Plasma insulin in pancreatic disease'. Gut, 11:524-531, 1970.
- Bank, S., Jackson, W.P.U., Keller, P., and Marks, I.N. 'Serum insulin response to glucose in pancreatic diabetes'. Postgrad. Med. J., 44:214-217, 1968.
- Bank, S., Marks, I.N., Lurie, B., Novis, B.H., and Barbezat, G.O. 'Precalcific pancreatitis'. S. Afr. Med. J., 46:2093-2097, 1972.
- Bank, S., Marks, I.N., Moshal, M.G., Efron, G., and Silber, R. 'The pancreatic function test - method and normal values'. S. Afr. Med. J., 37:1061-1066, 1963.

- Chey, W.Y., Shay, H., Nielsen, O.F., and Lorber, S.H.
'Evaluation of tests of pancreatic function in chronic
pancreatic disease'. J. Amer. Med. Ass., 201:347-350,
1967.
- Hanscom, D.H. 'Diagnostic tests in pancreatic disease'.
Med. Clin. N. Amer., 52:1483-1492, 1968.
- Marks, I.N. 'The natural history of calcific pancreatitis
in the Western Cape'. Trans. Coll. Physicians S. Afr.,
12:54-78, 1968.
- Rogers, J.B., Howard, J.M., and Parent, F.W. 'Serum
insulin levels in patients with chronic pancreatitis'.
Amer. J. Surg., 119:171-176, 1970.
- Yalow, R.A., and Berson, S.A. 'Immunoassay of endogenous
plasma insulin in man'. J. Clin. Invest., 39:1157-
1175, 1960.
- Youngs, G.R., Agnew, J.E., Levin, G.E., and Bouchier,
I.A.D. 'A comparative study of four tests of pancrea-
tic function in the diagnosis of pancreatic disease'.
Quart. J. Med., 42:597-618, 1973.

INSULIN RESERVE IN PATIENTS WITH CHRONIC PANCREATITIS

B. I. JOFFE

M.B. W'srand, M.R.C.P.

S. BANK

M.B. Cape Town, M.R.C.P.

W. P. U. JACKSON

M.D. Cape Town, F.R.C.P.

P. KELLER

Ph.D. Freiberg

I. G. O'REILLY

A. I. VINIK

M.B. W'srand, F.C.P., S.A.

S. HENDRICKS AND L. SCHATZ

Reprinted from THE LANCET, October 26, 1968, pp. 890-892

INSULIN RESERVE IN PATIENTS WITH CHRONIC PANCREATITIS

B. I. JOFFE

M.B. W'srand, M.R.C.P.

RESEARCH ASSOCIATE

S. BANK

M.B. Cape Town, M.R.C.P.

CONSULTANT GASTROENTEROLOGIST

W. P. U. JACKSON

M.D. Cape Town, F.R.C.P.

ASSOCIATE PROFESSOR OF MEDICINE

P. KELLER

Ph D. Freiburg

CHIEF RESEARCH OFFICER

I. G. O'REILLY

TECHNICIAN

ENDOCRINE RESEARCH AND GASTROINTESTINAL UNITS,
GROOTE SCHUUR HOSPITAL, AND DEPARTMENT OF MEDICINE,
UNIVERSITY OF CAPE TOWN

A. I. VINIK

M.B. W'srand, F.C.P., S.A

SENIOR LECTURER, DEPARTMENT OF MEDICINE AND
CHEMICAL PATHOLOGY, UNIVERSITY OF NATAL

With technical assistance from

S. HENDRICKS AND L. SCHATZ

Summary Sixteen patients with unequivocal evidence of chronic pancreatitis were subjected to intensive β -cell stimulation by combined intravenous injection of glucagon and tolbutamide after oral glucose. The serum-immunoreactive-insulin responses of the whole group were significantly impaired when compared with normal controls. The degree of impairment seemed to be proportional to the degree of glucose intolerance. It is postulated that the diabetic syndrome of chronic pancreatitis represents an example of acquired insulinopenia and is thus a valuable clinical model for assessing the effects of this in man.

Introduction

MANY patients with chronic or chronic relapsing pancreatitis develop impaired glucose tolerance and overt diabetes. (Comfort et al. 1946, Marks and Bank 1963, Chey et al. 1967). Their diabetic syndrome is characterised by a fluctuant course, rarity of ketoacidosis, severe

hypoglycaemic episodes on insulin therapy, and virtual absence of microangiopathy (Bank 1966, Marks 1968). Studies on plasma-immunoreactive-insulin levels in this condition have showed normal or moderately raised fasting values (Keller, Bank, Jackson, Marks, and O'Reilly 1965, Peters et al. 1966a), while responses after oral glucose have been reported as being either impaired or variable (Peters et al. 1966b, Bank, Jackson, Keller, and Marks 1968). Recently published data on procedures for assessing β -cell reserve (Ryan et al. 1967, Ryan and Schwartz 1967) have prompted us to further evaluate this facet in our patients. In the present study, the insulin secretory capacity of a group of patients with chronic pancreatitis has been examined after the combined injection of glucagon and tolbutamide, given 30 minutes after an oral glucose load.

Patients, Controls, and Methods

Pancreatic subjects.—Sixteen patients with unequivocal features of chronic pancreatitis were tested as outpatients: fifteen showed radiological evidence of pancreatic calcification, and in one the diagnosis was confirmed at laparotomy. Alcohol was considered to be the main aetiological factor. There were fourteen men and two women ranging from 39 to 65 years of age. Six had frankly diabetic glucose-tolerance tests, three were borderline, and seven had normal curves (Jackson 1964). No patient had previously received insulin. Five of the diabetics were taking oral hypoglycaemic agents and they were instructed to discontinue therapy for at least 5 days before testing. There was no evidence of hepatic or renal disease in any patient and no family history of diabetes.

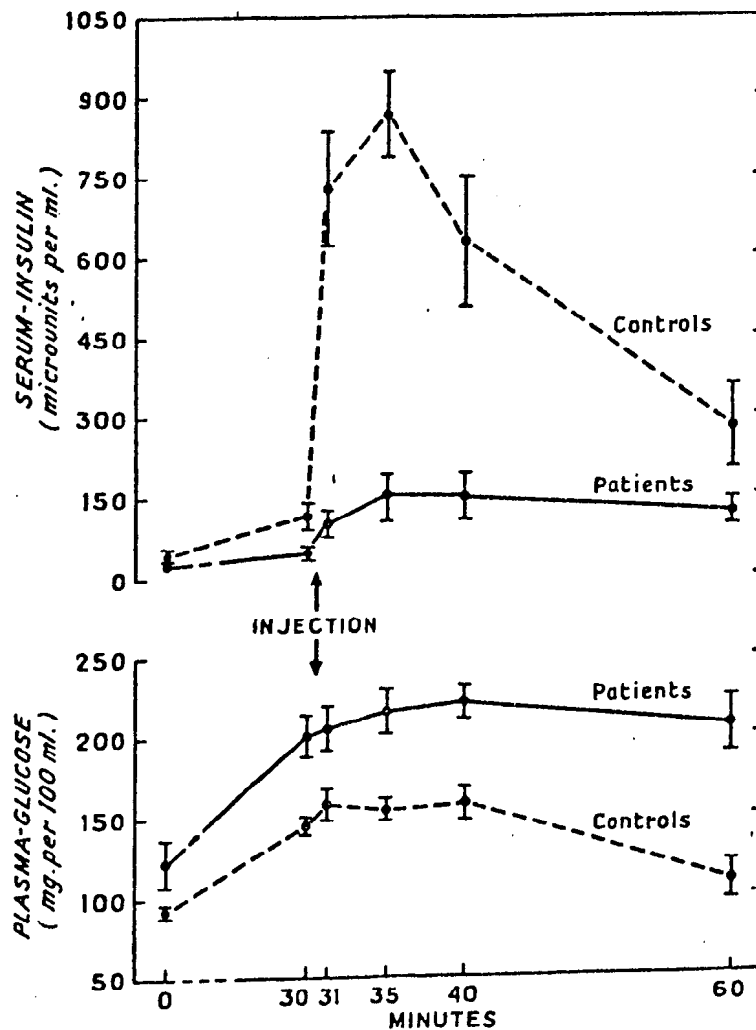
Controls.—Ten healthy, non-obese, active adults (nine men and one woman) with no clinical or laboratory features of pancreatic disease served as control subjects. Their ages ranged from 25 to 54 years. None had clinical evidence, or a family history, of diabetes, and their glucose-tolerance tests were normal. They were well nourished and received an adequate carbohydrate intake before testing.

Patients in each group were tested at rest, after an overnight fast. Venous blood was obtained from, and intravenous injections were administered into, indwelling polyethylene cannulas placed in antecubital veins. A dose of 75 g. of oral glucose was followed 30 minutes later by the rapid intravenous administration of 0.5 g. tolbutamide (Hoechst) and 1 mg. crystalline glucagon (Lilly); samples were taken fasting, 30 minutes after oral glucose, and at 1, 5, 10, and 30 minutes after the combined injection—i.e., at 31, 35, 40, and 60 minutes. Plasma-glucose was determined on the 'AutoAnalyzer' by the modified ferricyanide method of Hoffman (1937). Insulin was measured in serum by radioimmunoassay (Hales and Randle 1963). Plasma non-esterified fatty-acids (N.E.F.A.) were estimated by a modification of the method of Dole (1956). In addition samples

of glucagon from the batch used were periodically submitted to immunoassay for insulin contamination.

Results

The accompanying figure shows the mean ($\pm$ S.E.M.) plasma-glucose and serum-immunoreactive-insulin levels of the pancreatitis and control subjects during the test. The mean plasma-glucose levels were somewhat higher in the pancreatitis group, owing partly to the inclusion of those with diabetic glucose-tolerance tests. Although the fasting serum-insulin levels showed no significant difference ($P < 0.02$), the patients with chronic pancreatitis had a significantly impoverished insulin response 30 minutes



Mean concentrations ($\pm$ S.E.M.) of plasma-glucose and serum-insulin following combined glucagon and tolbutamide injection, given 30 minutes after an oral glucose load.

PLASMA-GLUCOSE AND SERUM-IMMUNOREACTIVE-INSULIN VALUES (MEAN $\pm$ S.E.M.) IN PATIENTS WITH CHRONIC PANCREATITIS, SEPARATED ACCORDING TO THEIR GLUCOSE-TOLERANCE TESTS, AND IN CONTROLS

Glucose-tolerance test	No.	Plasma-glucose (mg. per 100 ml.) at the following times (min.)						Serum-insulin (microunits per ml.) at the following times (min.)					
		0	30	31	35	40	60	0	30	31	35	40	60
<i>Patients with chronic pancreatitis</i>													
Normal ..	7	91 ± 7	167 ± 8	171 ± 15	176 ± 13	179 ± 14	161 ± 26	28 ± 5	53 ± 19	168 ± 40	241 ± 85	273 ± 80	149 ± 33
Borderline ..	3	113 ± 8	186 ± 7	195 ± 8	216 ± 16	226 ± 16	219 ± 20	15 ± 3	27 ± 4	56 ± 22	81 ± 11	119 ± 24	82 ± 24
Diabetic ..	6	154 ± 32	236 ± 26	246 ± 23	257 ± 20	253 ± 21	256 ± 21	24 ± 6	38 ± 6	42 ± 7	57 ± 14	54 ± 17	62 ± 23
Controls ..	10	92 ± 4	143 ± 4	156 ± 9	154 ± 6	156 ± 10	108 ± 12	33 ± 7	117 ± 23	724 ± 108	867 ± 79	623 ± 128	258 ± 77

after glucose ingestion ($P < 0.01$), and especially after the combined injection ($P < 0.001$ at 31, 35, and 40 minutes, and < 0.02 at 60 minutes).

The accompanying table shows the mean ($\pm$ S.E.M.) plasma-glucose and serum-insulin values in the three subgroups of patients with chronic pancreatitis, separated according to the state of their glucose tolerance. Although the number of patients in each subgroup was relatively small and there was some overlap, the serum-insulin responses tended to correlate with the degree of glucose tolerance in the samples taken after the combined injection. Thus, patients with pancreatic disease and normal glucose tolerance had the highest insulin output, diabetics showed the least response, and those with borderline tolerance were at an intermediate level. Even in the "normal" pancreatitis subgroup, the maximum mean ($\pm$ S.E.M.) output obtained (273 ± 80 microunits per ml., at 40 minutes) was significantly below ($P < 0.001$) that of the control subjects (867 ± 79 microunits per ml., at 35 minutes).

All glucagon samples assayed contained less than 5 microunits of immunoreactive insulin per μ g. Mean fasting plasma N.E.F.A. levels were somewhat greater in the pancreatitis subjects (mean level 699 μ eq. per litre) than in the controls (mean 577 μ eq. per litre). In both groups, however, there was a prompt fall 30 minutes after oral glucose, a slight rise immediately after the combined injection, and then a continued fall during the remainder of the test, so that the 60-minute levels were similar (mean level in patients with pancreatitis 363 μ eq. per litre; mean level in controls 384 μ eq. per litre).

Discussion

The present study provides striking support for the concept of impaired insulin reserve in patients with severe chronic pancreatitis. When presented with an acute maximal β -cell stimulus, using agents that may act on separate insulin-releasing mechanisms (Ryan et al. 1967), these patients had a diminished insulin output compared with a group of suitable controls. This was seen even when their glucose tolerance was normal, and there seemed to be progressive diminution with deteriorating glucose tolerance.

The patients with "pancreatic" diabetes were not totally deficient in insulin, and managed to increase their mean fasting level just over twofold after intensive stimulation. Part of this rise must be attributed to the insulin contamination in the glucagon samples used, although a maximum addition of less than 9 microunits per ml. to the

serum-immunoreactive-insulin values could be expected on this account (Crockford et al. 1966). What little reserve they have, however, is clearly inadequate for maintaining normal glucose homeostasis.

Our findings seem to show that the diabetic syndrome in patients with chronic pancreatitis is an example of acquired β -cell insufficiency. Many of its puzzling clinical features—for example, virtual absence of clinical angiopathy—need to be interpreted in this context. Thus the syndrome provides a valuable clinical model for assessing the consequences of acquired insulinopenia in man—in contrast to maturity-onset type diabetes mellitus, in which there may be a degree of insulin antagonism and resulting compensatory hyperinsulinism (Kipnis and Stein 1964, Vallance-Owen 1964). The insulin responses after intensive β -cell stimulation in patients with chronic pancreatitis and in those with maturity-onset diabetes are at present being investigated.

We thank Dr. I. N. Marks for allowing us to study patients under his care; Dr. B. L. Pimstone, whose helpful advice and criticism played an important part in the preparation of this manuscript; Mr. K. Samsodien, who rendered valuable technical assistance; and Miss P. Rear for typing the manuscript. Supplies of tolbutamide were kindly provided by Hoechst Pharmaceuticals and supplies of glucagon by Lilly Laboratories, Isando, Transvaal. The work was supported by the South African Council for Scientific and Industrial Research.

Requests for reprints should be addressed to B. I. J., Department of Medicine, Medical School, Observatory, Cape Province, South Africa.

REFERENCES

- Bank, S. (1966) *S. Afr. med. J.* 40, 342.
 — Jackson, W. P. U., Keller, P., Marks, I. N. (1968) *Post-Grad. med. J.* 44, 214.
 Chéy, W. Y., Shay, H., Nielsen, O. F., Lorber, S. H. (1967) *J. Am. med. Ass.* 201, 347.
 Comfort, M. W., Gambill, E. F., Baggenstoss, A. H. (1946) *Gastroenterology*, 6, 239, 376.
 Crockford, P. M., Porte, D., Jr., Wood, F. C., Jr., Williams, R. H. (1966) *Metabolism*, 15, 114.
 Dole, V. P. (1956) *J. clin. Invest.* 35, 150.
 Hales, C. N., Randle, P. J. (1963) *Biochem. J.* 88, 137.
 Hoffman, W. S. (1937) *J. biol. Chem.* 120, 51.
 Jackson, W. P. U. (1964) On Diabetes Mellitus; chap. 8. Springfield, Illinois.
 Keller, P., Bank, S., Jackson, W. P. U., Marks, I. N., O'Reilly, I. G. (1965) *Lancet*, ii, 1211.
 Kipnis, D. M., Stein, M. F. (1964) *Ciba Fdn Colloq. Endocr.* 15, 156.
 Marks, I. N. (1968) *Trans. Coll. Physns S. Afr.* 12, 54.
 — Bank, S. (1963) *S. Afr. med. J.* 37, 1039.
 Peters, N., Dick, A. P., Hales, C. N., Orrell, D. H., Sarner, M. (1966a) *Gut*, 7, 277.
 — — — — (1966b) *Lancet*, i, 95.
 Ryan, W. G., Nibbe, A. F., Schwartz, T. B. (1967) *ibid.* i, 1255.
 — Schwartz, T. B. (1967) *Diabetes*, 16, 514.
 Vallance-Owen, J. (1964) *ibid.* 13, 241.

The first paper provides striking support for the concept of impaired insulin reserve in chronic pancreatitis - even in patients whose glucose tolerance is apparently normal. This raises the possibility that nondiabetic patients with chronic pancreatitis are, in fact, 'prediabetic' subjects. In an attempt to unmask their 'latent' diabetic state, a steroid augmented glucose tolerance test might be revealing. Results of this investigation are presented in the next paper.

TRIAMCINOLONE-AUGMENTED GLUCOSE TOLERANCE IN NONDIABETIC
PATIENTS WITH CHRONIC PANCREATITIS

B.I. JOFFE, W.P.U. JACKSON, AND S. BANK
M.B., M.R.C.P. M.D., F.R.C.P. M.B., F.R.C.P.

Department of Medicine, Witwatersrand University Medical
School, Johannesburg, and the Gastrointestinal and Endocrine
Research Units of Cape Town University Medical School,
South Africa.

Running Heading

Triamcinolone glucose tolerance in pancreatitis

Correspondence

Dr. B.I. Joffe, Department of Medicine, Witwatersrand
University Medical School, Johannesburg, South Africa.

The
POSTGRADUATE MEDICAL JOURNAL

PUBLISHED BY BLACKWELL SCIENTIFIC PUBLICATIONS FOR THE FELLOWSHIP OF POSTGRADUATE MEDICINE

Editor: IAN GILLILAND, M.D., F.R.C.P.

c/o London House,
Mecklenburgh Square,
London W.C.1

Telephone: 01 837 8888 ext 299

1 May 1973

Dr.B.I.Joffe,
Department of Medicine,
Witwatersrand University Medical School,
Johannesburg,
South Africa

Dear Dr.Joffe,

The Editor is pleased to accept your paper 'Triamcinolone-augmented glucose tolerance in non-diabetic patients with chronic pancreatitis' for publication in the journal

Yours sincerely.

J. Leach
Editorial Assistant

SUMMARY Seven nondiabetic patients with chronic pancreatitis were shown to have a diminished acute insulin secretory response after intensive beta cell and intravenous tolbutamide stimulation. In an attempt to unmask their "latent" diabetic state, triamcinolone-augmented glucose tolerance tests were performed, some days after documenting normal standard 50 g oral glucose tolerance tests. A matched group of nondiabetic controls was similarly investigated. Although the steroid-augmented glucose tolerance tests showed marked impairment in the patients, becoming frankly diabetic in 3 cases, the normal control subjects reacted in a similar though less striking fashion. There was no significant difference between the mean glucose values in the 2 groups. The ability of patients with chronic pancreatitis to maintain normal glucose tolerance in the face of diminished insulin output is commented on. We conclude that, as an ancillary investigation for diagnosing chronic pancreatitis, the triamcinolone glucose tolerance test is unreliable.

Triamcinolone-augmented glucose tolerance in nondiabetic patients with chronic pancreatitis

Introduction

Although chronic pancreatitis is frequently complicated by diabetes, there are, nevertheless, a substantial number of patients who maintain normal glucose tolerance (Bank et al., 1968; Anderson et al., 1970). Recent studies (Joffe et al., 1968; Deckert et al., 1972) have indicated that even when glucose tolerance is apparently unaffected in chronic pancreatitis, insulin reserve has already been significantly decreased. Thus nondiabetic patients with chronic pancreatitis could be regarded as "prediabetic" subjects (Rogers, Howard and Pairent, 1970). This being the case, an investigation that may be expected to unmask this "latent" diabetic state would be a steroid-augmented oral glucose tolerance test (GTT). A study was therefore designed to assess the diagnostic value of an oral GTT augmented with triamcinolone (Navarette and Torres, 1965) in a group of nondiabetic patients with chronic pancreatitis, with reference to their insulin secretory capacity.

Patients and Methods

Patients and Controls

Seven nonobese patients with well-proven chronic pancreatic disease were studied. There were 6 men and 1 woman, ranging from 40 to 54 years of age. The diagnosis of pancreatitis was confirmed in each case on the basis of gross abnormality in the secretin/pancreozymin pancreatic function test (Bank et al., 1963). Furthermore, radiological evidence of pancreatic calcification was observed in 5 cases and chemical evidence of steatorrhea in 2 cases. Alcohol was thought to be of aetiological importance in all except one instance (where the cause was unknown); despite this, clinical, biochemical and histological evidence of liver disease was uniformly absent. All the patients had recent documentation of a normal 50 g oral GTT. There was no known family history of diabetes, although one patient had a brother with calcific pancreatitis and impaired carbohydrate tolerance. A group of 7 healthy nonobese subjects, matched with the patients as regards age and sex, acted as controls. None had a family history of diabetes or evidence of pancreatic disease. Their oral GTT's were normal.

Experimental design

The insulin secretory capacity of the patients and controls was first established using the techniques of: (a) intensive beta cell stimulation with a combination of 75 g oral glucose, followed 30 minutes later by the combined intravenous administration of $\frac{1}{2}$ g tolbutamide and 1 mg glucagon (Ryan, Nibbe and Schwartz, 1967); and (b) intravenous administration of 1 g tolbutamide alone (undertaken some days later). In each test, serum samples for immunoreactive insulin determinations were obtained fasting and after stimulation. Since the 5 minute post-injection sample in each test generally represented the peak insulin response, this (together with the fasting sample) was used for subsequent analysis. Oral GTT's were then performed, at a later date, in both groups of subjects. For the

standard GTT, 50 g of glucose was administered orally after an overnight fast and employing the usual precautions (Jackson, 1964). Triamcinolone-augmented GTT's were done at least 2 days later, using triamcinolone 8 mg 11 hours and 1 hour before the 50 g oral glucose load.

Methods

Glucose was determined $\frac{1}{2}$ hourly for 2 hours on capillary whole blood using a Technicon Auto-Analyzer and the modified ferricyanide method of Hoffman (1937). In addition, hourly urine samples were tested for glycosuria with Testape. Serum insulin during the intensive beta cell stimulation and tolbutamide tests were measured by radio-immunoassay (Hales and Randle, 1963).

Criteria for analysis of GTT's

For both the standard GTT and the triamcinolone GTT the same criteria were used (Jackson et al., 1972). Normal: all blood glucose levels below 120 mg/100 ml fasting, 185 maximum and 140 at 120 minutes. Borderline: one high value only. Diabetic: at least 2 high values.

Results

Table 1 indicates the acute insulin secretory capacity of the nondiabetic patients with chronic pancreatitis, together with that of the matched controls, as evidenced by their fasting and early insulin responses to intensive stimulation and tolbutamide alone. Fasting insulin levels were similar in the 2 groups, but the patients produced less than half the peak insulin output of the controls after intensive stimulation. A similar, although statistically less impressive, response was noted after tolbutamide alone. (Mean 30 minute % blood glucose falls after tolbutamide were similar in the 2 groups, at 35% in patients and 43% in controls).

The results of the standard and triamcinolone-augmented GTT's in the 2 groups are outlined in Table 2. Standard GTT's were normal in both groups, as anticipated; none of the differences between the mean values were statistically significant. Regarding triamcinolone GTT's, a statistically significant deterioration (compared to standard GTT) occurred in both groups ($p \leq 0.05$ at 60, 90 and 120 minutes). Although the mean glucose level was generally higher in the pancreatitis patients than in the controls during the triamcinolone test, at no time did it become significantly greater. Of interest was the observation that the mean triamcinolone GTT had, in fact, become "diabetic" in the chronic pancreatitis patients, while still remaining "normal" in the controls.

Glycosuria was uniformly absent during standard GTT's. It was detected in all 7 chronic pancreatitis patients during the triamcinolone GTT, but also in 4 of the 7 controls.

Table 3 summarises the fate of individual triamcinolone GTT's in the 2 groups, analysed according to the criteria set out earlier. The test became diabetic in 3 patients and 1 control.

Discussion

The primary object of the present study was to ascertain whether a steroid-augmented glucose tolerance test would be a useful ancillary investigation in chronic pancreatitis, by unmasking the diabetes susceptibility of those patients who preserve normal glucose tolerance in the face of diminished insulin reserve. Although marked deterioration in the triamcinolone GTT was, indeed, noted and nearly half the tests became diabetic, much of the impact of these observations was lost in view of the fact that normal controls reacted in a similar, though less striking, manner. This lack of specificity of the triamcinolone GTT has recently been commented on in relation to offspring of diabetic couples (Jackson et al., 1972). It would thus appear that an abnormal triamcinolone GTT in a nondiabetic patient with suspected chronic pancreatitis is of uncertain diagnostic reliability.

The pathogenesis of steroid "diabetes" is not very clear, but direct antagonism of insulin at a cellular level seems to be an important factor (Berger et al., 1966). This results in compensatory hypersecretion of insulin, both from the acutely releasable and slowly responding functional insulin pools in the beta cell (Porte and Bagdade, 1970), and if this is inadequate, impaired carbohydrate tolerance will ensue. In chronic pancreatitis, the defect in insulin output appears to mainly involve its early secretion from the acutely releasable insulin pool (Porte and Bagdade, 1970), so that a steroid-augmented GTT may not be the most effective means of revealing this abnormality. Agents that selectively compromise the early release of insulin from the beta cell, such as epinephrine, diazoxide and mannoheptulose (Levine, 1970) might have greater diagnostic merit in this regard.

Finally, the ability of patients with chronic pancreatitis to maintain normal glucose tolerance in the face of considerably diminished insulin secretory capacity is of interest. It implies a

state of insulin sensitivity in chronic pancreatitis, and this has indeed been demonstrated after exogenous insulin administration (Joffe, Bank and Marks, 1968). Reasons for this are speculative, although decreased secretion of anti-insulin factors, such as growth hormone (Vinik et al., 1970), and pancreatic glucagon (Persson et al., 1971) may be partly responsible.

Acknowledgements

We should like to thank Dr. I.N. Marks for allowing us to study patients under his care, Mr. M.G. Toyer for helping with the glucose tolerance tests, Mrs. R.E. Joffe for typographical assistance, and the South African Medical Research Council for financial aid.

References

- ANDERSON, M.F., DAVISON, S.H.H., DICK, A.P., HALES, C.N. and OWENS, J. (1970) Plasma insulin in pancreatic disease. Gut, 11, 524.
- BANK, S., MARKS, I.N., MOSHAL, M.G., EFRON, G. and SILBER, R. (1963) The pancreatic function test - method and normal values. South African Medical Journal, 37, 1061.
- BANK, S., JACKSON, W.P.U., KELLER, P. and MARKS, I.N. (1968) Serum insulin response to glucose in 'pancreatic diabetes'. Postgraduate Medical Journal, 44, 214.
- BERGER, S., DOWNEY, J.L., TRAISMAN, H.S. and METZ, R. (1966) Mechanism of cortisone modified glucose tolerance test. New England Journal of Medicine, 274, 1460.
- DECKERT, T., KOLENDORF, K., PERSSON, I. and WÖRNING, H. (1972) Insulin secretion after tolbutamide and after secretin in patients with pancreatic diseases. Acta medica Scandinavica, 192, 465.
- HALES, C.N. and RANDLE, P.J. (1963) Immunoassay of insulin with insulin-antibody precipitate. Biochemical Journal, 88, 137.
- HOFFMAN, W.S. (1937) A rapid photoelectric method for the determination of glucose in blood and urine. Journal of Biological Chemistry, 120, 51.
- JACKSON, W.P.U. (1964) On Diabetes Mellitus, p. 113. Thomas, Springfield, Illinois.
- JACKSON, W.P.U., CAMPBELL, G.D., MARINE, N., MAJOR, V. and SEEDAT, Y.K. (1972) Triamcinolone-augmented glucose tolerance in offspring of diabetic couples. Metabolism, 21, 807.

- JOFFE, B.I., BANK, S., JACKSON, W.P.U., KELLER, P., O'REILLY, I.G. and VINIK, A.I. (1968) Insulin reserve in patients with chronic pancreatitis. Lancet, 2, 890.
- JOFFE, B.I., BANK, S. and MARKS, I.N. (1968) Hypoglycaemia in pancreatitis. Lancet, 2, 1038.
- LEVINE, R. (1970) Mechanisms of insulin secretion. New England Journal of Medicine, 283, 522.
- NAVARETTE, N.J. and TORRES, I.H. (1965) A triamcinolone-glucose tolerance test in early diagnosis of diabetes. Diabetes, 14, 481.
- PERSSON, I., GYNTELBERG, F., HEDING, L.G., and BOSS-NIELSEN, J. (1971) Pancreatic-glucagon-like immunoreactivity after intravenous insulin in normal and chronic pancreatitis patients. Acta Endocrinologica, 67, 401.
- PORTE, D. and BAGDADE, J.D. (1970) Human insulin secretion: an integrated approach. Annual Review of Medicine, 21, 219.
- ROGERS, J.B., HOWARD, J.M. and PAIRENT, F.W. (1970) Serum insulin levels in patients with chronic pancreatitis. American Journal of Surgery, 119, 171.
- RYAN, W.G., NIBBE, A.F. and SCHWARTZ, T.B. (1967) Beta-cytotrophic effects of glucose, glucagon and tolbutamide in man. Lancet, 2, 1255.
- VINIK, A.I., JOFFE, B.I., JOUBERT, S.M. and JACKSON, W.P.U. (1970) Growth hormone response to insulin-induced hypoglycaemia in diabetes secondary to chronic calcific pancreatitis. Journal of Clinical Endocrinology and Metabolism, 31, 86.

TABLE 1. Fasting and peak insulin responses (mean $\pm$ SEM) after intensive beta cell and intravenous tolbutamide stimulation in nondiabetic patients with chronic pancreatitis and normal controls

Group	No. of Subjects	Serum Insulin (uU/ml) after Stimulation		
		Fasting	5 min. after Intensive Stimulation	5 min. after Tolbutamide
Chronic pancreatitis	6	28 $\pm$ 6	400 $\pm$ 148	66 $\pm$ 16
Normal controls	7	33 $\pm$ 7	867 $\pm$ 79	113 $\pm$ 23
Significance		NS	< 0.05	NS

TABLE 2. Effect of triamcinolone augmentation on glucose tolerance in nondiabetic patients with chronic pancreatitis and normal controls. All values are means $\pm$ SEM

Time	Blood Glucose (mg/100 ml) after Glucose Administration			
	Chronic Pancreatitis (7)		Normal Controls (7)	
	Standard GTT	Triamcinolone GTT	Standard GTT	Triamcinolone GTT
Fasting	90 $\pm$ 4	95 $\pm$ 5	87 $\pm$ 3	96 $\pm$ 6
30 min	113 $\pm$ 13	163 $\pm$ 14	140 $\pm$ 10	157 $\pm$ 7
60 min	147 $\pm$ 16	206 $\pm$ 19	139 $\pm$ 10	177 $\pm$ 13
90 min	117 $\pm$ 7	184 $\pm$ 16	112 $\pm$ 9	150 $\pm$ 14
120 min	98 $\pm$ 11	156 $\pm$ 9	78 $\pm$ 8	124 $\pm$ 13

There is no significant difference between the 2 groups, for either the standard or the triamcinolone GTT values.

TABLE 3. Fate of individual triamcinolone GTT's in nondiabetic patients with chronic pancreatitis and normal controls

Result of Triamcinolone GTT	Chronic Pancreatitis (7)	Normal Controls (7)
Remained normal	1	2
Boderline	3	4
Diabetic	3	1

Turning to the syndrome of 'pancreatic' diabetes (ie. diabetes secondary to chronic pancreatitis), further elucidation of its pathogenesis was sought by employing the classical acute insulinogenic stimulus, tolbutamide.

Brief Notes and Comments

Effect of Intravenous Tolbutamide on Serum Insulin Levels in Pancreatic Diabetes

B. I. Joffe, M.R.C.P., S. Bank, M.R.C.P., W. P. U. Jackson, F.R.C.P.,
A. I. Vinik, F.C.P. (S.A.) and P. Keller, Ph.D., Cape Town, South Africa

with technical assistance from A. Wouters and L. Schatz

SUMMARY

Intravenous tolbutamide was administered to seven patients with diabetes secondary to chronic calcific pancreatitis who had not previously received insulin. A matched group of normal controls was similarly investigated. The pancreatic diabetic patients were found to respond to tolbutamide with a significantly impaired serum insulin rise compared to the control group, while their fall in plasma glucose was delayed and significantly less pronounced. The relationship between insulin responses in pancreatic and in primary diabetes is briefly discussed and therapeutic implications of the findings are considered. DIABETES 18:499-501, July, 1969.

Chronic pancreatitis is often complicated by the development of diabetes.^{1,2} Recent investigations with the use of insulin radioimmunoassay have shown that insulin responses after glucose^{3,4} and intensive beta cell stimulation⁵ are diminished in this situation. In the present study the effect of intravenous tolbutamide alone on the pancreatic insulin secreting capacity of patients with diabetes secondary to chronic pancreatitis has been examined in an attempt to elucidate further the pathogenesis of the syndrome and because of possible therapeutic implications.

MATERIAL AND METHODS

The subjects of the study were seven lean patients with unequivocal clinical and investigative features of chronic pancreatitis; all had radiological evidence of pancreatic calcification. Alcohol was believed to be related to the etiological factor. Despite this, hepatic disease was not detected clinically, biochemically or histologically in any patient. The presence of diabetes had previously been confirmed on the basis of a diabetic oral glucose tolerance test.⁶ Pertinent characteristics of these patients are given in table 1. No patient had previ-

From the Endocrine Research Group of the Council for Scientific and Industrial Research and Gastrointestinal Unit, Groote Schuur Hospital, and the Department of Medicine, University of Cape Town, Cape Town, South Africa. Dr. A. I. Vinik's present address is University of Natal, Department of Chemical Pathology, Congella, Durban.

TABLE 1
Characteristics of patients studied

Patient	Age	Sex	Weight (per cent of ideal)	Fasting plasma glucose* (mg. per 100 ml.)	Therapy
A.F.	51	M	94	281	chlorpropamide
R.P.	53	F	100	195	chlorpropamide
P.B.	51	M	97	97	diet
M.O.	67	M	80	292	chlorpropamide
J.D.	42	M	100	159	chlorpropamide
M.C.	42	M	91	110	none
M.S.	59	M	96	121	chlorpropamide
Mean	52		94	179	

*Value during present test

ously received insulin, although five were taking chlorpropamide; none was ketotic. Familial diabetes was excluded as far as possible by a careful systematic inquiry.

Seven active, healthy, nonobese volunteers (six males, one female), belonging to a similar age group served as normal controls. None had a family history of diabetes, and their glucose tolerance tests were normal.

All subjects received an adequate carbohydrate intake prior to testing, and in those taking chlorpropamide the drug was stopped for four days before the test. It was felt that with a half-life of thirty-five hours, drug activity would be slight at the time of testing. After an overnight fast, each subject received an intravenous injection of 1 gm. tolbutamide over three minutes. Venous blood was obtained via an indwelling cannula placed in an antecubital vein. Samples for plasma and serum were taken at fasting and at 5, 10, 20, 30, 60 and 90 minutes after the end of the injection. They were separated and stored at -20° C. until analyses were made.

Plasma glucose was determined by the ferricyanide method of Hoffman⁷ modified for the AutoAnalyzer. Serum immunoreactive insulin (IRI) was assayed by the radioimmunoassay procedures of Hales and Randle,⁸ as modified by the Radiochemical Centre, Amersham Data Sheet 5616.

RESULTS

Serum insulin (IRI) response (figure 1)

There was no significant difference between the fasting IRI levels of the two groups ($p < 0.5$). In the normal subjects,

the mean IRI level rose promptly to a peak of $113 \mu\text{U./ml.}$ after five minutes, with subsequent gradual decline to the fasting level at 90 min. On the other hand, in the pancreatic diabetic patients the IRI response to tolbutamide was small, with a peak of only $28 \mu\text{U./ml.}$ at five minutes. The differences between the normal and pancreatitis groups were statistically significant at 5, 10 and 20 minutes ($p < 0.005$, $p < 0.01$, $p < 0.02$ respectively).

Plasma glucose response (table 1 and figure 1)

In the patients with pancreatitis the mean $\pm$ S.E.M. fasting plasma glucose value (179 ± 30 mg. per 100 ml.) was almost double the corresponding value (91 ± 4 mg. per 100 ml.) for the normal controls ($p < 0.02$). The normal subjects had a sharp decline in plasma glucose with a maximum fall of 43 per cent of the mean fasting value at thirty minutes. In the pancreatic diabetics, the fall in glucose was delayed and significantly less pronounced ($p < 0.001$ at 10, 20 and 30 minutes and $p < 0.05$ at sixty minutes). When the area under the curve was related to the mean increment in insulin area during the tolerance test however, the ratio obtained (0.9) was similar to that in the normal subjects (1.0). This suggests that the diminished glucose fall in the patients with pancreatitis simply reflected deficient insulin secretion (and not endogenous insulin resistance).

DISCUSSION

The findings in the present study further support the thesis of impaired insulin reserve in patients who develop diabetes secondary to chronic pancreatitis. Tolbutamide, a known insulinogenic stimulus, caused only slight increments in serum IRI in these subjects when compared to normal controls. Associated with this, the fall in blood glucose was diminished.

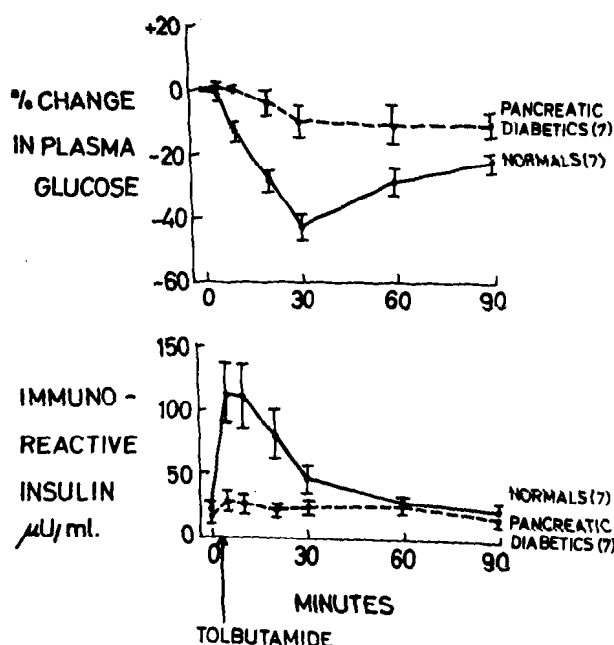


FIG. 1. Effect of intravenous tolbutamide on plasma glucose and serum immunoreactive insulin in normal subjects and pancreatic diabetics (mean $\pm$ S.E.M.)

In addition, the mean fasting serum IRI level was not significantly different in the two groups, despite the nearly two-fold greater mean fasting plasma glucose level in the pancreatic diabetic patients.

The possibility that factors other than pancreatic disease could have contributed to the poor insulin response after tolbutamide warrants consideration. Five of the patients were taking chlorpropamide prior to testing and a decreased insulin secretory response to glucose after months of therapy has been demonstrated.⁹ The changes in insulin levels were generally small; also the drug was discontinued for some days prior to testing in our study to minimize any similar effect. All the pancreatic diabetic patients were lean, and, since obesity leads to hyperinsulinism,¹⁰ it is feasible that leanness per se might be associated with a diminished pancreatic response to insulinogenic stimuli. This point must remain speculative, however, since there is little direct supporting evidence.

Comparison of the insulin responses in pancreatic diabetes with those in "primary" diabetes is of interest. In the light of recent observations,¹¹⁻¹³ a comparable group of middle-aged, nonobese, moderately severe primary diabetics could also be expected to show insulinopenia, although possibly not to the same extent. Indeed the results in our patients approach those reported in juvenile diabetes mellitus after intravenous tolbutamide.^{14,15}

Our findings also suggest that the majority of patients with pancreatic diabetes are unlikely to respond well to oral sulfonylurea agents because of their marked insulinopenia. The known unpredictability of the intravenous tolbutamide tolerance test in determining the likely response of patients to oral therapy¹⁶ and the abnormal sensitivity to exogenous insulin that patients with pancreatic diabetes manifest¹⁷ have prompted us, however, to investigate further this problem by means of a controlled trial. Preliminary results unfortunately are not encouraging.

ACKNOWLEDGMENT

This report forms part of the work of the joint University of Cape Town/C.S.I.R. Endocrine Research Group.

We wish to thank Dr. I. N. Marks for allowing us to study patients under his care and Dr. B. L. Pimstone for helpful advice and criticism. Mr. K. Samsodien, Mr. I. G. O'Reilly, Mr. P. Balk and Mr. S. Hendricks rendered valuable technical assistance. We are indebted to Mrs. E. Orkin for typing the manuscript. Supplies of tolbutamide were kindly given by Messrs. Hoechst Pharmaceuticals (Pty.) Ltd.

REFERENCES

- 1 Marks, I. N., and Bank, S.: The aetiology, clinical features and diagnosis of pancreatitis in the South Western Cape. *S. Afr. Med. J.* 37:1039, 1963.
- 2 Chey, W. Y., Shay, H., Nielsen, O. F., and Lorber, S. H.: Evaluation of tests of pancreatic function in chronic pancreatic disease. *JAMA* 201:347, 1967.
- 3 Peters, N., Dick, A. P., Hales, C. N., Orrell, D. H., and Sarner, M.: Exocrine and endocrine pancreatic function in diabetes mellitus and chronic pancreatitis. *Gut* 7:277, 1966.
- 4 Ohlsen, P.: Endocrine and exocrine pancreatic function in pancreatitis. *Acta Med. Scand. Supp.* 484, 1968.
- 5 Joffe, B. I., Bank, S., Jackson, W. P. U., Keller, P., O'Reilly, I. G., and Vinik, A. I.: Insulin reserve in patients

the mean IRI level rose promptly to a peak of $113 \mu\text{U./ml.}$ after five minutes, with subsequent gradual decline to the fasting level at 90 min. On the other hand, in the pancreatic diabetic patients the IRI response to tolbutamide was small, with a peak of only $28 \mu\text{U./ml.}$ at five minutes. The differences between the normal and pancreatitis groups were statistically significant at 5, 10 and 20 minutes ($p < 0.005$, $p < 0.01$, $p < 0.02$ respectively).

Plasma glucose response (table 1 and figure 1)

In the patients with pancreatitis the mean $\pm$ S.E.M. fasting plasma glucose value (179 ± 30 mg. per 100 ml.) was almost double the corresponding value (91 ± 4 mg. per 100 ml.) for the normal controls ($p < 0.02$). The normal subjects had a sharp decline in plasma glucose with a maximum fall of 43 per cent of the mean fasting value at thirty minutes. In the pancreatic diabetics, the fall in glucose was delayed and significantly less pronounced ($p < 0.001$ at 10, 20 and 30 minutes and $p < 0.05$ at sixty minutes). When the area under the curve was related to the mean increment in insulin area during the tolerance test however, the ratio obtained (0.9) was similar to that in the normal subjects (1.0). This suggests that the diminished glucose fall in the patients with pancreatitis simply reflected deficient insulin secretion (and not endogenous insulin resistance).

DISCUSSION

The findings in the present study further support the thesis of impaired insulin reserve in patients who develop diabetes secondary to chronic pancreatitis. Tolbutamide, a known insulinogenic stimulus, caused only slight increments in serum IRI in these subjects when compared to normal controls. Associated with this, the fall in blood glucose was diminished.

In addition, the mean fasting serum IRI level was not significantly different in the two groups, despite the nearly two-fold greater mean fasting plasma glucose level in the pancreatic diabetic patients.

The possibility that factors other than pancreatic disease could have contributed to the poor insulin response after tolbutamide warrants consideration. Five of the patients were taking chlorpropamide prior to testing and a decreased insulin secretory response to glucose after months of therapy has been demonstrated.⁹ The changes in insulin levels were generally small; also the drug was discontinued for some days prior to testing in our study to minimize any similar effect. All the pancreatic diabetic patients were lean, and, since obesity leads to hyperinsulinism,¹⁰ it is feasible that leanness per se might be associated with a diminished pancreatic response to insulinogenic stimuli. This point must remain speculative, however, since there is little direct supporting evidence.

Comparison of the insulin responses in pancreatic diabetes with those in "primary" diabetes is of interest. In the light of recent observations,¹¹⁻¹³ a comparable group of middle-aged, nonobese, moderately severe primary diabetics could also be expected to show insulinopenia, although possibly not to the same extent. Indeed the results in our patients approach those reported in juvenile diabetes mellitus after intravenous tolbutamide.^{14,15}

Our findings also suggest that the majority of patients with pancreatic diabetes are unlikely to respond well to oral sulfonylurea agents because of their marked insulinopenia. The known unpredictability of the intravenous tolbutamide tolerance test in determining the likely response of patients to oral therapy¹⁶ and the abnormal sensitivity to exogenous insulin that patients with pancreatic diabetes manifest¹⁷ have prompted us, however, to investigate further this problem by means of a controlled trial. Preliminary results unfortunately are not encouraging.

ACKNOWLEDGMENT

This report forms part of the work of the joint University of Cape Town/C.S.I.R. Endocrine Research Group.

We wish to thank Dr. I. N. Marks for allowing us to study patients under his care and Dr. B. L. Pimstone for helpful advice and criticism. Mr. K. Samsodien, Mr. I. G. O'Reilly, Mr. P. Balk and Mr. S. Hendricks rendered valuable technical assistance. We are indebted to Mrs. E. Orkin for typing the manuscript. Supplies of tolbutamide were kindly given by Messrs. Hoechst Pharmaceuticals (Pty.) Ltd.

REFERENCES

- 1 Marks, I. N., and Bank, S.: The aetiology, clinical features and diagnosis of pancreatitis in the South Western Cape. *S. Afr. Med. J.* 37:1039, 1963.
- 2 Chey, W. Y., Shay, H., Nielsen, O. F., and Lorber, S. H.: Evaluation of tests of pancreatic function in chronic pancreatic disease. *JAMA* 201:347, 1967.
- 3 Peters, N., Dick, A. P., Hales, C. N., Orrell, D. H., and Sarner, M.: Exocrine and endocrine pancreatic function in diabetes mellitus and chronic pancreatitis. *Gut* 7:277, 1966.
- 4 Ohlsen, P.: Endocrine and exocrine pancreatic function in pancreatitis. *Acta Med. Scand.: Supp.* 484, 1968.
- 5 Joffe, B. I., Bank, S., Jackson, W. P. U., Keller, P., O'Reilly, I. G., and Vinik, A. I.: Insulin reserve in patients

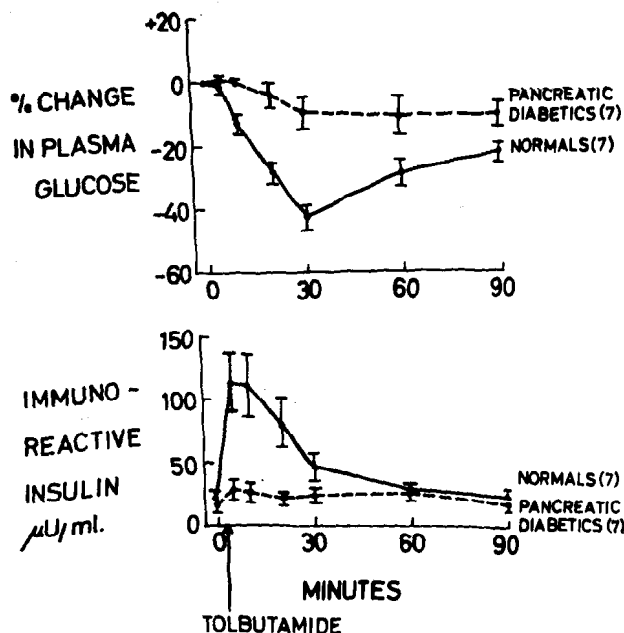


FIG. 1. Effect of intravenous tolbutamide on plasma glucose and serum immunoreactive insulin in normal subjects and pancreatic diabetics (mean $\pm$ S.E.M.)

BRIEF NOTES AND COMMENTS

- with chronic pancreatitis. *Lancet* 2:890, 1968.
- Johnson, W. P. U.: In "On Diabetes Mellitus." Springfield, Illinois: Charles C Thomas, 1964, chapter 8.
- 11 Hoffman, W. S.: A rapid photoelectric method for determination of glucose in blood and urine. *J. Biol Chem.* 120:51, 1937.
- 12 Hales, C. N., and Randle, P. J.: Immunoassay of insulin with insulin antibody precipitate. *Biochem. J.* 88:137, 1963.
- 13 Reaven, G., and Dray, J.: Effect of chlorpropamide on serum glucose and immunoreactive insulin concentrations in patients with maturity-onset diabetes mellitus. *Diabetes* 16:487, 1967.
- 14 Karam, J. H., Grodsky, G. M., and Forsham, P. H.: Excessive insulin response to glucose in obese subjects as measured by immunochemical assay. *Diabetes* 12:197, 1963.
- 15 Seltzer, H. S., Allen, E. W., Herron, A. L., Jr., and Brenner, M. L.: Insulin secretion in response to glycemic stimulus: relation of delayed initial release to carbohydrate intolerance in mild diabetes mellitus. *J. Clin. Invest.* 46:323, 1967.
- 16 Buchanan, K. D., and McKiddie, M. T.: Factors determining the plasma insulin response to oral glucose in diabetes mellitus. *Diabetes* 16:466, 1967.
- 17 Colwell, J. A., and Lein, A.: Diminished insulin response to hyperglycemia in prediabetes and diabetes. *Diabetes* 16:560, 1967.
- 18 de Belle, R. Belmonte, M. M., and Colle, E.: Effect of intravenous tolbutamide in juvenile diabetes mellitus. *Diabetes* 16:215, 1967.
- 19 Parker, M. L., Pildes, R. S., Chao, K., Cornblath, M., and Kipnis, D. M.: Juvenile diabetes mellitus, a deficiency in insulin. *Diabetes* 17:27, 1968.
- 20 Creutzfeldt, W., and Söling, H.: Oral Treatment of Diabetes. Berlin, Springer-Verlag, 1961, p. 56.
- 21 Joffe, B. I., Bank, S., and Marks, I. N.: Hypoglycaemia in pancreatitis. *Lancet* 2:1038, 1968.

The preceding paper implies that patients with 'pancreatic' diabetes are unlikely to respond well to oral sulphonylurea agents because of their marked insulinopaenia. This hypothesis is submitted to formal study in the following experimental design.

*Reprinted from The Journal of the British Society of Gastroenterology—GUT
Volume 13, page 285, 1972. Copyright © 1972 Gut. All rights of reproduction of this
reprint are reserved in all countries of the world*

Effect of oral hypoglycaemic agents on glucose tolerance in pancreatic diabetes

B. I. JOFFE, W. P. U. JACKSON, S. BANK, AND
A. I. VINIK

British Medical Association, Tavistock Square, London WC1H 9JR

Effect of oral hypoglycaemic agents on glucose tolerance in pancreatic diabetes

B. I. JOFFE, W. P. U. JACKSON, S. BANK, AND A. I. VINIK

From the Department of Medicine, Witwatersrand University Medical School, Johannesburg, the Gastro-intestinal and Endocrine Research Units of Cape Town University Medical School, and the Chemical Pathology Department of Natal University, South Africa

SUMMARY The short-term therapeutic effect of oral hypoglycaemic agents has been assessed in 12 patients with symptomatic diabetes secondary to chronic pancreatitis (pancreatic diabetes). In six patients who had moderate to severe carbohydrate intolerance, associated with severe insulinopaenia during arginine infusion, the potent sulphonylurea chlorpropamide produced no change in the fasting blood glucose level after two weeks of treatment. This contrasted with the significant reduction produced in a matched group of maturity-onset primary diabetics. The six patients with milder diabetes, and a greater (although still subnormal) insulin secretory capacity, showed an improvement in oral glucose tolerance during the first hour following glucose administration while on chlorpropamide. When the biguanide phenformin was substituted for chlorpropamide in five of these patients, a statistically insignificant improvement in glucose tolerance was observed during treatment.

Applications of these findings to the practical management of pancreatic diabetes are briefly considered.

Chronic pancreatitis is frequently complicated by diabetes (pancreatic diabetes). Recent studies utilizing immunoassay procedures (Joffe, Bank, Jackson, Keller, O'Reilly, and Vinik, 1968; Anderson Davison, Dick, Hales, and Owens, 1970) have indicated that when carbohydrate intolerance supervenes, insulin reserve is often considerably diminished. However, treatment of the diabetes with exogenous insulin may be complicated by severe hypoglycaemic episodes (Bank, 1966). A study was therefore designed to assess the short-term effect of oral hypoglycaemic agents in pancreatic diabetics with reference to their insulin-secretory status. The results of blood glucose concentrations and glucose tolerance before and after treatment are reported in this paper.

Patients and Methods

PATIENTS

Twelve non-obese patients with proven chronic pancreatic disease were studied. There were 10 men

and two women, ranging from 30 to 67 years of age. The diagnosis of pancreatitis was confirmed on the basis of a gross abnormality in at least two aspects of the pancreatic function test, namely, a low volume of pancreatic secretion (normal > 140 ml) measured 80 minutes after secretin or pancreozymin stimulation; a mean bicarbonate level of 50 m-equiv/litre or less (normal > 65 m-equiv/litre); and a mean amylase value of 4.0 Pimstone units/ml or less (normal > 5.0 Pimstone units/ml). Furthermore, radiological evidence of pancreatic calcification was observed in 11 of these patients, while steatorrhoea (faecal fat excretion > 5 g per day) was present in two-thirds of cases. Alcohol was thought to be of aetiological importance in all instances; despite this, clinical, biochemical, and histological evidence of liver disease was absent in all except one case. Six of the 12 patients had had clinical diabetes for longer than a year (maximum duration seven years) and in the remainder symptomatic diabetes was recently discovered. Only one had previously suffered from ketosis. None gave a family history of diabetes, had previously received regular insulin therapy, or was taking drugs known to affect carbohydrate metabolism.

EXPERIMENTAL DESIGN

After stabilization on a 2000 calorie 'diabetic' diet, patients were arbitrarily divided on the basis of fasting blood sugar determinations into two groups: those with elevated fasting levels, ie, above 120 mg/100 ml, were labelled 'moderate to severe' diabetics and those with normal fasting values designated as 'mild' diabetics. Each group consisted of six patients.

Arginine and chlorpropamide studies

The insulinogenic effect of arginine, a potent stimulus to beta cell activity (Floyd, Fajans, Conn, Knopf, and Rull, 1966), was estimated in the two groups in an attempt to establish their insulin secretory capacity. For this purpose, 30g arginine infusion studies were performed after an overnight fast in four of the severe pancreatic diabetics, all six mild patients, and also in seven non-obese normal male controls. Plasma samples for immunoreactive insulin determinations were obtained fasting, at the completion of the 30-minute infusion period, and half hourly for a further hour. The fasting and peak insulin values recorded during the test in each patient were used for analysis.

In the moderate to severe group, therapy was then instituted with 500 mg of chlorpropamide daily and after two weeks a repeat fasting blood glucose level obtained in each case. For comparison a group of seven recently diagnosed maturity-onset primary diabetics of matched age and severity were similarly investigated. The six mild pancreatic diabetics were subjected to formal 50 g oral glucose tolerance tests and then treated with chlorpropamide in an average daily dose of 375 mg. After a two-week period repeat glucose tolerance tests were performed. In five of these patients chlorpropamide was then withdrawn and a further glucose tolerance test carried out a month later; it was felt that with a biological half-life of about 36 hours, 'carry-over' chlorpropamide activity would be negligible at this stage. Thereafter they were given phenformin (in a dose of 50 mg sustained release capsule twice a day) for a two-week period at the end of which a final glucose tolerance test was done.

All tolerance tests were performed at rest, after an overnight fast; patients who were tested while on oral agents took their usual morning dose one to two hours before the start of the test.

METHODS

Glucose was determined half-hourly for two hours on capillary whole blood, using a Technicon Auto-Analyzer and the modified ferricyanide method of Hoffman (1937). Plasma insulin during the arginine infusions was measured by radioimmunoassay (Hales and Randle, 1963).

Results

Table I indicates the insulin secretory capacity of the two pancreatic diabetic subgroups, together with that of normal controls, as evidenced by their fasting and peak plasma immunoreactive insulin responses to intravenous arginine. Although fasting levels were similar, a tendency for insulin reserve to diminish with deteriorating carbohydrate tolerance was apparent. Numbers were too small for statistical evaluation of results.

Group	No. of Subjects	Plasma Insulin (μ U/ml) after Arginine	
		Fasting	Peak
Moderate to severe pancreatic diabetics	4	9 ± 1	12 ± 2
Mild pancreatic diabetics	6	9 ± 2	21 ± 4
Controls	7	10 ± 2	41 ± 7

Table I Fasting and peak plasma insulin responses (mean $\pm$ SEM) after 30 g arginine infusions in the severe and mild pancreatic diabetics as well as in seven controls

The effect of chlorpropamide (in a uniform dose of 500 mg daily) on fasting blood glucose levels in the six patients with moderate to severe pancreatic diabetes is shown in Table II. The drug produced no appreciable change in the mean fasting value, compared with the significant fall observed in the group of maturity-onset primary diabetics.

Diabetic Group	No. of Subjects	Age	Blood Glucose (mg/100 ml)		Significance
			Before Treatment	After Treatment	
Pancreatic	6	46	237 ± 25	241 ± 25	NS
Primary	7	51	187 ± 17	130 ± 15	

Table II Effect of chlorpropamide on fasting blood glucose levels (mean $\pm$ SEM) in moderate to severe pancreatic and primary diabetics

Table III summarizes the changes in glucose tolerance induced by chlorpropamide in the six patients with mild pancreatic diabetes. Significant improvement in the mean fasting, 30-, and 60-minute glucose values occurred during therapy but later levels showed no significant differences.

Table IV outlines the effect of phenformin on glucose tolerance in five of these mild pancreatic diabetics when it was substituted for chlorpropamide (after the latter had been withdrawn for a month). Except for the fasting level, which showed no

- Reaven, G., and Dray, J. (1967). Effect of chlorpropamide on serum glucose and immunoreactive insulin concentrations in patients with maturity-onset diabetes mellitus. *Diabetes*, 16, 487-492.
- Sevel, D., Bristow, J. H., Bank, S., Marks, I., and Jackson, P. (1971). Diabetic retinopathy in chronic pancreatitis. *Arch. Ophthalm.*, 86, 245-250.
- Siperstein, M. D., Unger, R. H., and Madison, L. L. (1968). Studies of muscle capillary basement membranes in normal subjects, diabetic, and prediabetic patients. *J. clin. Invest.*, 47, 1973-1999.
- Sterne, J. (1964). The present state of knowledge on the mode of action of the antidiabetic diguanides. *Metabolism* 13 791-798.

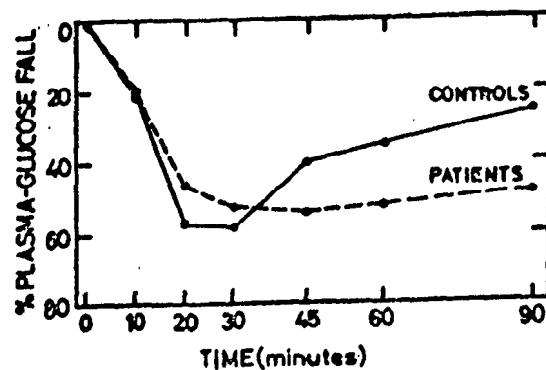
Insulin sensitivity in chronic pancreatitis has been mentioned in the previous paper. The following short communication provides evidence to support this contention.

HYPOGLYCAEMIA IN PANCREATITIS

SIR,—We are interested in the preliminary communication of Dr. Sutton and Dr. Taghizadeh (Sept. 28, p. 712), for there seems to be some relation between their findings and our studies in patients with pancreatitis.

8 patients with chronic calcific pancreatitis, due to alcohol, were given an intravenous injection of crystalline insulin (0.1 unit per kg. body-weight) after an overnight fast. 7 had diabetic glucose-tolerance tests (almost all with normal *fasting* blood-sugar levels) but none of the patients had previously received insulin therapy. A matched group of healthy non-obese controls, without family history of diabetes, was similarly investigated.

As the accompanying figure indicates, pancreatitis subjects responded with a slightly delayed but significantly prolonged ($P < 0.05$ at 45, 60, and 90 minutes) fall in plasma-glucose com-



Mean % plasma-glucose fall, from fasting, in 8 patients with chronic pancreatitis and healthy controls after intravenous administration of insulin (0.1 unit per kg. body-weight).

pared with the control group. In addition the pancreatitis patients invariably showed clinical evidence of hypoglycaemia during the latter stages of the test.

The prolonged hypoglycaemia in the pancreatitis group is unlikely to have been primarily due to defective compensatory glycogenolysis, since most of the patients were previously found to have entirely normal liver function and histology. Delay in

degradation of the injected insulin is a possible explanation but, like Dr. Sutton and Dr. Taghizadeh, we feel that pancreatic glucagon insufficiency may have been important. It is tempting to postulate that these patients, already deficient in insulin reserve,¹ are similarly lacking in stores of pancreatic glucagon with which to help maintain glucose homeostasis. Recently established techniques of plasma-glucagon immunoassay,^{2,3} may well provide the answer.

An important clinical application of these findings is to emphasise the need for caution in administering insulin to subjects with "pancreatic diabetes" if serious hypoglycæmia is to be avoided. This complication has previously been found to be an important cause of death in such patients.⁴

Endocrine Research and Gastrointestinal Units,
Department of Medicine,
University of Cape Town, South Africa.

B. I. JOFFE
S. BANK
I. N. MARKS.

1. Joffe, B. I., Bank, S., Jackson, W. P. U., Keller, P., O'Reilly, I. G., Vinik, A. I. *Lancet*, Oct. 26, 1968, p. 890.
2. Hazzard, W. R., Crockford, P. M., Buchanan, K. D., Vance, J. E., Chen, R., Williams, R. H. *Diabetes*, 1968, 17, 179.
3. Eisentraut, A., Ohneda, A., Parada, E., Unger, R. H., *ibid.* p. 321.
4. Bank, S. *S. Afr. med. J.* 1966, 40, 342.

Author's note

The above communication was cited in two editorial reviews:

- 1) Glucagon. *Lancet*, Nov. 9th, 1968: page 1021.
- 2) Diabetes and Pancreatitis. *Lancet*, Nov. 16th, 1968: page 1070.

In an attempt to determine the cause of prolonged hypoglycaemia after insulin administration in 'pancreatic' diabetes, we measured concomitant growth hormone responses - since growth hormone is an important insulin 'antagonist'. Results are reported in the following publication.

GROWTH HORMONE RESPONSE TO INSU-
LIN-INDUCED HYPOGLYCEMIA IN
DIABETES SECONDARY TO
CHRONIC CALCIFIC
PANCREATITIS

A. I. VINIK, B. I. JOFFE, S. M. JOUBERT, AND
W. P. U. JACKSON



Reprinted from

*THE JOURNAL OF
CLINICAL ENDOCRINOLOGY AND METABOLISM*

Vol. 31, No. 1, July, 1970, pp. 86-88

Published for The Endocrine Society by
J. B. Lippincott Company, Publishers
Philadelphia, Pennsylvania

Printed in the U.S.A.

Growth Hormone Response to Insulin-Induced Hypoglycemia in Diabetes Secondary to Chronic Calcific Pancreatitis

A. I. VINIK,¹ B. I. JOFFE,² S. M. JOUBERT,¹ AND W. P. U. JACKSON²

ABSTRACT. Human growth hormone (HGH) responses to insulin-induced hypoglycemia were measured in 6 patients with diabetes secondary to chronic calcific pancreatitis (pancreatic diabetes). A group of carefully matched control subjects was similarly investigated. Despite induced hypoglycemia of a magnitude not significantly different from the controls at 30 min, and significantly greater at 45 and 60 min, patients

with pancreatic diabetes responded with significantly impaired peak HGH levels. The interpretation of these findings is uncertain, although the observation that children with cystic fibrosis of the pancreas show similarly blunted responses suggests that a pancreatic stimulus to HGH secretion may be lacking. (*J Clin Endocr* 31: 86, 1970)

ABNORMAL sensitivity to exogenously administered insulin has been demonstrated in patients who develop diabetes secondary to chronic pancreatitis (pancreatic diabetes) (1). Pancreatic glucagon insufficiency may be partly responsible, and preliminary data of Aguilar Parada and associates (2) tend to support this hypothesis. However, as insulin sensitivity can occur in human growth hormone (HGH) deficiency, it was of interest to measure the HGH responses during insulin-induced hypoglycemia in pancreatic diabetes.

Materials and Methods

Six lean patients (5 males and 1 female) with well-proven chronic pancreatic disease—all showing radiologically demonstrable pancreatic calcification—were studied. Chronic alcoholism was considered to have been an etiological factor in all cases. Despite this, biochemical evidence of hepatic dysfunction was uniformly absent. No patient was hypoalbuminemic or uremic and there was no known family history of diabetes. The mean age of the patients was 57 yr (range 50–64 yr). All had diabetic glucose tolerance curves (3)—although, except in one instance, the fasting blood sugar was normal. None had previously received insulin therapy (2, taking oral sulfonylurea drugs, were instructed to discontinue them before testing). No patient showed ketosis or admitted to recent heavy consumption of alcohol. None were taking drugs known to suppress the HGH response to insulin hypoglycemia (4, 5).

Received December 15, 1969.

¹ Sub-dept. of Chemical Pathology, University of Natal Medical Faculty.

² Endocrine Research Unit, University of Cape Town Medical School, South Africa.

The “control” subjects comprised 6 age and sex matched healthy, non-obese, laboratory attendants with normal glucose tolerance and no family history of diabetes.

Subjects in each group were tested at rest, after an overnight fast. An indwelling polythene cannula was placed in an antecubital vein for blood sampling and a fasting specimen obtained. Crystalline insulin was then given intravenously into the opposite forearm (in a dose of 0.1 U/kg body weight). Further samples were taken at 30, 45, 60 and 90 min after the injection.

Plasma glucose was determined, immediately, on the AutoAnalyzer by the modified ferricyanide procedure (6). HGH was measured (on deep frozen plasma samples, at a later date) by a modified radioimmunoassay method of Morgan and Lazarow³ (7).

Results

Table 1 shows the plasma glucose and HGH levels of the pancreatitis and control subjects during the test. Despite induced hypoglycemia of a magnitude not significantly different from the controls at 30 min, and significantly greater at 45 and 60 min, the patients with pancreatic diabetes responded with significantly impaired mean HGH levels at 45 and 60 min (the times of maximum concentration in both groups). This is more strikingly brought out when increases in HGH produced by hypoglycemia (Δ HGH)—calculated by subtracting the basal from the peak value in each patient—are compared. The difference between the mean value

³ HGH H51147BC, and antibody, supplied by the Endocrine Study Section of the NIH, Bethesda, Md, was used for preparation of standards and labeled hormones.

Growth Hormone Response to Insulin-Induced Hypoglycemia in Diabetes Secondary to Chronic Calcific Pancreatitis

I. VINIK,¹ B. I. JOFFE,² S. M. JOUBERT,¹ AND W. P. U. JACKSON²

ABSTRACT. Human growth hormone (HGH) responses to insulin-induced hypoglycemia were measured in 6 patients with diabetes secondary to chronic calcific pancreatitis (pancreatic diabetes). A group of carefully matched control subjects was similarly investigated. Despite induced hypoglycemia of a magnitude not significantly different from the controls at 30 min, and significantly greater at 45 and 60 min, patients

with pancreatic diabetes responded with significantly impaired peak HGH levels. The interpretation of these findings is uncertain, although the observation that children with cystic fibrosis of the pancreas show similarly blunted responses suggests that a pancreatic stimulus to HGH secretion may be lacking. (*J Clin Endocr* 31: 86, 1970)

ABNORMAL sensitivity to exogenously administered insulin has been demonstrated in patients who develop diabetes secondary to chronic pancreatitis (pancreatic diabetes) (1). Pancreatic glucagon insufficiency may be partly responsible, and preliminary data of Aguilar Parada and associates (2) tend to support this hypothesis. However, as insulin sensitivity can occur in human growth hormone (HGH) deficiency, it was of interest to measure the HGH responses during insulin-induced hypoglycemia in pancreatic diabetes.

Materials and Methods

Six lean patients (5 males and 1 female) with well-proven chronic pancreatic disease—all showing radiologically demonstrable pancreatic calcification—were studied. Chronic alcoholism was considered to have been an etiological factor in all cases. Despite this, biochemical evidence of hepatic dysfunction was uniformly absent. No patient was hypoalbuminemic or uremic and there was no known family history of diabetes. The mean age of the patients was 57 yr (range 50–64 yr). All had diabetic glucose tolerance curves (3)—although, except in one instance, the fasting blood sugar was normal. None had previously received insulin therapy (2, taking oral sulfonylurea drugs, were instructed to discontinue them before testing). No patient showed ketosis or admitted to recent heavy consumption of alcohol. None were taking drugs known to suppress the HGH response to insulin hypoglycemia (4, 5).

Received December 15, 1969.

¹ Sub-dept. of Chemical Pathology, University of Natal Medical Faculty.

² Endocrine Research Unit, University of Cape Town Medical School, South Africa.

The “control” subjects comprised 6 age and sex matched healthy, non-obese, laboratory attendants with normal glucose tolerance and no family history of diabetes.

Subjects in each group were tested at rest, after an overnight fast. An indwelling polythene cannula was placed in an antecubital vein for blood sampling and a fasting specimen obtained. Crystalline insulin was then given intravenously into the opposite forearm (in a dose of 0.1 U/kg body weight). Further samples were taken at 30, 45, 60 and 90 min after the injection.

Plasma glucose was determined, immediately, on the AutoAnalyzer by the modified ferricyanide procedure (6). HGH was measured (on deep frozen plasma samples, at a later date) by a modified radioimmunoassay method of Morgan and Lazarow³ (7).

Results

Table 1 shows the plasma glucose and HGH levels of the pancreatitis and control subjects during the test. Despite induced hypoglycemia of a magnitude not significantly different from the controls at 30 min, and significantly greater at 45 and 60 min, the patients with pancreatic diabetes responded with significantly impaired mean HGH levels at 45 and 60 min (the times of maximum concentration in both groups). This is more strikingly brought out when increases in HGH produced by hypoglycemia (Δ HGH)—calculated by subtracting the basal from the peak value in each patient—are compared. The difference between the mean value

³ HGH H51147BC, and antibody, supplied by the Endocrine Study Section of the NIH, Bethesda, Md, was used for preparation of standards and labeled hormones.

TABLE 1. Plasma glucose and growth hormone concentrations in control subjects and pancreatic diabetics during insulin tolerance test

during insulin tolerance test											
Time (min)	Plasma glucose mg/100 ml					Plasma HGH ng/ml					Δ HGH* ng/ml
	0	30	45	60	90	0	30	45	60	90	
<i>Control subjects</i>											
IO	94	48	48	58	—	0.0	0.0	27.0	30.0	—	30.0
MS	93	41	59	54	60	0.0	0.0	28.0	26.0	25.0	28.0
EA	84	31	43	52	64	6.7	56.0	15.5	11.5	5.7	49.3
TS	102	36	62	65	78	0.0	0.0	39.5	30.1	24.0	39.5
KS	93	41	60	62	68	0.0	0.0	17.0	37.0	12.1	37.0
LS	100	25	50	49	52	7.8	1.9	21.0	47.0	28.0	39.2
Mean	94	37	54	57	64	2.4	9.7	24.7	30.3	19.0	37.2
SEM	3	3	3	2	4	1.5	—	3.6	4.8	4.3	3.1
<i>Pancreatic diabetics</i>											
AA	99	37	44	51	51	2.9	—	16.0	17.5	12.0	14.6
PB	102	40	45	53	83	0.8	2.9	7.7	14.5	12.1	13.7
DK	79	36	30	28	20	1.2	0.4	11.4	18.0	15.3	16.8
GN	174	74	55	40	40	0.0	0.0	1.2	2.0	0.8	2.0
DM	98	53	45	51	—	2.3	11.9	17.0	17.5	—	15.2
MS	81	40	36	40	44	3.2	9.9	16.0	11.4	12.5	12.8
Mean	106	47	43	44	48	1.7	5.0	11.6	13.5	10.5	12.5
SEM	14	6	4	4	10	0.5	2.5	2.5	2.5	2.5	2.2
p (vs. normals)	NS	NS	< .05	< .02	NS	NS	NS	< .02	< .02	NS	< .001

* Increase in GHG produced by hypoglycemia and calculated by subtracting the basal from the peak value.

in normals (37.2) and in pancreatic diabetics (12.5) is highly significant ($p < .001$).

Discussion

Plasma GHG values in the control subjects during the intravenous insulin tolerance test are similar to those reported by other workers (8, 9). Patients with diabetes secondary to severe chronic pancreatitis were by no means totally deficient in GHG reserve; nevertheless, in comparison with the control responses, a significant impairment emerged. In considering possible reasons for our observation, the effect of the diabetes *per se* is uncertain since there are reports of blunted (10), normal (11) and variable (12) growth hormone responses after induced hypoglycemia in "primary" diabetes. Chronic alcoholism was a common etiological factor in the patients studied, but there is little evidence to suggest that prolonged alcoholic consumption has a directly adverse effect on anterior pituitary function in man.

Of particular interest, however, is the observation that children with cystic fibrosis of the pancreas show a similarly impaired GHG response to hypoglycemia (13). This has not been substantiated by Handwerger and co-workers (14)—but they did not compare results with those of unaffected subjects. It is tempting to postulate that children with cystic fibrosis and patients with chronic pancreatitis respond poorly because they lack a pancreatic stimulus to GHG secretion. Glucagon has been associ-

ated with increases in GHG secretion when injected into healthy infants and adults (15, 16), but a recent study (17) casts doubt as to any physiological role of glucagon in this connection. The subnormal GHG responses in both diseases might also be explicable on a malnutritional basis—although the report of raised growth hormone levels in protein-calorie malnutrition (18) makes this unlikely.

Whether the impoverished growth hormone secretion shown above is an isolated pituitary disorder, or reflects a more widespread disturbance of anterior pituitary (or even hypothalamic) function, is currently being evaluated.

Practical implications of our findings are uncertain, but insulin sensitivity, rarity of ketosis and even relative freedom from diabetic retinopathy that pancreatic diabetics seem to enjoy (19) could be related.

Acknowledgments

The study was financed, in part, by the South African Medical Research Council and Atomic Energy Board. Valuable technical aid was rendered by Mr. M. G. Toyer, Mr. K. Samsodien and Mr. S. James. Mrs. R. Joffe kindly assisted with typing. We are grateful to Drs. I. N. Marks and S. Bank for allowing us to study patients under their care.

References

1. Joffe, B. I., S. Bank, and I. N. Marks, *Lancet* 2: 1038, 1968.
2. Aguilar-Parada, E., A. M. Eisentraut, and

TABLE 1. Plasma glucose and growth hormone concentrations in control subjects and pancreatic diabetics during insulin tolerance test

Time (min)	Plasma glucose mg/100 ml					Plasma HGH ng/ml					Δ HGH* ng/ml
	0	30	45	60	90	0	30	45	60	90	
<i>Control subjects</i>											
IO	94	48	48	58	—	0.0	0.0	27.0	30.0	—	30.0
MS	93	41	59	54	60	0.0	0.0	28.0	26.0	25.0	28.0
EA	84	31	43	52	64	6.7	56.0	15.5	11.5	5.7	49.3
TS	102	36	62	65	78	0.0	0.0	39.5	30.1	24.0	39.5
KS	93	41	60	62	68	0.0	0.0	17.0	37.0	12.1	37.0
LS	100	25	50	49	52	7.8	1.9	21.0	47.0	28.0	39.2
Mean	94	37	54	57	64	2.4	9.7	24.7	30.3	19.0	37.2
SEM	3	3	3	2	4	1.5	—	3.6	4.8	4.3	3.1
<i>Pancreatic diabetics</i>											
AA	99	37	44	51	51	2.9	—	16.0	17.5	12.0	14.6
PB	102	40	45	53	83	0.8	2.9	7.7	14.5	12.1	13.7
DK	79	36	30	28	20	1.2	0.4	11.4	18.0	15.3	16.8
GN	174	74	55	40	40	0.0	0.0	1.2	2.0	0.8	2.0
DM	98	53	45	51	—	2.3	11.9	17.0	17.5	—	15.2
MS	81	40	36	40	44	3.2	9.9	16.0	11.4	12.5	12.8
Mean	106	47	43	44	48	1.7	5.0	11.6	13.5	10.5	12.5
SEM	14	6	4	4	10	0.5	2.5	2.5	2.5	2.5	2.2
p (vs. normals)	NS	NS	< .05	< .02	NS	NS	NS	< .02	< .02	NS	< .001

* Increase in HGH produced by hypoglycemia and calculated by subtracting the basal from the peak value.

in normals (37.2) and in pancreatic diabetics (12.5) is highly significant ($p < .001$).

Discussion

Plasma HGH values in the control subjects during the intravenous insulin tolerance test are similar to those reported by other workers (8, 9). Patients with diabetes secondary to severe chronic pancreatitis were by no means totally deficient in HGH reserve; nevertheless, in comparison with the control responses, a significant impairment emerged. In considering possible reasons for our observation, the effect of the diabetes *per se* is uncertain since there are reports of blunted (10), normal (11) and variable (12) growth hormone responses after induced hypoglycemia in "primary" diabetes. Chronic alcoholism was a common etiological factor in the patients studied, but there is little evidence to suggest that prolonged alcoholic consumption has a directly adverse effect on anterior pituitary function in man.

Of particular interest, however, is the observation that children with cystic fibrosis of the pancreas show a similarly impaired HGH response to hypoglycemia (13). This has not been substantiated by Handwerger and co-workers (14)—but they did not compare results with those of unaffected subjects. It is tempting to postulate that children with cystic fibrosis and patients with chronic pancreatitis respond poorly because they lack a pancreatic stimulus to HGH secretion. Glucagon has been associ-

ated with increases in HGH secretion when injected into healthy infants and adults (15, 16), but a recent study (17) casts doubt as to any physiological role of glucagon in this connection. The subnormal HGH responses in both diseases might also be explicable on a malnutritional basis—although the report of raised growth hormone levels in protein-calorie malnutrition (18) makes this unlikely.

Whether the impoverished growth hormone secretion shown above is an isolated pituitary disorder, or reflects a more widespread disturbance of anterior pituitary (or even hypothalamic) function, is currently being evaluated.

Practical implications of our findings are uncertain, but insulin sensitivity, rarity of ketosis and even relative freedom from diabetic retinopathy that pancreatic diabetics seem to enjoy (19) could be related.

Acknowledgments

The study was financed, in part, by the South African Medical Research Council and Atomic Energy Board. Valuable technical aid was rendered by Mr. M. G. Toyer, Mr. K. Samsodien and Mr. S. James. Mrs. R. Joffe kindly assisted with typing. We are grateful to Drs. I. N. Marks and S. Bank for allowing us to study patients under their care.

References

1. Joffe, B. I., S. Bank, and I. N. Marks, *Lancet* 2: 1038, 1968.
2. Aguilar-Parada, E., A. M. Eisentraut, and

Characterisation of the diabetic syndrome complicating chronic pancreatitis would be incomplete without measurement of serum lipids in this situation. A preliminary report of fasting serum cholesterol, phospholipid and triglyceride levels is presented in the next paper.

PRELIMINARY REPORT

Serum Lipid Levels in Diabetes Secondary to Chronic Pancreatitis

By B. I. JOFFE, L. KRUT, S. BANK, I. N. MARKS AND P. KELLER

The mean fasting level of serum cholesterol and phospholipids in 20 patients with diabetes secondary to chronic pancreatitis (pancreatic diabetes) was significantly lower than levels found in matched groups of essential diabetics and normal controls. Mean fasting triglyceride values showed no significant differences between the three groups, although lowest in the pancreatitis patients. A low

intake, or malabsorption, of dietary fat appear unlikely to have been primarily responsible for the relative hypolipidemia in pancreatic diabetes. The possible significance of these observations to the pathogenesis of diabetic microangiopathy is briefly discussed and the value of the serum cholesterol level as a diagnostic aid indicated. (*Metabolism* 19: No. 1, January, 87-90, 1969)

CHRONIC PANCREATITIS may be complicated by the development of diabetes (pancreatic diabetes).¹ In this situation steatorrhoea is often present.² The blood lipid composition could be affected by either complication, and a preliminary investigation into this aspect of chronic pancreatic disease was therefore undertaken.

MATERIALS AND METHODS

Twenty patients (17 males and 3 females) with unequivocal evidence of chronic pancreatitis (19 showing radiologically demonstrable pancreatic calcification) were studied.

From the Endocrine Research, Lipid Research and Gastro-Intestinal Units, Department of Medicine, and Groote Schuur Hospital, University of Cape Town, Cape Town, South Africa.

Received for publication June 20, 1969.

Supported in part by the South African Council for Scientific and Industrial Research.

B. I. JOFFE, M.B., B.Ch., M.R.C.P.: Research Associate, Endocrine Research Unit. L. KRUT, M.D.: Chief Research Officer, Lipid Research Unit. S. BANK, M.B., M.C.R.P.: Consultant Gastroenterologist, Groote Schuur Hospital. I. N. MARKS, M.B., F.R.C.P.E.: Part-time Head, Gastro-Intestinal Unit. P. KELLER, Ph.D.: Research Officer, Endocrine Research Unit.

EDITORIAL COMMENT: With increased fragmentation of the formerly simple "diagnosis" of diabetes mellitus, there has been increased interest in primary or secondary diabetes. True "pancreatic diabetes" is said to be relatively rare and presumably a complete pancreatitis is one of the means of achieving this state. It then becomes an interesting means of studying some of the blood lipids which are frequently mentioned in the literature as being as important as blood glucose levels in following the course of diabetes. This neat project not only suggests the possibility of association between blood lipid levels and development of subsequent microangiopathy, but further suggests that serum cholesterol might help differentiate between "essential" and pancreatic diabetes. Admittedly this would involve a relatively small number of cases but any bit of evidence shedding light on the enigma of diabetes is welcome.—*Leo P. Krall, M.D.*

Table 1.—Comparison of Fasting Serum Lipid and Glucose Levels in Pancreatic Diabetics, Essential Diabetics, and Normal Controls

	Cholesterol (mg. %)	Phospholipids (mg. %)	Triglycerides (mg. %)	Glucose (mg. %)
Pancreatic Diabetics	152 ± 8*	167 ± 8*	83 ± 6	138 ± 19
Essential Diabetics	223 ± 15	260 ± 17	107 ± 13	173 ± 25
Normal Controls	212 ± 10	229 ± 13	88 ± 9	84 ± 2

All values represent mean ± SEM.

* $P < .001$ compared with each of the other two groups.

Alcohol was considered to have been related to the aetiological factor in all except one case (where the cause was unknown). Despite this, biochemical evidence of hepatic dysfunction was uniformly absent. There was no known family history of diabetes in any patient. The mean age of the patients was 51 years (range 34 to 69 years). All had diabetic glucose tolerance curves and were receiving either dietary (5 patients), oral sulphonylurea (5 patients), or insulin therapy. None was ketotic, and none admitted to recent *heavy* alcohol consumption.

A group of 13 "essential" diabetics, matched as closely as possible with the pancreatic diabetics as regards age (mean 46 years), sex (10 males and 3 females), race, body weight (all nonobese), socio-economic status, severity of diabetes and therapy was also selected for study. The majority of these patients had a "positive" family history of diabetes. Again, no patient showed ketosis. A similar number of apparently healthy control subjects, matched with the pancreatitis patients as regards the above criteria, where pertinent, were also investigated.

Each subject was bled after an overnight fast, those on specific anti-diabetic therapy receiving no treatment during the preceding 24 hours. Venous blood was analysed for serum cholesterol,³ phospholipid,⁴ triglyceride,⁵ and glucose (Auto Analyzer) content. Ten of the pancreatic diabetics had 72-hour stool collections analyzed for fecal fat.⁶

A dietary history was obtained from each subject, with particular attention to the amount of dietary fat consumed.

RESULTS

As indicated in Table 1, patients with pancreatic diabetes have mean fasting cholesterol and phospholipid values that are significantly lower ($p < .001$) than those of both the essential diabetics and the normal controls. The mean fasting triglyceride level in the pancreatic diabetics is slightly lower than in the essential diabetics, but the difference is not statistically significant (p just $> .05$).

Mean values for each class of lipid in the essential diabetics are slightly higher than in normal controls but none of these differences are statistically significant.

Mean fasting serum glucose levels in the pancreatic diabetics are not significantly different ($p > .1$) from corresponding values in essential diabetics, indicating a comparable degree of diabetic severity in the two groups.

The average daily fecal fat excretion in the pancreatitis patients studied was 12.3 Gm. (range 3 to 45 Gm.). Of interest was the finding that two of three patients without steatorrhoea (fecal fat excretion less than 5 Gm. per day) had among the lowest serum cholesterol levels in the group (105 mg. % and 126 mg. %).

The dietary history of the pancreatic diabetics suggested that, within the limits of this crude method of analysis, their habitual consumption of fat was comparable to that of the essential diabetic group both in quality and quantity.

Dietary restriction of carbohydrate was similar in both groups of diabetic patients.

DISCUSSION

Although the association of pancreatitis with various forms of hyperlipemia has been recently reviewed,⁷ this study highlights another aspect of disordered lipid metabolism occurring in pancreatic disease. Remarkably low mean levels of cholesterol and phospholipid were found in twenty patients with severe chronic pancreatitis and secondary diabetes. Despite their accompanying disturbance of carbohydrate metabolism, and endogenous insulinopenia,⁸ *fasting* triglyceride levels were not elevated.

It seems unlikely that simple malabsorption of ingested fat can completely account for these findings, particularly as fat assimilation has been shown to be minimally impaired even after massive pancreatectomy for chronic pancreatitis.⁹ Lack of dietary fat does not appear to be an important factor and the possible existence of a more fundamental disturbance of lipid, notably cholesterol, metabolism warrants further consideration.

Serum lipids may be of importance in the pathogenesis of diabetic microangiopathy¹⁰ and of special relevance is the view that this complication is uncommon in pancreatic diabetes.^{11,12} If the latter can be more fully substantiated, the findings reported here would strengthen the evidence for an association between certain blood lipid levels and the development of diabetic microangiopathy.

The susceptibility of pancreatic diabetics to atherosclerosis is at present under review.

A point of practical value to emerge from this study is that the serum cholesterol concentration may aid in differentiating between "essential" and pancreatic diabetes, a distinction that is not always clinically apparent.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the technical assistance of Mr. M. G. Toyer and Mrs. I. Kramer.

REFERENCES

1. Marks, I. N., and Bank, S.: The etiology, clinical features and diagnosis of pancreatitis in the South Western Cape. *S. Afr. Med. J.* 37:1039, 1963.
2. Bishop, R. P.: The diagnosis of pancreatic disease. *Amer. J. Gastroent.* 49:112, 1968.
3. Abell, L. L., Levy, B. B., Brodie, B. B., and Kendall, F. E.: A simplified method for the estimation of total cholesterol in serum and determination of its specificity. *J. Biol. Chem.* 195:357, 1952.
4. Bartlett, G. R.: Phosphorous assay in column chromatography. *J. Biol. Chem.* 234:466, 1959.
5. Young, G., and Eastman, R.: A micro-method for the determination of serum triglycerides. *S. Afr. J. Lab. Clin. Med.* 9: 28, 1963.
6. Van de Kamer, J. H., Huinink, H. den B., Weyers, H. A.: Rapid method for the determination of fat in feces. *J. Biol. Chem.* 177: 347, 1949.
7. Banks, P. A., and Janowitz, H. D.: Some metabolic aspects of exocrine pancreatic disease. *Gastroenterology* 56:601, 1969.
8. Joffe, B. I., Bank, S., Jackson, W. P. U., Keller, P., O'Reilly, I. G., and Vinik, A. I.: Insulin reserve in patients with chronic pancreatitis. *Lancet* 2:890, 1968.

9. Kalser, M. H., Leite, C. A., and Warren, W. D.: Fat assimilation after massive distal pancreatectomy. *New Eng. J. Med.* 279:570, 1968.

10. Chester, E. M., and Barker, B. Q.: The role of lipid thrombi in the pathogenesis of diabetic retinopathy. *Arch. Int. Med.* 120:397, 1967.

11. Marks, I. N.: The natural history of calcific pancreatitis in the Western Cape. *Trans. Coll. Physicians S. Afr.* 12:54, 1968.

12. Siperstein, M. D., Unger, R. H., and Madison, L. L.: Studies of capillary basement membranes in normal subjects, diabetic and prediabetic patients. *J. Clin. Invest.* 47:1973, 1968.

As a follow-up study to the previous publication, oral fat tolerance tests were performed in nine patients with chronic pancreatitis and additional information about the nature of their altered lipid metabolism thereby obtained.

Oral Fat Tolerance Studies in Chronic Pancreatitis

by

B. I. JOFFE, M.B., M.R.C.P.

L. KRUT, M.D.

D. MENDELSON, M.D.

and

H. C. SEFTEL, M.B., Dip. Med.

Johannesburg, South Africa

Reprinted from

American Journal Gastroenterology

Volume 59, Number 6, Pages 522 to 527, June, 1973

Oral Fat Tolerance Studies in Chronic Pancreatitis

B. I. JOFFE, M.B., M.R.C.P.

L. KRUT, M.D.

D. MENDELSON, M.D.

and

H. C. SEFTEL, M.B., Dip. Med.

Johannesburg, South Africa

INTRODUCTION

A variety of alterations in lipid metabolism may occur in pancreatitis.¹ The development of an intense, transient hypertriglyceridemia has occasionally been noted in the acute attack.^{2,3} Chronic pancreatic disease (in the absence of an underlying hyperlipidemic state) is associated with a normal fasting serum triglyceride level and remarkably low cholesterol and phospholipid concentrations, despite coexistent diabetes mellitus.⁴ The extent to which maldigestion of dietary fat alone can account for the relative hypolipidemia in chronic pancreatitis is uncertain. Fat assimilation, even after massive distal pancreatectomy for pancreatitis, has been shown to be only slightly impaired⁵ and steatorrhea may be minimal or absent. It seemed of interest, therefore, to perform oral fat tolerance tests in patients with chronic pancreatitis in an attempt to elucidate further the nature of their altered lipid metabolism.

MATERIALS AND METHODS

Nine patients (seven males and two females), with unequivocal clinical and investigative⁶ evidence of chronic pancreatitis and all showing radiologically demonstrable pancreatic calcification, were studied. Their mean age was 53 years (range 47-67 years) and their mean body weight 91 per cent (range 71 to 117 per cent) of ideal. Alcohol was considered to have been an etiological factor in all cases. Despite this, biochemical evidence of hepatic dysfunction was detectable in only one patient (whose subsequent handling of fat did not differ from the others in this group). Serum albumin levels were normal in all cases. All had diabetic glucose tolerance curves and were receiving either dietary (three patients), oral sulphonylurea (one patient) or insulin therapy. None was ketotic at the time of the test or admitted to recent heavy alcohol consumption. There was no known family history of diabetes.

A group of five apparently healthy, nonobese male control subjects with a mean age of 55 years (range 52 to 61 years) and normal glucose tolerance, was similarly investigated.

From the Carbohydrate-Lipid Research Unit, Department of Medicine, University of the Witwatersrand Medical School.

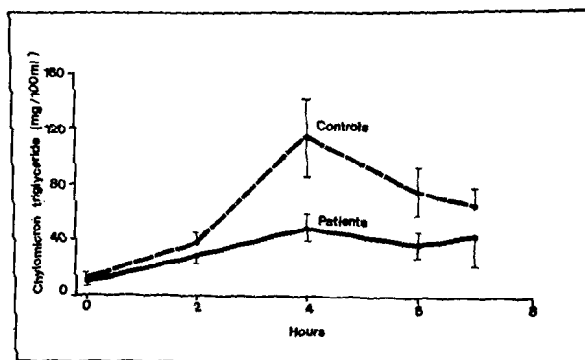


Fig. 1—Serum chylomicron triglyceride values during oral fat tolerance study in nine patients with chronic pancreatitis and in five normal controls. Vertical bars at each point indicate $\pm$ SEM.

Each subject was tested after an overnight fast. Those patients on specific antidiabetic, or pancreatic extract replacement therapy received no treatment in the 24-hour period preceding the test. After a fasting venous blood sample was obtained, each subject ate a standardized meal containing 70 gm. of butter fat (and 150 gm. of carbohydrate).⁷ Additional venous blood samples were collected at two, four, six and seven hours after the start of the meal. The subjects remained at rest during the experiment and did not smoke.

Blood samples were allowed to clot at room temperature and the serum separated by centrifugation. An aliquot of each serum sample was retained for triglyceride determination⁸ and the remainder ultracentrifuged (1.2×10^6 g min.) to separate the chylomicrons.⁹ Triglycerides were re-estimated in the subnatant serum.

The difference between the two triglyceride determinations on each serum sample was taken to represent the chylomicron triglyceride concentration and to reflect dietary fat absorbed in the postprandial state. The progressive rise of triglyceride which occurred in the subnatant fractions of serum during the test was thought to reflect, at least in part, incorporation of some of the chylomicrons into very low density lipoprotein (VLDL) triglyceride. Calculation¹⁰ of the area under each of these curves gave an estimate of the total chylomicron and VLDL triglyceride responses following the meal.

Fasting serum samples were also analyzed for total cholesterol¹¹ and glucose (auto analyzer) concentrations. Finally, at a later date, six of the pancreatitis patients had 72-hour stool collections measured¹² for fecal fat excretion.

RESULTS

Mean ($\pm$ SEM) serum chylomicron triglyceride values during the seven-hour fat tolerance test in the patients and controls are shown in Figure 1. The patients

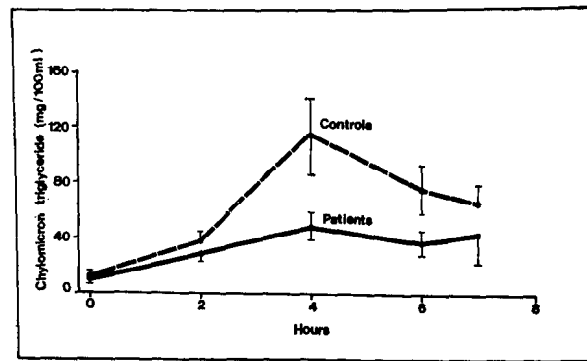


Fig. 1—Serum chylomicron triglyceride values during oral fat tolerance study in nine patients with chronic pancreatitis and in five normal controls. Vertical bars at each point indicate $\pm$ SEM.

Each subject was tested after an overnight fast. Those patients on specific antidiabetic, or pancreatic extract replacement therapy received no treatment in the 24-hour period preceding the test. After a fasting venous blood sample was obtained, each subject ate a standardized meal containing 70 gm. of butter fat (and 150 gm. of carbohydrate).⁷ Additional venous blood samples were collected at two, four, six and seven hours after the start of the meal. The subjects remained at rest during the experiment and did not smoke.

Blood samples were allowed to clot at room temperature and the serum separated by centrifugation. An aliquot of each serum sample was retained for triglyceride determination⁸ and the remainder ultracentrifuged (1.2×10^6 g min.) to separate the chylomicrons.⁹ Triglycerides were re-estimated in the subnatant serum.

The difference between the two triglyceride determinations on each serum sample was taken to represent the chylomicron triglyceride concentration and to reflect dietary fat absorbed in the postprandial state. The progressive rise of triglyceride which occurred in the subnatant fractions of serum during the test was thought to reflect, at least in part, incorporation of some of the chylomicrons into very low density lipoprotein (VLDL) triglyceride. Calculation¹⁰ of the area under each of these curves gave an estimate of the total chylomicron and VLDL triglyceride responses following the meal.

Fasting serum samples were also analyzed for total cholesterol¹¹ and glucose (auto analyzer) concentrations. Finally, at a later date, six of the pancreatitis patients had 72-hour stool collections measured¹² for fecal fat excretion.

RESULTS

Mean ($\pm$ SEM) serum chylomicron triglyceride values during the seven-hour fat tolerance test in the patients and controls are shown in Figure 1. The patients

TABLE II
COMPARISON OF FASTING SERUM CHOLESTEROL AND GLUCOSE CONCENTRATIONS
IN CHRONIC PANCREATITIS AND NORMAL CONTROLS

Group	Number	Cholesterol (mg. %)	Glucose (mg. %)
Chronic pancreatitis	9	143 $\pm$ 11	167 $\pm$ 34
Normal controls	5	214 $\pm$ 7	85 $\pm$ 10

All values represent mean $\pm$ SEM.

It would appear, from their lesser degree of chylomicronemia, that total fat absorption was reduced in the patients. There was also some inverse correlation between their total chylomicron responses and amount of steatorrhea. It was of interest, however, that no evidence of diarrhea occurred in the patients during the test period itself, suggesting that their fat absorption might have continued at a slower rate for a more prolonged period. Unfortunately, delayed serum samples were not available to assess this possibility.

There was some indirect evidence to suggest that plasma chylomicron clearance might also have been impaired, although this needs to be interpreted with caution.

Removal of dietary fat from plasma is presumably related to the activity of the lipoprotein lipase system; this system has been shown to be insulin-dependent.¹³ Since the patients with pancreatitis were all diabetic, with severely limited insulin reserve,¹⁴ impaired chylomicron removal might well be anticipated. It has recently been shown, however, that the major portion of chylomicron triglyceride cleared from the plasma is initially directed into pools other than VLDL.¹⁵ Therefore, the method by which chylomicron clearance was assessed in our study does not provide the most sensitive index of this process. A more appropriate assessment of this aspect of lipid metabolism, such as the disappearance rate of intravenously administered chylomicron particles, would need to be undertaken for definitive conclusions to be drawn.

The striking hypocholesterolemia in chronic pancreatitis was previously reported.⁴ The direct correlation between serum cholesterol and total chylomicron response in the patients suggests that exocrine pancreatic secretions critically influence the serum cholesterol concentration as well as the absorption of dietary triglyceride. Whether these functions are mutually dependent, or whether pancreatic secretions effect serum cholesterol concentrations by mechanisms independent of their role in the assimilation of dietary triglyceride, remains to be determined. Additional support for the role of pancreatic secretions in determining

3. Bagdade JD: Diabetic lipaemia complicating acute pancreatitis. *Lancet* 2:1041-1043, 1969.
4. Joffe BI, Krut L, Bank S, et al: Serum lipid levels in diabetes secondary to chronic pancreatitis. *Metabolism* 19:87-90, 1970.
5. Kalser MH, Leite CA, Warren WD: Fat assimilation after massive distal pancreatectomy. *New Eng J Med* 279:570-576, 1968.
6. Bank S, Marks IN, Moshal MG, et al: The pancreatic function test—methods and normal values. *S Afr Med J* 37:1061-1066, 1963.
7. Bouchier IAD, Bronte-Stewart B: Alimentary lipaemia and ischaemic heart disease. *Lancet* 1:363-366, 1961.
8. Young C, Eastman R: A micromethod for the determination of serum triglycerides. *S Afr J Lab Clin Med* 9:28-31, 1963.
9. Krut LH, Barsky RF: Effect of enhanced glucose utilization on postprandial lipaemia in ischaemic heart disease. *Lancet* 2:1136-1138, 1964.
10. Mann JI, Truswell AS, Pimstone BL: The different effects of oral sucrose and glucose on alimentary lipaemia. *Clin Sci* 41:123-129, 1971.
11. Abell LL, Levy BB, Brodie BB, et al: A simplified method for the estimation of total cholesterol in serum and determination of its specificity. *J Biol Chem* 195:357-366, 1952.
12. Van de Kamer JH, Huinink H den B, Weyers HA: Rapid method for the determination of fat in feces. *J Biol Chem* 177:347-355, 1949.
13. Schnatz JD, Williams RH: The effects of acute insulin deficiency in the rat on adipose tissue lipolytic activity plasma lipids. *Diabetes* 12:174-178, 1963.
14. Joffe BI, Bank S, Jackson WPU, et al: Insulin reserve in patients with chronic pancreatitis. *Lancet* 2:890-892, 1968.
15. Bergman EN, Havel RJ, Wolfe BM, et al: Quantitative studies of the metabolism of chylomicron triglycerides and cholesterol by liver and extrahepatic tissues of sheep and dogs. *J Clin Invest* 50:1831-1839, 1971.
16. Bell CC, Swell L: Effect of total pancreatectomy on cholesterol absorption and serum cholesterol level in man. *Proc Soc Exp Biol Med* 128:575-577, 1968.

3. Bagdade JD: Diabetic lipaemia complicating acute pancreatitis. *Lancet* 2:1041-1043, 1969.
4. Joffe BI, Krut L, Bank S, et al: Serum lipid levels in diabetes secondary to chronic pancreatitis. *Metabolism* 19:87-90, 1970.
5. Kalser MH, Leite CA, Warren WD: Fat assimilation after massive distal pancreatectomy. *New Eng J Med* 279:570-576, 1968.
6. Bank S, Marks IN, Moshal MG, et al: The pancreatic function test—methods and normal values. *S Afr Med J* 37:1061-1066, 1963.
7. Bouchier IAD, Bronte-Stewart B: Alimentary lipaemia and ischaemic heart disease. *Lancet* 1:363-366, 1961.
8. Young C, Eastman R: A micromethod for the determination of serum triglycerides. *S Afr J Lab Clin Med* 9:28-31, 1963.
9. Krut LH, Barsky RF: Effect of enhanced glucose utilization on postprandial lipaemia in ischaemic heart disease. *Lancet* 2:1136-1138, 1964.
10. Mann JJ, Truswell AS, Pimstone BL: The different effects of oral sucrose and glucose on alimentary lipaemia. *Clin Sci* 41:123-129, 1971.
11. Abell LL, Levy BB, Brodie BB, et al: A simplified method for the estimation of total cholesterol in serum and determination of its specificity. *J Biol Chem* 195:357-366, 1952.
12. Van de Kamer JH, Huinink H den B, Weyers HA: Rapid method for the determination of fat in feces. *J Biol Chem* 177:347-355, 1949.
13. Schnatz JD, Williams RH: The effects of acute insulin deficiency in the rat on adipose tissue lipolytic activity plasma lipids. *Diabetes* 12:174-178, 1963.
14. Joffe BI, Bank S, Jackson WPU, et al: Insulin reserve in patients with chronic pancreatitis. *Lancet* 2:890-892, 1968.
15. Bergman EN, Havel RJ, Wolfe BM, et al: Quantitative studies of the metabolism of chylomicron triglycerides and cholesterol by liver and extrahepatic tissues of sheep and dogs. *J Clin Invest* 50:1831-1839, 1971.
16. Bell CC, Swell L: Effect of total pancreatectomy on cholesterol absorption and serum cholesterol level in man. *Proc Soc Exp Biol Med* 128:575-577, 1968.

In view of the relative hypolipidaemia accompanying the hyperglycaemia in most pancreatic diabetics, an intriguing question that arises is whether they are less susceptible than primary diabetics to ischaemic heart disease. The final brief communication reveals that this is, indeed, the case.

ISCHEMIC HEART-DISEASE AND PANCREATIC DIABETES

SIR,—As your recent editorial¹ emphasises, 50 years after the discovery of insulin, reasons for the predilection of patients with diabetes mellitus to ischaemic heart-disease (I.H.D.) still remain obscure. One comparatively uncommon, but important, variety of diabetes which might shed some light on this problem is that complicating chronic pancreatitis (pancreatic diabetes). By contrast with genetic diabetics, a relative hypolipidaemia accompanies the hyperglycaemia in the majority of these patients.²

In order to assess the prevalence of I.H.D. in pancreatic diabetes, electrocardiographic studies were performed in 39 cases. All had unequivocal clinical and investigative evidence of chronic pancreatitis and all but 3 showed radiologically detectable pancreatic calcification; only 2 gave a positive family history of diabetes. Standard, 13-lead, resting electrocardiograms were combined with serial post-exercise tracings to provoke any latent ischaemic changes—a manoeuvre surprisingly infrequently employed in the assessment of coronary heart-disease in diabetes.³ A group of 30 genetic diabetics, matched for age, sex, race, socio-economic background, body weight,

TABLE 1—CLINICAL DATA AND FREQUENCY OF ELECTROCARDIOGRAPHIC EVIDENCE OF I.H.D. IN PANCREATIC AND GENETIC DIABETICS

Group	No.	Age (yr.)*	Sex (M/F)	Duration of diabetes (yr.)*	Prevalence of I.H.D.	
					No.	%
Pancreatic diabetics	39	50	33/6	5.8	7	18
Genetic diabetics	30	46	28/2	6.4	11	37

* Mean values.

duration of diabetes, and therapy, was similarly studied; none of them had previously diagnosed I.H.D. Tracings were analysed "blind" for ischaemic changes, according to diagnostic criteria outlined by Schamroth,⁴ by two observers (B. I. J. and H. C. S.). Due consideration was given to the possibility that isolated T-wave changes may have been caused by alcohol⁵—the commonest aetiological factor in the pancreatic diabetics.

Electrocardiographic evidence of I.H.D. was found twice as frequently in the genetic diabetics as in the pancreatic diabetics (table 1). It is noteworthy, however, that those pancreatic diabetics showing electrocardiographic evidence of I.H.D. had significantly higher fasting serum cholesterol

TABLE II—CHARACTERISTICS OF PANCREATIC DIABETICS SHOWING ELECTROCARDIOGRAPHIC EVIDENCE OF I.H.D.

	No.	Duration of diabetes (yr.)*	Therapy (% on insulin)	Serum-cholesterol (mg./100 ml.)*	Serum-triglyceride (mg./100 ml.)*
Patients with I.H.D.	7	8.7 ± 2.6	86	208 ± 23	133 ± 28
Patients without I.H.D.	32	5.0 ± 0.7	53	155 ± 11	86 ± 7
Significance		N.S.	N.S.	P < 0.05	P < 0.05

* Mean ± S.E.M.

and triglyceride levels than did pancreatic diabetics without these changes (table II). Dietary background, age, and duration of diabetes were not significantly different in the two subgroups, although an apparently greater proportion of the I.H.D. patients was receiving insulin therapy.

Although numbers are small, our findings seem to suggest that the level of serum-lipids may be a more critical factor in the pathogenesis of diabetic coronary heart-disease than the hyperglycaemia itself. The discouraging results of attempting to reduce mortality in borderline and mild diabetics by lowering the blood sugar alone may thus not be surprising.

We are grateful to Prof. W. P. U. Jackson for allowing us to study patients under his care and to the South African Medical Research Council for financial assistance.

Department of Medicine,
Witwatersrand University,
Medical School, Johannesburg,
and Gastro-intestinal Service,
Groote Schuur Hospital,
Cape Town, South Africa.

B. I. JOFFE
B. NOVIS
H. C. SEFTEL
L. KRUT
S. BANK.

1. *Lancet*, 1971, i, 957.
2. Joffe, B. I., Krut, L., Bank, S., Marks, I. N., Keller, P. *Metabolism*, 1970, 19, 87.
3. Lundbaek, K. in *Causal Factors of Myocardial Infarction* (Symposium Schlob Reinhartshausen/Rhein); p. 63. Stuttgart, 1969.
4. Schamroth, L. *An Introduction to Electrocardiography*; p. 35. Johannesburg, 1964.
5. Burch, G. E., Giles, T. D. *Am. J. Med.* 1971, 50, 141.

ADDENDUM

Since the publication of papers included in this thesis, a number of articles have appeared in the literature which confirm or complement the investigative data presented. Thus it has been confirmed that patients with chronic pancreatitis have diminished insulin reserve after intensive beta-cell stimulation (Kajubi, 1971) and that pancreatic diabetics have virtually no insulin response following intravenous tolbutamide (Varsano-Aharon, Echemendia, Yalow and Berson, 1970). The sensitivity of patients with pancreatic disease to (endogenous) insulin has also been commented on by Deckert, Kolendorf, Persson and Worning (1972). An additional factor that could be responsible for this is deficient pancreatic glucagon secretion, according to the data of Persson, Gyntelberg, Heding and Boss-Nielsen (1971). Aspects of lipid metabolism in pancreatitis were discussed by Banks (1971) in a recent review. With regard to vascular complications, evidence of diabetic retinopathy was found only one quarter as frequently in pancreatic diabetics as in a matched group of essential diabetics (Sevel, Bristow, Bank, Marks and Jackson, 1971).

References

- Banks, P.A. 'Acute pancreatitis'. Gastroenterology, 61:382-397, 1971.
- Deckert, T., Kolendorf, K., Persson, I., and Worning, H.

'Insulin secretion after tolbutamide and after secretin in patients with pancreatic diseases'. Acta Med. Scand., 192:465-470, 1972.

Kajubi, S.K. 'Beta-cell mass of the pancreas'. Lancet, 2:438, 1971.

Persson, I., Gyntelberg, F., Heding, L.G., and Boss-Nielsen, J. 'Pancreatic-glucagon-like immunoreactivity after intravenous insulin in normal and chronic pancreatitis patients'. Acta Endocr. (Kbh.), 67:401-404, 1971.

Sevel, D., Bristow, J.H., Bank, S., Marks, I., and Jackson, P. 'Diabetic retinopathy in chronic pancreatitis'. Arch. Ophthal., 86:245-250, 1971.

Varsano-Aharon, N., Echemendia, E., Yalow, S., and Berson, S.A. 'Early insulin responses to glucose and to tolbutamide in maturity-onset diabetes'. Metabolism, 19:409-417, 1970.