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The Use of an oral hypoglycemic agent mellitus

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THE USE OF AN ORAL HYPOGLYCEMIC AGENT (TOLBUTAMIDE) IN THE MANAGEMENT OF DIABETES MELLITUS

by

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INTRODUCTION

Diabetes mellitus is characterised by certain changes in carbohydrate, fat and protein metabolism. (10, 36)

The diabetic shows a depletion of body carbohydrates due to loss of glucose from the body. (8) The liver glycogen stores are diminished, and in addition, there appears to be a lack of phosphorylated glucose intermediary metabolites. (15)

The changes in fat metabolism are apparently intimately connected with the carbohydrate derangement. (8, 15) The body fat depots are decreased with increased oxidation of fat and increased production of ketone bodies (acetoacetic and B-hydroxybutyric acids). There is little production of fat or fatty acids from carbohydrate. It would appear that "lipogenesis is dependent upon efficient glycolysis". (15) A hyperlipemia is sometimes present with an increased serum cholesterol level and fatty infiltration of the liver.

The body protein stores are also depleted in the uncontrolled diabetic. (3, 10) There is failure both of storage and of synthesis, and an increased amount of nitrogen is lost from the body in the urine. The increased serum amino acid level sometimes found in the diabetic probably results from decreased protein synthesis, though it may be due to increased rate of protein catabolism. (36) This amino acid rise may also reflect a primary or secondary liver dysfunction.

All of the above-mentioned carbohydrate, fat and protein changes are reversible by administration of insulin.

There are apparently several different means of classifying diabetes mellitus. The more widely used classification, one which can be utilized

for the great majority of diabetics, is essentially descriptive and consists of three rather distinct symptom complexes. (12, 39, 40) Lawrence describes these three types as follows.

Type I: The diabetes of these patients usually begins before the age of 40, and is often referred to as juvenile diabetes because of the frequent onset before the age of twenty. The type I diabetic is subject to ketosis, but is also very insulin-sensitive. His usual daily insulin requirement is 40+ units per day, about equal to the need of a totally pancreatectomized human. Renal, vascular and ocular complications are not often seen in this group. The hepatic changes most often seen, even with control of the diabetic state, is fatty metamorphosis, though this is by no means a constant finding. Another point is that the insulin requirements generally increase as the disease progresses regardless of diet control. Lawrence also includes in this group those patient who fit the above description but who have insulin needs of between 60 and 100 units per day, in addition to the rare patient who requires hundreds or even thousands of units per day. This latter highly insulin-resistant phase is transient and the patient later reverts to his usual diabetic state. (22) On the basis of various clinical and laboratory observations Lawrence believes that the basic defect in type I patients is a pancreatic insulin deficiency. In those who are insulin-resistant this deficiency is complicated by the presence of some insulin antagonist.

Type II: This diabetic is generally an obese woman, older than forty years of age. (Some are between twenty and forty.) The women outnumber the men two to one. These patients commonly complain of polyphagia, polyuria and polydypsia prior to diagnosis. They are not

subject to ketosis. These patients are often referred to as adult diabetics, though Lawrence suggests the term lipoplethoric. The adult diabetic can usually be controlled by diet and weight reduction, but may also require insulin in amounts somewhat less than 40 units per day. This patient, while not subject to ketosis except in the face of infection, coronary thrombosis, or low carbohydrate diet, is heir to the various complications of diabetes, such as vascular lesions, retinopathy, cataracts and nephropathy. There are no typical or constant hepatic changes seen in this group. The condition of the liver is dependent upon the nutritional state of the patient, the degree of control of the diabetes, and the duration of the diabetes. It would seem that the type II diabetic produces endogenous insulin, according to laboratory and clinical findings.

Type III: This is a very rare type of diabetes usually having its onset in children and young adults. These patients have no ketosis, but are hyperglycemic and insulin-resistant. The most striking physical feature is the absence of fat depots. For this reason, Lawrence terms this type lipoatrophic diabetes. Even though fat depots are lacking, a marked hyperlipemia is present when there is an existing hyperglycemia. If the diabetes is adequately controlled by sufficient insulin, the lipemia drops to normal levels. Hepatomegaly with eventual cirrhosis and possible splenomegaly are also present, as is an increased basal metabolic rate without thyrotoxicosis. It is not known whether or not these patients produce an active insulin.

Another method of classification is based on the amount of excretion of choline in the urine. (19) Czaky found choline excretion increased in the so-called adult diabetic, with or without fatty livers, and normal

or decreased in other diabetics. Though it is not known whether or not hepatic abnormalities are primary or secondary findings in diabetes, it is well recognized that in certain cases treatment directed to the liver, e.g., the use of lipotropic agents, may control the diabetes. (21, 43, 48)

Himsworth divides diabetes into two categories. (31) These are insulin-sensitive--those with an absolute lack of insulin--and insulin-insensitive--those with a lack of some sensitizing factor, or possibly (a) an excessive amount of glucose released from the liver overwhelming the insulin present, (b) lack of glucose storage capability in the liver, or (c) inability of insulin to act, for whatever reason. He felt that ingestion of carbohydrates caused the body to become more sensitive to insulin by elaboration of an insulin-sensitizing factor. The diabetes could thus result from a deficit of insulin, or a relative or absolute excessive demand for insulin.

The suggestion has been made that diabetes mellitus in the elderly patient is only a reflection of a compensatory increase in blood sugar secondary to decreased cell membrane permeability. (66) It has been shown that the rate of use of peripheral glucose remains the same at normal as well as increased blood sugar levels.

There are several well established methods of producing diabetes, though the basic metabolic defect is still obscure, even in these cases. Pancreatectomy will cause diabetes by eliminating the Islets of Langerhans. Administration of alloxan will accomplish the same result. An excess of anterior pituitary hormone, either endogenous or exogenous, will produce a diabetic state. Growth hormone seems to act directly while the effect of adreno-corticotropic hormone (ACTH) is mediated through the adrenal cortex. Hyperadrenalism or administration of cortisone may cause diabetes. The

thyroid gland seems to be implicated also in that the hyperthyroid patient may show hyperglycemia and increased production of ketone bodies. (36) But the serum cholesterol and blood lipid levels in these individuals are normal or decreased rather than increased.

There are some who believe that the basic defect in the diabetic lies in the sulfhydryl metabolism. (32) It has been shown that colloidal sulphur in small doses will lower blood glucose levels (29) and that glutathione may reduce the experimentally induced hyperglycemia of ACTH administration. Glutathione also protects the beta-cells of the Islets of Langerhans from the toxic effect of alloxan. (42) Lazarow showed that anterior pituitary extract injection causes a decreased glutathione content of the tissues, as does ACTH. He also demonstrated that thiouracil and thyroidectomy caused increased concentrations of free sulfhydryl groups in the tissues and thus protection of the beta-cells against alloxan toxicity. Insulin also causes an increased glutathione level, and thiouracil has some beneficial effect in mildly diabetic rats. The possibility is suggested that the diabetes of some patients has an extra-pancreatic origin and only later is there beta-cell involvement.

It has been shown that liver homogenates from starved or fat fed rats are capable of destroying insulin activity at a lesser rate than homogenates from carbohydrate fed rats. (62) It has also been observed that many diabetics have a subnormal circulating insulin and excrete less insulin than the normal. On this basis, a group led by Mirsky suggests that in the majority of diabetics, the disease process is due to an increased rate of tissue destruction of insulin by the enzyme insulinase. (52)

Ever since Banting and Best first reported the hypoglycemic action of a pancreatic extract in 1922, attempts have been made to explain the

mode of action of insulin—it is still not clearly understood. (4) One of the more widely accepted explanations is that given by the Cori's. (17, 18, 69) They demonstrated that insulin was capable of releasing hexokinase from inhibition by a hormone elaborated by the anterior pituitary. This results in increased production of glucose in its active form, glucose-6-phosphate. It has been shown since that time, however, that there is no difference between the hexokinase activity of normal or alloxan diabetic animals. (61) This explanation, therefore, may be questionable. It has been suggested that insulin causes an increased cell permeability, thus allowing glucose to enter the cell for metabolism. (44, 62) Another group supports the idea that insulin acts upon the glucose—glycogen equilibrium in the liver, favoring a shift to the right. (41)

Attempts have been made to correlate liver function studies and histologic appearance of the liver with duration of diabetes and insulin sensitivity. (28, 70, 71) While results are not conclusive, the indication is that while liver function studies may not give a true picture of the microscopic appearance of the liver, the degree of fatty metamorphosis often parallels insulin insensitivity, and also correlates somewhat with duration of the diabetes and obesity of the patient. It does not correlate at all with the previous control of the diabetes.

It has been demonstrated that destruction of the hypophysis causes amelioration of the diabetic state, as does adrenalectomy, with subsequent increased sensitivity to insulin. (15, 17, 62, 69) Steroid diabetes, i.e., one produced by hyperadrenalism or by administration of cortisone, is insulin insensitive. (11)

Best seems quite impressed with the apparent relationship between the growth hormone and insulin. (3) Growth hormone causes protein

anabolism, and insulin is essential for this activity. (17, 36) In normal animals there is an increased secretion of insulin in response to administration of somatotropin. In the absence of somatotropin, insulin is itself capable of acting as the growth hormone. This relationship needs further exploration.

For many years attempts have been made to find oral therapies for the treatment of diabetes mellitus. Various oral insulins have proved either ineffective or impractical. (46) One of the first substances to be explored was Synthalin, a guanidine compound. Its hypoglycemic effect was due to hepatotoxicity with a subsequent derangement of glycogen synthesis. It was soon found, however, that Synthalin was too toxic and its use was abandoned.

In 1942 Janbon found, while studying the therapy of typhoid fever, that a thiodiazol sulfonamide was able to cause a hypoglycemia in some of the patients. (80) Following this, Loubatieres and others investigated a number of related compounds and found many to be effective in causing hypoglycemic reactions. (27, 47, 81) In 1955, the use of p-amino-benzene-sulfonamido-butylurea (BZ55, Carbutamide) for the control of diabetes, replacing exogenous insulin was reported. (1, 7, 24) Unfortunately, in 1956 it was shown to be too toxic and was removed from clinical use. A similar non-bacteriostatic compound, 1-butyl-3-p-tolylsulfonylurea (D860, tolbutamide, Orinase), also having hypoglycemic effects in diabetic patients, is at present undergoing clinical and laboratory evaluation. This paper presents a series of diabetic patients treated with tolbutamide.

CASE PRESENTATIONS

Six diabetic patients, two men and four women, ranging in age from 54 to 77 years, were placed on Orinase routine while in Douglas County Hospital for various problems other than diabetes. The known duration of the diabetes ranged between 14 days and 22 years. None of these patients had had previous episodes of diabetic coma. In order to better select the patients for the Orinase therapy prior to actually placing them on the tolbutamide, an oral "Orinase test" was performed. (16) This consisted of cessation of insulin therapy for three days. On the morning of the fourth day, the fasting blood sugar level was determined, and the patient was then given three grams of the oral hypoglycemic agent. If at the end of four hours, the blood sugar had decreased by 20% or more, the chances were that this patient would respond favorably to Orinase. It has been previously demonstrated, however, that this is not a completely reliable test, and that all patients with onset of diabetes past the age of 20 deserve a trial period of tolbutamide before declaring them unsuitable for this regimen. (20, 45) As it turned out, the diabetes of two patients with responses of less than 20% was not well controlled after two weeks of Orinase therapy, while one patient had a response of less than 20% and was well regulated by Orinase. At no time have any of the patients exhibited either clinical or laboratory signs of toxicity, such as skin rash, malaise, fever, renal dysfunction, red blood cell or white blood cell depression, or abnormal hepatic function tests attributable to the Orinase therapy. These patients have been on Orinase plus the diabetic diet control for periods of between 32 and 125 days. In all instances, the oral hypoglycemic agent plus diabetic diet were used to completely replace the insulin program. Immediately following the Orinase test, the dosage of Orinase was reduced daily until by the fourth day, a level of 1.0 gm. per day was given. The amount was later varied as deemed necessary.

Following the description of each patient is a table in which are recorded the results of the routine laboratory tests made in conjunction with evaluation and control of each patient. The values are expressed in gram %, milligram %, or % of normal, as appropriate. The following abbreviations are used: FBS (fasting blood sugar), Cholest. (cholesterol), TSP (total serum protein), A/G (albumin/globulin), ceph. floc. (cephalin flocculation), BSP (bromsulfalein), and Proth. (prothrombin).

1) J.F. This is a moderately obese 54 year old white man who entered the hospital for repair of an inguinal hernia. A routine urine check coupled with an elevated blood sugar, sluggishness and weight loss of 6 pounds in the past three months disclosed a previously undiagnosed case of diabetes mellitus. His diabetes was controlled with 25 units of NPH insulin per day. The fasting blood sugars ranged between 160 mg.% and 124 mg.% while on insulin therapy. On the 28th hospital day, the Orinase test was carried out. The response was an 11% drop in blood sugar. Liver biopsy with Silverman needle was taken after 20 days of Orinase therapy. Control of diabetes was excellent with 1.0 grams Orinase daily. See Fig. 1.

Hosp. days	FBS	Cholest. & esters	TSP	A/G	48 hr. ceph. floc.	45 min. BSP	Proth. time
28	110	282/172	5.30	3.06/2.24	-	0	90
35	112	302/180	5.05	2.97/2.08	-	0	100
42	110	296/176	5.05	2.70/2.35	-	0	94
49	100	290/178	5.65	2.88/2.77	-	0	90
56	94	302/200	4.55	2.88/1.67	-	0	90
60	117	Patient discharged					

2) M.B. This is a well nourished, not obese, 54 year old white woman who entered the hospital with generalized arteriosclerosis and peripheral vascular insufficiency. She had had a right mid-thigh amputation two years earlier for gangrene. The diagnosis of diabetes mellitus had been made 22 years ago, and she was controlled on 35 units

of NPH insulin per day plus diabetic diet. Her fasting blood sugar levels normally ranged between 110 and 170 mgm.%. On the 5th hospital day she was given the Orinase test. The response was a 22% drop in blood sugar. A liver biopsy was performed with a Silverman needle on the 26th day of therapy. Control of diabetes was excellent with dosage of 1.0 gram. Orinase daily. See Fig. 2.

Hosp. days	FBS	Cholest. & esters	TSP	A/G	48 hr. ceph. floc.	45 min. BSP	Proth. time
5	212	261/160	5.45	2.70/2.75	-	0	100
13	113						
19	97	260/158	5.85	2.97/2.88	-	0	94
26	113	258/154	5.20	2.97/2/23	-	0	95
33	117	256/150	5.05	2.88/2.17	-	0	100
38	Patient discharged						
39	110	248/148	5.65	2.97/2.68	-	0	90
45	106	250/150	5.65	3.10/2.55	-	0	95
52	106	203/125	5.65	2.70/2/95	-	0	100

3) L.S. This is a moderately obese 71 year old white man who entered the hospital with pansinusitis and atrophic rhinitis. Diagnosis of diabetes mellitus was made after a positive routine clinitest of the urine and a subsequent elevated (175 mgm.%) blood sugar level. He was at first controlled on 25 units of NPH insulin per day plus diabetic diet. His fasting blood sugar levels normally ranged between 110 and 150 mgm.%. On the 50th hospital day he was given the Orinase test. The response was a 22% drop in blood sugar. Control of diabetes was satisfactory on 1.25 grams Orinase daily. See Fig. 3.

Hosp. days	FBS	Cholest. & esters	TSP	A/G	48 hr. ceph. floc.	45 min. BSP	Proth. time
50	112	185/117	5.65	2.79/2.86	++	0	100
60	135	185/108	6.86	3.20/3.65	+	0	100
67	143						
77	120	210/130	6.00	2.70/3.30	tr	0	94
86	Patient discharged						
91	145	188/110	6.50	3.25/3.25	++	0	100
98	141	210/127	6.85	3.45/3.40	tr	0	100
105	143	221/130	6.85	3.86/2.99	tr	0	100

113	147	162/100	7.1[illegible]	3.65/3.50	tr	0	100
119	150		6.8[illegible]	3.55/3.30	-	0	100
126	126	220/132	6.2[illegible]	2.70/3.50	-	0	100
133	143	205/127	6.6[illegible]	3.25/3.25	-	0	100
140	150	221/132	6.4[illegible]	3.45/2.95	-	0	100
147	145	181/128	6.2[illegible]	3.35/2.85	-	0	100
154	155	220/130	7.6[illegible]	3.35/4.30	-	0	100
161	168	190/128	6.0[illegible]	3.00/3.00	-	0	100
168	162	183/130	5.85	2.45/3.40	-	0	100
175	177	180/129	6.6[illegible]	3.45/3.15	-	0	100

4) A.H. This is a well nourished, not obese, 64 year old Negro woman who entered the hospital with a plantar abscess and a diagnosis of endarteritis obliterans. She had had a mid-thigh amputation of her left leg 3 years ago, and she had been controlled on 20 units of NPH insulin per day plus diabetic diet. Her fasting blood sugar normally varied between 120 and 140 mgm.%. On the 95th hospital day she was given the Orinase test. The response was a 29% drop in blood sugar. A liver biopsy was performed with a Silverman needle after 113 days of Orinase therapy. Control of diabetes was excellent on dosage of 1.0 gram Orinase daily. See Fig. 4.

Hosp. days	FBS	Cholest. & esters	TSP	A/G	48 hr. ceph. floc.	45 min. BSP	Proth. time
95	124	221/120	6.00	2.79/3.21	-	0	94
105	131	199/98	7.20	3.06/4.14	-	0	94
112	128						
122	120	210/115	6.40	3.25/3.15	-	0	90
134	110	162/114	5.85	2.79/3.06	-	0	94
136	Patient discharged						
141	164	168/76	6.40	3.15/3.25	tr	0	88
148	152	196/94	7.35	3.15/4.20	-	0	90
155	196	143/90	6.85	3.15/3.70	-	0	94
163	143	210/120	6.60	3.25/3.25	tr	0	94
169	127	198/100	6.40	3.06/3.34	-	0	94
176	139	181/88	7.45	2.88/4.57	-	0	90
183	147	192/102	6.40	3.15/3.25	-	0	90
190	132	203/110	6.60	3.06/3.54	-	0	90
197	168	196/106	6.00	2.85/3.15	-	0	94
204	162	210/100	6.40	2.90/3.50	-	0	94
211	147	200/112	6.00	2.07/3.93	-	0	100
218	177	196/106	6.20	3.06/3.14	-	0	95
225	165						

5) J.A. This is a slightly obese, 75 year old Negro woman who entered the hospital with an upper respiratory infection. She had had diabetes for 20 years, and was controlled by 10 units of NPH insulin per day with diabetic diet. Her fasting blood sugar levels normally ranged between 110 and 190 mgm.%. She had diabetic retinopathy and an occasional cast in her urine. On the 26th hospital day she was given the Orinase test. The response was a 44% drop in blood sugar. Control of diabetes was excellent on dosage of 1.25 grams Orinase daily. See Fig. 5.

Hosp. days	FBS	Cholest. & esters	TSP	A/G	48 hr. ceph. floc.	45 min. BSP	Proth. time
26	110	278/145	6.60	3.06/3.54	-	0	100
36	164	221/114	7.15	3.06/4.09	-	0	94
43	150						
53	143	320/215	6.50	2.97/3/53	-	0	90
62	Patient discharged						
67	148	312/200	7.35	3.06/4.29	-	0	94
74	148	349/255	7.15	3.25/3.90	-	0	94
81	160	369/260	6.85	3.15/3.70	-	0	94
89	145	320/210	6.70	3.45/3.25	-	0	100
95	147	380/250	6.60	3.25/3.35	-	0	100
102	132	369/265	6.60	3.06/3.54	-	0	100
109	147	375/270	6.85	3.35/3.50	-	0	100
116	135	380/256	6.40	3.35/3.05	-	0	100
123	145	344/144	6.00	2.93/3.07	-	0	95
130	145	370/256	6.00	3.15/2.85	-	0	100
137	147	340/238	6.60	2.97/3.63	-	0	100
144	131	360/250	6.00	2.70/3.30	-	0	100
151	139	350/245	5.65	2.70/2.95	-	0	100

6) M.D. This is a moderately obese, 77 year old white woman who entered the hospital for removal of cataracts. She had hypertension and arteriolar nephrosclerosis. The diagnosis of diabetes had been made 1 year previously. She was controlled by 35 units of NPH insulin per day with diabetic diet. Her fasting blood sugar levels normally ranged between 130 and 170 mgm.%. On the 27th hospital day she was given the Orinase test. The response was a 40% drop in blood sugar. Control of diabetes was excellent on dosage of 1.25 grams Orinase daily. See Fig. 6.

Hosp. days	FBS	Cholest. & esters	TSP	A/G	48 hr. ceph. floc.	45 min. BSP	Proth. time
27	105	320/215	5.65	3.35/2.30	-	0	100
38	183	330/235	6.40	3.35/3.05	-	0	100
45	150						
49	Patient discharged						
54	198	298/180	5.65	2.70/2.95	-	0	94
61	193	306/224	5.85	3.35/2.50	-	0	88
68	160	330/200	6.00	3.15/2.85	-	0	90
75	191	268/188	5.75	3.35/2.40	-	0	100
76	Return to hospital for second cataract removal.						
83	199						
90	131	303/202	5.55	3.06/2.49	-	0	100
97	135	298/182	5.20	2.97/2.28	-	0	100
105	117						
115	Patient discharged						
119	184	312/200	5.20	3.06/2.14	-	0	95
126	177	298/185	5.35	2.45/2.90	-	0	90
133	177	206/120	5.20	2.97/2.23	-	0	90
140	147	250/120	6.10	3.40/2.70	-	0	94
146	148	235/110	5.75	2.53/3.22	-	0	95

Three liver biopsies were obtained using the Silverman needle. A portion of each tissue was fixed in Carnoy's solution, and the other part in formalin-calcium chloride solution. The tissues were sectioned at 5μ and then stained routinely with hematoxylin-eosin (Figs. 7-9). In addition they were stained for glycogen with Best's carmine (Figs. 10-12), and for lipids with oild red O (Figs. 13-15). All biopsies were taken 2 hours after a normal meal. Tissues were obtained from J.F., M.B., and A.H., as noted above. All of the tissues appear to be well within normal limits, both on the basis of histological appearance and histochemical staining reactions. There are, however, differences within the group. J.F. showed a little fatty infiltration with a heavy deposit of lipid droplets and a small amount of glycogen deposition. He also had a very slight amount of periportal round cell infiltration. M.B. showed a very little fatty change with only an occasional vacuole and a moderate number of stained lipid droplets, with slightly more glycogen deposition than J.F. There was a very minimal amount of periportal round cell infiltration.

A.H. showed minimal fatty changes with a lesser number of lipid droplets than the other two, and only a rare vacuole. The glycogen deposition in this case was the heaviest of the three patients. There was no evidence of periportal inflammation. The fat and glycogen distribution was uniform throughout the tissues with no peripheral or central lobular pattern. The only apparent reciprocal arrangement was with regards relative quantity of fat and glycogen. It was noted, in addition to the above findings, that the liver of J.F. showed many nuclear vacuoles, that of M.B. very few, and that of A.H. almost none. These vacuoles were interpreted as glycogen deposition within the nuclei.* However, they did not take the stain for either glycogen or fat. Since intra-nuclear glycogen vacuoles are not a constant finding in diabetes and since there is no apparent correlation between duration of diabetes, severity of the diabetes, or degree of control and the finding of these vacuoles, little significance was attached to their presence. (65) All three patients did display, however, an occasional, small intra-nuclear granule of glycogen, as demonstrated histochemically. There seemed to be no difference between patients, in this respect. None of the biopsy material showed any signs of cytotoxicity.

*The author is indebted to Drs. H. W. McFadden and C. A. McWhorter for this and other observations concerning the tissues.

DISCUSSION

The role of the oral hypoglycemic agents is still being explored and explanation of the mode of action of these compounds is a subject still requiring much work. Certain observations are well agreed upon, others are controversial.

Tolbutamide seems to give best results in those diabetics who might have been controlled by weight loss and diet alone, and therefore in the adult, obese diabetic patient. (45) It can be used in other patients also, and each diabetic probably deserves a trial with a sulfonylurea before it is concluded that he can not be aided by it. (58) The duration of the diabetes does not seem important. Some workers feel that if it has been present 20 years or more, tolbutamide will not be effective, but there is disagreement, and the correlation between duration and efficacy of a sulfonylurea is not well established. (16, 68, 74) The age of the patient at the onset of the disease process correlates much better (see below). It has been fairly well demonstrated that those patients who have been in acidosis are generally not aided by tolbutamide. (45) In the present series no attempt was made to see if the insulin dose could be reduced in patients taking Orinase. The interest centered only in those patients who could be completely freed from the use of insulin. The severity of the diabetes, therefore, played a part. Orinase is apparently able to replace up to 30 to 35 units of insulin per day, and may be useful in reducing the insulin requirements in patients using 100 or more units per day. (54, 76, 88) It is also reported as having decreased markedly the insulin requirement in a lipoatrophic patient. (50) The main circumstances in which an oral sulfonylurea is of no value at all involve times of stress, as with an acute febrile infection, and

acidosis. (58) Aside from clinical evaluation, a laboratory method of determining potential efficacy of tolbutamide is the Orinase test as previously stated. The Orinase can be given either orally or intravenously. After the test dose, if the blood sugar is depressed 20% or more, after oral administration, or 26% or more, after intravenous administration, the patient is probably a suitable candidate for trial. (13, 16) The intensity of the response, however, is no absolute guide to the final dosage. One worker uses the criterion of absence of ketonuria 24 hours after stopping insulin as favoring a good response to sulfonylurea therapy. (76) Most patients are well controlled on 1.0 gram of Orinase per day, either in single or divided dosage. Some have been maintained on as much as 3.0 grams per day with good results. The dosage has an inversely proportional relationship to the fasting blood sugar in most instances. However, the physician should not allow the ease of administration of an oral hypoglycemic agent to lull the patient into a sense of false security regarding non-regulation of diet. In the series reported here, the blood sugar levels were usually decreased by repeated and detailed diet instructions, rather than by an increased Orinase dosage.

Though almost every diabetic should be tried on an oral sulfonylurea regimen before stating categorically that he is not suitable for this type of therapy, it is well established that the juvenile diabetic (all of those with onset at less than 20 years of age, and 1/3 of those with onset between 20 and 40 years of age) will not respond to the sulfonylureas. This observation in itself gives some insight into a possible mode of action of tolbutamide (see below). Some investigators, however, have claimed favorable results with a few juvenile diabetics. (5, 20, 35)

There are relatively few contraindications to the use of tolbutamide. As noted above, it is useless for treating a patient in acidosis or an increased blood sugar associated with stress. Patients with ulcer symptoms sometimes experience an exaccerbation of discomfort when placed on tolbutamide, and sometimes a dermatitis may flare up. (20) One worker, however, reports that a diabetic patient with ulcerative colitis has had no recurrence of the colitis during 9 months of Orinase use. (88)

Side effects are infrequent. With tolbutamide they are generally reported as occurring in less than 1% of cases. (74, 82, 88) Only rarely is a leukopenia seen, and it may be corrected by simply discontinuing the Orinase therapy. (25) In one instance, the Orinase was resumed with no ill effects. Dermatitis rarely occurs. There have been a few cases of jaundice, but none definitely attributable to the tolbutamide. There have been no reports of "sulfa" toxicity or of renal complications. Hypoglycemic reactions are unusual, but when they occur can be treated with oral or intravenous glucose. An incipient ketosis, based on routine urine checks, can be treated with insulin in the usual manner. It must be remembered that oral sulfonylurea therapy represents a new therapeutic regimen, and that the effects of long term administration are not yet known.

Laboratory methods have been employed in the attempt to explain the mode of action of the sulfonylureas. In many respects the results are controversial. The principal hypotheses as to their action include anti-glucagon agents, antagonists to diabetogenic hormones, inhibitors of hepatic enzyme systems, insulin-like action, anti-insulinase agents, and stimulants to insulin production.

One of the earlier interpretations regarding the mechanism was that they acted as anti-glucagon agents, either peripherally or by attacking the alpha-cells of the pancreas directly. (1, 7, 24) Glucagon, it will be remembered, is a substance probably produced by the pancreatic alpha-

cells which is said to cause an increased blood sugar level by a lytic action on liver glycogen. (37) Most of the evidence today is against the anti-glucagon explanation. Tolbutamide produces no hypoglycemic effect in severe alloxan diabetic animals, nor does it block the hyperglycemic effect of administered glucagon. (9, 78) The pancreas of the tolbutamide treated animal has a normal glucagon content, and the alpha-cells show no histologic evidence of any change after a course of Orinase administration. (6, 59)

A number of workers have investigated the action of the sulfonylureas on hormones and endocrine glands capable of producing a hyperglycemic state. The conclusions reached regarding adrenal and pituitary glands are fairly well agreed upon, namely, that tolbutamide does not act to depress the adrenal or pituitary systems. (26, 60, 75) In fact, an animal is rendered more sensitive to tolbutamide (just as to insulin) by adrenalectomy, and the hyperglycemia caused by cortisone administration is unaffected by sulfonylureas. (33, 79) Also, both normal and hypophysectomized dogs show an equal response to sulfonylureas; and, tolbutamide does not affect the increased blood sugar caused by the diabetogenic factor of the anterior pituitary. (73) The effect of the sulfonylureas on the thyroid gland does not seem quite so clear-cut. Tolbutamide appears to have a mild anti-thyroid effect, as indicated by a slight decrease in protein-bound iodine value and radio-active iodine "pickup", but with levels remaining within normal limits. (14, 38, 49, 57) It should be recalled that thiouracil or thyroidectomy causes an increased concentration of free sulfhydryl groups in the tissues. The higher level apparently protects the beta-cells of the pancreas and may cause a decreased blood sugar. This particular phase of action probably deserves further investigation.

Another locus of action has been proposed for Orinase, namely the liver, but most of the evidence is against this explanation. It was suggested that tolbutamide inhibited hepatic gluconeogenesis and hepatic release of glucose, or that there was improved hepatic glucose, ketone body and fatty acid utilization. (59, 60, 86) It has been well demonstrated in vitro, however, that tolbutamide has little effect on glucose-6-phosphatase activity and that the concentration of tolbutamide needed to inhibit glucose production from liver slices is excessively high. (2, 6, 63) (Application of in vitro results to in vivo circumstances may be done only with caution.) Dulin observed that tolbutamide was able to exert a hypoglycemic effect in hepatectomized animals, and that in fasted, intact animals, tolbutamide caused decreased blood sugar with an increase in liver glycogen content. (75, 83) In normally fed rats, tolbutamide caused decreased blood sugar with diminished liver glycogen. No muscle glycogen changes have been observed with tolbutamide administration. (51) Also against an hepatic site of action is the absence of variation from normal in the liver function tests. (77) In the present series there are no abnormalities which can be attributed to Orinase therapy. It should be noted here that the geriatric patient may normally show an inverted or decreased serum A/G ratio. (34) Microscopic study of liver biopsy specimens revealed neither evidence of disturbed morphology in general, nor cytotoxicity in particular. One rather interesting and possibly significant observation has been made concerning the detoxified form of tolbutamide. Orinase is excreted almost entirely in the urine. The detoxified conjugated form is p-carboxy-benzene-sulfonamido-butylurea. (78) It is highly soluble and therefore the chances of crystalluria are slight. (23) The excreted substance is apparently without metabolic

effect. Kinsell reported that of two juvenile diabetics treated with tolbutamide, one had a good response while the other did not. (35) In the first case, the greater part of the compound was excreted in its conjugated form. In the second, the greater part was excreted free.

The possibility of an insulin-like action has been suggested for the sulfonylureas, but the majority of reports do not support this idea. (26, 44, 78) Aside from the previously mentioned observations that the sulfonylureas are ineffective against the hyperglycemia associated with glucagon, cortisone, anterior pituitary extract injections or severe alloxan diabetes, several other phenomena have been reported which are inconsistent with an insulin-like action of tolbutamide. There is no potentiation of exogenous insulin administered to labile diabetics, though it is potentiated by high doses of Orinase in normal and pancreatectomized animals. (32, 38, 81) Sulfonylureas are without effect in eviscerate animals. Tolbutamide does not stimulate glucose uptake by muscle in vitro, as insulin does. (67, 89) The blood pyruvic and lactic acid levels are unchanged, and the glucose tolerance test curve is either unchanged or slightly raised by Orinase. (57, 59, 78, 85)

One group of workers favors the idea that the sulfonylureas act by inhibition of insulinase, the hormone which destroys insulin. (53, 54, 55, 81) Mirsky believes that the inhibition is on a non-competitive basis, and therefore, advises a great deal of caution in the use of the sulfonylureas. If it were true that most diabetes is the result of increased destruction rather than diminished production of insulin, as Mirsky contends, then it might be suspected that more diabetics, notably juveniles, could be aided by Orinase, and also that more adult diabetics would have decreased circulating insulin levels than are reported. (30) The explanation offered by Mirsky for failure of Orinase in juvenille

diabetics is that the continued increased demands for insulin have exhausted the beta-cells of the pancreas, so that insulin is no longer being produced. (54) While high doses of Orinase may potentiate exogenous insulin, and there may be a prolonged hypoglycemia with exogenous insulin plus Orinase in patients previously unresponsive to tolbutamide, the fact remains that the juvenile diabetic is not generally aided by the oral sulfonylureas. Mirsky reports decreased insulinase activity of the liver 60 minutes after giving tolbutamide, but Vaughan reports no such anti-insulinase activity in vitro. (63, 84)

The action of Orinase which has received the greatest study and which seems to be acceptable to most workers is that the sulfonylureas stimulate production and release of insulin by the beta-cells of the pancreas, even though Best is of the opinion that there is no increased insulin production or release. (9) Since no blood pyruvic or lactic acid level changes occur after administration of tolbutamide, Moorhouse concludes that either there is no increased insulin production, or that exogenous insulin differs from endogenous insulin in certain properties, a conclusion not without merit. (56, 85) It may be that the effect is similar to the beta-cell stimulation caused by carbohydrate or protein ingestion. (29) Himsworth found that repeated small intravenous doses of carbohydrate caused an increased insulin sensitivity. (31) The possibility exists that continued stimulation of beta-cells may lead to their exhaustion. However, Beaser reported that after 6-10 months of therapy with Orinase, several diabetic patients were returned to their previous insulin dosage, indicating no loss of Islet cell function. (72) It has also been noted that "most materials which stimulate insulin secretion will, when given over a period of time, stimulate the growth of the Islets in the rat." (3)

Administration of BZ55 to rats was observed to cause an increase in Islet size. (80) It has also been reported that a diminution of beta-cell granulation occurred following administration of the sulfonylureas. (64, 90) This finding was interpreted as indicating increased insulin production. The observation that tolbutamide has no effect in pancreatectomized animals coupled with the fact that jubenile diabetics generally do not respond is certainly compatible with the idea that endogenous pancreatic insulin must be present if sulfonylureas are to exert hypoglycemic action. (68, 79, 80, 81) It should be recalled that both depancreatized and juvenile diabetics generally use about 40 units of insulin per day, and that the pancreas of the juvenile diabetic often shows complete fibrosis or hyalinization of the Islets of Langerhans.

The effects of tolbutamide on the deposition of liver glycogen, as mentioned earlier, are compatible with the theory of an increased production of insulin, as are the histochemical and histologic studies of liver biopsies reported in this paper. While all liver specimens appeared to be within normal limits, it is interesting to note that the patient receiving tolbutamide for the shortest period of time, 20 days, had the most fatty infiltration and the least glycogen, while the liver of the patient receiving tolbutamide for the longest period of time, 113 days, had the least fatty infiltration and the most glycogen. The liver of the patient receiving Orinase for 26 days was approximately intermediate between the other two, but closer in appearance to the liver of 20 days therapy. See Figs. 10-15.

One observation that seems to be compatible with any of the above suggested mechanisms of action of tolbutamide is that a number of patients who received a course of oral sulfonylurea therapy had no apparent need for insulin after the sulfonylurea was discontinued. (87, 88)

The phenomenon which is not readily understandable in the light of any one of the hypotheses alone is that tolbutamide may replace 30-35 units of insulin in some patients, and up to 1500 units per day in others, as seen in a lipoatrophic diabetic.

It would seem that the sulfonylureas are capable of exerting a hypoglycemic effect in more than one manner. At the present time, however, the preponderance of evidence seems to favor the mechanism of an increased insulin production, in all probability by the beta-cells of the Islets of Langerhans. This and the other suggested mechanisms will be more clearly defined only after a great deal more work both with insulin and the oral hypoglycemic agents.

SUMMARY

1. A series of six adult diabetic patients ranging in age from 54 to 74, with newly discovered and long standing cases of diabetes is presented. The patients had previously been controlled with diet regulation and insulin dosages of from 10 to 35 units. All of these patients were placed upon an oral sulfonylurea (Orinase) routine. Of these patients, 5 had had positive Orinase test responses, while 1 had not.

2. Between 1.0 and 1.25 grams of Orinase per day were required in addition to diet regulation for adequate control of the diabetes.

3. Liver biopsies were taken from three patients after 20, 26, and 113 days of Orinase therapy, respectively. All specimens showed normal histologic and histochemical (glycogen and lipid) appearance.

4. Liver function tests were performed on all patients. No abnormalities attributable to Orinase could be demonstrated.

5. No untoward side reactions were observed in any of the patients on Orinase therapy.

CONCLUSIONS

1. Tolbutamide is a suitable oral hypoglycemic agent for selected, adult diabetic patients.

2. Tolbutamide plus diet regulation will replace at least 35 units of insulin.

3. Duration of the diabetes is apparently not well correlated with success or failure of tolbutamide therapy.

4. The oral Orinase test is not a completely accurate criterion for prejudging the efficacy of tolbutamide therapy.

5. The absence of a history of ketosis favors chances of the successful use of tolbutamide.

6. The incidence of untoward side effects is less than 1%.

7. Orinase does not cause abnormalities to appear in selected hepatic liver function tests.

8. Orinase does not cause abnormal histologic appearance of the liver.

9. The content and distribution of lipid and glycogen in the liver of the patient on Orinase therapy are comparable to those of diabetic patients well controlled by insulin.

10. It is suggested that Orinase acts by stimulating the beta-cells of the pancreas.

FIG. 1 J.F.

x--liver biopsy o--discharge from hospital

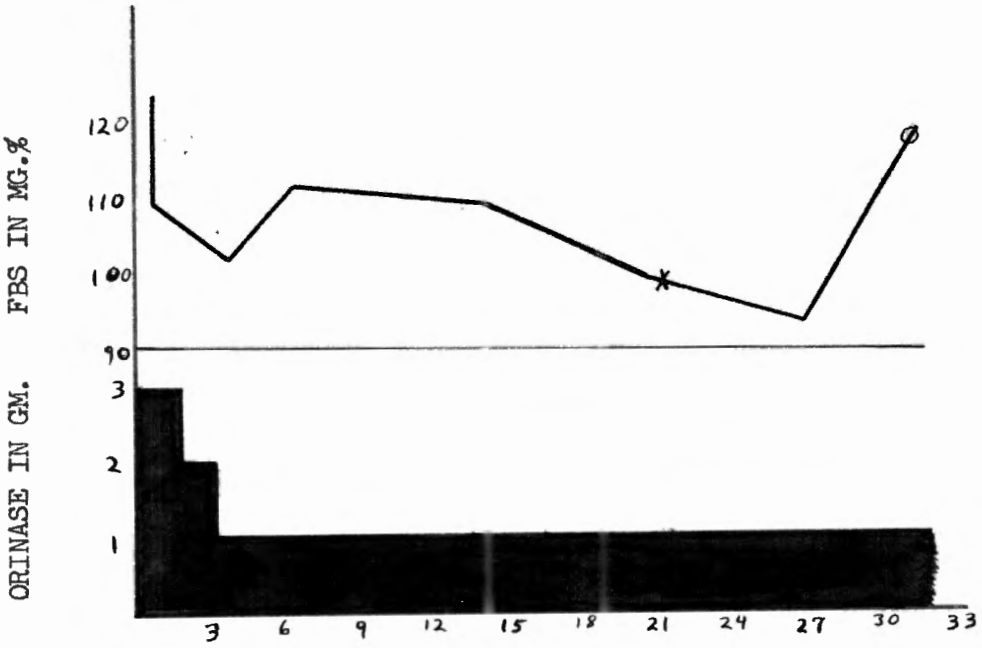


FIG. 2 M.B.

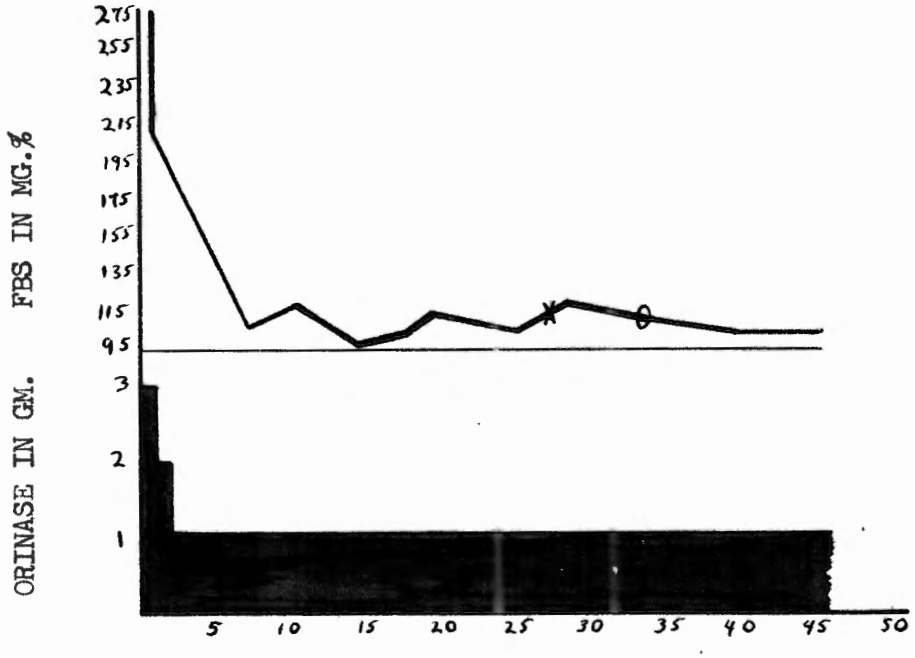


FIG. 3 L.S.

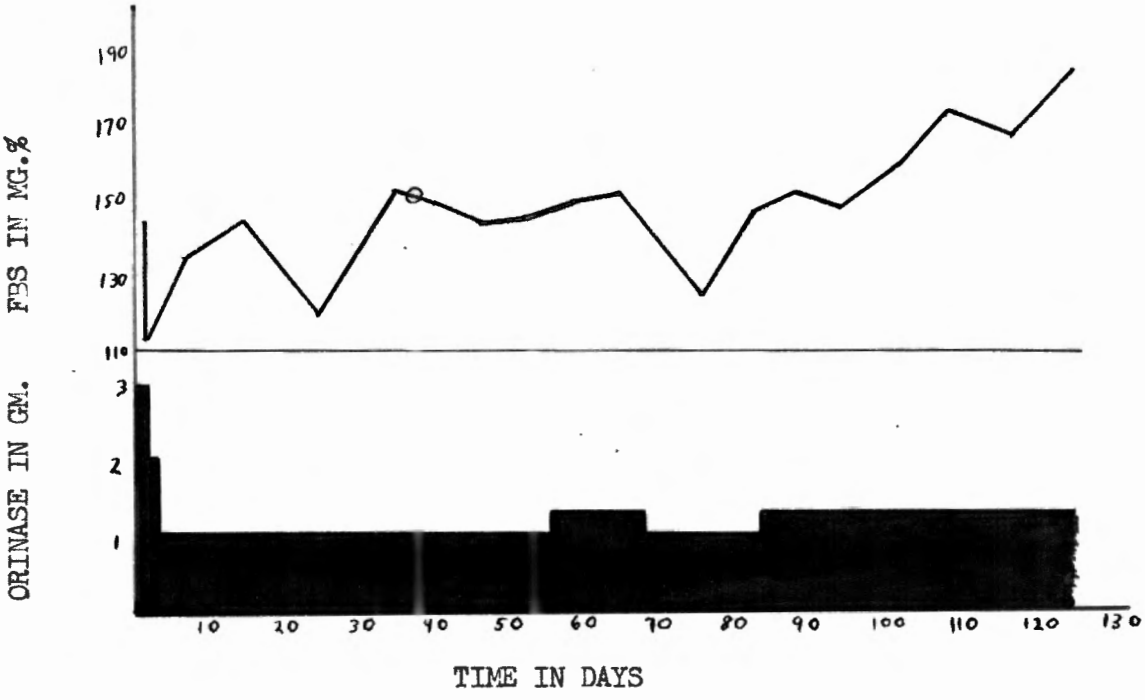


FIG. 4 A.H.

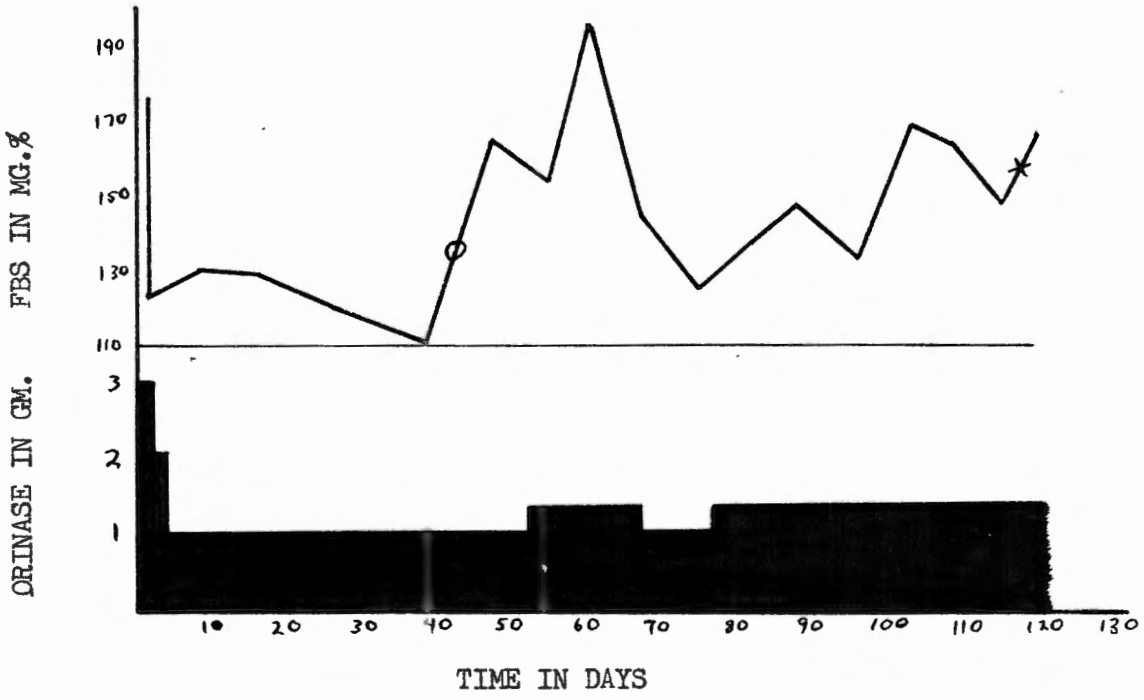


FIG. 5 J.A.

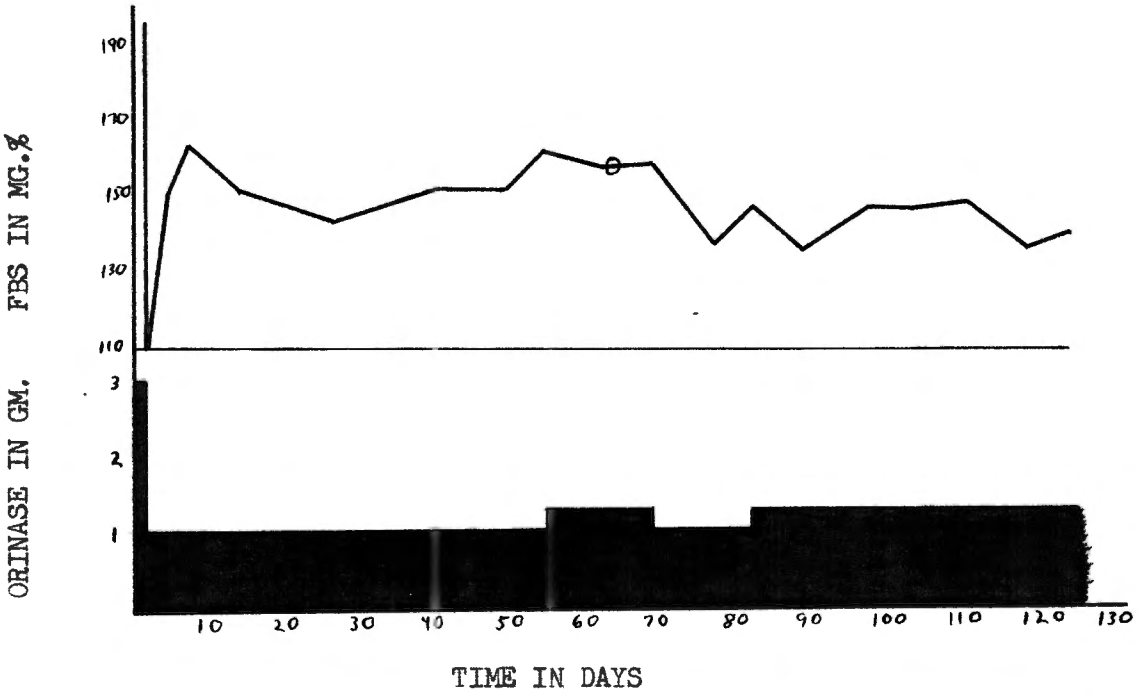
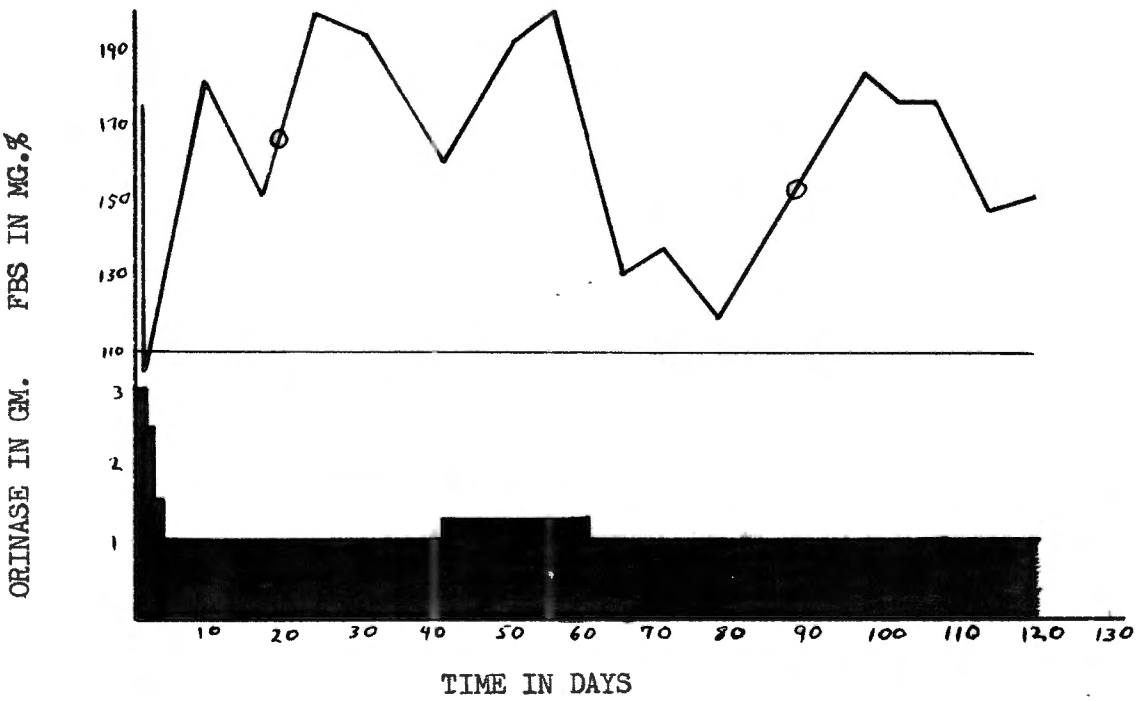


FIG. 6 M.D.



EXPLANATION OF PHOTOMICROGRAPHS

PLATE I

Hematoxylin-eosin stain

It is readily seen that the tissues pictured are essentially normal. J.F. has a few more fat vacuoles than has M.B., while A.H. shows none. x220

PLATE II

Best's carmine stain for glycogen

A.H. is seen to have the greatest amount of glycogen with rather distinct granules of the material. J.F. shows the least glycogen deposition, and M.B. has only a small amount more. The non-staining lipid vacuoles (A) and intra-nuclear vacuoles (B) are apparent. x420

PLATE III

Oil red O stain for lipids

The greatest droplet size and concentration are seen in association with the liver of J.F. The least amount of lipid is seen in the photomicrograph of the liver specimen taken from A.H. The lipid content of the liver of M.B. is between the other two in density, but lies closer to that of J.F. x420

PLATE I

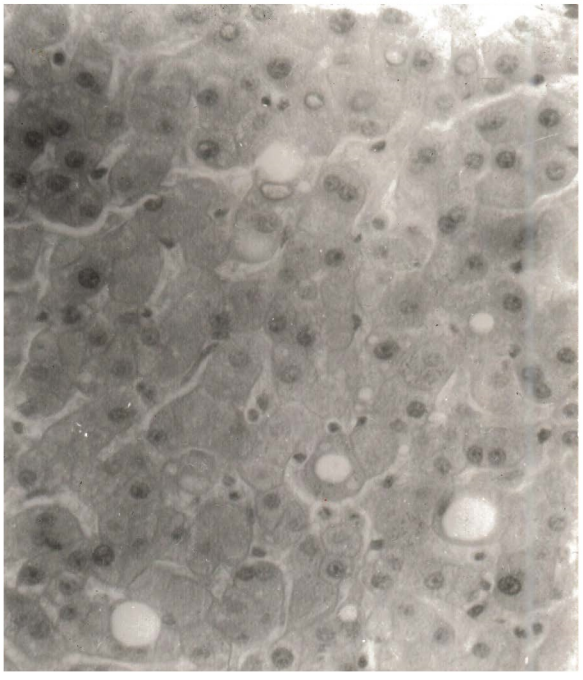


FIG. 7 J.F.

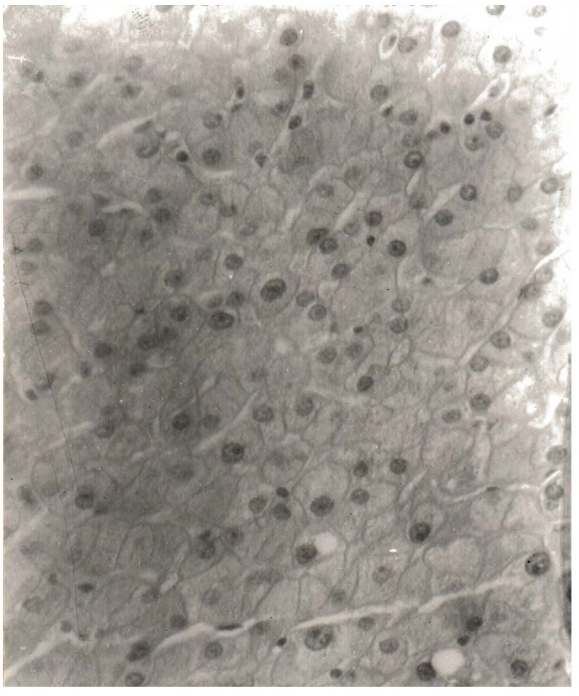


FIG. 8 M.B.

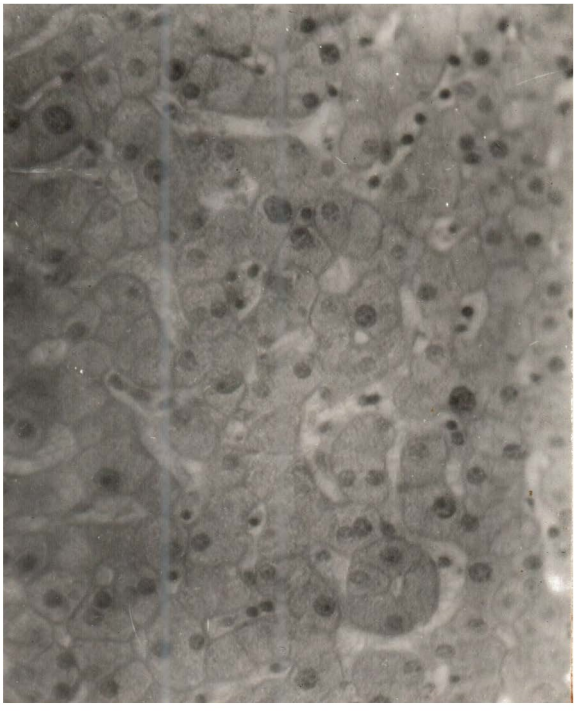


FIG. 9 A.H.

PLATE II

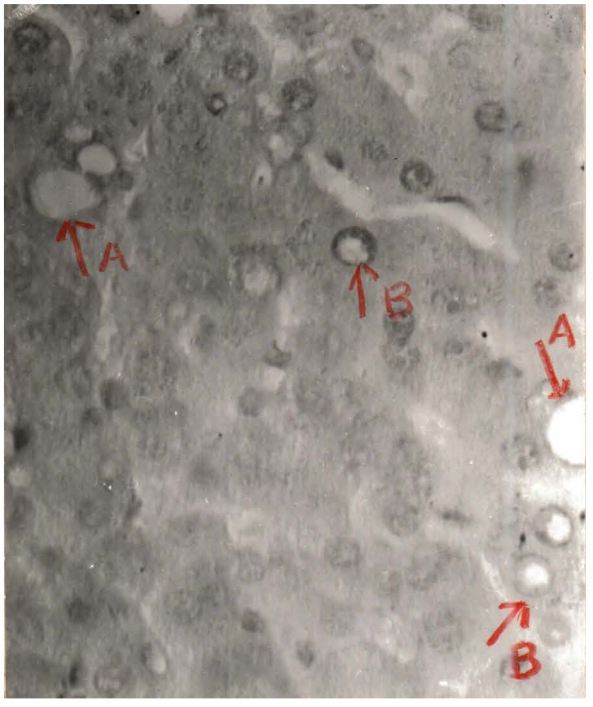


FIG. 10 J.F.

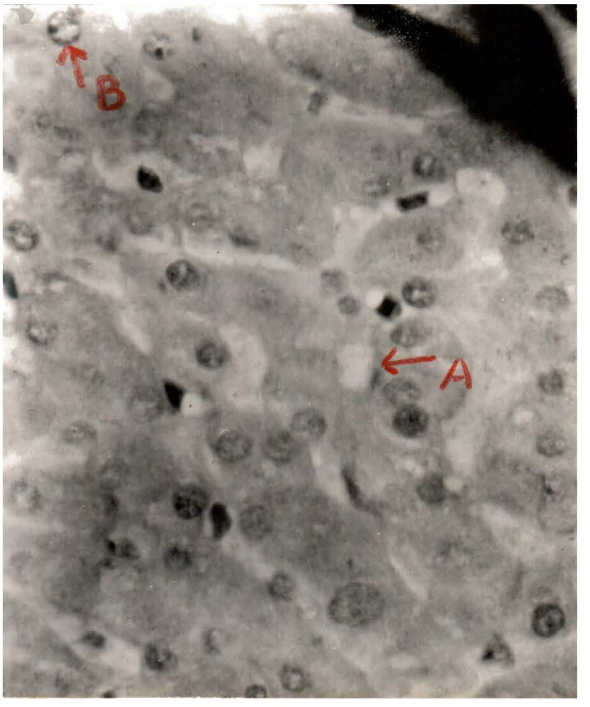
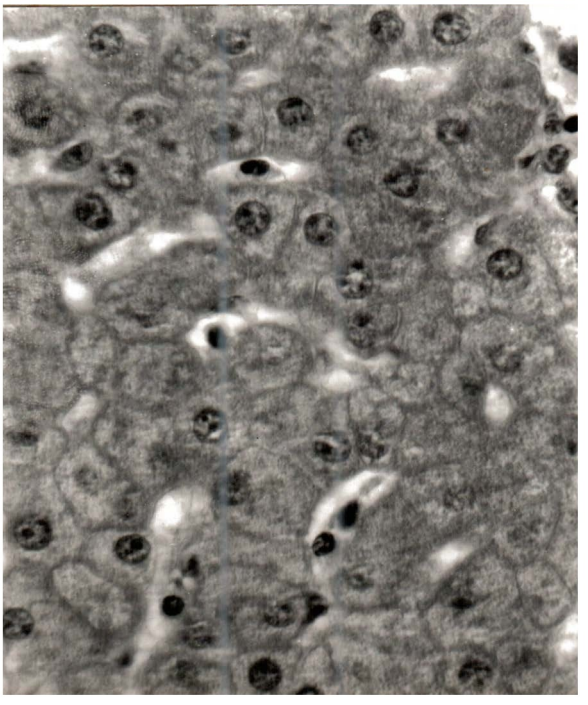


FIG. 11 M.B.



IG. 12 A.H.

PLATE III

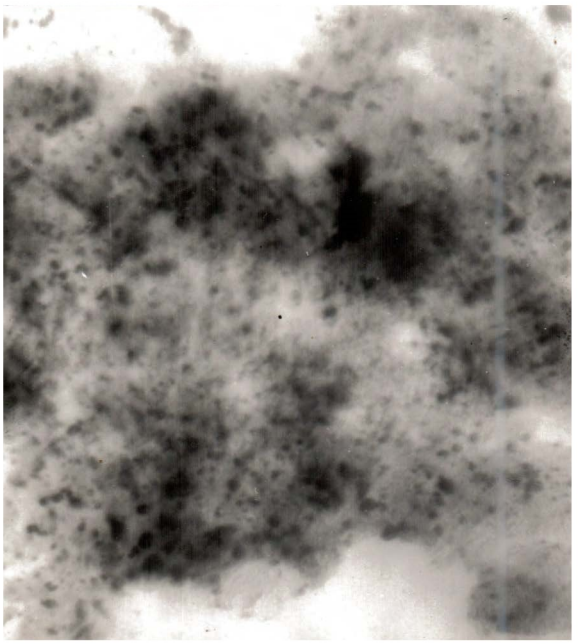


FIG. 13 J.F.

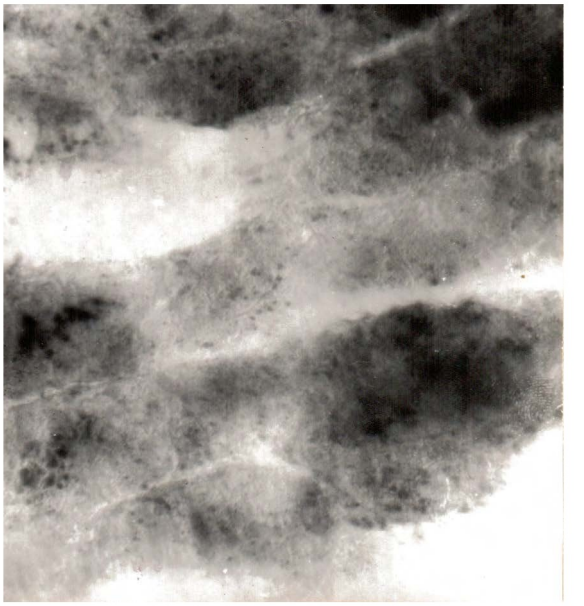


FIG 14 .B.

FIG. 15 A..Ho

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The following are abstracts of papers presented at the "Conference on the Effects of the Sulfonylureas and Related Compounds in Experimental and Clinical Diabetes" held February 14 and 15 by the New York Academy of Sciences. These articles will appear in full published form at a later date. (1957)

72. Beaser, S.B. Further experience with the use of sulfonylureas in diabetes.

73. Bergenstal, D.M., Lubs, H.A., Hallman, L.F. and Striker, J.A. Effects of tolbutamide on the diabetes of acromegaly and on the blood sugar in patients with altered endocrine states.

74. Dolger, H. Experience with the sulfonylurea management of 500 cases of diabetes on an ambulatory basis.

75. Dulin, W.E. and Johnston, R.L. Studies concerning the role of the liver in the hypoglycemic response of animals to Orinase.

76. Duncan, G.G. Clinical experiences with the sulfonylureas in diabetes mellitus.

77. Elrick, H. and Purnell, R. Peripheral and hepatic action of tolbutamide.

78. Fajans, S.S., Louis, L.H., Hennes, A.R., Wajchenberg, B.L., Johnson, R.D., Gittler, R.D., Ackerman, I.P. and Conn, J.W. Metabolic effects of sulfonylureas in normal men and in various types of diabetic patients.

79. Houssay, B.A., Penhos, J.C., Teodosio, N., Bowkett, J. and Apelbaum, J. Action of the hypoglycemic sulfonamides in experimental animals subjected to various endocrine conditions.

80. Loubatieres, A.L. The development of our knowledge concerning the hypoglycemic sulfonamides between 1942 and 1955.

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82. Marble, A. and Camerini-Davalos, R. Clinical experience with sulfonylurea compounds in diabetes.

83. Miller, W.L. Studies on the absorption, mechanism of action, and excretion of tolbutamide in the rat.

84. Mirsky, I.A. The sulfonylureas and insulinase activity.

85. Moorhouse, J.A., Kark, R.M. and Gelman, D.D. Effects of tolbutamide on the metabolism of fructose and glucose.

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87. Sherry, S. The use of tolbutamide in the management of adult diabetes.

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89. Wick, A.N. The effect of sulfonylureas on the peripheral utilization of carbohydrates in animals.

90. Volk, B.W., Goldner, M.G., Weisenfeld, S. and Lazarus, S.S. Functional and histological studies concerning the action of sulfonylureas.