The Syndrome of Narcolepsy and Diabetogenic Hyperinsulinism in the American Negro

Its Relationship to the Pathogenesis of Diabetes Mellitus, Obesity, Dysrhythmias, and Accelerated Cardiovascular Disease

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Tell me not, in mournful numbers,
Life is but an empty dream! —
For the soul is dead that slumbers,
And things are not what they seem.

—LONGFELLOW

Let us then blush, in this so ample, and so wonderful field of nature, (where performance still exceeds what is promised) to credit other mens traditions only, and thence coine uncertain problems, to spin out thorney and captious questions. *Nature* her selfe must be our adviser; the path she chalks must be our walk; for so while we confer with our own eies, and take our rise from meaner things to higher, we shall be at length received into her Closet-secrets.

— WILLIAM HARVEY[1]

INTRODUCTION

THIS contribution was prompted by two events: 1) a recent series of editorials and letters written by distinguished clinicians and investigators[2-5] "in order to denounce the teachings . . . that the brain of the Negro is physically inferior to that of the white"; and 2) an increasing awareness of the frequency with which the syndrome of narcolepsy and diabetogenic ("functional") hyperinsulinism I have described [6-9] occurs in Negro patients. My prime purpose herein is to present evidence for the following: 1) a significant segment of Negro patients whom I see are afflicted with narcolepsy, a readily treatable disorder; and 2) this manifestation represents the interaction of both a genetic diathesis and long-standing metabolic insults to the brain, chiefly reactive hypoglycemia. While these conclusions admittedly must be conditioned by the limited number of patients studied to date, it is hoped that this presentation will spur the obtaining of comparable data on larger population groups.

In order to avert any misunderstanding of intent, I believe it proper both to reiterate and to second the opposition expressed by Ingle concerning "the dogma of both equalitarians and racists because both groups rationalize valued judgments behind the facade of flimsy evidence"[2], and Penfield's conviction[3] that "the innate intellectual capacity of white, mulatto and Negro is probably the same." It is my belief that this preliminary probe into certain medical and behavior genetics of the American Negro has been carried out in compliance with Halstead's prerequisites that 1) "the ghost of racist dogma must be laid to rest before any comprehensive investigation of the important scientific problem posed by race can be undertaken", and 2) "the scientific yield of such efforts will depend directly on the freedom to make *free* inquiry."[5] The following commentary by Albert Einstein[10] also conveys a perspective pertinent to this study:

It is difficult even to attach a precise meaning to the term 'scientific truth.' So different is the meaning of the word 'truth' according to whether we are dealing with a fact of experience, a mathematical proposition or a scientific theory . . . *Scientific research can reduce superstition by encouraging people to think and survey things in terms of cause and effect.* Certain it is that a conviction, akin to religious feeling, of the rationality or intelligibility of the world lies behind all scientific work of a high order . . . Denominational traditions I can only consider historically and psychologically; they have no other significance for me. (Italics author's).

By way of further introduction, it is desirable to orient the reader as to the manner in which these clinical observations and convictions germinated. As a consulting physician and the author of two texts on diagnostic problems[11,12], I am continually confronted with a variety of perplexing situations. Approximately five years ago, I began to become aware of the *extraordinary* frequency with which patients presenting themselves

in this context had both true (but unrecognized) narcolepsy and "functional" hyperinsulinism.[6-9] Their recurrent hypoglycemia was frequently assoated with diabetes mellitus (overt or occult). In an accrued experience of 232 patients with this disorder, the correct diagnosis had not been previously in a *single* instance. These patients variously presented with the subtle manifestations of narcolepsy (particularly undiagnosed "fatigue" or "tiredness", and "refractory hypothyroidism"), obesity (due to the summation of narcoleptic hypokinesia and hypoglycemic-induced orexia), or other common manifestations and consequences of repeated hypoglycemic stress. The latter included vascular headaches, cerebral dysrhythmias, peripheral neuropathies, angina pectoris, cardiac arrhythmias, peptic ulcer and alcoholism — all of which had defied standard medical management. The clinical, laboratory, electroencephalographic, electrocardiographic and experimental bases for these assertions are detailed elsewhere.[8,9,13] Concomitantly, I become increasingly impressed with the high incidence and severity of this syndrome among Negro patients, both within the realm of my private (and predominently white) consultation practice, and as a visiting physician attending indigent patients on a general medical ward or in a cardiac clinic. Although more white patients with this disorder have been encountered, the severity of the narcolepsy, the frequency of unrecognized diabetogenic hyperinsulinism, and the notably low electroencephalographic voltages in the Negro group justify a presentation of this unique experience, however controversial.

CLINICAL DATA

The pertinent data concerning 31 personally-observed Negro patients afflicted with both narcolepsy and recurrent hypoglycemia are summarized in Table 1.

Sex Distribution. There were 23 females (74.2%) and 8 males (25.8%). This finding contrasts with the widespread belief that narcolepsy is predominently a disease of men, and underscores its great subtilty among women.

Age Range. These patients ranged in age from 13 to 76 years. A further breakdown of their average ages based upon the presence of diabetes mellitus and obesity is found in Table 1. The majority of patients who were seen in their second and third decades gave narcoleptic symptomatology clearly dating back to the first decade. The older average age of the diabetic obese (DO) group also is noteworthy. It is of interest that the major features of this syndrome apparently had never been diagnosed in the three patients over the age of 60 years, notwithstanding prolonged doctoring.

Obesity. Most of these patients, 25 or 80.6%, were obese according to the criteria used (viz., 10 lbs. or more above the upper limits of their desirable weight). Some patients who had been overweight were not classified as obese if they did not meet these criteria when seen. (See Case NN-5 in Case Histories).

Diagnostic Criteria for Narcolepsy. The following features of narcolepsy were specifically sought:

1. The hallmark of *irresistible drowziness and actual sleep* in the absence of physical fatigue, after an adequate night's sleep, and with proper motivation (e.g., while driving, during dental work, or in the course of a medical interview) was present in *every* patient.

2, 3, 4. *Cataplexy, hypnogogic hallucinations, and sleep paralysis* were admitted by 24 (77.4%), 23 (74.2%), and 23 (74.2%) patients, respectively. (The "narcoleptic tetrad" refers to combined presence of narcolepsy and these 3 features.[14])

5. A definite or highly suggestive *family history of narcolepsy* was obtainable from 20 patients. An adequate family history could not be obtained from 7 patients.

6. *Electroencephalographic evidence of marked drowziness or sleep* was found in 10 of the 12 patients who underwent such study. Technical considerations and the need for instituting therapy prior to electroencephalographic study probably accounted for its absence in the remaining patients.

7. *A dramatic clinical response to the trial of relatively small doses of an analeptic agent* — notably methylphenidate hydrochloride (Ritalin) — was forthcoming in the majority of instances where such a therapeutic test was given.

At least six of the above seven diagnostic criteria, or five of six when electroencephalograms or a reliable family history could not be obtained, were found in 21 (67.7%).

Although a history of severe infection (e.g., pneumonia, rheumatic fever) was occasionally obtained, it was absent in the predominant majority. No documented instance of encephalitis was encountered.

Recurrent Hypoglycemia due to "Functional Nondiabetic Hyperinsulinism". This diagnosis was made in 9 patients. The criteria included the occurrence of typical hypoglycemic symptomatology

TABLE 1. SUMMARY OF DATA ON 31 NEGRO PATIENTS WITH BOTH NARCOLEPSY AND RECURRENT HYPOGLYCEMIA

	GROUP I (NO) Nondiabetic obese	*GROUP II (NN) Nondiabetic nonobese*	*GROUP III (DO) Diabetic obese*	*GROUP IV (DN) Nondiabetic nonobese*	*TOTALS*
Patients	4	5	21	1	31
Females	4 (100%)	3 (60%)	15 (71.4%)	1 (100%)	23 (74.2%)
Males	0	2 (40%)	6 (28.6%)	0	8 (25.8%)
Average age (years)	32	27	41	37	34.2
Over 60 years	0	0	3 (14.3%)	0	3 (9.7%)
F.H. narcolepsy	3 (75%)	4 (80%)	12 (56.1%)	1 (100%)	20 (64.5%)
F.H. diabetes mellitus	3 (75%)	2 (40%)	10 (47.6%)	1 (100%)	16 (51.6%)
Fasting hyperglycemia	—	—	11 (52.4%)	0	11 (35.5%)
Narcolepsy	4 (100%)	5 (100%)	21 (100%)	1 (100%)	31 (100%)
Cataplexy	4 (100%)	5 (100%)	14 (66.7%)	1 (100%)	24 (77.4%)
Hypnogogic hallucinations	4 (100%)	5 (100%)	14 (66.7%)	0	23 (74.2%)
Sleep paralysis	4 (100%)	5 (100%)	13 (61.9%)	1 (100%)	23 (74.2%)
Complete narcoleptic tetrad	4 (100%)	5 (100%)	12 (56.7%)	0	21 (67.7%)
Previous thyroid therapy	1 (25%)	0	1 (4.8%)	0	2 (6.4%)
Vascular headaches	3 (75%)	4 (80%)	18 (85.7%)	1 (100%)	6 (83.9%)
Recurrent edema	2 (50%)	3 (60%)	13 (61.9%)	1 (100%)	19 (61.3%)
Neuropathy (including leg cramps and "restless legs")	1 (25%)	2 (40%)	14 (66.7%)	1 (100%)	18 (58.1%)
Angina Pectoris	0	2 (40%)	6 (28.6%)	0	8 (25.8%)
Cardiac arrhythmias	2 (50%)	1 (20%)	7 (33.3%)	0	10 (32.3%)
Hypertension	1 (25%)	0	9 (42.9%)	0	10 (32.3%)
Alcoholism	0	1 (20%)	2 (9.5%)	0	3 (9.7%)
Patients studied by EEG	1 (25%)	2 (40%)	8 (38%)	1 (100%)	12 (38.7%)
Low-voltage fast activity	0 of 1	1 of 2	4 of 8	1 of 1	6 of 12
High-voltage spiking	1 of 1	2 of 2	3 of 8	1 of 1	7 of 12
High-voltage paroxysmal slowing	0 of 1	2 of 2	2 of 8	0	4 of 12
14-and-6/sec., 14/sec., or 6/sec.	1 of 1	0 of 2	2 of 8	1 of 1	3 of 12
Low-voltage (pre-glucose)	0 of 1	1 of 2	3 of 8	0	4 of 12

several hours after eating, its prompt response to the ingestion of food or sugar, and the absence of diagnostic hyperglycemia in both morning *and* (when performed) afternoon glucose tolerance tests.

Recurrent Hypoglycemia Associated with Diabetes Mellitus. Fasting hyperglycemia or impaired glucose tolerance was found in the remaining 22 patients. Diabetes mellitus had been previously known or suspected, however, in only seven patients. Fasting hyperglycemia was recorded on at least one occasion in 11 patients. Impaired glucose tolerance by either morning or afternoon testing was found in 14 patients whose fasting blood glucose concentrations either were normal or in the equivocal range (i.e., between 120 mg. % and 130 mg. % Folin Wu.)

As noted earlier, these patients were classified according to the presence or absence of diabetes mellitus and obesity (Table 1). The breakdown was as follows:

Nondiabetic obese (NO) group — 4 patients
Nondiabetic nonobese (NN) group — 5 patients
Diabetic obese (DO) group — 21 patients
Diabetic nonobese (DN) — 1 patient

A *family history of diabetes mellitus* could be obtained from 16 patients (51.6%). It is significant, however, that five were in the nondiabetic groups (NO and NN).

No patient fulfilled the standard diagnostic criteria for "organic" hyperinsulinism due to islet-cell neoplasia. Similarly, the diagnoses of adrenocortical hyperfunction and pheochromocytoma were specifically excluded by appropriate studies whenever these possibilities were raised.

There was no evidence of sickle-cell anemia in any patient. Although hemoglobin electrophoretic studies were not routinely performed in outpatients, the sickle-cell trait could be demonstrated in only one patient.

LABORATORY STUDIES

Fasting Glucose Concentrations. Blood glucose determinations were done in all patients, chiefly by the Folin-Wu method. The method of reducing potassium ferricyanide to potassium ferrocyanide (using the automatic Technicon apparatus) was employed in some studies. Hyperglycemia in the fasting state — arbitrarily defined as exceeding 120 gm. per cent, was found on at least one occasion in 11 patients. No patient had a fasting glucose concentration below 75 mg. per cent.

Morning Glucose Tolerance Testing. Glucose tolerance tests were carried out for four to six hours during the morning after the ingestion of a 100 gm. glucose load in 23 patients. Attempts were made to avoid or minimize carbohydrate restriction prior to such testing. Impaired morning glucose tolerance — i.e., glucose concentrations arbitrarily exceeding 180 mg. per cent at any time, and greater than 130 mg. per cent at three hours, was found in 13 patients. The average blood glucose concentrations in the diabetic (DO and DN) and nondiabetic (NO and NN) groups were as follows:

	Diabetic Groups	*Nondiabetic Groups*
Fasting	113 mg.%	98 mg.%
½ hour	192 mg.%	124 mg.%
1 hour	195 mg.%	114 mg.%
2 hours	158 mg.%	113 mg.%
3 hours	118 mg.%	82 mg.%
4 hours	89 mg.%	80 mg.%

A decline of the glucose concentration to 70 mg. per cent or less, or a nadir level of at least 15 mg. per cent below the fasting glucose concentration, especially when accompanied by a reproduction of the patient's clinical attack, was regarded as confirmatory of reactive hypoglycemia. The reasons for selecting the 70 mg. per cent level and the discrepancies frequently encountered in this "biochemical twilight zone" (particularly among diabetic patients in whom testing was terminated at four hours) have been considered previously.[8,13] It is further pointed out that the 3-hour, 4-hour and even 5-hour averages tend to be misleadingly elevated because of the frequent rebound rise of the blood glucose concentration after a maximal decline — presumably reflecting hypoglycemia-induced adrenal stimulation. (See Discussion.) The lowest individual levels encountered in the diabetic and nondiabetic groups were 48 mg. per cent at 4½ hours and 30 mg. per cent at 3 hours, respectively.

Afternoon Glucose Tolerance Testing. Glucose tolerance tests were performed during the afternoon on seven patients, of whom six proved to be diabetic. This method is considered elsewhere in detail.[8,13] A routine was followed wherein the patient ate a "good" breakfast at least 4 hours prior to ingesting 100 gm. glucose, and then remained active before and during the test — in effect simulating customary daily activity. The test was usually concluded 4 hours after the glucose ingestion unless a severe hypoglycemic reaction necessitated its premature cessation. The average blood glucose concentrations were as follows:

	Diabetic Groups	*Nondiabetic Groups*
Pre-glucose	90 mg.%	102 mg.%
½ hour	242 mg.%	160 mg.%
1 hour	182 mg.%	132 mg.%
2 hours	156 mg.%	111 mg.%
3 hours	108 mg.%	98 mg.%
4 hours	81 mg.%	79 mg.%

It is pointed out that only the glucose tolerance test of Case NN-2 (See Case Reports) comprises the nondiabetic column.

The following two important findings and insights were derived from afternoon testing: 1) there were six patients, two with nondiabetic morning tests, and four with borderline morning responses (i.e., a single peak glucose concentration ranging between 180 mg. per cent and 190 mg. per cent) who evidenced unequivocal impairment of glucose tolerance *only* in afternoon glucose tolerance tests; and 2) the majority of patients experienced marked clinical and chemical intensification of their hypoglycemic responses during the afternoon (the reaction often exactly simulating their spontaneous clinical attacks).

Serial Serum Potassium Levels were determined before and hourly for 4 hours after the glucose loading in 2 diabetic patients. Their concentrations declined from an average fasting level of 4.33 mEq/L to an average minimal level of 3.71 mEq/L. This response is comparable to that found in 18 white patients with diabetogenic hyperinsulinism who were studied in a similar manner.

Serial Serum Sodium Levels were determined fasting and hourly for four hours after glucose loading in two female patients who had suffered with "idiopathic" recurrent edema. Their sodium

concentrations increased from an average fasting level of 141.5 mEq/L to a maximal average of 145.5 mEq/L. This response was associated with a *prompt* exacerbation of abdominal distention and gain in weight in one. A comparable electrolyte and clinical response occurred in 14 white patients with this syndrome who were so studied.

Representative changes of the concomitant blood glucose, sodium and potassium concentrations after glucose loading during a morning study are illustrated by Case DO-7. This 35-year old female with longstanding obesity (250 lbs.), the narcoleptic tetrad, recurrent hypoglycemia (more convincingly demonstrated by afternoon testing), hypertensive cardiovascular disease, and migraine gave the following results:

	Blood Glucose	*Serum Sodium*	*Serum Potassium*
Fasting	82 mg.%	143 mEq/L	4.2 mEq/L
½ hour	196 mg.%	142 mEq/L	3.5 mEq/L
1 hour	192 mg.%	140 mEq/L	3.8 mEq/L
2 hours	114 mg.%	140 mEq/L	4.1 mEq/L
3 hours	115 mg.%	143 mEq/L	3.7 mEq/L
4 hours	98 mg.%	148 mEq/L	5.3 mEq/L

Similar electrolyte responses during the course of both morning and afternoon studies are cited elsewhere.[8,13]

Studies of Adrenal Function were performed in 11 patients. They included several or all of the following: determination of urinary 17-ketosteroid and 17-hydroxycorticosteroid excretion before and after corticotropin; the 24-hour catecholamine excretion; the eosinophil response to corticotropin; and the determination of serum electrolytes. Although these studies were generally indicative of normal adrenal function, slight to moderate elevation of the 17-ketosteroid and 17-hydroxycorticosteroid output was noted in several.[8] This finding — along with the ensuing decreased titers following dietotherapy — has been explained on the basis of hypoglycemic-induced adrenal stimulation.[8,15,18]

X-rays of the Skull and Sella Turcica were normal in 6 of 7 patients so studied. Slight enlargement of the sella turcica was present in Case DO-14. (See Case Reports.)

Studies of Thyroid Function were carried out in the majority of patients. These parameters included several or all of the following: determination of the protein-bound iodine or butanol-extractable iodine, the serum cholesterol, the timed Achilles tendon reflex (SD interval) with the Kinemometer, and the radioactive iodine uptake. Except for the hypercholesterolemia associated with diabetes and the occasional absence of ankle jerks in patients with diabetic neuropathy, they were essentially within normal limits. Thyroid surgery had been performed because of hyperthyroidism in two subsequently euthyroid patients.

Serial Plasma Insulin-Like Activity (ILA) Assays were determined by the rat epididymal fat pad assay method on specimens obtained from four patients both before and at ½, one and two hours after glucose loading. The fasting ILA was normal in all. ILA rose as anticipated after glucose ingestion, the increase being particularly strik-

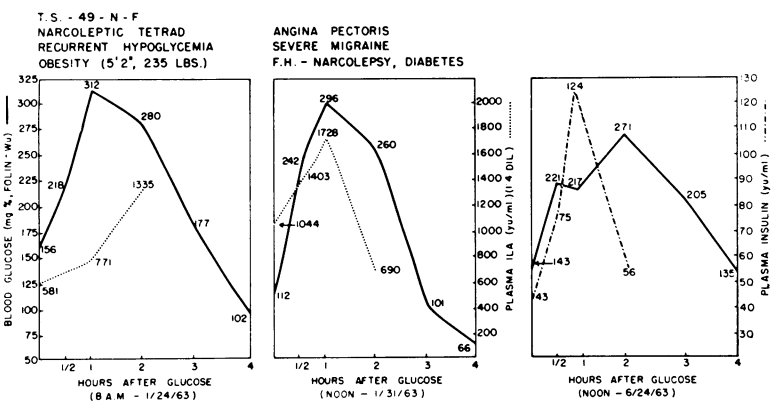

Fig. 1. "Decompensation" of both the plasma insulin and insulin-like activity response to an afternoon glucose load in an untreated obsese diabetic (Case DO-8). (See Case Reports) Also note her exaggerated reactive hypoglycemia during the initial earlier afternoon study when insulinogenesis was relatively less impaired.

ing among the diabetic patients.[19] Serial plasma insulin by the immunoassay method[19] also was done in two patients; their responses were comparable.

The writer's concept that *diabetes mellitus represents a "high-output failure"* of insulinogenesis was supported by 1) comparative morning and afternoon glucose tolerance testing (*vide supra*), 2) ILA assays and plasma insulin assays carried out in previously-untreated diabetic patients, and 3) the morning and afternoon responses to 1 gm. intravenous tolbutamide (Orinase) in three patients. The results obtained in Case DO-8 are illustrative. This 49-year old obese newly-discovered diabetic female (See Case Histories) predictably experienced intensification of her hypoglycemic symptomatology (notably hunger, "weakness", and chest pain) during the late afternoon. No insulin or oral hypoglycemic therapy had been administered prior to study. She evidenced failure of insulinogenesis after glucose loading *only* during afternoon study. The results of concomitant blood glucose concentrations and ILA (1:4 dilution) obtained after glucose loading in the morning and afternoon (Fig. 1) were as follows:

Morning test (1-24-63)
(Wt. 220 lbs.)

	Blood glucose	*ILA*
Pre-glucose	156 mg.%	581 μ units/ml.
½ hour	218 mg.%	
1 hour	312 mg.%	771 μ units/ml.
2 hours	280 mg.%	1335 μ units/ml.
3 hours	177 mg.%	
4 hours	102 mg.%	

(Afternoon test (1-31-63)
(Wt. 218 lbs.)

	Blood glucose	*ILA*
Pre-glucose	112 mg.%	1044 μ units/ml.
½ hour	242 mg.%	1403 μ units/ml.
1 hour	296 mg.%	1728 μ units/ml.
2 hours	260 mg.%	690 μ units/ml.
3 hours	101 mg.%	
4 hours	66 mg.%*	

* Clinical hypoglycemic reaction.

Plasma was subsequently obtained during a repeat afternoon glucose tolerance test, and assayed for insulin by the immunoassay method. The results were as follows:

Afternoon test (6-24-63)
(Wt. 226 lbs.)

	Blood glucose	*Plasma insulin*
Pre-glucose	143 mg.%	43 μ units/ml.
½ hour	221 mg.%	75 μ units/ml.
1 hour	217 mg.%	124 μ units/ml.
2 hours	271 mg.%	56 μ units/ml.
3 hours	205 mg.%	
4 hours	135 mg.%	

Intravenous tolbutamide testing was performed both while fasting and at 4:30 p.m. (after she had eaten lunch about 4 hours prior to testing). The results of the blood glucose concentrations and the percentage declines in relation to the pre-tolbutamide levels were as follows:

Morning test (7-19-63)
(Wt. 212 lbs.

Pre-Injection	153 mg.%	
10 minutes	145 mg.%	(94.1%)
20 minutes	143 mg.%	(93.5%)
30 minutes	135 mg.%	(88.2%

Afternoon test (9-11-63)
(Wt. 216 lbs.)

Pre-Injection	101 mg.%	
10 minutes	93 mg.%	(92.1%)
20 minutes	87 mg.%	(86.1%)
30 minutes	93 mg.%	(92.1%)

ELECTROENCEPHALOGRAPHIC STUDIES

Electroencephalograms were recorded before and after glucose loading for periods of four to five hours in three patients, and for periods of 1½ hours or longer after glucose in nine patients. A standard monopolar recording technic (employing 14 electrodes and an 8-channel Grass unit) was used by the same technician. Attempts were made to discontinue all medication (especially barbiturates and analeptics) for three days. This interval was reduced to only one day, however, in those patients who required an analeptic effect because of occupational or driving hazards. All tracings were interpreted independently by the writer and a consultant electroencephalographer (William Everts, M.D.).

Profound low voltages and prompt sleep patterns characterized the pre-glucose electroencephalograms of four patients. (Figs. 2-4.) Comparable patterns were not found in the many more (62) white narcoleptic patients who have been studied under identical circumstances. There was no evidence of hypothyroidism in these patients with low voltage either clinically or biochemically (e.g., the butanol-extractable iodine level of patient W.W. in Fig. 2 was 4.2 mg. per cent).

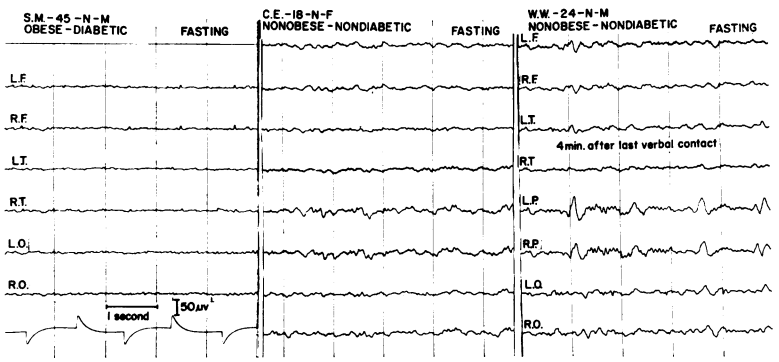

Fig. 2. Pre-glucose electroencephalograms in three Negro patients afflcted with severe narcolepsy and diabetogenic hyperinsulinism. The low-voltages and the prompt onset of parietal "humps" and sleep spindles in W.W. are noteworthy.

Progressive drowziness and sleep was readily induced (i.e., within 30-60 minutes) by glucose ingestion in 10. This was evidenced both clinically and by sustained replacement of occipital alpha rhythm with low-voltage slow waves, followed by the appearance of striking parietal "humps" and sleep spindles (Figs. 5 and 6). (It was also a frequent occurrence during glucose tolerance testing.) The majority of these patients had long recognized the sleep-inducing effect of meals. One described this phenomenon as "I get sleepified after I eat."

In the uninterrupted studies, glucose-induced sleep was followed by increasing "alertness" at varying intervals. This was evidenced by a return of occipital alpha rhythm, frequent eye blinking, and muscle tension artifacts. Although these changes in cortical activity were clearly related to declining blood glucose concentrations, they could not be correlated with specific levels in every instance — especially among the diabetic patients. This threshold, however, generally approximated 70 mg. per cent, and *not* 50 mg. per cent. Correlative electroencephalographic and chemical sequences in several patients are depicted in Figs. 5 and 6.

Intravenous methylphenidate hydrochloride (Ritalin) was injected in small doses (2.5-5 mg.) via the side tubing of a continuous slow saline infusion at the height of glucose-induced sleep. Striking cortical activation was consistently produced within 30 seconds to 3 minutes (Figs. 7 and 8). There was no response to a preceding control infusion of the lyophilized powder base of the methylphenidate hydrochloride mixed with its diluent.

Cortical activation occurred within 1-5 minutes after injecting *intravenous crystalline insulin* (20 units) under comparable circumstances. This response has been illustrated elsewhere[8,9] and documented by others.[20,21]

The activation induced by *intravenous tolbutamide* (1 gm.) was much less impressive. Its onset was considerably more delayed than that following insulin — i.e., it did not occur in two patients until their blood glucose concentrations had declined below 70 mg. per cent (Fig. 8.)

The greater analeptic effect of methylphenidate over relative hypoglycemia was illustrated by two young and severely narcoleptic patients. Case NN-3 (an 18-year old female) had not yet awakened from deep sleep 30 minutes after receiving an infusion of 1 gm. tolbutamide even though her blood glucose concentration was 70 mg. per cent.

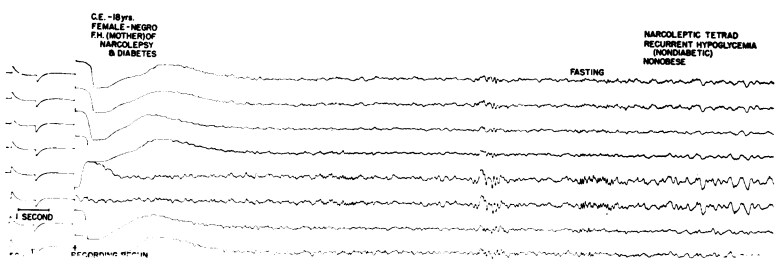

Fig. 3. Spontaneous sleep pattern in a young narcoleptic Negro female. Note the dramatic appearance of sleep spindles and parietal "humps" within one minute after the recording was begun.

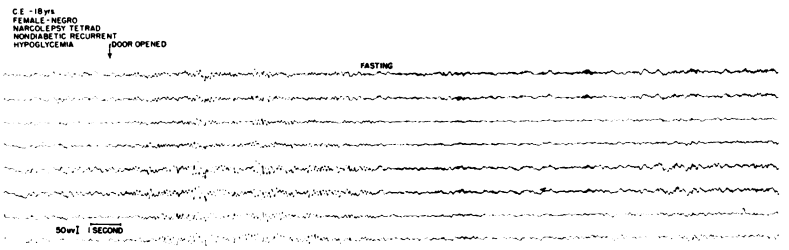

Fig. 4. Demonstration of the prompt return of sleep in the severely narcoleptic patient depicted in Fig. 3 after she was awakened by opening door.

(Fig. 8.) Case DO-11 (a 24-year old male) demonstrated slight cortical activation 72 minutes after intravenous tolbutamide when his blood glucose concentration was 67 mg. per cent. Within 1 minute, both patients then responded dramatically to intravenous methylphenidate (2.5 mg. and 5.0 mg., respectively) after a comparable amount of the lyophilized powder base mixed with the diluent had produced no effect.

The most striking electroencephalographic findings were the presence of unequivocal and generally multiple *dysrhythmias* in 10 of the 12 patients so studied. The pre-glucose EEG of one of those without dysrhythmia was characterized by low voltage. A history of frank clinical seizures — even when sought in retrospect — could not be elicited from a single patient. These dysrhythmias consisted chiefly of diffuse paroxysmal high-voltage spike activity (seven patients), frequent bursts of low-voltage fast (20-30/second) activity over the frontal and parietal areas (six patients), diffuse paroxysmal high-voltage slowing (notably over the parietal and mid-temporal areas) (four patients), and either 14-and-6/sec., 14/sec., or 6/sec. activity (three patients). Some representative dysrhythmias are shown in Figs. 9 and 10. Other dysrhythmias encountered in patients with the syndrome of narcolepsy and diabetogenic hyperinsulinism have included a "mitten" pattern, abnormal frontal and parietal fast activity accentuated by hyperventilation, and psychomotor variant pattern.[8,9] The familial incidence of dysrhythmias in patients with this syndrome is depicted in Fig. 10.

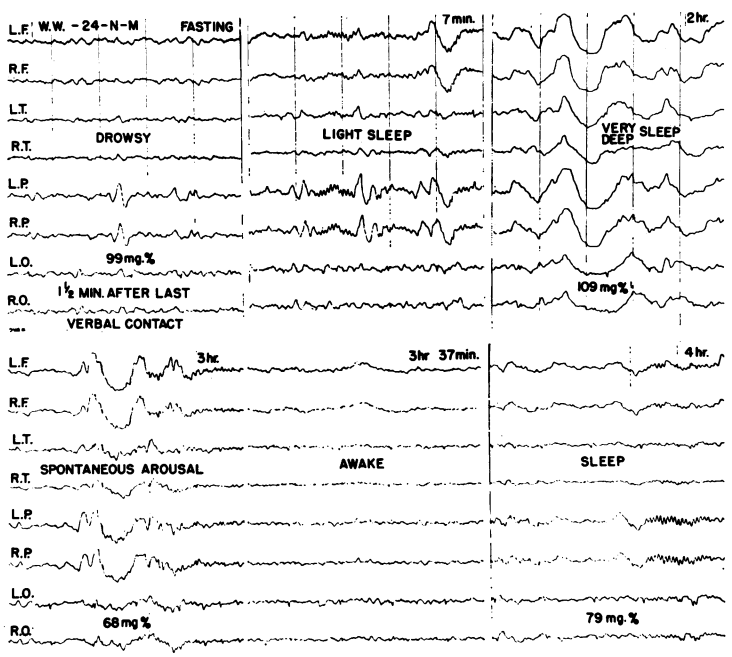

Fig. 5. Electroencephalographic and biochemical observations during glucose-induced sleep and subsequent reactive hypoglycemia-induced arousal in a severely narcoleptic young Negro male. Note the threshold glucose concentration of approximately 70 mg.% (Folin-Wu) below which the analeptic effect occurred and above which sleep recurred.

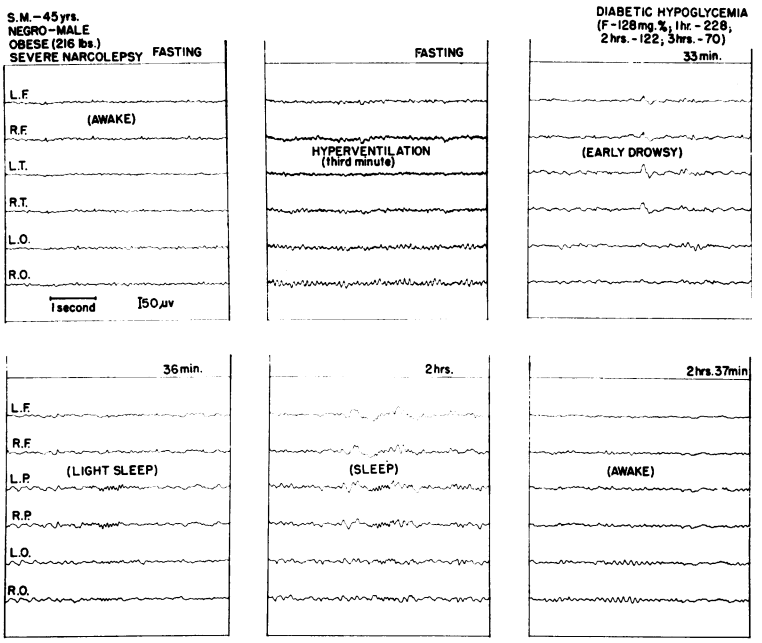

Fig. 6. Electroencephalographic sequence of glucose-induced sleep and subsequent spontaneous arousal associated with reactive hypoglycemia in an obese and severely narcoleptic diabetic Negro.

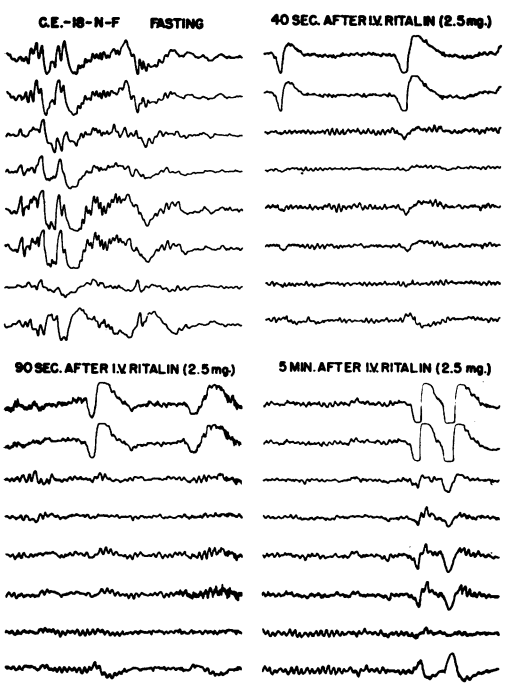

Fig. 7. Demonstration of the prompt analeptic effect in a severely narcoleptic young female after injecting Ritalin (2.5 mg.) into a continuous saline infusion during spontaneous sleep. A preceding injection of Ritalin base mixed with its diluent had failed to produce any effect.

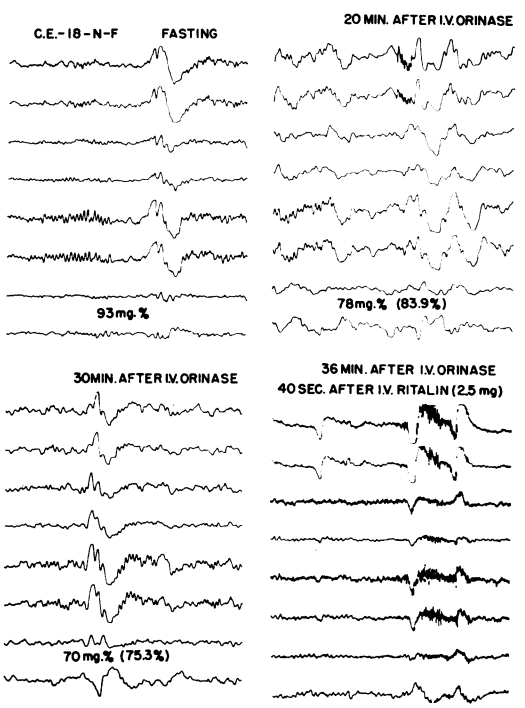

Fig. 8. Demonstration of the prompt analeptic effect of intravenous Ritalin (2.5 mg.) in a severely narcoleptic young female after intravenous tolbutamide had not yet effected such a response—even though the blood glucose concentration declined to 70 mg.%.

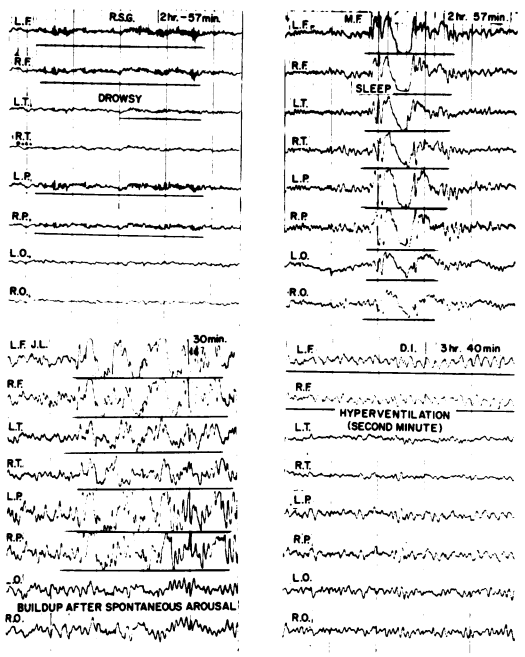

Fig. 9. Representative dysrhythmias in patients with the syndrome of narcolepsy and diabetogenic hyperinsulinism, including low-voltage fast (20-30/second) discharges (chiefly over the frontal and parietal leads), paroxysmal slowing, and paroxysmal high-voltage spike activity.

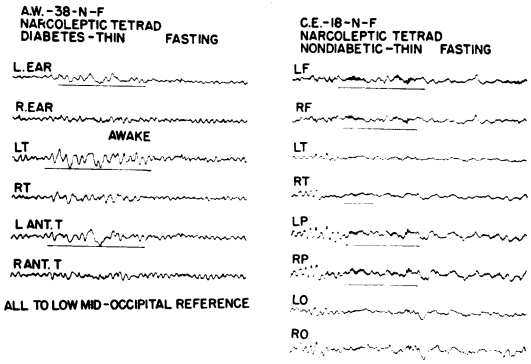

Fig. 10. Representative dysrhythmias in a thin diabetic female with severe narcolepsy (Case DN-1) and her severely narcoleptic daughter (Case NN-3). (See Case Reports)

FREQUENT PRESENTING FEATURES AND ASSOCIATED COMPLICATIONS

Classic *migraine* and so-called *histaminic cephalgia* ("histamine headaches") were present in 26 patients (83.9%). The writer has repeatedly and unequivocally demonstrated that hypoglycemia can both precipitate and *exactly* reproduce such attacks of headache in these patients. [8,13,22] (See Cases DO-8, DN-1, NN-3, NN-5, NO-1, and DO-14.)

Recurrent edema ("idiopathic" edema) was a prominent feature in 19 female patients (61.3%). (See Cases DN-1, NN-3, DO-8, NN-5, NO-1, and DO-14.) On the basis of the data presented earlier[8] and that of others[23], such edema is believed to be related to the inhibition of sodium excretion with associated retention of water which follows glucose ingestion. Reference was made to the dramatic reproduction of edema in these patients either during or following glucose tolerance testing.

Severe *peripheral neuropathies, leg cramps and "restless legs"* were prominent in 18 patients (58.1%). The neuropathies were characterized more often as an intense burning discomfort or lancinating pains, especially in the lower extremities. These features occurred both with and without demonstrably impaired glucose tolerance. (See Cases DN-1 and NO-1.) Severe leg cramps or the "restless legs" phenomenon, or both — generally occurring during the night — also were common complaints. (See Cases NO-1 and DO-14.) A corrective diet aimed at minimizing hypoglycemia effected *prompt* and oft-dramatic improvement in virtually every patient, even after numerous drugs (e.g., quinine, diphenhydramine) and a variety of physical maneuvers had proved ineffective.

Classic angina pectoris and paroxysmal tachycardia were present in eight (25.8%) and ten (32.3%) patients, respectively. (See Cases DO-8, NN-5 and DO-14.) In many instances, these features had resisted standard therapeutic measures, but were *promptly* checked after the underlying role of recurrent hypoglycemia was appreciated and treated by diet. *Episodic cardiac pain or arrhythmias occurring more than three hours after eating or during the early morning hours always should raise the possibility of a triggering hypoglycemic mechanism.*[8,13,24,25] These arrhythmias can be logically explained on the basis of hypoglycemia-induced myocardial hypoxia, hyperepinephrinemia and hypokalemia.

Accelerated hypertension was encountered in ten patients (32.3%),[8] of whom 9 were in the diabetic obese group. The majority had not received thiazide drugs prior to glucose tolerance testing.

Significant *psychiatric features,* notably anxiety and depression, were present in several patients. Aggravation of such disability often could be correlated with their cyclic hypoglycemia. (See Case

NN-2.) The importance of this association was further underscored by the following experiences: 1) their failure to exhibit clinical improvement after prolonged formal psychiatric therapy and psychotropic medications in high dosage; and 2) their gratifying response to a regimen essentially centered about a corrective diet and analeptic therapy. The writer believes that the *symptom* of narcolepsy per se is *not* indicative of a fundamental psychiatric disorder, but rather a *nonspecific* expression of deranged cerebral function.

Unnecessary thyroid substance was being taken or had been used over prolonged periods by two patients on the basis of their "low metabolism". The frequency with which narcoleptic patients are so treated because of an erroneous diagnosis of hypothyroidism or "metabolic insufficiency" deserves reemphasis.

Excessive alcohol was being consumed by three patients who drank primarily, but unknowingly, for the short-lived amelioration ("relaxation") of their disabling hypoglycemic symptoms, especially tremors and "nervousness". Derangement of liver function was absent or minimal in those with impaired glucose tolerance. Since there is increasing evidence[26,27] that alcohol ingestion can precipitate or exaggerate hypoglycemia, in at least some individuals, it is apparent that a vicious cycle may be induced thereby. Many patients with the syndrome of narcolepsy and diabetogenic hyperinsulinism have consistently observed that 1) alcoholic beverages (particularly wine) in small amounts will promptly induce somnolence, and 2) the ingestion of alcohol is frequently followed by a severe hypoglycemic attack (generally during the early morning hours.)

TREATMENT

The limitations of space allow for only a brief summary of those therapeutic measures and general recommendations which have been found most helpful in managing patients with the syndrome of narcolepsy and diabetogenic hyperinsulinism.

Diet. Recurrent hypoglycemia can be controlled by a diet which is 1) high in protein, 2) devoid of sugar and concentrated carbohydrate, 3) adequate in fat, and 4) encompasses the concept of "scientific nibbling" (i.e., seven or more small feedings per day.) Because of their accelerated circadian insulinogenesis, many of these patients require snacks at increasingly frequent intervals (i.e., every 1½-2 hours) both as the day progresses and during the night. There is an increasing body of clinical and experimental evidence which supports the value of "nibbling" in correcting obesity, hyperlipemia and atherosclerosis.[28] These patients were supplied with a list of relatively inexpensive sugar-free foods (e.g., matzos, dietetic biscuits, Jewish rye bread, shredded wheat, Grape nuts, dietetic canned foods) that could be purchased in local markets and readily incorporated into their dietary programs. Excessive fluid intake with meals should be avoided because of the possible "dumping" effect so induced.

Owing to their relatively high-protein and low-fat content, *dietary formulas* in liquid, wafer, soup or casserole form — of which Metrecal* is the prototype — proved helpful and convenient in managing both the recurrent hypoglycemia and obesity of selected overweight patients, especially in combination with analeptic therapy (Fig. 11). (Also see Case DO-14.) The details of administration are presented elsewhere.[29,30] The chief difficulty encountered with these formulations (especially the wafers) was the reactive hypoglycemia experienced by an occasional patient in response to

* Kindly supplied by Mead Johnson & Co., Evansville, Ind.

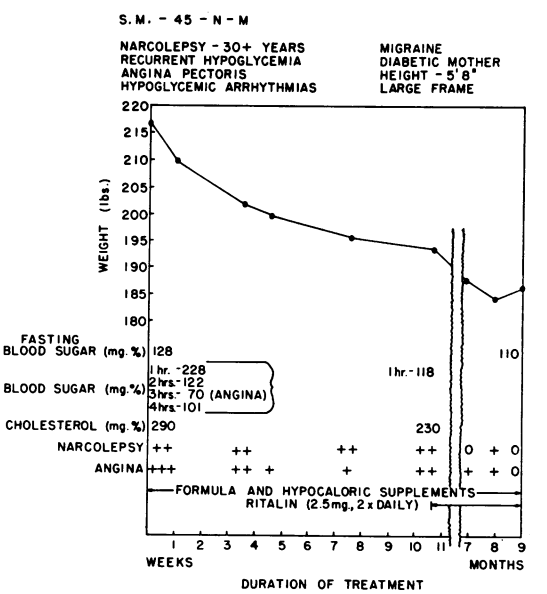

Fig. 11. Example of successful reducing in an obese diabetic Negro male by means of a combined regimen of analeptic therapy and frequent small feedings of a formula diet and hypocaloric supplements. Note the ensuing normalization of his fasting glucose and cholesterol concentrations.

even the relatively small amounts of sugar contained therein.

Analeptic Therapy. Methylphenidate hydrochloride (Ritalin)† has proved to be a highly effective analeptic agent that is usually free of sympathomimetic side effects in the dosages employed. Most patients proved remarkably responsive to relatively small doses — viz, 2.5-10 mg. before meals, 2 or 3 times daily. While an occasional patient preferred *pipradrol hydrochloride (Meratran)*§ over methylphenidate hydrochloride, the reverse has been found to be the case in the majority of those who sampled both agents. Some patients required as much as 60-80 mg. methylphenidate daily. The safety of methylphenidate even in geriatric patients was shown in another study wherein 195 patients over the age of 60 years were uneventfully given this drug (either alone or in combination with reserpine) for "improving senile behavior".[31] The writer encouraged his patients to experiment in arriving at the optimal dosage and frequency of their analeptic medication. For example, many found that the taking of 5 mg. Ritalin every 3 hours during the day was preferable to 10 mg. before meals. Similarly, while some noted that they required more in the morning but less in the afternoon (to minimize insomnia), others found it necessary to increase their dosage during the afternoon.

Although most narcoleptic patients cannot forego their analeptic drug without a prompt relapse, an appreciable number were able to reduce dramatically, or even discontinue, such medication. (See Case Reports.) This clinical phenomenon is believed to represent the beneficial effect on cerebral function of dietotherapy aimed at checking recurrent hypoglycemia. Such a contention is supported by the improvement of dysrhythmias and the diminution or absence of sleep in response to glucose that has been found by repeat electroencephalography after instituting a corrective diet.[9,10]

Other contraindications. Inasmuch as the vast majority of patients with this syndrome are *not* hypothyroid, *needless thyroid therapy should be discontinued.*

Excessive smoking must be curtailed since this habit can cause or aggravate post-prandial hypoglycemia.[32] These patients also should be advised to *avoid alcoholic beverages, excessive caffeine, and sweetened cola-containing liquids* for similar reasons.[26,27]

Management of Diabetes Mellitus. By recognizing diabetes mellitus before it has become manifest in its classic form — and especially prior to the total "decompensation" of insulinogenesis — dietary measures can be instituted to prevent or delay its clinical onset, and minimize or reverse its complications. Stress must be placed upon the *strict* avoidance of added sugar in the diet (a matter requiring continuing vigilance), the ingestion of small meals, weight reduction, the prevention of obesity, and the 24-hour prevention of reactive hypoglycemia by means of frequent nibbling. *On such a regimen, diagnostic hyperglycemia no longer could be demonstrated in seven patients among the writer's total series who were subjected to repeat morning or afternoon glucose tolerance testing, or both.* Three were not obese[13]. (See Case DO-14.) Decidedly improved afternoon glucose tolerance also has been found in others.

Particular pains should be taken to prevent insulin-induced hypoglycemic reactions in the sizable group of diabetic patients who fail to either manifest or appreciate their cerebral, autonomic responses to severe hypoglycemia.[33] Such individuals may experience hypoglycemic coma or convulsions without warning. Several attempts were made to treat adult patients with "early" diabetogenic hyperinsulinism by means of tolbutamide (Orinase) or phenformin (DBI), chiefly because of the purported beneficial effect of these drugs during this crucial period.[34,35] The ensuing intensification of hypoglycemic symptomatology and their clinical exacerbations, however, do *not* appear to justify the "prophylactic" use of these drugs — at least in the present context. This policy is consistent with the following observations and current convictions of the writer: 1) the demonstration of a lessened hypoglycemic effect by afternoon intravenous tolbutamide testing in untreated "early" diabetics[13] (*vide supra*); 2) the phenomenon of "secondary tolbutamide failure" (which is regarded as iatrogenically-induced total decompensation); and 3) accruing evidence that *recurrent hypoglycemic stress with its various endocrine and metabolic sequelae plays a crucial role in the genesis of diabetes mellitus and its complications.*[13,36,37]

Management of Recurrent Edema. Patients who

† Kindly supplied by Ciba Pharmaceutical Co., Summit, N.J.
§ Kindly supplied by Wm. S. Merrell Co., Cincinnati, Ohio

are subject to recurrent edema should be counseled concerning the avoidance of excessive intake of salt and water — as well as sugar — and lying down during the day. Diuretic agents must be used judiciously in these individuals. Several patients with a reversed diurnal excretion of urine volume have experienced dramatic symptomatic relief and an initial diuresis with synthetic oxytocin (Syntocinon) administered either by injection or nasal spray.[8,37,38]

Anti-Epileptic Therapy. Diphenylhydantoin (Dilantin) was given to a number of patients with dysrhythmias when their episodic headaches, severe anxiety, other neurologic or psychiatric features, or the desire to resume alcohol did not abate after they had attempted to adhere to the basic program outlined above. The dosage was generally 0.1 gm. thrice daily. These experiences support those of others who have observed clinical and electroencephalographic improvement following the administration of this drug to labile diabetics.[39]

Nandrolone Phenpropionate. Nandrolone phenpropionate (Durabolin)* has consistently proved highly helpful in managing the neuropathies of many patients—particularly diabetics—after standard measures (viz., parenteral vitamin B_{12}, multivitamins, the avoidance of leg crossing) were ineffective.[9,37] The dosage ranged from 12.5-25 mg. intramuscularly. The drug was injected into the deltoid area every 5-7 days initially. Marked relief of neuritic discomfort was generally forthcoming within 34 weeks. In many instances such benefit was either accompanied by or followed a significant decrease in the SD interval (timed Achilles reflex). No instance of hepatic or hematopoietic toxicity has been observed in a prolonged experience with nandrolone phenpropionate.

REPRESENTATIVE CASE REPORTS

Cases DN-1 and NN-3: Non-obese Negress with classic narcolepsy and recurrent hypoglycemia associated with previously-unrecognized diabetes mellitus; recurrent edema aggravated her rheumatic heart disease; also peripheral neuropathy, severe headaches, and cerebral dysrhythmia; classic narcolepsy, recurrent hypoglycemia, recurrent edema, and dysrhythmia also present in her non-obese daughter.

A 37-year old Negro female (Case DN-1) was initially seen in medical consultation prior to surgery for a mass in her left breast. She had been treated for long-standing rheumatic heart disease, mitral stenosis and aortic stenosis, and was receiving digitalis. When seen, there was no significant enlargement of the heart or evidence of congestive failure. Her pulse was regular and normal. There was no peripheral edema. A moderate hypochromic anemia was present. Her sickle-cell preparation was negative.

The patient appeared markedly drowsy at the initial interview. On further questioning, she gave a striking history of narcolepsy of many years duration, but which had become increasingly worse during the previous three years. Sleep paralysis and cataplexy were also experienced; she denied hypnogogic hallucinations. Concommitantly, she had been experiencing intense recurrent hypoglycemic episodes in the mid-morning and mid-afternoon. If she did not eat frequently, she would become extremely "nervous" and develop a severe throbbing headache. She also had symptoms consistent with a peripheral neuropathy, and was subject to recurrent edema of the hands (which bore no relationship to her periods.)

The patient's glucose tolerance test was typically diabetic. The results were as follows: fasting — 82 mg.%; ½ hour — 173 mg.%; 1 hour — 236 mg.%; 2 hours — 276 mg.%; 3 hours — 246 mg.%; and 4 hours — 88 mg.%. There was 4+ glucosuria in all specimens from 30 minutes to 3 hours. Her fasting serum sodium was 140 mEq/L.; the highest rise (143 mEq/L.) of hourly serum sodium concentrations after glucose occurred at 2 hours. She slept for several hours after ingestion of the glucose, following which she became increasingly alert and intensely hungry. Owing to her cardiac status, the test was terminated at 4 hours. Her electroencephalogram revealed a severe dysrhythmia, chiefly consisting of paroxysmal high-voltage slowing and spiking in the left hemisphere (maximal in the left mid-temporal area) (Fig. 10).

On a program of abstinence from sugar and concentrated sweets, frequent snacks, Ritalin (5 mg.) before breakfast and lunch, and continuation of her previous cardiac program, she experienced gratifying clinical improvement in all respects. She then underwent breast surgery uneventfully.

The 18-year-old daughter (Case NN-3) of this patient was subsequently seen because her mother described her as "always being tired". She was found to have severe and classic narcolepsy. It apparently had been present most of her life, but was becoming worse in recent years. This condition had made it virtually impossible for her to concentrate during school. Her drowsiness was strikingly exaggerated following meals. She gave a history of typical cataplexy, sleep paralysis, frequent auditory hallucinations, and marked insomnia (i.e., awakening between 1-2 a.m.) She had found that she would feel more comfortable and could return to sleep if she drank some milk or juice during the night. She also experienced intense hunger approximately 3 hours after eating, recurrent abdominal swelling that bore no relationship to her periods, and increasing nervousness".

The results of her glucose tolerance test were as fol-

* Kindly supplied by Organon, Inc., West Orange, N. J.

lows: fasting — 98 mg.%; 1 hour — 128 mg.%; 2 hours — 148 mg.%; 3 hours — 80 mg.%; and 4 hours — 87 mg.%. She slept during the first 2½ hours of the test, but then experienced increasing tremulousness and hunger. Her pre-glucose electroencephalogram revealed 1) low voltage, and 2) parietal "humps" and sleep spindles *within one minute* after both last verbal contact with the technician (Fig. 3) and purposeful arousal (Fig. 4). During her periods of drowsiness, she exhibited 20-30/second low-voltage activity, particularly over the frontal areas (Fig. 10). On a program of abstinence from sweets, frequent feedings, and Ritalin (5 mg. before meals), this patient experienced gratifying clinical improvement. It was particularly evidenced by her improved ability to work as a clerk. There was a concomitant decrease of her 20-30/second frontal activity in an electroencephalogram obtained one month later.

Cases DO-8 and NN-2: Obese Negress with diabetogenic hyperinsulinism, the narcoleptic tetrad, migraine, angina pectoris, recurrent edema, and dysrhythmias; severe "functional" hyperinsulinism and the narcoleptic tetrad in her son since early childhood; both experienced benefit with diet and analeptic therapy.

A 49-year-old Negro widow (Case DO-8) was seen initially for longstanding hypertensive vascular disease. She had twice experienced toxemia of pregnancy 13 and 9 years previously. She was receiving digitalis, chlorothiazide, reserpine and guanethidine because of her longstanding dyspnea on slight exertion and orthopnea. She had been fat since her early teens. Her weight fluctuated between 205 and 220 lbs. during the past several years. She was 5 ft. 2 in. Numerous attempts at weight reduction with various diets and amphetamine-type agents had been tried by many physicians — all to no avail. She volunteered that she felt much better when taking amphetamine drugs, but experienced a profound "letdown" when they were discontinued. She ate only one meal daily, generally about 3 p.m.

Further questioning confirmed the presence of longstanding typical narcolepsy. She experienced marked heaviness of the eyes that interfered with viewing television or reading a newspaper except for brief periods. If she did not force herself to remain active, she could sleep as long as five hours following her main meal. She also experienced the following: 1) intense sleep paralysis, striking hypnogogic hallucinations, and cataplexy for many years; 2) recurrent dizziness, shaking and nervousness — falling and bruising her knee during one recent episode; 3) recurrent insomnia; 4) severe headaches with associated scotomata; 5) recurrent abdominal swelling; and 6) retrosternal oppression, particularly on hurrying. A partial pelvic ablation had been done at the age of 40 years.

The patient had six children. The third oldest was fat. Her 13-year old child (*vide infra*) had been sent home on numerous occasions because of "nerves" or sleeping in class. Her mother had diabetes mellitus.

The pertinent findings on physical examination included marked obesity, a blood pressure of 160/110, good pedal pulsations, and markedly tortuous fundal vessels with both hemorrhages and microaneurysms. There was no enlargement of the thyroid.

She was found to have both hyperglycemia and a typical diabetic glucose tolerance curve (See "Laboratory Studies"). Other studies were as follows: cholesterol — 180 mg.%; uric acid — 7.1 mg.%; NPN — 29.5 mg.%; 24-hour urinary catecholamines — 2.59 mg.; and protein-bound iodine — 8.04 mcg.%. The results of her ILA and plasma insulin assays were detailed earlier (Fig. 1). Electroencephalography revealed the presence of paroxysmal low-voltage 18-24/second activity in both frontal leads, 14/second positive spike activity in both hemispheres, and high-voltage negative spike seizure activity in the left and right frontal areas.

Within several weeks after instituting a regimen of Ritalin (5 mg. 3 times daily) and frequent small feedings of formula and hypocaloric supplements, her narcoleptic symptoms abated and she lost ten pounds. Her blood pressure concomitantly declined to 136/80 and 130/80 on 2 subsequent visits.

The 13-year-old son (Case NN-2) of this patient was seen at her request because he had been repeatedly sent home from school since the age of 6 years for daydreaming, sleeping during class, or becoming "very nervous". He had mild pneumonia at the age of 6 months. Even during his first several years, he was noted to be a highly "nervous" child, and was frequently subject to spontaneous shaking and profuse sweats. These symptoms could be promptly relieved by eating something sweet.

This patient was subject to profound drowziness and sleep, especially after meals. He frequently fell asleep while watching television or in church — as well as during school. His history also revealed the presence of classic cataplexy, sleep paralysis and hypnogogic hallucinations for at least the preceding 5 years. He had been subject to severe headaches for at least 10 years; they predictably became aggravated during the night, and were associated with severe leg cramps and marked insomnia. On no occasion, however, had a convulsion or fit ever been observed. He was subject to hay fever.

He weighed 101 lbs., and was 5 ft. in height. The physical examination was not remarkable. His morning glucose tolerance test on 1-28-63 gave the following results: fasting — 102 mg.%; ½ hour — 160 mg.%; 1 hour — 132 mg.%; 2 hours — 111 mg.%; 3 hours — 98 mg.%; and 4 hours — 79 mg.%. In view of his maternal diabetic background, an afternoon glucose tolerance test performed on 2-8-63. The results were as follows: pre-glucose — 92 mg.%; ½ hour — 158 mg%; 1 hour — 123 mg.%; 2 hours — 116 mg.%; 3 hours — 71 mg.%; and 4 hours — 79 mg.%. He experienced increasing hunger, sweats and nervousness — comparable to his "nervous attacks" during school — after the third hour.

The patient was then placed on a diet devoid of sugar and sweets, frequent feedings *around the clock* (including school hours and during the night), and

Ritalin (5 mg. before meals.) His subsequent course after one year's observation has been gratifying in all respects, especially with reference to his performance in school, freedom from narcoleptic and hypoglycemic symptomatology, and continued growth.

Case NN-5: Patient with the narcoleptic tetrad, nondiabetic functional hyperinsulinism, and symptomatic angina pectoris, palpitations and migraine; also hypertension, gout, recurrent edema, and previous obesity; family history of probable narcolepsy; striking clinical improvement on dietotherapy.

This 49-year-old Negro female was seen because of hypertension and angina pectoris of 5 and 3 years duration, respectively. She would frequently awaken during the night with chest pain or palpitations. Recurrent hypoglycemic symptoms were experienced for which she had been using considerable sugar and jelly. Classic narcolepsy, sleep paralysis, cataplexy, and hypnogogic hallucinations were present at least 3 years. At one time, she had weighed 156 lbs. Other features of the history included recurrent swelling of the abdomen, severe "sick" headaches, and typical gout during the preceding year. Her serum uric acid levels ranged from 7.95 mg.% to 11.8 mg%. A spontaneous menopause had occurred at the age of 41 years. A younger sister was described as being sleepy much of the time.

The only pertinent finding on physical examination was a blood pressure of 160/116. She weighed 135 lbs. She was 5 ft. 3 in., and of medium frame. The results of a morning glucose tolerance test were as follows: fasting — 94 mg.%; ½ hour — 108 mg.%; 1 hour — 60 mg.%; 2 hours —90 mg.%; 3 hours — 61 mg.%; and 4 hours — 84 mg.%. During the early course of this study, she became markedly "tired". She subsequently experienced progressive nervousness, nausea and palpitations. Other studies were as follows: cholesterol — 252 mg.%; 24-hour catecholamine excretion — 8.5 mg.; serum sodium — 141 mEq/L; and serum potassium — 4.7 mEq/L. An afternoon glucose tolerance test was not performed for fear of inducing a severe anginal attack.

The patient was counselled concerning the necessity of eating frequent meals and abstaining from sugar. Other symptomatic measures were instituted, including small maintenance doses of an estrogenic preparation. On this program, her angina pectoris, palpitations, hypoglycemic symptomatology and narcolepsy subsided—even without specific analeptic therapy.

Case NO-1: School teacher with incapacitating vascular headaches of both the migraine and "histamine cephalgia" types, the narcoleptic tetrad, and severe functional hyperinsulinism; also peripheral neuropathy, recurrent edema, nocturnal leg cramps and insomnia; probable narcolepsy in her mother and son; gratifying remission on a corrective diet and analeptic therapy.

This 39-year old Negro high school teacher presented with severe and persistent headaches, especially over the right temple. She described features that were characteristic of both migraine and "histamine headaches" (e.g., her homolateral eye would frequently tear and the nostril on the same side feel stuffed.) Notwithstanding the use of Sansert for several months, her headaches recurred. She experienced severe nausea during the attacks. They often awakened her about 1-2 a.m.

She also had a longstanding weight problem, having weighed as much as 175 lbs. She was 5 ft. 4 in., and of moderate frame. She predictably experienced increasing hunger about 3 p.m., and would take several crackers with some benefit. Because of her overweight problem, however, she not only did so reluctantly, but ate little or no lunch. A profound tendency to drowziness had been present "as long as I can remember", but was increasing in recent years. On her free days, she slept as long as 3 hours after lunch. Paradoxically, she frequently awakened during the night because "I am a light sleeper". She also experienced the following: 1) typical auditory hallucinations (particularly hearing the telephone ringing), sleep paralysis, and cataplexy; 2) an intense "burning" discomfort in the lower extremities for 5 years which frequently prevented her from sleeping; 3) recurrent severe leg cramps during the night; and 4) recurrent edema. A hysterectomy had been performed about 5 years previously. Her maternal aunt was diabetic. Her mother required frequent naps. Her 13-year old son was having increasing difficulty both during school and with his homework because of inability to concentrate. He also complained of recent headaches, and had become markedly overweight.

Aside from moderate obesity (143 lbs.), the physical examination was noncontributory. The results of a morning glucose tolerance test were as follows: fasting — 112 mg.%; 1 hour — 129 mg.%; 2 hours — 116 mg.%; 4 hours — 54 mg.%. She experienced a severe headache, palpitations and marked "nervousness" as the last specimen was being taken.

On a program of abstinence from sugar and sweets, frequent feedings, Ritalin (5 mg. before meals), and small doses of an estrogenic preparation, this patient experienced a total and persistent remission of her headaches, narcolepsy and nocturnal leg cramps. Her increased affectiveness as a teacher has been particularly gratifying.

Case DO-14: Young obese patient with hypertensive vascular disease, headaches, the narcoleptic tetrad, and diabetogenic hyperinsulinism; also nocturnal leg cramps, probable angina pectoris, recurrent edema, hyperlipemia and hypercholesterolemia; gratifying response of her headaches, tinnitus, narcolepsy, blood pressure, weight and serum lipids on formula and analeptic therapy.

This 37-year-old Negro maid was seen in consultation on 4-11-63 because of hypertensive vascular disease with severe headaches and tinnitus. Other features included the classic narcoleptic tetrad for more than 2 decades, typical recurrent hypoglycemic symptoms, severe leg cramps, probable angina pectoris, and recurrent edema. There was no past history or family history of diabetes mellitus. Her initial blood pressure was 170/110. Her weight was 164½ lbs. She was 5′ 3″ in height, and of medium body build. The results of

a morning glucose tolerance were as follows: fasting — 105 mg.%; 1 hour — 185 mg.%; 2 hours — 131 mg.%; 3 hours — 124 mg.%; 4 hours — 107 mg.%; and 2+ and 3+ glucosuria at 1 and 2 hours, respectively. The serum potassium was 5.3 mEq/L. Her sella turcia was perhaps slightly enlarged, but no gross impairment of the visual fields could be demonstrated. Financial considerations precluded further hormonal assay and radiographic study.

The patient was placed on Ritalin (10 mg. 3 times daily) and a dietary regimen consisting of formula (Metrecal) in liquid or wafer form every 3 hours with hypocaloric vegetables as desired. She was also maintained on her previous antihypertensive drug (Naclex). The formula diet was started on 4-18-63 when no further diuretic response from the thiazide drug was forthcoming. Her weight progressively declined to 156¼ lbs. on 4-27-63, 154½ lbs. on 5-15-63, 148½ lbs. on 6-6-63, 151¼ lbs. on 6-12-63, 144 lbs. on 6-29-63, and 142½ lbs. on 6-13-63. From 5-6-63, additional hypocaloric foods were added. By 8-10-63, her weight had declined to 139½ lbs., and by 10-5-63 to 134¾ lbs. The patient's hypertensive medication also was shifted to phenobarbital 30 mg. daily and Diupres-500 daily. Her blood pressure progressively declined to 160/110 on 4-27-63, 140/100 on 5-6-63, 140/90 on 6-12-63, 122/90 on 6-29-63, and 110/86 on 7-13-63. Her antihypertensive drugs were concomitantly reduced or omitted.

During the above period, the patient felt dramatically improved with reference to her headaches, tinnitus, narcolepsy, and ability to work. By taking frequent snacks — including one or two during the night — her recurrent hypoglycemic symptomatology (viz., weakness, dizziness, tremors and severe hunger) completely subsided. Her leg cramps, retrosternal oppression and recurrent edema also disappeared.

An afternoon glucose tolerance test was performed on 5-15-63 (approximately one month after treatment began) and revealed normalization of her previously impaired glucose tolerance. The results were as follows: pre-glucose — 83 mg.%; 1 hour — 155 mg.%; 2 hours — 120 mg.%; 3 hours — 107 mg.%; and 4 hours — 90 mg.%. Only a trace of glucosuria was found at 1 and 2 hours. The results of serial lipids and lipoprotein studies were as follows:

	4-22-63	5-10-63	5-15-63	9-11-63
Total lipids	1153 mg.%	795 mg.%	640 mg.%	841 mg.%
Cholesterol	324 mg.%		262 mg.%	277 mg.%
Phospholipids	300 mg.%		279 mg.%	266 mg.%
Phospholipid/cholesterol ratio	0.92:1		1.07:1	0.96:1
Triglycerides	529 mg.%		99 mg.%	298 mg.%
Lipalbumin	17.6%		13.9%	18.5%
Beta-lipoprotein	36.1%		55.8%	61.7%

DISCUSSION

Diagnostic Considerations

Although the syndrome of narcolepsy and diabetogenic hyperinsulinism is common — albeit unrecognized — in many facets of contemporary medical practice, its apparent frequency and severity in the Negro deserve emphasis. Accordingly, it now becomes the responsibility of physicians to seek out this disorder before making certain vague or potentially-hazardous misdiagnoses in Negroes that heretofore have often been used chiefly as diagnostic wastebaskets. In this regard, attention is specifically directed to such terms as "psychophysiologic phenomenon", "simple exogenous obesity", "refractory hypothyroidism", "metabolic insufficiency", "euthyroid hypometabolism", Pickwickianism, "metabolic obesity", "obesity as a depressive equivalent"[40], "chronic nervous exhaustion", "specific reading disability", premature menopause, and encephalitis. For example, the Council on Drugs of the American Medical Association has clearly asserted that there is little evidence to support the assumption that fatigue is due to metabolic "insufficiency" or "inefficiency".[41] Similarly, the absence of conclusive evidence that potassium and magnesium aspartates are of value in managing the "fatigue syndrome" [42] should come as no surprise if it is understood at the outset that this "disorder" represents a misnomer. It is therefore *mandatory* to ascertain whether patients presenting with the ubiquitous complaint of undiagnostic "fatigue" or "tiredness" are *really* using these terms to describe their pathologic drowziness.

The classic narcoleptic histories of these Negro patients, the striking pre-glucose low voltages found in the electroencephalograms of a significant number (Fig. 2), and their gratifying response to analeptic therapy would indicate that such stigmata as "laziness" "constitutional inadequacy," "racial inferiority" and "underdevelopment of the brain" which have been uncritically directed against many Negroes are at least as often related to their narcolepsy as to social status or economic disadvantages. Weil [43] has observed similar changes in the electroencephalographic voltages among several Negroes.

While an important basis for the failure to recognize narcolepsy is lack of physician awareness, the patient himself often contributes to the

confusion because of a poor history. Although the "phenomenon of denial" also has been encountered among white narcoleptics, it was particularly impressive among many Negro patients in this series. Such denial could be explained by the effect of pathologic drowziness in responding to questions, the accepting of this state as their norm, or the fear that admission of it would be regarded as "laziness." A therapeutic diagnostic test with small amounts of methylphenidate has proved of decided value in some patients who initially denied this symptom. After they experienced an analeptic effect, however, the history of severe and irresistible drowziness was often amplified in considerable detail.

Although every patient in this series had unequivocal pathologic drowziness as defined earlier, individuals have been encountered with "narcoleptic equivalents" and diabetogenic hyperinsulinism. For example, a 54-year-old obese Negro female was seen in consultation at the request of her ophthalmologist because of an extensive diabetic retinopathy. Even though she gave a history of typical hypnogogic hallucinations, cataplexy and sleep paralysis, a clearcut history of narcolepsy could not be elicited. She also had diabetogenic hyperinsulinism, as evidenced by a fasting blood glucose concentration of 122 mg. per cent, a 3-hour concentration of 126 mg. per cent, and a 4-hour decline to 78 mg. per cent with associated severe hunger and headache.

PATHOGENIC CONSIDERATIONS — HEREDITARY AND ACQUIRED

The syndrome of narcolepsy and diabetogenic hyperinsulinism is an *acquired,* albeit genetically-influenced, disorder which involves excessive insulinogenesis and deranged function of the hypothalamus and reticular activating system. It occurs in both sexes. The present observations indicate that the inheritance is one of incomplete or variable penetrance, and is importantly influenced by environmental factors. Of the latter, excessive carbohydrate ingestion by individuals who are enzymatically "poised" to exaggerated insulinogenesis is probably the most significant. Evidence for such overindulgence in sugar consumption by our society abounds in all directions — beginning with the nursery. The metabolic derangement of these patients is further compounded by habitual forced meal eating.

It is believed that the *nonspecific* symptom of narcolepsy and the high incidence of dysrhythmias in these patients are logically attributable largely to cerebral insults resulting from repeated hypoglycemic stress over prolonged periods, perhaps as early as the neo-natal period[9]. This conviction is also supported by the clinical and electroencephalographic observations made by others on diabetic patients who have experienced severe insulin reactions[44], patients with functioning islet-cell tumors[45-46], and patients with petit mal epilepsy[48]. The following are also of considerable related interest: 1) several narcoleptic diabetics who had scrupulously (and correctly) avoided insulin reactions, on occasion even in defiance of medical counsel to increase their dosage of insulin, were found to be free of dysrhythmias; and 2) improvement of both narcolepsy (as evidenced by cessation or reduction of analeptic drug requirements) and dysrhythmias has been found after instituting a corrective diet. For example, repeat electroencephalograms obtained in Case NN-3 (see Case Histories) revealed minimal 20-30/second frontal activity (as compared with her pretherapy recording obtained one month previously) following the institution of a diet aimed at minimizing severe episodic hypoglycemia.

If narcolepsy in the American Negro represents an aftermath of recurrent hypoglycemic stress, it could be regarded in a sense as a "disease of civilization." Perhaps the term "reversed Darwinism"[49] might be appropriately applied to the syndrome of narcolepsy and diabetogenic hyperinsulinism, especially when complicated by obesity. This is in keeping with the following comments of Wyler, "It is my suggestion, then, that fat-forming tendency is a condition of original selective value which has now, like the sickle trait, become disadvantageous to the bearer of environmental shift; that it represents not so much a homeostatic defect or an inborn error of metabolism as an evolutionary atavism".[49]

The writer's concept and evidence for diabetogenic hyperinsulinism is considered and documented elsewhere in detail.[8, 13] For the purposes of this discussion, it will suffice to indicate there is much clinical, biochemical and histologic data both from man and in animal experiments which support the contention that islet-cell hypertrophy

and "functional" hyperinsulinism characterize the "prediabetic" state. The findings obtained from *afternoon* glucose tolerance testing are consistent with the following convictions: 1) diabetes mellitus usually represents the aftermath of "high-output failure" ("decompensation", "exhaustion") of insulinogenesis, a belief further supported by concomitant plasma insulin and insulin-like activity assays; 2) there is a circadian acceleration of excessive insulinogenesis as the day advances; and 3) afternoon glucose tolerance testing offers a more satisfactory method for evoking these metabolic aberrations than either cortisone-glucose tolerance testing or tolbutamide (oral or intravenous) testing.[8, 13]

As noted earlier, it is believed that diabetogenic hyperinsulinism is fostered by many dietary habits which now characterize Western civilization — and which the Negro has adopted. These include the eating of only one or two large meals daily (especially by the obese) and the ingestion of excessive sugar. In commenting upon slavery of the American Negro as "the greatest biological experiment of all times" and the resultant removal of most undesirable genes from this race by means of selective breeding, one physician commented, "Most of the familial diseases, if they did exist, disappeared towards the end of slavery except for those that had come in from the white race."[50] It is pertinent that in a recent study of 93 per cent of the adult population of Evans County, Georgia, the increased prevalence of coronary heart disease among white males over Negro males disappeared when adjustments were made for social class and blood cholesterol levels.[51]

For reasons expressed previously[13], this issue of diet may be as important as that of heredity in the clinical evolution of diabetes mellitus and its alarming incidence in the American Negro. Owing to the current unchallenged emphasis upon diabetes mellitus as a heritable disorder, with the concomitant implications of irreversible predetermination, pessimism, and hopelessness, I would challenge this orientation if it is not also qualified by specific information concerning the diet. The following comprehensive statement of Danowski and his colleagues concerning the orientation of clinical research within the realm of certain complications to which the American Negro is uniquely prone deserves reiteration. "The genetic susceptibility, whatever it may be, of the African, West Indian and North American Negro to atherosclerosis, hypertension, myocardial infarction and other cardiovascular catastrophes appears to be conditioned by an as yet uncharacterized mixture of geographic, environmental, economic, social, dietary and psychologic variables."[52]

The *extraordinary* frequency of diabetes mellitus among the American Negro continues to impress the writer and others who are concerned with this problem. The predominance of obese Negro females with diabetogenic hyperinsulinism in this series coincides with the morbidity rates of diabetes mellitus. For example, the death rate in Florida from diabetes mellitus per 100,000 population during the year 1961 were as follows: white males — 13.6; white females — 13.6; nonwhite males—11.5; and nonwhite females—26.7.[54] Similarly, a multiphasic chronic disease detection survey among low-income Negro adults in Chicago during 1962 revealed a rate of probable diabetes mellitus of 177 per 1,000 — the overall rates for sex being 160 and 184 per 1,000 in men and women, respectively.[53]

The recent demonstration that hypglycemia is the most potent stimulus in man for the elaboration of diabetogenic growth hormone[55] is particularly pertinent.

RELATIONSHIP TO OBESITY AND HYPERLIPEMIA

The syndrome herein described also bears closely upon the increased incidence of obesity and hyperlipemia among American Negroes. As noted earlier, it is believed that obesity in our society largely represents the end-result of several complex processes which are simultaneously operative. These include increased appetite associated with episodic hypoglycemia, reduced caloric expenditure stemming from the hypokinesia of narcoleptic drowziness and prolonged sleep, and many metabolic adaptations to the habitual eating of large meals and excessive sugar. Danowski and his associates have recently shown that the concentrations of serum cholesterol, phospholipids and triglycerides are higher among Negro male prisoners in the 20-34 age range than among comparable white prisoners.[53] Without attempting to cover this subject exhaustively, the following observations are regarded as highly pertinent:

1. The relationship between carbohydrate intake and fat deposition, and the importance of adipose tissue in

oxidizing glucose and converting glucose to fat have been increasingly appreciated. For example, following the recognition that the albumin-bound nonesterified or free fatty acids (NEFA) serve as the major form of lipid transport from adipose tissue depots, it has been possible to study the process of fat mobilization and regulation in man by using this parameter.[58] One of the key factors found to affect fat mobilization is the availability and sufficiency of carbohydrate. It has been suggested that the ingestion of excessive carbohydrate can result in lipogenesis by a shift from oxidation via the Embden-Myerhof citric acid cycle to that of the "hexosemonophosphate shunt."[59]

2. There is evidence that two types of lipemia (hypertriglyceridemia) exist — i.e., one being induced by dietary fat, and the other by dietary carbohydrate.[60] In an affluent society where food is abundant, carbohydrate-induced lipemia is the more common occurrence. A convincing demonstration of the phenomenon of carbohydrate-induced lipemia is found in the markedly increased triglyceride and Sf-400 lipoprotein concentrations of hypertensive patients after being placed on a rice diet (which is high in carbohydrate and low in fat.)[61] The high content of palmitic, palmitoleic and oleic acids that predominate in the fat particles associated with carbohydrate-induced lipemia is noteworthy.[60]

3. Excessive insulin exerts a marked lipogenic effect. The ensuing deposition of fat in adipose tissue is variously attributable to the increased synthesis of fatty acids from glucose and other fatty acid precursors, the increased incorporation of fatty acids derived from dietary lipid into the neutral fat of adipose tissue, and the decreased rate of fatty acid liberation into the plasma from adipose tissue.[62] Further support for this concept is found in the observation that rats treated with insulin develop a type of obesity which is characterized by an increased number of adipose tissue cells.[63]

4. A high incidence of functional hyperinsulinism has been found in obese night-eaters.[64] Stunkard postulated that nocturnal bulimia and associated hypoglycemic manifestations represent a disturbance of the negative feed-back system by which insulin and other secretions become decreased or inactivated when the supply of carbohydrate is sharply curtailed.[64] Owing to the enhanced insulinogenesis triggered by ingesting large amounts of sugar for the relief of episodic hypoglycemia, however, such carbohydrate intake is self-defeating.

5. The increased incidence of diabetes mellitus, coronary heart disease and hypercholesterolemia among Yemenite Jews immigrating to Israel has been convincingly correlated with the change from a virtual sugar-free diet to one in which 25-30 per cent of the total carbohydrate intake consists of sucrose.[65]

RELATIONSHIP TO CARDIOVASCULAR DISORDERS

Certain cardiovascular disorders which are unique to or more prevalent in American Negroes merit reevaluation as consequences of diabetogenic hyperinsulinism, especially in the light of twofold and threefold greater prevalence rates of hypertension and electrocardiographic abnormalities among adult Negro diabetics and nondiabetics.[53]

1. The high incidence of toxemia of pregnancy (2½-4 times in excess of its occurrence among whites), the frequency of malignant hypertension and accelerated vascular disease, and increased surgical and obstetrical mortality in the American Negro due to cardiovascular complications are recognized facts.[66] Pathologic studies of Negroes in Haiti and the United States have revealed a striking increase in the incidence and severity of coronary atherosclerosis among the American group starting *as early as childhood*.[68]

2. The electrocardiographic patterns of S-T segment elevations and T-wave inversion or peaking in the precordial leads are accepted as "normal variants" among Negroes.[69, 70] For example, in one series of 131 adult Negro males, 14 (10.8%) were found to have a T-wave inversion pattern (persistent or transient) in the unipolar leads V_1-V_6.[66] Each of these individuals was thought to have a normal cardiovascular system and no clinical evidence for pericarditis. (Three even had normal pericardiums at the time of thoracotomy). The ST-segment elevation and tall peaked T-waves in male Negroes may simulate serious heart disease.[69]

3. The occurrence of heart failure during the postpartum period and in the absence of antecedent heart disease is unique among Negro patients.[72] Its familial nature also is pertinent. Several patients have been observed by the writer during pregnancies which ensued after a diagnosis of diabetogenic hyperinsulinism was made.[9] The postpartum course of all was characterized by intensified reactive hypoglycemia after it had been ameliorated during the latter part of gestation by the hormonal effects of pregnancy. Although information pertaining to a family history of diabetes mellitus has been included only infrequently in most reports of familial cardiomegaly", it is of interest that 1) the mother of two siblings with "heart disease of unknown cause in siblings" was diabetic, and 2) diabetes and coronary artery disease were found in the father's relatives among two other siblings with undetermined heart disease presented in this same report.[73]

4. The frequent absence of a history of angina pectoris among Negro patients with coronary insufficiency and "silent" myocardial infarction has received attention in the literature for many years. Hunter[74] made the following pertinent statement: "I believe that the absence of angina in the Negro cannot be explained by an inability to feel or to express pain. Likewise there is little evidence to support the contention that the Negro does not have angina because he lacks mental stress. On the contrary, mental stress is the common explanation for the high incidence of hypertension in the Negro." It is highly possible that the presence of severe narcolepsy either may interfere with their perception of severe pain or preclude subsequent accurate history-taking be-

cause of the "phenomenon of denial" which is encountered so commonly in such individuals. (*vide supra*)

5. The significantly higher sodium concentration of erythrocytes found in Negroes is of interest in view of the rise in serum sodium after glucose loading in patients with diabetogenic hyperinsulinism.

6. Frequent evidences of an excessive adrenergic discharge (sympathetic "storm") are observed among Negroes in response to a variety of physical and psychologic stress situations.[67] These include labile hypertension (noted among 70 per cent of surgical colored patients on admission in one series), the exaggerated cold pressor response, the frequent abrupt changes in blood pressure during general anesthesia, marked contraction of the superficial veins prior to intravenous injections, and the oft-heard generalization that Negroes tend to panic when confronted with mild stress (e.g., having blood drawn) or the necessity of making decisions or assuming responsibility (as in the Armed Forces).

A major common denominator of these "adaptations to civilization" probably resides in the unchecked sequelae of "metabolic hypoxia" associated with hypoglycemia and the hypoglycemic-induced release of epinephrine, norepinephrine and adrenocortical hormones.[15,18] For example, the observations that hypoglycemia is a potent stimulus to adrenal function,[56] and that epinephrine can induce edematous reactions in the large arteries[75] offer acceptable grounds for comprehending in part these unique pathologic diatheses of the American Negro. In observations concerning the electroencephalographic changes following insulin shock therapy, Zohman and Russek[76] noted: "... the lack of available carbohydrate as well as the increased work of the heart during hypoglycemic shock of long duration would suggest that anoxemia may be a factor in producing the cardiac changes." There is clinical and experimental evidence that norepinephrine can exert a deleterious effect on the myocardium,[84] and that epinephrine and norepinephrine can accelerate blood coagulation and favor thrombosis.[85]

It is impossible that the aforementioned electrocardiographic patterns may reflect alterations of cell membrane permeability caused by electrolyte changes associated with longstanding recurrent hypoglycemia (i.e., potassium influx and sodium efflux[6,8] *vide supra.*) (The frequent absence of a true correlation between T-wave changes and either the serum potassium level or the amount of potassium salt administered should be borne in mind.) The exaggeration of such T-wave inversion by hyperventilation and its normalization by the oral administration of potassium or by intravenous Probanthine also have led to the hypothesis that such a "juvenile pattern" represents an expression of hypervagotonia.[70] It is recognized that flattening or inversion of the T-waves in the bipolar or lateral V leads may be produced by a high-carbohydrate meal, and that these changes can be obviated by the simultaneous administration of potassium chloride.[71] Such a decrease in plasma potassium has been attributed to its deposition with glycogen in the liver and in skeletal muscle under the influence of insulin. It is of interest that the plasma potassium fell from 4.1 mEq/L to 3.6 mEq/L two hours after a high-carbohydrate meal and was associated with T-wave changes in one patient in whom such changes had been misinterpreted as representing coronary heart disease; after the addition of 3 gm. potassium chloride to the meal, these electrocardiographic changes were not found, even though his plasma potassium still dropped from 3.9 to 3.6 mEq/L.[71]

While the writer concurs with the necessity of not incurring the burden of needless iatrogenic disease in Negroes who are found to have S-T interval and T-wave variants, it is well that physicians not completely discard the potential significance of such changes. Thomas, Harris and Lassiter have aptly stated, "It is probable that the S-T segment and T-wave changes reported here are normal variations. However, one must consider the possibility that they may be precursors of future organic changes, especially since such changes occur in heart disease."[69] The normalization of these T-wave abnormalities *cannot* be used as evidence of their "functional" nature, however, since it has been shown that potassium salts are also capable of causing an upright deflection of organically-inverted T-waves.[77] Such normalization of inverted T-waves reflects a change in the repolarization process which is both rapid at onset and of a temporary nature (i.e., they revert to their original configuration within 2 hours[77]). The following discussion concerning the effects of insulin shock therapy on the electrocardiogram is pertinent: "It has been repeatedly shown that induced insulin shock in schizophrenia is frequently associated with electrocardiographic changes in the nature of depression of the S-T segments, flattening and inversion of the T-waves, and arrhythmias. It has also been observed that these electrocardio-

graphic alterations are transient in nature, disappearing in a matter of hours following the shock episode. Some observers, however have noted that these changes tend to become less and less reversible as the series of repeated hypoglycemic shocks progresses. Furthermore, inasmuch as some of these abnormalities were found to be present as long as six months after cessation of treatment, the question of permanent myocardial damage from this form of treatment requires consideration."[76]

RELATIONSHIP TO OTHER DISORDERS THOUGHT PECULIAR TO NEGROES

The local tissue and immunologic effects of prolonged diabetogenic hyperinsulinism may interreact with other heredofamilial traits to produce pathologic states which are thought peculiar to the Negro. The keloid diathesis offers such an instance. It may explain the apparent increased incidence of endomyocardial fibroelastosis among Negroes. For example, the preponderance of Negroes was striking in one series of 30 male patients (with a peak age incidence in the third decade) who had pathologic evidence of subendocardial fibrosis.[78] It is also of interest that "East African endomyocardial necrosis" bears a resemblance to endomyocardial fibroelastosis.[79]

The writer has inferred a similar mechanism to be operative in other unusual situations he has encountered which could not be otherwise explained. The following is a case in point:

A 20-year-old Negro female was seen in consultation at the request of her periodontist* because of progressive gingival enlargement for 1½ years. Concomitantly, there had been considerable migration of her teeth, resorption of the adjacent alveolar bone, and edema of the lower lip (Fig. 12). A biopsy of the gingiva revealed only a heavy fibrotic reaction. She also had been subject to pathologic drowziness and cataplexy since high school. As a result of her intense hunger (especially during the latter part of the afternoon), she had gained 50 lbs. during the preceding year. Her mother and one younger sibling were diabetic. Several siblings were severe "sleepyheads". Aside from marked obesity, severe gingival hyperplasia with epulis formation, and slight keloid formation at the site of several small scars, her physical examination was not remarkable. A morning glucose tolerance test revealed impaired tolerance and reactive hypoglycemia. Her blood total protein was 7.65 mg.%, with an albumin of 3.56 gm.% and a globulin of 4.09 gm.%. The blood calcium, phosphorus, alkaline phosphatase, sickle cell preparation, L.E. cell preparation, BSP retention, and serology were within normal limits. Her urinary calcium output was normal. The chest films were normal. Since such causes as leukemia, sarcoid, hyperparathyroidism and connective-tissue disorders appeared to have been convincingly ruled out, it was the writer's impression that this patient was an early diabetic, and that her gingival enlargement represented a local reaction to periodontitis with a superimposed keloid diathesis.

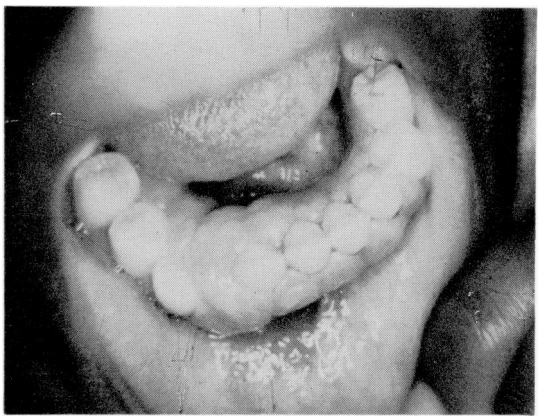

Fig. 12. Severe gingival hyperplasia and fibrosis with migration of teeth, resorption of alveolar bone and edema of the lower lip in a young female with narcolepsy, diabetogenic hyperinsulinism and a keloid diathesis. Extensive studies and biopsy appeared to rule out other possible local and systemic causes.

Diabetogenic hyperinsulinism also may offer a fundamental lead in understanding sarcoidosis. It has been repeatedly and convincingly demonstrated that sarcoidosis is neither a variant of pulmonary tuberculosis nor a specific clinical or pathologic disorder caused by any infectious agent that has as yet been defined. More fruitful inroads into the understanding of this enigma may well be achieved by pursuing the deranged immunologic response of patients who are so afflicted on the basis of the few available epidemiologic facts. The extraordinary incidence of this disease in the American Negro (18 to 1 over whites),[80] the incidence of diabetogenic hyperinsulinism and other incidences of altered reactivity (e.g., the high incidence of keloid formation) in this race, and the well-known antigenicity of excessive insulin suggest such an approach. Moreover, the finding that American Negroes tend to have higher average gamma globulin concentrations than their white counterparts (e.g., see above Case History) serves as another indicator of a widespread immunologic alteration among Negroes that bears no

* I am grateful to Dr. Marvin Rosenberg for permission to report this case and his photograph.

relation to infection with tuberculosis or syphilis,[81] and transcends geographic location.

PROPHYLACTIC AND THERAPEUTIC CONSIDERATIONS

Since the phenomenon of "anticipation" (or "antecedence") is operative in both narcolepsy and diabetes mellitus,[82] it has been possible to uncover many instances of this syndrome among children when parents who were so afflicted sought medical attention, and vice versa. One of the most gratifying rewards that has come from these efforts has been the intellectual rehabilitation of otherwise-gifted children who were seen in consultation initially because of their poor performance in school. A number of white and Negro narcoleptic children already have been encountered in whom serious consequences ensued because their pathologic drowziness was misinterpreted as voluntary inattentiveness, "laziness" or an emotional disorder by parents, teachers and physicians alike (See Case NN-2). Moreover, it has been consistently observed that the younger children of narcoleptic patients tend to be afflicted more severely with both narcolepsy and diabetogenic hyperinsulinism, perhaps due to intensification of the diabetogenic hyperinsulinism in their mothers as a result of both increasing age and repeated pregnancies.

A correct diagnosis of the syndrome of narcolepsy and diabetogenic hyperinsulinsm offers an important key to the prevention of certain potential complications. The most important are driving accidents due to falling asleep at the wheel, "high-output failure" (decompensation, "exhaustion") of insulinogenesis in patients with "early" (or partially compensated) diabetes mellitus, the management and prevention of hypoglycemic-induced angina pectoris, cardiac arrhythmias and vascular headaches, and the prevention of iatrogenic hypothyroidism or adrenocortical insufficiency stemming from the needless administration of thyroid substance or drugs related to cortisone. The importance of *strict* prevention of recurrent hypoglycemia in such patients who have diabetic relatives is further underscored by the increased elaboration of diabetogenic growth hormone that is so induced.[57]

Although effective therapy for this syndrome is readily and inexpensively available, treatment is often ineffective or suboptimal if not sufficiently panoramic in scope. This consideration applies in particular to the management of both major components if weight reduction is to be successful on a long-term basis. This common shortcoming in most reducing programs has been emphasized previously.[8,29,30]

The normalization or striking improvement of glucose tolerance by dietary measures aimed at preventing or minimizing severe recurrent hypoglycemia has been documented herein (see Case DO-14) and elsewhere.[8,13] Some patients were able to discontinue insulin therapy (e.g., as much as 80 units daily in Case DO-10). Such improvement of glucose tolerance in young patients with diabetogenic hyperinsulinism by means of a low-carbohydrate, high-protein diet also has been convincingly shown by others.[83] Similarly, it is imperative that pursuit of the fantasy of maintaning "strict chemical control" among most diabetic patients by resorting to excessive insulin or oral hypoglycemic drug therapy should *not* be condoned at the price of repeated hypoglycemic reactions.

Finally, if the aforementioned assertions concerning the deleterious effects of excessive ingestion of sugar and forced meal-eating are correct, then the public-health implications relative to the need for modifying both the nature of the diet and the eating habits of *all* Americans become obvious.

SUMMARY

The syndrome of true narcolepsy and diabetogenic ("functional") hyperinsulinism is described in 31 personally-observed Negro patients. The recurrent hypoglycemia was associated with demonstrable diabetes mellitus or impaired glucose tolerance in 21 patients (67.7%), which had not been suspected previously in 14.

Other frequent complicating features included obesity, vascular headaches (migraine, "histaminic" cephalgia), cerebral dysrhythmias, peripheral neuropathies, angina pectoris, cardiac arrhythmias, accelerated hypertension, recurrent ("idiopathic") edema, and alcoholism. The basis of these interrelationships are considered.

The technic and results of afternoon glucose tolerance testing in such patients are presented. Its potential value in the following situations is emphasized: 1) the uncovering of "early" diabetes mellitus among patients with recurrent hypo-

glycemia who have diabetic relatives and nondiabetic morning glucose tolerance tests; and 2) the convincing documentation of reactive hypoglycemia, with or without associated impaired glucose tolerance.

Other notable laboratory findings in these patients were: 1) the serial rise in serum sodium and plasma insulin or insulin-like activity after glucose loading, 2) the decline in serum potassium concentration after glucose loading, 3) the high incidence of dysrhythmias (generally multiple) in the absence of a history of seizures, and 4) the profound low-voltage electroencephalograms of several patients, even prior to glucose ingestion. Evidence is presented that diabetes mellitus represents the aftermath of "high-output failure" of insulinogenesis in these patients.

A rational program of therapy and prophylaxis based on the above observations is described. Since it is believed that *hypo*glycemia serves as the critical factor in the genesis of diabetes mellitus with its complications, the potential amelioration of diabetes mellitus by corrective dietotherapy alone is underscored. The need for early recognition and management of this disorder in the children of these patients is also stressed.

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THE GROWING NUMBER OF ELDERS

The number of people at ages 65 and over in the United States continues to grow rapidly, reaching a record high of 17⅔ million in July of 1963, a gain of one million since the 1960 Census. It is expected that they will total 20 million in 1970 and may number about 24½ million by 1980.

The elders have been increasing at a greater rate than the population as a whole, despite the large numbers of children born since the close of World War II. The proportion of the total population that is 65 and over has risen from 8.1 per cent in 1950 to 9.3 per cent at present, and will probably reach 10 per cent by 1980.

The increments to the population at ages 65 and over have been greater for women than for men. This is due largely to the fact that females have the higher survival rate at every period of life. Currently, there are 9⅘ million women at the older ages, or 2 million more than men; by 1980 it is likely that the excess will be as much as 3⅘ million. This means that the sex ratio at ages 65 and over will increase from 125 women per 100 men to 137 per 100.

In the years immediately ahead, the growth of the older population will continue to be most rapid at the more advanced ages, i.e., at 75 and over. Between 1960 and 1970 the number of men is expected to increase 7 per cent at ages 65-74 and by no less than 30 per cent at ages 75 and over. Men in the latter age group will probably comprise over 36 per cent of all men at ages 65 and over in 1970, compared with 32 per cent in 1960. Among the women, the proportion of elders that are in the age group 75 and over is likely to increase from 35 to 40 per cent.

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