The Etiology of Incapacitating, Brittle Diabetes

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Incapacitated brittle diabetic subjects are a small subset of insulin-dependent diabetic individuals who are unable to maintain a normal lifestyle because of frequent disruptions secondary to severe hyperglycemic and/or hypoglycemic episodes. Thirty incapacitated patients were referred for evaluation because the cause of their diabetic instability could not be determined by their personal physicians despite extensive patient training in correct diabetes management, frequent hospitalizations for observation, and multiple diagnostic testing. From the 30 patients, a diagnostic algorithm was developed (described in the companion article) from which the etiology of brittle diabetes could be established in 29. This article provides the clinical characteristics of each of the 30 patients, a description of the etiologic categories of brittle diabetes, and the clinical follow-up from the time that the etiologic diagnosis was established and treatment recommended. Although extensive medical records were sent with each patient, without prospective objective testing under rigidly controlled conditions, the correct etiologic diagnosis would not have been evident from the clinical presentation of the patient. Of equal importance in identifying the etiology of brittle diabetes was the acceptance and cooperation of the referring physician in providing close follow-up and repeat insulin challenge testing when necessary. In this referred patient population, eight subjects had factitious disease, eight were malingering, seven had communication deficits, two had gastroparesis, two had systemic insulin resistance, two had miscellaneous causes of brittle diabetes, and one patient remained undiagnosed. Using a prospective algorithmic approach to determine the etiology of brittle diabetes, not only is the cause of diabetic instability almost always identifiable, but a significant improvement in lifestyle is achieved in greater than 50% of the incapacitated individuals. DIABETES CARE 1985; 8:12–20.

The term "brittle diabetes" was coined by Woodyatt in 1934 to describe individuals with unexplained large changes in blood glucose concentration.[1] Since this clinical definition, many series of patients have been described, most without definitive pathogenic mechanisms being identified.[2–8] Furthermore, treatment of some of these patients with subcutaneous intensive insulin therapy has not necessarily improved their "brittle" diabetic state.[9] Our approach to the brittle diabetic individual (specifically, the incapacitated patient) has been to first identify the etiology of brittle diabetes before initiating treatment. The rationale for this approach is our belief that there are multiple, unrelated etiologies of brittle diabetes, and to be successful, corrective therapy must address the specific etiology inducing the brittle diabetic state. This approach is consistent with previous reviews of brittle diabetes,[10] except that actual procedures for defining the etiology of brittle diabetes mellitus have not been adequately described, nor has the percentage of patients with a specific etiology been given. In the companion article, a step-by-step (algorithmic) approach to identifying the etiology of brittle diabetes is described.[11] Using this algorithm, we prospectively studied 30 incapacitated brittle diabetic subjects and determined the etiology of brittle diabetes in 29. The importance of this approach is that once the etiology is established and therapy directed at the causative factor, greater than 50% of the patients can be rehabilitated or significantly improved. Furthermore, even if the patient's personal lifestyle is not altered, that of his physician and health care team usually is, since invasive diagnostic procedures in the patient are avoided and alternative explanations for the recurrent excessive glucose excursions do not have to be pursued.

METHODS

Patient selection. All patients were referred from physicians who were unable to establish the etiology of their patient's diabetic instability. Most referral physicians were endocrinologists or internists who specialized in diabetes care. Furthermore, 60% of the patients had been referred on at least one occasion for diagnostic purposes to other major medical centers located throughout the United States, without a specific etiology for brittle diabetes being identified. All patients were sent to us with extensive in-hospital records and outpatient self-monitoring of blood glucose data, emphasizing the problem of recurrent hospital admissions for diabetic ketoacidosis and/or hypoglycemic coma. No patient was refused referral for any reason. If the patient had no medical insurance, the cost of hospitalization, testing procedures, and travel were supported by the University of New Mexico Clinical Research Center grant. Patients were referred from throughout the United States and Canada. Only two of the 30 patients were referred by physicians from within the state of New Mexico.

TABLE 1
Etiologic classification and demographic data of 30 patients with incapacitating brittle diabetes

Patient	Age	Sex	Ht	Wt (lb)	Duration of diabetes (yr)	Diabetic complications*
Factitious disease						
1	30	F	5'10"	141	23	1, 2, 3
2	21	F	5'3"	164	2	—
3	21	F	5'6"	181	3	—
4	19	F	5'1"	128	9	—
5	8	F	3'8"	42	2	—
6	24	F	5'3"	154	8	—
7	28	F	5'6"	141	16	1
8	33	F	5'4"	111	9	1
Malingering						
9	16	F	5'7"	119	6	—
10	15	M	5'9"	136	2	—
11	18	F	5'8"	132	2	—
12	27	F	5'7"	142	10	—
13	18	F	5'4"	116	9	—
14	25	F	5'7"	140	7	—
15	14	M	5'5"	155	2	—
16	16	F	5'6"	134	7	—
Communicative disorders						
17	22	F	5'2"	138	20	1, 2, 3
18	19	F	5'8"	168	12	—
19	16	F	5'3"	117	11	—
20	14	F	5'3"	98	4	—
21	33	F	5'8"	128	23	1
22	29	F	5'11"	140	7	1, 3
23	35	M	5'9"	149	17	—
Diabetic gastroparesis						
24	19	M	5'6"	141	12	1, 3
25	32	M	5'6"	115	23	1, 2
Insulin resistance						
26	36	F	5'6"	130	1	1
27	43	M	5'8"	196	2	—
Miscellaneous						
28	30	F	5'6"	155	3	—
29	10	M	4'4"	79	4	—
Undiagnosed						
30	27	F	5'7"	136	7	—

*Abbreviations: 1, retinopathy; 2, nephropathy; and 3, neuropathy.

Previous patient therapy. Before referral, all patients had been treated with multiple insulin injection regimens, usually referred to as intensive insulin therapy, for at least 1 yr.[12] In addition, 70% of the patients had unsuccessfully tried continuous subcutaneous insulin infusion with an external insulin pump. All patients had been instructed, on numerous occasions, in the correct diabetic approach to diet, exercise, and illness. In 16 of the patients, intramuscular insulin injections had also been attempted, with variable short-term results. In all but one patient, the intramuscular injections had to be given by another person because of the pain involved. However, none of the patients were willing to continue this approach because of the discomfort induced by this route of insulin delivery.

Approach to patients. On admission to the University of New Mexico Clinical Research Center, all patients underwent a history and physical examination and screening tests described in the companion article.[11] The mean total glycosylated hemoglobin on admission to our Clinical Research Center was 11.7 ± 3.3% SD (normal values 4.6–6.1%) for the 30 patients, confirming poor diabetes control. Informed consent was obtained from each subject, and also from one parent if the subject was under 18 yr of age. In addition, each procedure was again explained to the patient on the day before testing to ensure both an understanding of the test procedure and the reason for doing it. Results were provided to the patient as soon as they became available.

Regardless of the patient's previous history of testing procedures in other medical centers, all decisions on the etiology of brittle diabetes were based on tests performed by the authors or on results from blood drawn and sent by the authors to specific laboratories for specialized assays. This approach was essential because patient manipulation of the previous test results in other hospitals could not be excluded. During the initial period of testing (usually 1–2 wk), severe restrictions were placed on all patient activities to prevent surreptitious food ingestion and manipulation of insulin injections. Patients were confined to the University of New Mexico Hospital's Clinical Research Center (a 10-bed section of the hospital reserved for the study), were not allowed to have visitors (except parents), and all procedures such as insulin injections and capillary blood glucose monitoring were performed by nurses trained in these techniques. All direct insulin challenge testing for hypoglycemic activity was performed by a physician (one of the authors), with an assigned nurse in attendance at all times to observe the subject. These extensive precautions were necessary because the manipulative subject can rapidly alter blood glucose concentration by surreptitiously ingesting food or injecting additional insulin. Despite these precautions, on several occasions be-

tween insulin challenge tests (usually at night), unexplained hypoglycemic seizures and hyperglycemic episodes occurred, all of which were later shown to have occurred in manipulative patients.

Demographic data. Demographic data of the 30 patients used to formulate the algorithm in the companion article are described in Table 1, grouped according to etiologic diagnosis. The majority of the patients (77%) were women, similar to that reported in other studies of brittle diabetic subjects.[13] Mean age of the entire group was 17.7 ± 8.7 (SD) yr, and all but seven of the patients were within 20% of ideal body weight.[14] Duration of diabetes ranged from 1 yr to 23 yr, with a mean of 14.6 ± 9.1 SD. All patients except two were C-peptide–negative after both glucose and glucagon stimulation.[15] The first of these two patients was demonstrated to be malingering, and the second patient had anti-insulin-receptor antibodies. The clinical problem in 28 of the patients was recurrent hyperglycemia and ketoacidosis. In the remaining two, recurrent hospital admissions for hypoglycemic coma and seizures were characteristic.

Close long-term follow-up was attempted in all patients by having the patients send copies of their glucose records directly to the authors after their return home. In addition, frequent telephone contact with the referring physician was maintained until the patient's brittle diabetes was resolved and/or corrective therapy begun. The final outcome (i.e., results of treatment) of the patient's condition was determined by personal contact with the referring physician by one of the authors (Table 2). Three categories were used to describe the change (or lack of change) in the brittle diabetic state after establishment of an etiologic diagnosis. The category "unchanged" indicates that the patient still requires frequent hospitalization to establish diabetes control at a rate similar to that experienced before referral. The term "improved" indicates that the rate of hospitalization for diabetes has decreased by at least 50% from the 12 mo immediately before referral and the physician believes that the quality of the patient's life has improved. The term "rehabilitated" indicates that the patient no longer requires hospitalization for unexpected episodes of hyperglycemia or hypoglycemia and is able to carry on a normal daily lifestyle, be it attending school, raising a family, or maintaining gainful employment.

RESULTS

Etiologic diagnosis. Table 2 provides the etiologic categories of the 30 brittle diabetic subjects participating in the diagnostic algorithm.[11] For some of the categories, specific individualized diagnoses could be identified based on specific tests described in the companion article.[11] For most patients, an additional diagnosis or characteristic that may have been related to the primary etiologic diagnosis was also present. The choice as to which etiologic diagnosis was the cause of the brittle diabetic state was based on the authors' assessment of the severity of the disability and its direct contribution to the diabetic instability. For 29 of the 30 patients, a definitive etiology could be determined. Factitious disease was strongly suspected in the one undiagnosed patient, but all testing could not be completed because the patient was frequently uncooperative (would not permit blood withdrawal) and developed a spontaneous remission (she is no longer "resistant" to insulin and no longer has brittle diabetes). Of the remaining 29 patients, eight had factitious disease, eight were malingerers, seven had communication disorders, and six had miscellaneous causes of incapacitating, brittle diabetes.

The two largest categories of patients with incapacitating, brittle diabetes were factitious disease and malingering. Factitious disease is defined as a medical condition that is fabricated or simulated by a patient and is not associated with ulterior motives or material advantages other than achievement of patient status.[16] This group was the most difficult in which to establish the etiology, and often required extensive insulin challenge retesting and extremely close long-term observation and follow-up. The clinical characteristics of patients with factitious disease were that they: (1) appeared to be intelligent; (2) had an extensive understanding of diabetes; (3) were familiar with the administration of the hospital (timing of nursing shifts and vital signs, location of food carts); and (4) were knowledgeable in the control of infusion devices such as IVACs or IMEDs. These characteristics are similar to those reported in another series of patients with factitious fever.[17] Four of the eight patients in this category had completed training and had previously worked as practical or registered nurses before becoming incapacitated by brittle diabetes. In one of the patients, the referring physician had suspected that factitious disease might be present, but was unable to prove it, even in a hospital setting. We believe that the reason we were able to identify factitious disease was the implementation of strict patient rules during the initial hospital admission (described above), and the specific training of our Clinical Research Center nurses on the ever-present possibility of factitious disease. Of importance was the fact that in four of these patients the specific manipulation was detected by the Clinical Research Center nurses and not by the authors. Manipulation included several different approaches, such as replacement of insulin in the insulin bottle with water; injecting insulin surreptitiously to produce hypoglycemic seizures; injecting saliva to produce an abscess at the insulin injection site; stealing food from other patients and from our hospital gift shop to induce hyperglycemia; injecting heparin through the intravenous lines to induce a bleeding diathesis; crimping intravenous insulin infusion catheters to induce hyperglycemia and ketoacidosis; drinking hot water (immediately before the nurse took an oral temperature) to induce factitious fever; and injecting contaminated material into the intravenous infusion lines to induce recurrent polymicrobial gram-negative sepsis. Thus, patient manipulation was not necessarily limited to directly altering blood glucose concentration but always resulted in prolonging the patient's hospital stay, sometimes for as long as 3 mo. Treatment of factitious disease was successful in only four patients (50%), in spite of the fact that all subjects were referred for psychological counseling. Of interest is that one of the patients with this etiologic diagnosis was receiving psychological counseling before being referred to us. During her evaluation by us, and before our making the correct

TABLE 2
Long-term follow-up of patients with incapacitating, brittle diabetes

Patient	Etiology of brittle diabetes	Additional diagnoses or characteristics	Duration of follow-up (mo)	Results of treatment
1	Factitious disease	Drug addiction	12	Improved
2	Factitious disease	Depression	16	Improved
3	Factitious disease	Superior intelligence	14	Improved
4	Factitious disease	Pathologic behavior	25	No change
5	Factitious disease	Recurrent sepsis, factitious bleeding diathesis	12	Deceased
6	Factitious disease	Obesity	25	No change
7	Factitious disease	—	8	No change
8	Factitious disease	Depression	7	Improved
9	Malingering	—	14	Improved
10	Malingering	School phobia	30	Rehabilitated
11	Malingering	Disease denial	20	No change
12	Malingering	Spouse manipulation	33	Rehabilitated
13	Malingering	School phobia	33	No change
14	Malingering	Spouse manipulation	16	Improved
15	Malingering	School phobia	19	Rehabilitated
16	Malingering	Pragmatic language disorder	3	Improved
	Communicative disorders			
17	Receptive plus expressive language deficits	Low intellectual functioning	8	No change
18	Receptive language deficits	—	21	Rehabilitated
19	Auditory processing deficits	—	14	Rehabilitated
20	Receptive plus expressive language deficits	Pragmatic language disorder	14	Rehabilitated
21	Receptive language deficits	Depression	12	Improved
22	Receptive language deficits	—	10	Rehabilitated
23	Receptive language deficits	Pragmatic language disorder	14	Improved
24	Diabetic gastroparesis	Depression	15	No change
25	Diabetic gastroparesis	Depression	3	Improved
	Insulin resistance			
26	Systemic	Systemic lupus erythematosus	4	Rehabilitated
27	Systemic	Memory and auditory processing deficits	6	Improved
	Miscellaneous			
28	Drug addiction	Depression	24	Rehabilitated
29	Seizure disorder	Memory deficit	7	Rehabilitated
30	Undiagnosed	Insulin allergy	18	Spontaneous remission

diagnosis, our staff psychiatrist evaluated the patient and stated that she was "a mentally normal female with good family support."

Eight patients were malingering, which is distinguished from factitious disease by the fact that these patients use diabetes to avoid responsibilities of life, such as attending school or being gainfully employed,[18] whereas patients with factitious disease do not exhibit identifiable ulterior motives for their manipulative behavior.[16] In all malingering patients, an ulterior motive could be identified when family members and the patient's physician and health care team were interviewed. The majority of patients in this category were teenagers, and avoidance of school or social peer pressure was often readily evident.[19] These patients' behavior also differed from those with factitious disease in that the former group's manipulation was restricted to omitting their insulin injections and noncompliance with a diabetes diet. Episodes of diabetic ketoacidosis were almost always related to an identifiable event, such as an argument with a family member (or spouse) or an impending exam at school. When this etiologic diagnosis was made, corrective approaches were discussed with the patient, family, and physicians. Behavioral modification was usually recommended under the guidance of a psychologist specializing in altering teenage manipulative behavior. For the teenage patients, we usually recommended a "contract" approach be used between the physician and

the patient.[20] Seventy-five percent of the patients with this diagnosis improved or were rehabilitated with treatment (Table 2).

Seven patients had communicative disorders directly contributing to their diabetic instability. This term describes patients whose sensory input is intact (normal vision and hearing) but who have difficulty processing the information received and formulating responses.[21–24] Thus, their interpretation of diabetes instructions or how to respond to unexpected changes in blood glucose concentration often differed markedly from the interpretation of the same information by the referring physician. These deficits were evident only after extensive psycholinguistic testing, the details of which are described in the companion article.[11] Of interest was the fact that two of these patients were part-time volunteer instructors in their hometowns for teaching diabetes care to other diabetic individuals. Thus, although these patients had sufficient basic knowledge to care for diabetes, they had extreme difficulty formulating and completing an appropriate plan of action to deal with their own diabetic instability. Our approach to these patients was to identify their strengths (in addition to their deficits) and to recommend to the referring physician and their family how to compensate for the communication deficits. Recommendations for each patient had to be individualized, but an example for one of the patients with receptive language deficits is indicative of the approach. In this patient, failure to correctly fill an insulin syringe frequently led to progressive hyperglycemia and recurrent hospitalization. The many sequential steps required to correctly fill an insulin syringe and inject the insulin (13 steps) resulted in excessive mistakes by the patient.[25] This problem was overcome by having the patient's father preload all syringes with insulin. In this patient, no admissions for diabetic ketoacidosis have been necessary since undertaking this approach (21 mo). In another patient, who had auditory processing deficits (i.e., her hearing was within normal limits, but her ability to centrally process the instructions was impaired), we recommended that all instructions be provided in written form and that the patient reiterate the current diabetes management strategy to her physician on each visit. This type of approach, in which communication deficits are overcome by reinforcing other communicative skills (listening, speaking, reading, and writing), is a standard technique used to instruct learning-impaired children and adults.[26] Eighty-six percent of patients with communicative disorders improved when appropriate therapy was initiated (Table 2).

Two patients referred for brittle diabetes were addicted to narcotics (physician-prescribed drugs). One patient was taking hydromorphine intramuscularly for migraine headaches, and the other anileridine phosphate for peripheral neuropathy. Neither patient was aware of the presence of drug addiction or the signs and symptoms of narcotic withdrawal, which eventually precipitated diabetic ketoacidosis. After diagnosis, both patients were medically withdrawn from narcotics. The first patient has been rehabilitated and has been working full-time as a secretary for the past 2 yr. The second (in whom drug addiction was a secondary diagnosis) also exhibited factitious disease (as a primary diagnosis) but has improved and responded to behavioral modification. Neither of the referring physicians was aware of the possibility of drug addiction, which emphasizes the usefulness of a urinary narcotic drug screen in all patients with recurrent diabetic ketoacidosis.[11] The presence of "needle tracks" is of no value in drug-addicted brittle diabetic individuals because they can claim that the puncture sites are secondary to repeated insulin infusions for diabetic ketoacidosis.

Two of the 30 subjects had severe gastroparesis such that matching gastrointestinal food absorption to subcutaneous insulin absorption was extremely difficult. This diagnosis was suspected by one referring physician, but the importance of it was not appreciated. Both subjects developed frequent severe hypoglycemia after subcutaneous insulin injection, despite recent meal ingestion, followed by severe hyperglycemia 4–10 h after the meal when foodstuffs were finally absorbed and the effect of insulin had waned. Both patients have been treated with metoclopramide, with one experiencing symptomatic relief, but not demonstrating a radiographic increase in gastric emptying as has been previously reported.[27] Improvement in one of the patients occurred when the majority of foods were given in liquid form (which empties more readily from the stomach[28]), and by intentionally decreasing his insulin dose (and delaying its injection to after the meal) so that his blood glucose concentration remained above 100 mg/dl. Although the other patient also improved when the above approach was used during his stay in our Clinical Research Center, his referring physician did not accept our diagnosis and continued him on long-term intravenous insulin therapy (for apparent subcutaneous insulin resistance) with no long-term clinical improvement.

Two of the 30 patients demonstrated subnormal responsiveness to both intravenous and subcutaneous insulin challenge testing. One patient had borderline IgG insulin antibody titers of 0.4 mU/ml pork and 0.41 mU/ml beef (values >2.0 mU/ml are considered clinically significant)[29] and normal red cell insulin receptors on two occasions.[30] Since the rise in plasma free insulin following both subcutaneous and intravenous insulin challenge testing was within normal limits,[31] we believe he has a "cellular insulin postreceptor defect."[32] However, he did respond to large doses of subcutaneous short-acting insulin (0.5 U/kg) if sufficient time was allowed for its hypoglycemic activity to occur (6 h). He was placed on 50 U short-acting insulin every 12 h (3 a.m. and 3 p.m.) and fed two meals per day (breakfast and supper). On this regimen, his blood glucose could be well controlled and recurrent hospitalization for severe hyperglycemia ceased. The second patient with insulin resistance was demonstrated to have anti-insulin-receptor antibodies in spite of her own endogenous insulin secretion.[33] She had a clinical history of systemic lupus erythematosus and acanthosis nigricans 2 yr before referral, but was currently in remission on no medication. When referred, her glucose varied between 500 mg/dl and 1000 mg/dl, which resulted in severe visual impairment (in spite of receiving 50 U of short-acting insulin subcutaneously every 6 h). This patient dramatically improved

by being placed on a low-carbohydrate diet and increasing her salt and water intake, thus maintaining a state of overhydration. Following this approach, her kidneys were able to significantly enhance peripheral glucose disposal, and maintain her glucose between 200 mg/dl and 300 mg/dl. She can now perform all her duties as a housewife, although she does have polyuria.

The final patient in whom an etiologic diagnosis could be made had type I diabetes plus a concomitant seizure disorder (despite large dosages of anticonvulsant medication). When the patient's blood glucose concentration declined rapidly (for example, following exercise) or reached hypoglycemic levels (probably secondary to the variable absorption of NPH insulin[34]), he would experience a grand mal seizure. The extreme muscular contractions associated with these seizures lowered his glucose concentration even further, resulting in profound hypoglycemia, attaining levels of 20 mg/dl on several occasions. This patient's brittle diabetes (and frequency of seizures) was greatly improved by restricting his exercise and using only short-acting insulin on a schedule of five daily injections. He is currently doing well (attending school full-time) and receiving insulin from an external insulin pump.

DISCUSSION

This article provides the clinical description of the 30 patients from whom the diagnostic algorithm in the companion article was derived. These patients are a select group in that their brittle diabetes was sufficiently incapacitating to warrant referral to a university medical center. In addition, the etiology of their brittle diabetes could not be established by the referring physician, even though all patients had been hospitalized frequently. What is encouraging from our results is that the etiology of brittle diabetes could be established in 97% of these patients (1) when a sequential diagnostic approach was followed,[11] and (2) when necessary, the referring physician was willing to pursue close surveillance (long-term follow-up) until a diagnosis was established. The importance of this approach is emphasized by the fact that, when correctly diagnosed, more than 50% of the patients were improved or rehabilitated and returned to a productive lifestyle. Although the cost savings of this approach varied with each patient, the hospital bills alone in several of the referred patients ranged between $30,000 and $80,000 per year.

Several questions may be raised by this study, including: (1) Why was the physician unable to establish the correct etiologic diagnosis before referring the patient to us? (2) Why wasn't therapy successful in all patients once the correct etiologic diagnosis was established? (3) What approach should the busy practicing physician take to the brittle diabetic patient to establish the correct etiologic diagnosis? We believe that the reason the referring physician was unable to make the correct etiologic diagnosis is multifactorial. First, a step-by-step approach for establishing the etiology of brittle diabetes is not readily available, as it is for most medical diseases having multiple etiologies, the classical example being a "fever of unknown origin."[17,35,36] We hope that our algorithmic approach published in the companion article will provide a general guideline, which will undoubtedly have to be modified in the future as new diagnostic techniques become available.[11] A second reason for failure to establish an etiologic diagnosis before referral is that the referring physician's professional relationship to the patient was usually so close that objective investigation of factitious disease and malingering behavior was frequently not even considered. The major advantage that we had was that all patients were approached similarly, no matter what the referring physician stated or what the patient's previous medical records "proved." A third reason is that we have trained the nurses in our Clinical Research Center that multiple etiologies of brittle diabetes exist and have requested their active participation and observation of the patients. We were not aware of a similar participation in any of the diabetic health care teams routinely caring for the referred patients. In fact, several referring physicians reported to us that their diabetic support teams were emotionally upset at our suggesting that the patient was manipulating his disease. We initially had the same experience with our nursing staff when the first patient with factitious disease was diagnosed. However, with additional training and experience, our nurses now accept all etiologic diagnoses as possible and are actively kept informed on the patient's test results. On several occasions, the correct diagnosis involving manipulation was proven by our nurses when our insulin challenge testing was normal. A fourth reason was evident in the patients' extensive records, which indicated that testing for resistance to subcutaneously injected insulin was frequently conducted when the patient (1) had recently eaten, (2) was severely dehydrated, or (3) was permitted to inject his own insulin injections and/or monitor his blood glucose concentration. In the first situation, the absorption of carbohydrate probably masked the expected hypoglycemic effect of insulin. In the second, the hypoglycemic response to subcutaneous insulin injection could be impaired or delayed, either because of the dehydration-induced decreased blood flow to the skin or because of the presence of elevated circulating levels of free fatty acids, as originally proposed by Randall.[37] In the third situation, patient manipulation probably participated in the "nonresponsiveness" to insulin. Thus, it is important to test the patient for insulin sensitivity when adequate rehydration is established and metabolic substrates are reasonably well controlled, such as after an overnight infusion of intravenous insulin.[38] We strongly recommend that all insulin injected for the insulin challenge testing be done by the patient's physician, and not by his nurse or associate, and that a new bottle of insulin be used to ensure full potency. A fifth reason for the difficulty in making the etiologic diagnosis of brittle diabetes is that a patient, even in the hospital, cannot be observed at all times. Unavoidable periods during which the patient is in the bathroom or the attending nurse must respond to an emergency elsewhere in the hospital give the patient the opportunity to manipulate his diabetes control. This situation was undoubtedly true even in our Clinical

Research Center. However, if the physician is persistent in determining the etiology of brittle diabetes, the manipulative patient will eventually be identified. A final explanation for the difficulty of the referring physician in making the correct etiologic diagnosis was that a manipulative patient may not perform these manipulative acts while in the hospital under close observation. Thus, close, long-term follow-up by the referring physician may be necessary, accompanied by immediate rehospitalization and repeat insulin challenge testing as soon as an unexplained episode of hyper- or hypoglycemia occurs. One of our patients had to be rehospitalized three times by the referring physician before malingering was confirmed, since during our evaluation, all test results repeatedly fell within normal limits and the brittle diabetes state could not be duplicated.

The second question raised by our study was why treatment was not successful in all patients once the correct etiologic diagnosis of the brittle diabetes was established. One reason was that appropriate therapy is not available for all etiologic categories. The most difficult etiologic diagnosis to treat was factitious disease, because the "reason" that the patient performed manipulation was never understood. Our success rate with this etiologic diagnosis (50%) was similar to another large series of factitious disease in patients with recurrent infections.[17] Our approach to patients with factitious disease is to refer them for psychiatric care in hopes of providing psychotherapy and preventing permanent self-induced injury. Unfortunately, one of these patients died secondary to recurrent sepsis despite the fact that self-induced disease was accepted by the referring physician. We believe it is important for the patient's physician not to ostracize these patients, since they will seek medical treatment from other unsuspecting physicians and manipulation will continue. In contrast to factitious disease, most other etiologic categories of brittle diabetes are amenable to corrective therapy. Both communication and behavioral disorders can often be sucessfully treated.[39] In the former, speech/language pathologists are the appropriate specialists,[23,26] whereas psychologists are appropriate for most behavioral problems. In general, physicians do not have the training or time necessary to deal with either of these etiologic diagnoses. Unfortunately, both of these diagnoses require patient cooperation, which cannot be enforced by the physician. The subjects with these etiologic diagnoses who did not improve were unwilling to follow the recommendations of their physicians for specialized help in these areas.

A second reason for failure of the subject to benefit once the correct etiology of brittle diabetes was established was resistance of the referring physician to the diagnosis. This was usually experienced when the diagnosis was factitious disease or malingering. It is understandable for a physician who has spent many nights treating his patient for diabetic ketoacidosis to resist being told that the correct diagnosis involves patient manipulation. Resistance of physicians to this diagnosis has been previously reported.[40] Unfortunately, if the physician will not accept the correct etiologic diagnosis (as occurred in three cases), no corrective therapy will be instituted and, in fact, none of these patients improved. Finally, it must be recognized that insulin-dependent diabetes is a disease in which the individual must have constant access to insulin and syringes to stay alive. Thus, in contrast to the suicidal psychiatric patient whose access to sedative drugs can be medically restricted to prevent overdosage, the physician cannot restrict the patient's means to manipulate his diabetes. Since approximately half the patients referred to us exhibited manipulative behavior, treatment must rely on behavior modification, which is not always successful.[39]

The third question refers to the correct approach for the physician providing care for an extremely brittle diabetic patient. We believe that the first step is not to immediately hospitalize the patient and start insulin challenge testing. Instead, the patient should undergo training in the correct technique of insulin injections and diabetes care (including diet, self-monitoring of blood glucose, exercise, and response to illness).[12] Training programs are now widely available throughout the United States and many are sponsored by chapters of the American Diabetes Association. Lack of appropriate knowledge has been identified as the principal cause in many diabetic subjects characterized by poor diabetes control, and up-to-date knowledge in the control of blood glucose concentration will frequently improve metabolic stability in many individuals.[41] However, if the patient is well-trained in diabetes care techniques and still cannot function without recurrent hospitalization for poor diabetes control, initiation of the diagnostic algorithm outlined in the companion article is recommended.[11] If the patient responds normally to intravenous and subcutaneous insulin challenge testing (which occurs in approximately 90% of cases), the etiology of the incapacitating, brittle diabetes is considerably narrowed.[11] An algorithmic approach should be followed to the extent that the physician's facilities permit. Most important, the physician must keep in mind the possibility that manipulative behavior is ever present and that he cannot intuitively tell which patient is a manipulator.[42] A review of the entire patient record and clinical course by a physician colleague who does not know the patient may be particularly helpful in obtaining an objective opinion. However, once the physician has reached the point where he is unable to proceed with the differential diagnosis of the brittle diabetic individual, referral of the patient to a medical center with diabetes expertise is appropriate. We strongly recommend against using "shotgun" therapy for the many etiologies of incapacitating brittle diabetes because of the potential hazards involved.[43] Unfortunately, many of these approaches were used in most of the patients before referral to us, sometimes resulting in life-threatening complications, particularly sepsis from permanent intravenous insulin delivery catheters.[44]

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