The Electroencephalogram of Patients with Diabetes Mellitus

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In 1946 Greenblatt, Murray and Root[1] reported a high incidence of "cerebral dysrhythmia" in diabetic patients with frequent severe insulin reactions ("problem" diabetics). Their findings have since been confirmed by the studies of Fabrykant and Pacella[2] and Wilson.[3] Greenblatt and others[1] found that 51 per cent of the 35 "problem" cases studied had abnormal electroencephalograms whereas, in a comparable control group of 40 patients with uncomplicated diabetes the incidence of abnormal EEGs was not increased over that in normal persons. Except for one patient in the control group, all were taking insulin. Long duration of diabetes did not appear to alter the incidence of "cerebral dysrhythmia". Administration of insulin over long periods of time had no apparent effect on the EEGs. Fabrykant and Pacella[2] also showed that the abnormalities were not due to the effect of the administered insulin. Six of the seven labile diabetics whom they studied had abnormal or borderline EEGs. Wilson[3] found eight cases of extremely labile diabetes in a series of 100 consecutive diabetic patients admitted to the hospital. Five of the eight cases had abnormal tracings. On the other hand, Strauss, Ostow, and Greenstein report a normal EEG in 23 cases of diabetes[4].

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In none of the reported studies have the criteria and type of EEG abnormality been clearly defined. No information is available in regard to the EEG and the level of blood sugar. Furthermore, the emphasis has been mainly on the "labile" or "problem" diabetic. For these reasons it was felt that a re-evaluation of the relationship of the EEG to diabetes would be in order. An attempt has been made to define more clearly the incidence, type, and distribution of electroencephalographic abnormalities in the general diabetic population and the influence of nine factors which might effect EEG.

METHOD OF STUDY

Patients. 81 patients with diabetes mellitus were used in this investigation. They were selected to obtain a wide range in age, duration of diabetes, insulin requirements, and stability of their carbohydrate metabolism. No patients with a personal or family history of convulsions prior to the onset of diabetes were included. All patients were ambulatory and they had not recently been in coma or insulin shock at the time of EEG study. They were classified into two main groups, the *relatively unstable group* (U) of 35 patients and the *relatively stable group* of 46 patients in accordance with criteria set forth in a previous paper.[5] The latter group was further subdivided into those receiving insulin (SC, 26 patients) and those controlled by diet alone (SS, 19 patients). Of those 19 patients, four had no symptoms of diabetes but did have mildly abnormal glucose tolerance tests. The mean ages and ranges of groups U, SC, and SS were 36.8 years (15-76), 58.9 years (25-76 years), and 54.6 years (22-75 years) respectively. While the three groups were comparable in age range, most of the young patients fell into group

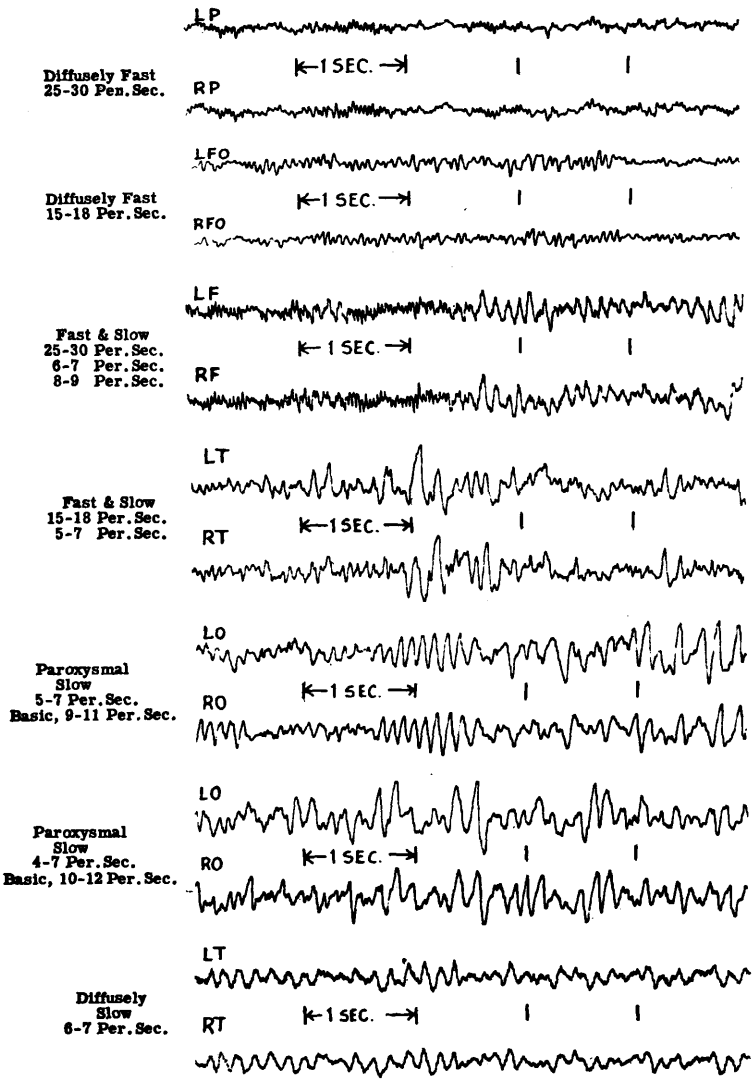

FIGURE 1 Examples of the different types of "abnormal" EEG's in the 81 patients studied.

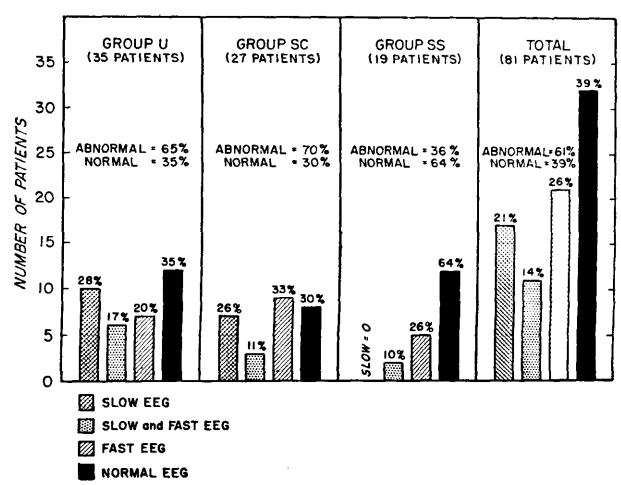

FIGURE 2 Incidence and type of "abnormal" EEG's among Group U (the relatively unstable group), Group SC (the relatively stable group receiving Insulin) and Group SS (the relatively stable group controlled by diet alone). For fuller explanation of group classification see text.

U. Groups U and SC were comparable in respect to amount and type of insulin used.

It should be emphasized that no sharp line of demarcation exists between stable or unstable patients or between those receiving and those not receiving insulin; nor can precise definitions be formulated. Nevertheless, the two major groups possess certain distinguishing features. The *relatively unstable group* is difficult to control; wide unpredictable swings in blood sugar levels are prone to occur unexpectedly with resultant waves of hypoglycemia and/or hyperglycemia and glycosuria; reactions to insulin tend to be frequent, severe, difficult to eliminate and aggravated by attempts to maintain normal blood sugar levels; ketosis develops rapidly. In

contrast, control is easy in the *relatively stable group;* fluctuations in blood sugar levels are decidedly less; reactions to insulin tend to be infrequent, explainable, and usually avoidable; ketosis is usually the result of gross neglect, infections, or both.

Neurological and Psychiatric Screening. Neurological examination was conducted on all patients to rule out the existence of organic disease of the central nervous system. In addition it was deemed advisable to screen all the patients used in the study by means of a mental status examination. This was limited to examination of the sensorium and included the following: 1) Orientation as to person, place and time. 2) Memory, recent and remote. 3) Retention. 4) Serial numbers repeated backward and forward. 5) Calculation. 6) Reading, writing, and speech. 7) Serial subtraction of 3 or 7 from 100. 8) Assessment of abstract thinking by use of proverbs, Kohs blocks and Goldstein stick procedures.

Electroencephalography. A Grass, 6 channel, model III C, electroencephalograph was used with 8 electrodes, routine placement, scalp-to-scalp and scalp-to-ear tracings. Twenty-two patients had one EEG, 53 patients had 2 EEGs from one to six months apart, and 6 patients had 3 EEGs. Repeat EEGs were different on only four occasions. Records containing more than random activity of slower than 8 per second or faster than 13 per second were regarded as "abnormal". Only fast activity of amplitude *greater than 20 microvolts* was classed as "abnormal". This follows the classification of Gibbs.[6] The significance of the so-called "abnormals" will be discussed later.

Blood Sugar Determination. Specimens of oxalated venous blood were obtained at the beginning and end of each EEG 137 times and analyzed for "true" blood sugar.

RESULTS

The following types of "abnormality" were noted in this series: 1) Bursts of high voltage slow activity, 2) Diffuse slowing, 3) Bursts of slow and fast activity, 4) More or less continuous fast activity of amplitude greater than 20 microvolts. Slow activity was bilateral, synchronous and not localized. Fast activity was more prominent in the anterior half of the brain and fell roughly into two ranges, 15-18 per second and 25-30 per second. Examples of each type of abnormality are illustrated in Figure 1.

The incidence and type of abnormal EEGs in the patients studied are summarized in Figure 2. In the total series 17 (21 per cent) had slow activity (S), 11 (14 per cent) had both fast and slow (FS), and 21 (26 per cent) had fast activity (F), a total of 61 per cent "abnormals". Among groups U and SC the incidence of "abnormals" was 65 per cent and 70 per cent respectively, while among SS it was 36 per cent with no S records. The 4 asymptomatic patients in group SS, noted above, had normal EEGs. The only statistically significant correlation between distribution of EEG type and classification of patients was in the lower incidence of slow activity (S and SF records) in the SS group as compared to that in the other groups ($P=.036$).

The incidence and type of EEG was analyzed statistically with respect to nine other variables which might conceivably be related to the EEG abnormality. The data were analvzed in two ways, the incidence of each type of EEG, (S, SF, F, and N), and the incidence of records with slow activity (S and SF) and records with fast activity (F and SF) against all others. Statistical analysis by the Chi square test yielded P values greater than 0.05, except in a few instances which will be mentioned below.

Blood sugar level at the time of the tracing. The lowest and highest blood sugars recorded were 32 and 602 mg. per 100 cc. respectively. Most of the blood sugar values fell between 100-300 mg. per 100 cc. Further, there were 14 patients whose blood sugar differed by more than 100 on repeat examination. No gross difference in the two EEGs was observed in any of these patients. On two occasions the blood sugar was less than 50 mg. per 100 cc., but was in the normal range when repeated; in neither instance was the EEG slow. Blood sugars were over 400 on 7 occasions, but no consistent trend as far as the type of EEG was observed. It is clear from these data that the EEG abnormalities cannot be accounted for on the basis of variations in the blood sugar level.

Age. The incidence of slow activity (S and SF) was greater in the younger age group (15-30) years and in the older age group (56-80), but this was not statistically significant. On the other hand, the fast activity (F and SF) was significantly more common in ages over 30, ($P=.038$). The rising incidence of fast activity with age will be discussed below.

Age at Onset of Diabetes. Records with slow activity (S and SF) were fairly well scattered among all the patients, but fast records tended to be more common among the patients whose diabetes began after the age of 30, that is, among the older patients, a correlation already noted.

Duration of Diabetes. There was no indication that the duration of diabetes influenced the type of EEG found among these patients.

Incidence of Coma or Acidosis. The patients were divided into three groups: 1) 19 with one or more episodes of coma or severe acidosis; 2) 13 who had had mild acidosis and ketonuria, but no coma; 3) 49 who had no recorded acidosis. No statistically significant differences were found as regards the distribution of EEG abnormalities in the three groups ($P>0.05$). Thus no evidence was obtained that any of the abnormalities resulted from the effects on the brain of previous acidosis or coma.

History of Insulin Reactions. (Table 1) There was a significantly greater incidence of records with slow activity (S and SF) among the patients who had had frequent insulin reactions in the past ($P=0.026$). In no instance had the patient had an insulin reaction immediately prior to the EEG. No other significant correlations were noted. We do not regard this as evidence that the insulin reactions are responsible for the slow activity because 15 patients with frequent severe insulin reactions had no slow activity in the EEG, while 8 patients with no insulin reactions did have slow EEG activity.

TABLE 1 EEG AND INCIDENCE OF INSULIN REACTIONS

EEG Type	Number of Patients with Frequent Reactions	Occasional Reactions	No Reactions
Slow (S)	10	4	3
Fast and Slow (FS)	5	1	5
Fast (F)	6	2	12
Normal (N)	9	4	20
Total	30	11	40

Presence of Retinopathy. Since retinopathy might mirror changes in the central nervous system, its incidence was compared with types of EEG. No significant correlation was found with slow activity, but fast activity was more common among patients with retinopathy ($P=0.013$). Since all but one of the patients with retinopathy was over 50 years in age, the greater incidence of fast activity may be accounted for on that basis.

Mental Status and Neurological Examination. No patient demonstrated any marked dementia, but eleven manifested minimal signs, including some concretization of thought; some recent memory disturbance; some decrease in span of attention, but without gross defects of memory, confabulation, disorientation, etc. Changes of this magnitude are frequently discovered among the older patients in this hospital when carefully examined. Seven of these 11 were over 70 years of age, the youngest was 53. Five had slow EEGs; one had mixed fast and slow; one had a fast record, and four had normal records. These data suggest that some of the slow activity in the older age group might be accounted for on the basis of organic brain disease, but this hardly explains the occurrence of slow activity in the 22 other patients who showed no evidence of dementia. Statistically there was no significantly greater incidence of records with slow activity among the patients with dementia. ($P=0.14$). Among the 11 patients with dementia the incidence of EEG abnormalities is about what has been reported in the literature.[7, 8, 9]

The neurological screening revealed the following:

One patient, a 24 year old woman with unstable diabetes, also had Friedreich's ataxia. She had no evidence of dementia. The EEG was classified as slow, but with no focal abnormalities.

Three patients had hemiparesis, presumably on a vascular basis. One had minimal dementia and a slow EEG, a second had no dementia and a slow EEG. The third patient, a 59 year old woman, suffered a left hemiplegia in 1935, with residual weakness still present in 1950. Her EEG showed fast activity on the left, frequency 15-20 per second, voltage 20-90 mv, and a dominant frequency of about 16 per second. On the right the doninant frequency 10 per second, with only small amounts of 16 per second activity. We classified this record as abnormally fast and considered the slower activity (actually within normal range) on the right as secondary to the earlier stroke.

One patient had the residuals of poliomyelitis contracted in infancy. She had no dementia. The EEG was classified as fast. There were six patients with peripheral neuropathy. Three had slow EEGs, one had a fast EEG, and 2 had normal EEGs. Three of the patients with abnormal EEGs also had dementia. One patient had a herniated nucleus pulposus and had a normal EEG.

One patient with a left-sided Bell's palsy had a normal EEG. A 23 year old woman with possible early multiple sclerosis had a normal EEG. A 33 year old woman had severe head trauma at age 16 but neurological examination in 1950 showed no abnormalities. EEG showed fast and slow activity, with no focal abnormalities. A 22 year old man had had a convulsion since the development of diabetes. His EEG was normal.

Thus careful neurological screening provided no evidence for neurological disease as an explanation for the EEG abnormalities.

Other Systemic Diseases. Since diabetics as a population show a high incidence of other systemic disorders, especially those related to vascular disease, we also analyzed our material from this point of view. None of these patients was delirious (although 11 had mild dementia as already discussed) so that EEG abnormalities could not be explained on such a basis.[10] There were 49 patients who had such complications and a number had more than one. In the series as a whole no significant correlation was found between EEG and the presence or absence of complications other than diabetes.

Twenty-seven patients had heart disease related to arteriosclerosis and/or hypertension. The distribution of EEG abnormalities was identical with that in the total group of 81 diabetics.

Nine patients had renal disease, including pyelonephritis and intercapillary glomerulosclerosis. Five had abnormal EEGs, including one S and four F. The one patient with the slow EEG had chronic azotemia, but no evidence of delirium.

Other complications included generalized and peripheral arteriosclerosis (without gross renal or cardiac disease), 7 cases; latent syphilis, 2 cases; pernicious anemia in remission, 2 cases; operated carcinoma of the breast, 4 cases; cirrhosis of the liver, 2 cases; asthma, 2 cases; mild hypothyroidism, 1 case. The small numbers did not permit any statistical evaluation.

COMMENTS

Our findings confirm the observations of previous investigators reporting the occurrence of abnormal electroencephalograms among diabetic patients. In the total series of 81 patients, the incidence of records with slow activity (S and SF) was 35 per cent, a significant difference from the 10 per cent which is generally accepted as the incidence in the so-called "normal" population. The incidence of diabetics whose EEGs showed fast activity (F and SF) was 40 per cent.

There would be no disagreement among electroencephalographers as to the significance of the slow activity which we have classified as "abnormal." More controversial would be the interpretation of the fast activity. We have designated as "abnormal" fast only activity of greater than 13 cycles per second occupying the bulk of the record and having an amplitude greater than 20 microvolts. Gibbs[11] reports among 1,000 adult controls 6 per cent with slightly fast activity and less than one per cent with very fast activiy. (F_1 and F_2 respectively, according to Gibbs' nomenclature.) Gibbs is vague in defining the difference between F_1 and F_2; "F_1, slightly fast; moderate amount of activity faster than 12 per second; F_2, very fast; large amount of activity faster than 12 per second. The amount is considered in terms of amplitude and frequency of the fast activity; the percentage of time it is present and the number of leads in which it appears."[11] We would assume from his description that the records which we have classified as fast correspond more closely to his F_2 category. According to Gibbs the incidence of slightly fast (F_1) electroencephalograms increases with age, being 3 per cent at age 15-18 and reaching 25 per cent by age 70.[11] Among our patients, the incidence of fast activity (F and FS) as defined by us was 15 per cent in the age group 15-30 years; 46 per cent in the group from 31-55 years; and 49 per cent in the group above 55 years. Since most of our records probably fall in the F_2 classification, which Gibbs regards as abnormal at any age, the incidence of fast records would be significant according to Gibbs. Yet Strauss and others[4] would classify Gibbs' F_1 and F_2 as normal. Mundy-Castle[12] studied the incidence of beta rhythm (14-30 per second) in the EEGs of normal adults. He reported 6.6 per cent of 211 normal adults as having some beta activity of amplitude greater than 20 microvolts, with an incidence of 3.7 per cent among 161 young adults (mean age 22.4 years) and 16 per cent among 50 "normal seniles" (mean age 75.1 years) Walters [13] states "transient bursts of activity at 14-30 c/second are seen in many normal records . . ." but he gives no data as to incidence, amplitude or amount. Schwab considers fast activity abnormal if greater than 30 microvolts in amplitude.[14] Thus, although electroencephalographers in general are much less certain about the interpretation of fast records, the statistical data available on so-called normals indicates a much higher

incidence of fast records among diabetics than the general population. It exceeds the 26 per cent reported by Gibbs as the incidence among 730 adult epileptics.[6]

Greenblatt and others[1] found the incidence of abnormal EEGs to be high among "problem" diabetics but not to exceed the normal incidence among uncomplicated diabetics. No such clear-cut distinction was evident in our records. 45 per cent of the "unstable" (U) diabetics had records with abnormally slow activity (S and SF), while the incidence among the "stable" (SC and SS) group was 26 per cent. If we exclude from this last group the 4 patients who had transiently abnormal glucose tolerance curves but no symptoms (and who may not be diabetics), the incidence of slow activity would be 29 per cent. The difference in incidence between the two groups was not found to be significant on statistical analysis, nor was there any difference in the incidence of fast activity (F and SF), which was 37 per cent and 41 per cent respectively.

The meaning of these findings remains obscure. We find no support for the hypotheses that the abnormal EEG relates in any way to the severity or stability of the diabetes or that it is a consequence of complications of diabetes. The greater incidence of slow records among patients who had frequent insulin reactions cannot be regarded as evidence either that the insulin reactions caused the EEG abnormality or that the EEG abnormality rendered the individual more vulnerable to hypoglycemia, as others have suggested.[1, 2] A different type of experimental design is necessary to establish such conclusions. While many records do closely resemble those seen among epileptics, this hardly seems sufficient basis to relate the two disorders or to provide a rationale for the use of anticonvulsants.[2, 3] There is no reason to believe that the fast activity and the slow activity necessarily have the same significance. The slow activity did not correlate with the presence of delirium or dementia. In this regard there is some resemblance between the findings in diabetes and in Addison's disease, where there is also found a high incidence of paroxysmal and diffusely slow records unrelated to delirium.[10, 15, 16]

Fabrykant and Pacella[2] have suggested the possibility of a genetic or constitutional factor causing the EEG abnormalities. The inability to correlate the EEG with any of the variables mentioned has suggested to us a similar hypothesis. Further studies are planned to examine the possibility of a genetic determinant and/or of a metabolic defect.

SUMMARY

Electroencephalographic studies were performed on 81 patients with diabetes mellitus. Thirty-five patients belonged to the *relatively unstable group* and 46 patients to the *relatively stable group*. Of the latter, 26 patients were receiving insulin, while 19 were controlled by diet alone. Neurological and psychiatric screening examinations were performed on each patient. Blood sugar determinations were made at the beginning and end of each EEG 137 times.

The following types of "abnormality" were noted in this series: 1.) Bursts of high voltage slow activity; 2.) Diffuse slowing; 3.) Bursts of slow and fast activity; 4.) More or less continuous fast activity of amplitude greater than 20 microvolts. Slow activity was bilateral, synchronous and not localized. Fast activity was more prominent in the anterior half of the brain and fell roughly into two ranges, 15-18 per second and 25-30 per second.

In the total series 17 (21 per cent) had slow activity, 11 (14 per cent) had both fast and slow, and 21 (26 per cent) had fast activity, a total of 61 per cent "abnormals." There was no statistically significant difference in the distribution of EEG abnormalities in the 3 groups of diabetics except for a lesser incidence of slow activity among the stable diabetics not receiving insulin.

The incidence of slow activity was greater in the younger age group (15-30) years and in the older age group (56-80) but this was not statistically significant. Fast activity was significantly more common in ages over 30.

A significantly greater incidence of records with slow activity was noted among the patients who had had frequent insulin reactions in the past. However, 15 patients with frequent severe insulin reactions had no slow activity in their EEG records while 8 patients with no history of insulin reactions did have slow activity.

No significant correlations between EEG type and blood sugar, duration of diabetes, incidence of coma or acidosis, minimal dementia, or associated systemic or neurological disease could be made.

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DISCUSSION

DR. MAXIMILIAN FABRYKANT (*New York*): In a group of 16 labile diabetics studied with Drs. B. L. Pacella and J. H. Taterka, a normal electroencephalogram was obtained in only three. In the remaining 13 cases there was no uniformity in the recorded alterations of the EEG pattern. This is in agreement with data presented by Dr. Izzo and his associates. We were also unable to establish a definite correlation between the type and the degree of the disturbance in cerebral electroactivity and the degree of lability of diabetes, except for the fact that a marked distortion of the EEG was seen only in those who were subject to severe insulin reactions. Thus patterns consistent with convulsive tendency were recorded in six, and suggestive of focal brain pathology in three such patients.

While no sufficient information is available as yet to offer a satisfactory explanation for the development of EEG abnormalities in diabetes, some known facts seem to be significant in this connection. Inasmuch as we have obtained a disturbed brain wave pattern in nondiabetic blood relatives of several of our diabetic patients, we have previously suggested that the disordered cortical potentials may be genetic or constitutional in origin. Further studies revealed that EEG abnormalities may be found in apparent absence of a genetic factor in those who were repeatedly subjected to severe and prolonged insulin reactions.

True, there is no strict parallelism between the height of the blood sugar and the electroactivity of the brain. Critically low blood sugar values associated with normal EEG patterns were reported in various hypoglycemic states, including that due to pancreatic islet tumors. However, it is known that severe hypoglycemic episodes may produce injury to the brain. We therefore believe that some of the EEG abnormalities recorded in diabetic patients are genetic or constitutional in origin while others are secondary to repeated severe insulin reactions and reflect metabolic and functional disturbances of the brain cell resulting from severe hypoglycemia.

Dr. Izzo and his associates found no correlation between the frequency of insulin reactions and the alterations of the EEG. However, I find it significant that in their patients treated with diet alone the incidence of abnormal EEG tracings was only 36 per cent as against 65 per cent and 70 per cent in those who received insulin therapy. Thus their statistics do not necessarily support their view that the abnormal EEG is not in any way related to the severity of diabetes or to complications of this disease. Certainly, with regard to EEG abnormalities, the important point is not the frequency but rather the severity of insulin reactions.

Dr. Izzo and his associates find no rationale for the use of anti-convulsants in diabetes. To this I would take exception since it is recognized that anticonvulsants may be useful in certain nonepileptic conditions, and may even reduce the irritability and excitability in major psychoses. Our exceedingly satisfactory results with the use of anticonvulsive therapy in labile diabetes have been recently confirmed by D. R. Wilson (Canad. M. A. J. 65:462, 1951). Moreover, in our experience anticonvulsants may produce a marked improvement in the initially abnormal EEG patterns of labile diabetics.

The work of Dr. Izzo and his associates is of considerable interest. They have presented evidence that EEG alterations may be found in a surprisingly large proportion of diabetics, even in mild diabetics who received no insulin therapy. To my way of thinking, their work opens up new leads for a study of functional or structural brain changes which may be present in a great number of diabetic patients.