Quantitative electroencephalographic analysis of naturally occurring (schizophrenic) and drug-induced psychotic states in human males

Analysis of the quantified electroencephalogram of the left occipital lead (Drohocki's integrative method) of 21 normal male subjects revealed an average coefficient of variation in electrical energy of 15.4 per cent. In 25 male chronic schizophrenic patients, the mean coefficient of variation was 8 per cent. Placebo administration did not produce any significant change in either group. In the normal men, oral dosage with 0.3 μg per kilogram of D-N, N diethyl lysergamide (lysergic acid diethylamide, LSD-25) produced a 33 per cent decrease in variability without significant change in the mean energy content of the electroencephalogram. When the dose of lysergic acid diethylamide was increased to 1 μg per kilogram, a 25 per cent decrease in variability and 23 per cent reduction of the energy content of the electroencephalogram followed. In schizophrenic patients, lysergic acid diethylamide at 1 μg per kilogram orally did not affect the mean energy content but produced a 47 per cent increase in variability. The findings indicate that the electroencephalogram of male institutionalized chronic schizophrenics tends to be hyperregulated. Similar hyperregulation is produced in normal volunteers by threshold and larger doses of lysergic acid diethylamide.

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Since its beginnings, the measurement of the rhythmic electrical activity of the brain, the electroencephalogram, has remained a fascinating but rather elusive possibility for gaining knowledge of the functioning of the central nervous system. Most work with the electroencephalogram, both clinical and experimental, has consisted of qualitative analysis through visual inspection. Semiquantitative methods such as determination of distribution of electroencephalogram frequencies[4] or measurements of the alpha index are of great theoretic and practical interest. These are of necessity done on

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very limited lengths of recordings and can refer to only one individual at a time. Thus, they permit neither over-all, long range analyses nor, even more important, the establishment of mean or average characteristics in groups of subjects. Furthermore, these procedures do not define or allow precise calculations of variability, a very informative parameter in biologic systems.

Data from Drohocki's[2] integrator which can measure continuously and automatically the energy content of the electroencephalogram, analyzed by the statistical procedures suggested by the same author[3] and by Muñoz and Goldstein,[12] have opened other fields for electroencephalographic research. So far, most applications of these techniques in this country have been to animal experiments. It appeared promising to apply these methods to the analysis of electroencephalograms of normal volunteers and those of schizophrenic patients. It was also of interest to compare the effects of D-*N*, *N* diethyl lysergamide (lysergic acid diethylamide, LSD-25) upon the electroencephalograms of the two groups.

The present report will be divided into three parts. In the first part, the characteristics of the quantified electroencephalogram from normal subjects without drug and after placebo will be presented. This is most important since all those differences which are spontaneously present in schizophrenic patients or are brought about by drugs can then be described in relation to what will be defined as the "normal" electroencephalogram. In the second part, measurements obtained from the electroencephalograms of male chronic schizophrenic subjects will be described. Finally, the effects of lysergic acid diethylamide on normal subjects and psychotic patients will be discussed.

Procedure

Subjects. Three groups of subjects were utilized in these studies. The first consisted of 21 volunteers from the New Jersey Reformatory at Bordentown. Most were first offenders, and all were in the last 6 months of detention before release. Their age range was 21 to 30. The subjects were screened with medical history and physical examination, electrocardiogram, clinical electroencephalogram, Wechsler Adult Intelligence Scale, Minnesota Multiphasic Personality Inventory, and Rorschach test. This group of subjects will be referred to as reformatory volunteers.

The second group consisted of 9 male volunteers from the laboratory staff. Their age range was 19 to 48. This group will be designated as staff volunteers.

The third group consisted of 25 male schizophrenic patients from the Clinical Investigative Unit of the Bureau of Research. Their age range was 23 to 45. They were selected from the patients in the Clinical Investigative Unit on the basis of their ability to cooperate in the testing procedure. These patients had been transferred for intensive study from one or another of the four state hospitals of New Jersey during the past year. The criteria for selection were: age 20 to 45 years, diagnosis of schizophrenic reaction, little or no response to usual somatic therapies, and no neurologic abnormalities. In general, the life histories of these patients are typical of those found in "process" schizophrenics, with poorly developed premorbid personalities and no mature social or sexual relationships. Only one had been married. In the present mental condition, they covered a wide range, from well-preserved paranoids to severely regressed hebephrenics.

Eleven patients had received both electroconvulsive and insulin coma treatments. Another 10 patients had courses of electroconvulsive therapy but not insulin. The remaining 4 patients had neither electroconvulsive therapy nor insulin. The number of electroconvulsive treatments varied from zero to 128, and the period since administration varied from 2 to 21 years. The insulin comas were induced in courses of thirty to sixty treatments; unfortunately, the records are not clear as to the number and depth of comas actually produced.

All patients had been treated with one or several of the phenothiazine derivatives and some with other antipsychotic agents over periods varying from weeks to years. All had been free of medication for periods of from 1 month to more than a year at the time of the first electroencephalographic examination.

Methods. The method of quantification of the electroencephalogram was that of energy content measurements by the use of the electronic integrator first designed and built by Drohocki in 1948.[2] Numerous descriptions of the way in which this device operates have been published,[2, 3, 7] so only a brief account will be given here.

The integrator full-wave rectifies the successive waves of the electroencephalogram and via a modified relaxation oscillator and monostable multivibrator generates a train of pulses the frequency of which is directly proportional to the area under the rectified electroencephalogram. Since the electroencephalogram is a record of voltage varying in time, the area under the resulting curve is the product of electric potential times time. An electric potential may be defined as the amount of energy necessary to move a unit charge from one point to another. Its dimensions are therefore energy and unit charge. The unit charge, however, is a constant within any system so that pulses per unit time are directly proportional to the energy. In practical units, energy is expressed in joules or watt-seconds. The units in these studies, pulses per unit time, are directly proportional to the energy though quite difficult to express in actual dimensions of watt-seconds or joules, since by varying the gain or time constants of the integrator, the constant of proportionality between energy and pulse frequency can be altered. Therefore, immediately before the beginning of each run, the integrator was calibrated using the 50 μV rise and expotential decay which are common on many electroencephalographs. The settings were never changed after this calibration. In Fig. 1, an example of the integration process is presented. In this case, two integrators were used, set at two different constants of proportionality. One was set for an output of 3 pulses and the other for 13 pulses per calibration signal.

After a unit of time for summation was chosen, for instance 20 seconds, the number of pulses for thirty or more such periods successively was counted. The mean number of pulses per unit time could then be calculated. The term electrogenesis will be used to refer to such mean values. When successive electrogenic levels are plotted against time, one obtains what Drohocki[3] calls "electrochronograms."

Three features of this technique are to be noted. First, the integrative method is an averaging method; it expresses all electrical events during a certain time period in one

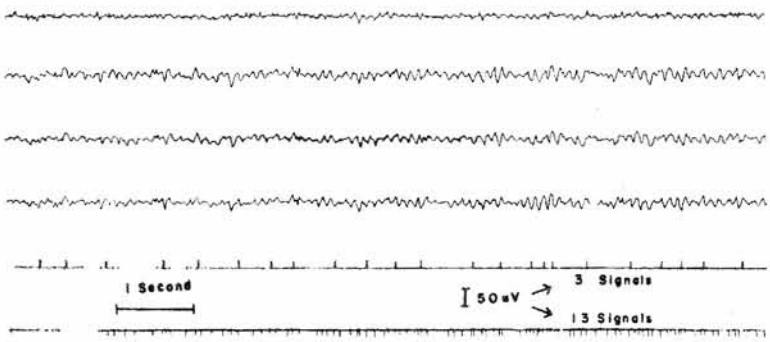

Fig. 1. Example of the integration of electroencephalograms. The sources are, from top to bottom, right temporal, right and left parietal, left occipital, integrator 1, and integrator 2. The proportionality coefficients of the integrators are respectively 3 and 13 pulses per 50 μv calibration signal. The pulses correspond to the electrical activity from the left occipital area.

value. Thus transients are masked unless they are of sufficient magnitude to distort the statistical parameters of the mean. Second, the integrator is frequency independent; when a certain cumulative energy occurs within a given time period, the total number of output pulses is the same, regardless of the number of waves. Third, with this type of analysis, electrogenesis increases in states of sedation or sleep and decreases in states of excitation or stimulation.

The experiments always began with a 10 minute control recording. This was followed by a 20 minute rest interval, at the beginning of which drug or placebo was given. After this interval, a second 10 minute recording was made, again followed by a 20 minute interval without recording. The procedure was repeated to yield four 10 minute records beginning 30, 60, 90, and 120 minutes after drug or placebo. During rest periods, the subjects were permitted to sit or move about or to read. They were not allowed to smoke or to drink anything.

Recordings were made on a Grass Model III electroencephalograph. Monopolar electrodes were placed on the frontal, temporal, parietal, and occipital areas of the scalp with both ears as reference. The output from the left occipital was processed through an integrator or through two set at different constants of proportionality to allow analysis of widely varying units of time. The occipital area was chosen because the voltage of the alpha complexes and the variability of the electroencephalogram are maximal in this area. Intervals in the control record of drowsiness or sleep or of alerting during which alpha waves become flattened or disappear were omitted from computations.

At no time did the subjects, the electroencephalogram technicians, the individual who gave the doses, or the persons who analyzed the records know what drug was administered.

Following the procedure described above, 15 reformatory volunteers were given 70 to 90 ml. of distilled water, with or without a capsule containing lactose. Next, to compare effects of a psychotomimetic agent in normal individuals with spontaneous findings in psychotic patients, these subjects were given lysergic acid diethylamide orally in 70 to 90 ml. of distilled water at two dose levels, 0.3 and 1.0 μg per kilogram. The same procedure was followed as for placebo.

Only control period recordings were obtained from the 9 staff volunteers.

Baseline recordings were obtained from the 25 patients for periods of 5 to 20 minutes. With one exception, they were able to lie still satisfactorily with their eyes closed. Some of them had occasional muscular movements, but sufficient lengths of records were obtained in which there was no artifact.

Three experiments were then performed with the patients as subjects. In the first, recordings were made as described: 10 minute control, followed by 10 minute recordings at 30, 60, 90, and 120 minutes after control. However, these patients were given nothing to drink or to swallow. Such dry runs were performed to determine whether any significant differences would appear between patients given no dose and those given placebo. Next, 5 patients were given placebos the same way as the normal persons. Finally, 10 patients were given 1.0 μg per kilogram of lysergic acid diethylamide.

Analysis of data. Throughout these studies, the unit of time was 20 seconds. In other words, the mean electrogenic levels and their statistical parameters during control periods and during the various experimental sampling periods were computed by breaking the different recording runs of each experiment into successive strips of 20 seconds. Thus from a 10 minute run, thirty values were obtained from which were calculated the mean and standard deviation for that run. Since each subject had a different characteristic level of electrical energy, no valid pooling could be performed on the crude, direct data. To obtain over-all means and also to compare subjects, the method of Muñoz and Goldstein[12] was fol-

Table I. *Representative example of data obtained in these studies and the way in which they were analyzed*

Successive 20 second intervals	Control period		Interval after placebo							
	Direct data (D)	Percentage transformed data (PT)	30 min.		60 min.		90 min.		120 min.	
			D	PT	D	PT	D	PT	D	PT
1	69	82	94	116	86	116	92	115	96	130
2	88	105	75	92	50	67	64	78	92	125
3	73	87	104	128	57	77	81	101	79	107
4	88	105	85	105	85	115	81	101	64	87
5	117	139	58	71	68	92	72	90	76	103
6	93	110	84	104	80	108	88	110	75	102
7	76	90	85	105	83	112	84	105	86	117
8	93	110	78	96	78	106	80	100	67	91
9	89	106	75	92	74	100	76	95	75	102
10	87	104	105	129	87	118	54	67	78	106
11	89	106	84	103	80	108	62	78	87	118
12	80	95	79	97	84	114	73	91	77	105
13	92	109	78	96	84	114	95	119	74	100
14	97	115	76	94	69	93	57	72	64	87
15	81	96	65	80	85	115	65	81	75	102
16	79	94	91	112	69	93	69	87	75	102
17	124	148	81	100	88	119	43	54	86	117
18	90	108	77	95	74	100	101	128	53	72
19	63	75	77	95	74	100	107	134	61	83
20	91	108	78	96	55	75	96	120	86	116
21	84	100	88	108	83	112	93	116	56	76
22	90	107	83	102	68	92	94	118	71	97
23	76	90	61	75	87	118	96	120	79	107
24	86	102	78	96	74	100	78	97	61	83
25	68	81	111	137	80	108	94	118	77	105
26	68	81	97	119	59	80	78	98	61	83
27	56	66	59	72	54	73	79	99	78	106
28	83	99	83	102	58	78	81	101	73	99
29	78	92	94	116	69	93	101	126	52	71
30	78	93	57	70	79	107	67	84	71	96
Means (direct data)	84.2		81.3		74.0		80.0		73.5	
Means (percentage transformed data)		100.0		100.0		100.0		100.0		100.0
Standard deviation (percentage transformed data)		16.0		15.6		15.3		19.5		16.4
Index	100.0		96.6		87.9		95.0		87.3	

lowed. The mean of each control period was adjusted to 100, and the means in succeeding periods of the experiment were expressed as

$$\frac{\text{mean under experimental condition}}{\text{mean during control period}} \cdot 100.$$

Variability was computed on the basis of the additivity of variance in normal distributions,[5] since, as shown below, the distributions were in fact normal. After successive values in each single run were transformed so that the mean was 100, the sum of the squares of the deviations of such transformed values from 100 was calculated. Finally, all such sums were added up and divided by the grand total number of all similar runs in all the subjects. This yielded, after dividing by the number of

degrees of freedom, an over-all variance. The same transformed data were used to plot the histograms of the frequency distributions.

To illustrate the type of data obtained and to clarify the way in which these were handled, a complete set of results from 1 subject, a reformatory volunteer, age 25, given a placebo, is presented in Table I. As can be seen, there are two related values. The first includes means from direct data (D means); in the second, these are adjusted so that the mean is 100 (percentage transformed or PT means). The successive means of the D columns are used to calculate the indices of the different sampling periods (last row on the table), while standard deviations refer to the sum of the deviations squared in relation to 100 in the PT columns. In subsequent tables, indicial changes will refer to averages of all indices calculated from samplings obtained at identical periods during the experiments, while standard deviations will be calculated from the sum of all the deviations squared of all subjects, again during the same periods of the recordings.

Results

Spontaneous electroencephalograms of reformatory volunteers. This phase of the study was completed on 21 subjects and involved eighty-six experiments. Nineteen of the subjects were recorded four times each, the remaining 2 five times each. Hence, the differences in weighting of the final results by each subject are negligible. Whenever the same subject was recorded more than once, a minimum of 7 days elapsed between the successive sessions. Altogether, 2,501 measurements were obtained with 20 seconds as the unit time.

For individuals, the standard deviations (as calculated from the PT columns in Table I) ranged between 10.3 and 21.0, with an average of 15.4. Since the mean was set at 100, these values are also the coefficient of variation and therefore directly express the range of variability.

Three examples of the kinds and extents of variation encountered are presented in Fig. 2. Rather wide variations occur in values from successive 20 second unit times, but the distribution around the mean is

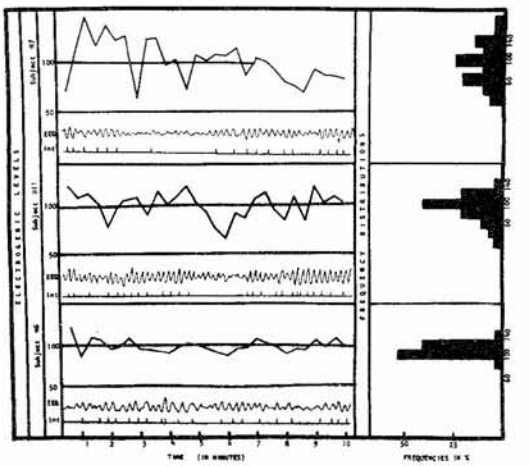

Fig. 2. Example of variation per unit time of electrical energy in 3 reformatory volunteers. Below each electrochronogram are 5 second strips of the actual record. On the right are the histograms of frequency distributions of the electrochronogram.

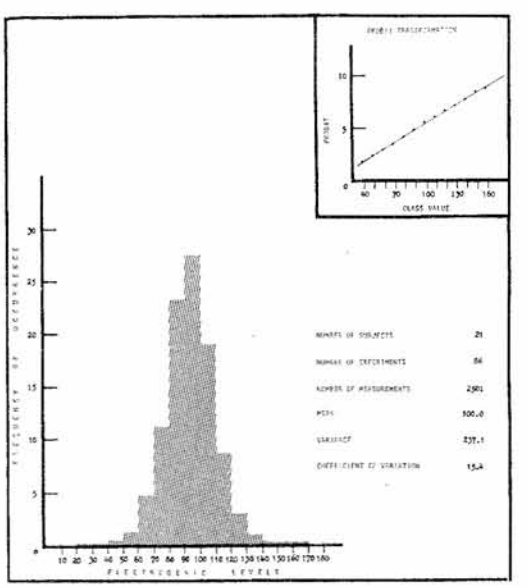

Fig. 3. Over-all frequency distribution histogram for all the reformatory volunteers. See text for explanation of probit transformation.

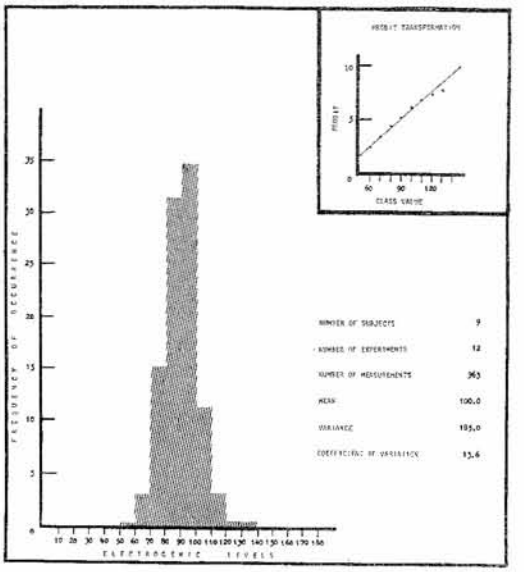

Fig. 4. Over-all frequency distribution histogram for all the staff volunteers.

symmetric. The main determinant of the variability is the magnitude of the deviations; the periods of oscillations do not vary appreciably. That the deviations are symmetrically distributed is shown at the right end of the figure. Differences in the extent of variability notwithstanding, the distributions are normal.

When an over-all frequency distribution is plotted from all values of all subjects, the pattern in Fig. 3 is obtained. An almost perfect Gaussian distribution is formed, and normalcy is confirmed by the probit transformation,[1] which yields a linear regression function. Since the distribution is normal, parametric statistical procedures may be used.

It is noteworthy that the limits of the distribution are rather wide (20 to 160) and that the standard deviation is fairly large, even for a biologic system.

Spontaneous electroencephalograms of staff volunteers. The distribution of the electrogenic levels from these 9 subjects (Fig. 4) was similar to that obtained from the reformatory group. However, the range of the standard deviation was somewhat smaller, 9.7 to 18.2, and the mean was also smaller, 13.6 instead of 15.4. This difference is not statistically significant; the F ratio[17] for variances in both groups is 1.28 which, with the degrees of freedom involved, is at the limit of the 0.05 confidence level. These results suggest that the reformatory volunteers are a valid control group, representative of normalcy insofar as this technique is concerned.

Spontaneous electroencephalograms of patients. The electroencephalograms of the patients were with a single exception characterized by markedly reduced variability. The range of the standard deviations was 3.0 to 11.8, with a mean of 8.0. Examples of one of the most variable of patient records, one of average variability, and one with low variability are presented in Fig. 5. The over-all distribution from all the patients appears in Fig. 6. This distribution also is normal. However, the limits of this distribution are much narrower than those of the volunteers. The two central class intervals contain 91 per cent of the area under the curve, while in the reformatory volunteers, these same class intervals contain only 50.6 per cent of the area. This difference is reflected in the smaller standard deviation of the patients, 42 per cent less than that of normal individuals.

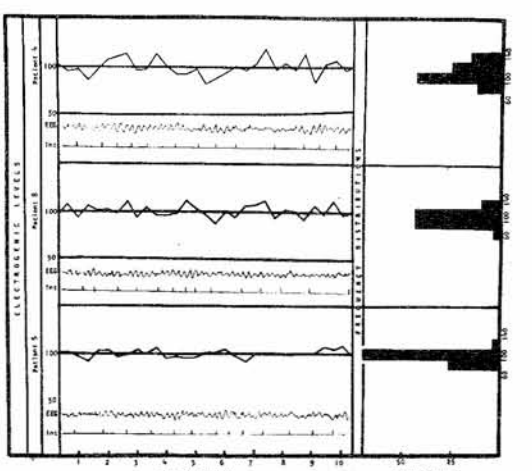

Fig. 5. Electrochronograms of 3 schizophrenic patients, for comparison with normal records in Fig. 2.

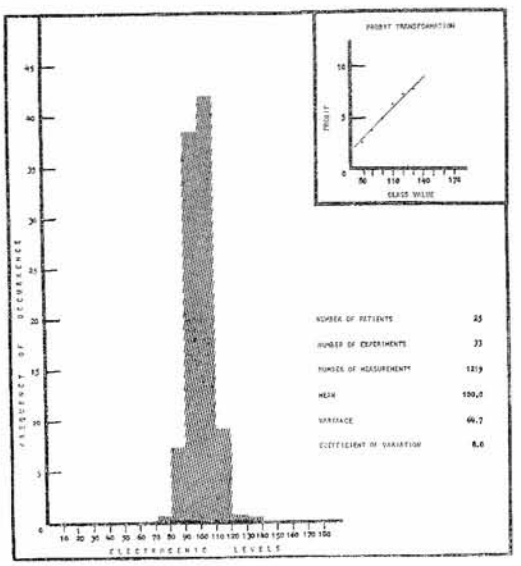

Fig. 6. Over-all frequency distribution histogram for all the schizophrenic patients.

Dry run and placebo electroencephalograms of patients. The dry run sessions produced no significant change (Table II) in mean electrogenesis or its variability. After 70 to 90 ml. of distilled water or 0.9 per cent saline, the electroencephalogram still remained unchanged (Table II). In dry runs and placebo trials, the F ratios were in the range of 1 to 1.8.

In both experimental procedures, the relatively small number of patients was considered to be sufficient since the range of the standard deviation of the means indicated that the error of the mean could not exceed 4 per cent of its value, even with such a small sample.

Effects of lysergic acid diethylamide on electroencephalograms of reformatory volunteers. These results are summarized in Table III. The 0.3 μg per kilogram dose of lysergic acid diethylamide produced no significant change in mean electrogenesis. However, there was a reduction in variability, the standard deviation decreasing by 31 per cent from 17.6 during the control period to 11.7 ninety minutes after drug administration. This was statistically significant, the F ratio being 2.3 ($p < 0.01$).

After 1.0 μg per kilogram of lysergic acid diethylamide, not only was there a decrease in variability but also a considerable and significant drop in the mean electrogenesis. A typical example of the change in a single subject appears in Fig. 7. By 90 minutes after dosage, mean electrogenesis was reduced 22.7 per cent, and over-all variability was reduced 40 per cent. In those experiments in which recordings were continued to a period 150 minutes after drug administration, mean electrogenesis and variability remained at the same level (Table III).

Decreases in mean electrogenesis and variability were found in all normal subjects but 1. In this single instance, there was no significant change in mean electrogenesis; a small apparent increase in vari-

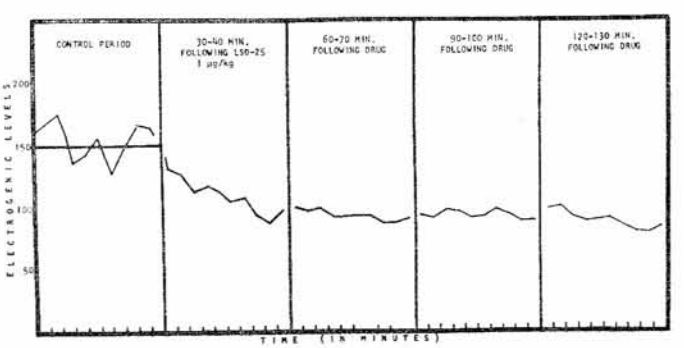

Fig. 7. Effects of lysergic acid diethylamide (1 μg per kilogram) in 1 reformatory volunteer. These are direct data, not transformed. To reduce the length of each measurement run, the unit time here is 1 minute, not 20 seconds.

Table II. *Cortical electrogenesis of male chronic schizophrenic patients (means ± standard deviations)**

Control period	Interval after control period			
	30 min.	60 min.	90 min.	120 min.
Effect of experimental procedure				
100.0 ± 6.4 (N = 149)	98.9 ± 7.4 (N = 141)	97.9 ± 7.9 (N = 137)	96.8 ± 6.5 (N = 137)	97.1 ± 7.3 (N = 128)
Effect of placebo administration (distilled water or 0.9 per cent saline)				
100.0 ± 6.8 (N = 146)	102.5 ± 7.1 (N = 150)	100.4 ± 7.3 (N = 150)	96.8 ± 9.4 (N = 147)	98.3 ± 8.4 (N = 149)

*The numbers in parentheses refer to the actual independent measurements upon which were computed the standard deviations.

Table III. *Effect of lysergic acid diethylamide on cortical electrogenesis in reformatory volunteers (means ± standard deviations)*

Dose of lysergic acid diethylamide (μg per Kg. orally)	No. of subjects	Control period	Interval after drug administration				
			30 min.	60 min.	90 min.	120 min.	150 min.
0.3	6	100 ± 17.6 (N = 171)	93.5 ± 16.8 (N = 179)	98.6 ± 14.3 (N = 179)	95.8 ± 11.7 (N = 179)	98.2 ± 12.8 (N = 180)	
1.0	13	100 ± 14.7 (N = 343)	93.8 ± 13.5 (N = 382)	85.3 ± 11.7 (N = 380)	77.3 ± 8.7 (N = 381)	78.0 ± 10.7 (N = 381)	74.1 ± 7.9 (N = 386)

Table IV. *Effect of lysergic acid diethylamide (1 μg per Kg.) on cortical electrogenesis in 10 male chronic schizophrenic patients (means ± standard deviations)*

Control period	Interval after drug administration			
	30 min.	60 min.	90 min.	120 min.
100 ± 7.3 (N = 282)	104.6 ± 13.4 (N = 270)	105.2 ± 11.2 (N = 270)	105.8 ± 14.5 (N = 233)	115.5 ± 10.3 (N = 190)

ability was also not significant. This subject also presented an unusual reaction to lysergic acid diethylamide, becoming catatonic 1 hour after drug administration and remaining in that state for more than 3 hours.

Effect of lysergic acid diethylamide on electroencephalograms of patients. In 10 patients, 1 μg per kilogram of lysergic acid diethylamide produced no significant change in mean electrogenesis (Table IV). The greatest apparent difference occurred 120 minutes after dosage, but t between this and the control period was only 1.7, which corresponds to $p = 0.1$. In contrast, the increases in variability were significant; F ratios ranged from 2 to 3.9 ($p = < 0.01$).

Discussion

A question which must always be considered in research of this kind is that of placebo reactions. On the basis of individual records after placebo, the reformatory volunteers could be separated into three categories (Table V). In the first were 7 subjects who showed no significant change

Table V. *Effect of placebo on cortical electrogenesis of reformatory volunteers (means ± standard deviations)*

Subject	Control period	Interval after drug administration			
		30 min.	60 min.	90 min.	120 min.
4	100.0 ± 13.3	106.0 ± 10.3	109.8 ± 15.2	107.9 ± 8.4	106.7 ± 23.2
6	100.0 ± 11.0	93.5 ± 17.1	98.8 ± 8.4	93.8 ± 14.7	93.2 ± 10.6
7	100.0 ± 10.2	102.1 ± 8.3	89.7 ± 14.0	104.0 ± 3.8	102.5 ± 9.6
9	100.0 ± 16.8	106.4 ± 7.0	106.4 ± 15.0	98.1 ± 10.1	104.6 ± 10.3
11	100.0 ± 13.3	108.6 ± 22.2	108.6 ± 24.9	112.2 ± 12.5	99.2 ± 7.2
13	100.0 ± 16.0	117.0 ± 15.6	107.3 ± 15.3	116.4 ± 19.5	90.1 ± 16.4
15	100.0 ± 17.7	106.4 ± 14.8	116.2 ± 15.0	96.9 ± 16.3	99.5 ± 12.2
1	100.0 ± 19.1	113.2 ± 17.4	112.2 ± 18.0	108.3 ± 23.7	112.0 ± 6.1
2	100.0 ± 16.4	113.8 ± 15.4	119.4 ± 13.7	121.0 ± 11.6	126.1 ± 13.7
10	100.0 ± 14.7	116.3 ± 19.3	117.6 ± 9.3	113.0 ± 5.2	110.0 ± 10.4
3	100.0 ± 11.5	88.7 ± 13.5	88.4 ± 12.1	103.0 ± 14.7	104.2 ± 14.1
5	100.0 ± 19.2	96.6 ± 17.2	87.9 ± 13.6	95.0 ± 18.4	87.3 ± 15.6
8	100.0 ± 11.6	91.8 ± 3.5	83.7 ± 18.8	64.4 ± 21.8	86.8 ± 4.3
12	100.0 ± 15.6	79.5 ± 14.9	86.3 ± 15.8	75.1 ± 24.1	95.8 ± 12.2
14	100.0 ± 15.1	84.7 ± 3.1	93.7 ± 6.2	80.8 ± 8.8	94.1 ± 4.8
General average*	100.0 ± 14.3	101.6 ± 14.2	101.1 ± 14.0	99.3 ± 14.4	100.8 ± 13.1

*Thirty observations in each period of each of the 15 subjects; therefore, the general average is obtained for each period from fifteen indices insofar as the means are concerned and 450 measurements for standard deviation calculations.

in electrogenesis at any time after placebo. The maximal effect observed was an increase of 17 per cent or a decrease of 6.5 per cent of the mean electrogenesis, both values well within the limits of significance. The standard deviations in single subjects of this group varied in no predictable way from one recording period to another. In some subjects, there were increases in the mean with decreases in standard deviation; in others, the opposite occurred; and in some, neither parameter changed. In the second category were 3 subjects with slight but significant effects consistent with sedation (increase in electrogenesis) after placebo. But once again, there was no reliable change in the standard deviation. The third category was made up of 5 subjects who reacted to placebo with significant effects of the kind usually observed when a stimulant is administered. But as in the other instances, there were no consistent changes in mean electrogenic levels. Subject 8, for instance, exhibited a decrease in variability 30 minutes after placebo; this was followed 30 minutes later by an increase to a level greater than control; and the increase was still greater 90 minutes after administration. When all results from all subjects were pooled, stable values emerged; all the individual differences cancelled each other so that there was no change in mean electrogenesis or in the standard deviation at any time. Hence, among the reformatory volunteers, as any other population, there were placebo reactors, but when averaging of an adequate sample was done, no significant change remained. The stability of the standard deviation on the group basis, as opposed to its irregularity on an individual basis, deserves particular mention, since it could afford a very sensitive method for measuring the efficacy of drugs and for distinguishing between true drug effects and placebo reactions.

Another question which can be raised concerns the difference in the age range of the groups (21 to 30 versus 23 to 45). There are no presently available definite indications that significant changes occur in

normal subjects between these age levels.[6] This may be simply a reflection of the lack of precision or sensitivity of qualitative electroencephalographic analytic procedures. In any case, there was a fair degree of overlap between the ages of the subjects in both groups. Separate analysis of the records of 7 patients whose ages were within the range of the reformatory volunteers yielded a coefficient of variation of 6.0, entirely consistent with that of the entire group of patients.

The observations and results reported here strongly suggest that contrary to what has sometimes been stated on the basis of qualitative judgments,[8] there is a difference between the spontaneous cortical electrical activity of normal subjects and of chronic schizophrenic patients. This difference is manifested in the greatly reduced variability of the electroencephalograms of the patients. This paradoxic stability[9] has been previously indicated by results from qualitative analysis[14] and statistical computations based on the alpha index.[10]

An objection to such a conclusion might be raised: schizophrenic patients, despite their frequent appearance of being withdrawn, are extremely sensitive to their environments. Anxiety caused by the experimental situation could lead to a state of sustained arousal with a low energy invariant electroencephalogram. However, recordings made during five successive periods (the dry runs) rather than during a single session showed no significant change in the standard deviations through the consecutive periods. And many patients were recorded two, three, or more times; the measurements obtained on such repeated sessions were always quite similar, always within what could be called the schizophrenic range. Thus, neither an increase in the interactions between the patients and the attending technicians and physicians nor the repeated exposure to and familiarization with the same environment changed the electrical hyperregulation.

Previous studies have shown that decreases in energy content and variability of the electroencephalogram typically accompany states of stimulation or excitation. Thus, Murphree, Jenney, and Pfeiffer[13] have shown that D-amphetamine produces in normal man a 20 per cent decrease in electrogenesis and a 35 per cent decrease in its variability. In correlated electroencephalographic and behavioral studies on rabbits, Goldstein* found that sedation induced by pentobarbital, accompanied by a 100 per cent increase in electrogenesis, could be reversed by intravenous administration of 2 to 5 μg per kilogram of lysergic acid diethylamide. Under the same conditions, Muñoz and Goldstein[12] found that an intravenous dose of 0.5 mg. per kilogram of DL-amphetamine had the same kind of stimulant effect.

When the quantified electroencephalographic parameters of normal subjects under lysergic acid diethylamide are compared with those of schizophrenic patients without any drug treatment, the similarities are striking. If such a similarity is more than a coincidence, it would suggest that the cerebral cortex of chronic schizophrenic patients is in a sustained state of excitation or even hyperexcitation. The very small variability regularly encountered in these patients may be simply a concomitant of the decrease in the mean. However, Pfeiffer and colleagues[15] have shown decreases of 20 per cent or more in electrogenesis accompanied by marked increases in variability in normal subjects after oral dosage with deanol (2-dimethylaminoethanol). Furthermore, in the present studies, decreases of variability occurred after threshold doses of lysergic acid diethylamide without significant change in energy content. It appears, therefore, that psychotic symptoms, whether in schizophrenic patients or induced by lysergic acid diethylamide in normal subjects, are accompanied by reduced energy content and reduced variability of the electroencephalogram.

It is of interest that no decrease in electrogenesis occurred in schizophrenic pa-

*L. Goldstein: Unpublished results.

tients after lysergic acid diethylamide. This might be due to an already highly stimulated state which might prevent any further change in the same direction. It is also noteworthy that lysergic acid diethylamide increased the variability of the electroencephalogram of schizophrenic patients rather than decreasing it as in normal individuals. It has been reported[16] that transient improvement sometimes occurs in schizophrenic patients given lysergic acid diethylamide. There is a possibility that this could be related to the increase in variability, but more data are needed.

At present, it is possible only to speculate regarding reasons for the hyperexcitation of these patients. This state could very well be due to the presence of an abnormal stimulating metabolite. It could also result from what Miller[11] calls "information input overload," i.e., an exaggerated input to the brain from the periphery accompanied by a decrease in the potentialities of the brain to handle such supramaximal charges.

It is hoped that future work using quantitative analytic electroencephalographic procedures and measuring drug effects in an objective manner may help to achieve a better understanding of mental disease in general and schizophrenia in particular.

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