action of cell-free *Aerobacter* enzyme showed marked pathogenizing activity. The pathogenizing activity must be, therefore, an intrinsic property of this levan.

It is suggested that the pathogenizing activity of a polysaccharide is a function of patterns which are specific to the colloidal state. The activity depends only in minor degree on the structure, configuration and manner of linkage of the individual repeating unit or on the presence of polar groupings in the carbohydrate polymer. There is no consistent relationship between the viscosity of the injected carbohydrate solution and the pathogenizing activity which it manifests.

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Electroshock Therapy by Stimulation of Discrete Cortical Sites with Small Electrodes.*

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Among the many phenomena observed during and following electroshock therapy are convulsion, loss of memory and profound stimulation of the autonomic nervous system. By using small electrodes (8 mm in diameter as contrasted to conventional electrodes of 5 cm^2) it was found that no convulsion resulted when the stimulus was applied through regions some distance from the motor strip, although the current used was sufficient to produce convulsions when applied to the motor strip itself. The conventional shock machine was used in the experiment. Fairly accurate control of current was possible by measuring the resistance of the subject.

Some degree of localization of the stimulation was possible. Observations made following stimulation of several chosen sites indicated that stimuli over the various regions produced different results. Correlating these observations with clinical results and information concerning other organic treatments used in mental disorders, has made possible some speculation concerning the factors which make electroshock treatment effective. It has also offered directions for further investigations into the mechanism of the psychoses.

Sites for stimulation through the frontal area were chosen in accordance to external skull landmarks. Site A was high on Area 4 (Brodmann) just posterior to the interauricular line. Site B was roughly through Brodmann's Area 11. Site C was roughly through Brodmann's Areas 9 and 10. Site D was a point midway between the orbit and auditory canal and 1 cm above the upper border of the zygomatic process. (Brodmann Area 38).

Observations of results following stimulation of the selected sites will be presented according to:

(A) Motor phenomena
(B) Autonomic nervous system phenomena
(C) Disturbance of intellectual function
(D) Clinical results

(A) Motor phenomena. Stimulation of Site A or Area 4 of Brodmann resulted in a typical tonic and clonic convulsion lasting 40 seconds to one minute. Stimulation of the other sites produced with considerable regularity a single extension "jerk" of all extremities.

(B) Autonomic nervous system phenom-

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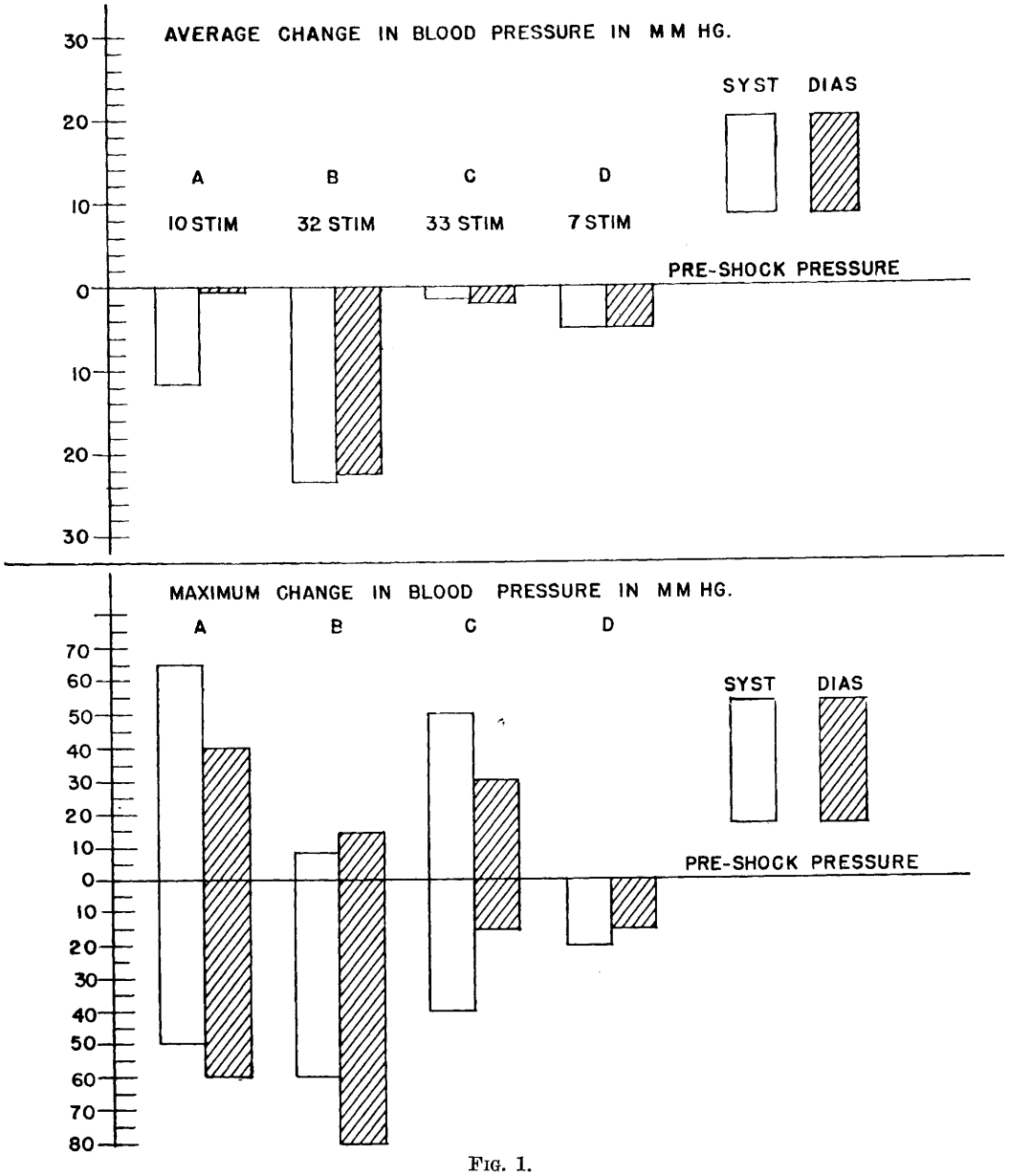

FIG. 1.
A. Average change in blood pressure. B. Maximum change in blood pressure.

ena. 1. Blood pressure (Fig. 1A and 1B).

Site A—Ten stimulations with convulsion. There was a rise of systolic and diastolic pressure in 2 cases and a fall in 8. Average systolic change was —11.5 mm; extremes +65 mm and —50 mm. Average diastolic change —0.5 mm; extremes +40 mm and —60 mm.

The time at which blood pressure was recorded in relation to the first deep respiration probably accounts for the inconsistent finding of 2 rises and 8 falls in pressure. With the cessation of respiration accompanying the tonic and clonic movements, there is a rise of pressure. With the first deep breath following the convulsion there is a rapid fall.

Site B—32 stimulations; blood pressure increased in 2, dropped in 30; average systolic change —23.6 mm; extremes —60

mm and +8 mm. Average diastolic change —22.3 mm; extremes —80 mm and +14 mm.

Site C—33 stimulations; average systolic change —1.4 mm; extremes +50 mm and —40 mm. Average diastolic change —2.0 mm; extremes +30 mm and —15 mm.

Six patients were stimulated in both Site B and Site C. In 3 of these cases Site B stimulation produced a fall, whereas C caused a rise. In the other 3 patients a drop was recorded after stimulation over both Site B and Site C. The fall after stimulation of Site B was, however, considerably greater.

Site D—7 stimulations. On 5 occasions there was no change. Twice the pressure dropped. Average change —5 mm in both systolic and diastolic pressure; extremes —20 mm systolic and —15 mm diastolic.

Summary. Stimulation at Site B produced a marked depressor effect after 30 of 32 stimuli. The effect of stimulation at Site C was not so consistent, the pressor response being noted with about the same frequency as the depressor. Over Site D there was no change in pressure following 70% of the stimulations. The effect of motor response on blood pressure changes is not important here as it was the same with excitation of each of the 3 sites.

2. Pulse rate. Recordings of pulse following stimulation of Site A are of no value because of the accompanying convulsion. After stimulation of Site B in 10 patients the rate was slowed in 7 and increased in 3. In contrast, after stimulation at Site C the rate speeded in 7 and slowed in 3. The rate was consistently slowed in 5 cases stimulated over Site D.

3. Pupillary response. Observations were made on 5 patients after stimulation at Site A and, on every occasion, the pupils were observed to dilate. Following stimulation at Site B, contraction was noted in 26 cases and dilation in but 3. Stimulation at Site C produced contraction in 22 cases and dilation in 23. Of 20 cases stimulated over Site D, 15 showed contraction and 5 dilation.

4. Peripheral vasomotor reaction. During the convulsion following Site A stimulation, the vasomotor reactions were not consistent. Usually, however, there was pallor immediately after stimulation, followed in a few seconds by a generalized flush. Toward the end of the convulsion cyanosis set in; but was followed again by flush with the initial deep respiration. One hundred ten stimulations over Site B were followed in every case by marked flushing of the skin. Almost invariably lacrimation was also noted. In 50 observations after stimulation at Site C, the flush was noted in two-thirds, but in the other one-third (15 cases) there was pallor of the skin. In 5 of the 15 cases which showed pallor, there was also profuse sweating. Site D stimulation produced very little change in peripheral vasomotor status.

5. Respiration. Slowing of respiratory rate, and often a period of prolonged apnea with mild cyanosis, was noted consistently following Site D stimulation. As Area 6B (Brodmann) was approached, this became more pronounced. Bucy[1] stimulated this area during a craniotomy on a patient and found that respiration temporarily ceased. His paper also refers to other work on cortical respiratory centers. Our findings support his conclusion that this area is a respiratory inhibitory center. It must, however, be considered that the apnea may have resulted from spread to medullary centers.

The only conclusion that can be drawn from these observations of autonomic phenomena occurring with focal stimulation of the brain through the skull is that there is a cortical autonomic level which when stimulated does exert a strong effect. The finding of different responses to stimulation of the various sites suggest localized areas of autonomic representation. However, by such diffuse stimulation one cannot hope to accurately localize autonomic function.

(C) Disturbance of intellectual function. Immediate effects: Following conventional electroshock treatment the patient remains dazed for 15 to 20 minutes. He has a blank, far away stare in his eyes and does not respond to the usual stimuli. He is often restless, and thrashes about aimlessly in bed. At times there is rather violent

[1] Bucy, P. C., and Chase, T. J., *J. Nervous and Mental Diseases*, 1936, **84**, 156.

motor activity. This marked confusion usually clears in 30 minutes to a few hours.

A review of the literature indicates that about 80% of cases develop a more lasting memory impairment which remains a few weeks to several months. Several authors[2,3] have suggested that some intellectual impairment may be irreversible. A few cases[3] are cited in which disturbances of memory remain 2 to 3 years following treatment.

Following stimulation over Site A (motor strip with convulsion) the recovery was more rapid. Patients could answer simple questions in less than 5 minutes. They did not develop the same dazed, far away look nor the marked hyperkinesia.

After stimulation of Sites B and C patients complained of anxiety and discomfort and were reluctant to continue treatment. There was no evident intellectual impairment.

Stimulation at Site D produced amnesia for several minutes. The patients appeared dazed and confused like those who had received conventional shock. The effect was, however, of shorter duration.

(D) Clinical results. Site A—(motor strip)—Results from stimulation of this area were essentially the same as with conventional therapy (*i.e.*, it was very effective in the treatment of affective psychoses—involutionals and manic depressive - depressed): with equivocal results in manic depressive—manic and schizophrenia. This method of administering convulsion did, we believe, possess an added advantage. Inasmuch as there was little memory loss and confusion, it was possible to administer psychotherapy in conjunction with electroshock therapy.

A case history will be briefly outlined to illustrate this: A 27-year-old, white female with a history of a mild depression 2 years previously, from which she spontaneously recovered in the course of 6 months, witnessed the bombing of Pearl Harbor during which her fiance was killed. After repatriation to the U. S. she spent 2 months nursing her fiance's mother through a nervous breakdown. She then took a job as stenographer at the San Diego Naval Base so as to be close to his friends. In an effort to forget she began to drink heavily and her morals became lax. (She had been raised strictly in the Catholic faith and attended Catholic boarding schools). Eventually pregnancy resulted and, taking the advice of a friend, she had an abortion performed. It was while convalescing from this that her psychosis developed, taking the form of schizo-depression with auditory hallucinations, delusions of persecution, self-abasement and attempted suicide. She entered the Pennsylvania Hospital a few days later and after the preliminary workup, electroshock treatments were begun. After 3 or 4 treatments she was so confused as to be unable to give her own name. Although all symptoms of psychosis disappeared several additional treatments were given. Approximately 7 to 10 days after the last treatment the confusion began to subside but, as her memory returned and before it was possible to begin psychotherapy, the symptoms of the psychosis returned. This procedure was repeated twice more, *i.e.*, treatment with improvement while confused, followed by relapse as memory returned. After the third relapse, shock treatment was instituted with small electrodes over the motor strip. No confusion or memory loss resulted and it was possible to administer psychotherapy shortly after the conclusion of the convulsion. The patient talked out her problems and remained well.

Site B stimulation was considerably less effective than was stimulation which produced a generalized convulsion as with Site A. Some patients, however, were benefited clinically and one made a complete recovery, but not until 20 to 25 treatments or many more than the customary number were given.

Site C—Results of stimulation of this area were essentially the same as those obtained from stimulation of Site B.

Site D—Stimulation of this area alone produced no clinical improvement. Analysis of data thus far accumulated suggests that:

1. Amnesia is not necessary to produce clinical improvement.

2. Respiratory complications can be les-

[2] Levy, N. A., Serota, H. M., and Grinker, R. R., *Arch. Neurol. and Psych.*, 1942, **47**, 1009.

[3] Brody, M. B., *J. Men. Sci.*, 1944, **90**, 777.

sened by avoiding Area 6B (Brodmann), the cortical respiratory inhibitory center.

3. Some benefits are derived from stimulation through the frontal lobes without convulsion, although results are considerably below those achieved with convulsion.

4. Stimulation through Site D (temporal cortex, basal ganglia and hypothalamus) which produced memory loss but little effect on the autonomic nervous system (except pupillary responses) resulted in no clinical improvement.

Frontal lobe stimulation (at Sites B and C) produced some clinical improvement. It was, however, considerably less effective than motor strip (Site A) stimulation. The autonomic nervous system was affected in stimulation of all these sites. The autonomic cortex is reported to extend from the central sulcus anteriorly to the frontal pole.[4,5] There is a marked difference in the duration of the effects of the stimulus in these 2 regions. When Sites B and C were stimulated the effect was for the duration of the stimulus only (0.3 to 0.6 second). When Site A was stimulated producing a convulsion there was a spread of the excitation over the entire motor strip and it continued throughout the convulsion (45 sec. to 1 min.)

It seemed possible, therefore, that profound excitation of the autonomic nervous system might be the reason for clinical improvement. If this were the case, it might be possible to obtain autonomic stimulation and, therefore, clinical improvement without convulsion by repeated stimulation through the frontal lobe anterior to the motor strip.

In an effort to further investigate this assumption repeated stimuli were given through the frontal lobes anterior to the motor strip. In this way more prolonged autonomic stimulation could be obtained, still without convulsion, and if the forementioned speculations were correct, that clinical results were obtained from excitation of the autonomic nervous system, our percentage of cures should have increased.

Six stimuli about 10 seconds apart were administered throughout the frontal area. The first patient resented this treatment and refused to permit it because of the intense anxiety produced by each shock (as mentioned above in discussion of results of Site B and C stimulations). To overcome this complication we first stimulated Site D. Amnesia resulted and, thereafter, the patient had no recollection of the treatment and submitted uncomplainingly (much as in conventional therapy) to further stimulation at other sites.

Before results are discussed it should be pointed out that even with 6 shocks of 0.5 second each, the duration of autonomic excitation is considerably less than that seen in the generalized convulsion (45 sec. to 1 min.)

Table I gives a comparison of the clinical results obtained with stimulation of the various sites. The one manic depressive-depressed case treated unsuccessfully with multiple stimuli was subsequently given a full course of conventional shock treatment with no improvement. He was transferred to a state institution.

Case history to illustrate this procedure. A 69-year-old, white female. Prepsychotic personality; meticulous, rigid. Married but not happy; 2 children. Because of financial difficulties after husband's death, lived with sister for 5 years before onset of illness. Did not get along with sister.

Present illness. Ostensibly precipitated by a flood which damaged her home in January 1943; became extremely agitated and depressed; threatened suicide; self-accusatory; believed herself destitute and penniless; entered Pennsylvania Hospital March 1943.

Physical examination. 1. Old fracture of right hip with shortening of right leg.

2. Hypertrophic arthritis.

X-ray of spine: Degenerative changes and narrowing of discs.

X-ray of hip: Old osteochondritis with obliteration of the joint space.

Orthodox shock therapy was advised against by the roentgenologist. The family could ill afford prolonged hospitalization in

[4] Kennard, M. A., *Illinois Monographs in the Medical Sciences*, 1944, **4**, 295.

[5] Fulton, J. F., *Physiology of the Nervous System*, second edition, New York, Oxford University Press.

TABLE I.
Summary of Clinical Results in Electro-shock Treatment with Small Electrodes.

	Manic Depressive-Depressed					Involutional Melancholia				
Site	A	B	C	D	Multiple stimuli	A	B	C	D	Multiple stimuli
Well	8	1	0	0	0	5	1	1	0	2
	63%	12.5%				83%	16%	16%		50%
Improved	2	4	3	0	0	1	2	2	0	1
	27%	50 %	50%			17%	34%	34%		25%
No change	1	3	3	2	1	0	3	3	2	1
	10%	37.5%	50%	100%	100%		50%	50%	100%	25%
Total No. of cases treated	11	8	6	2	1	6	6	6	2	4

a private institution and felt any therapy was preferable to state hospitalization.

Treatment was begun in May, 1943. She received 7 stimuli on each of 34 consecutive days, exclusive of Sunday, the first being directed through Site D so as to produce amnesia for the treatment. At the end of these periods all symptoms of her illness subsided and shortly she was discharged to her daughter. Regular follow-up letters indicate she continues to remain well.

Analysis of results of multiple stimuli. Although our cases are too few in number to permit definite conclusions the evidence is sufficient to make the following statements:

1. With multiple stimuli to that part of the frontal cortex that has autonomic representation the results appear to be better than with single stimulation.

2. The increased percentage of cures tends to support our hypothesis that stimulation of the autonomic nervous system may play a large role in the clinical results in electroshock therapy.

Other evidence to indicate the role of the autonomic nervous system in mental disorders.

1. The suggestion emphasized by these procedures, that the autonomic nervous system plays a major role in the affective mental disorders, is supported by frequent reports of findings of altered autonomic function in these psychoses. For example, in the involutional case there is insomnia, agitation, often elevated blood pressure, inability to eat, etc. Altered autonomic functions in depressed cases are also well known.

2. Clinical results reported with electronarcosis are at least as favorable as those reported with electroshock in the treatment of the affective disorders and are considerably better in the treatment of schizophrenia. In electronarcosis a smaller current than that used in electroshock is administered over a prolonged period. (60-cycle a.c. machine—initial current of 150 to 250 milliamperes for 30 seconds then decrease to level which permits respiration *i.e.*, 45 to 90 m.a. for up to 20 minutes). Frostig *et al.*[6] describe autonomic effects, motor phenomena and loss of consciousness with this procedure. The motor effects are perhaps less pronounced than with electroshock. There is an initial extensor spasm, then a few tonic and clonic movements, after which all variation between narcosis and marked hyperkinesia are seen for the duration of the treatment. The autonomic effects are quite variable. They are much more prolonged than with electroshock (dependent upon duration of treatment). The electrodes used in this treatment are 5 cm x 5 cm and the placement is over the temporal region. An extensive area of the brain is, therefore, stimulated much as in conventional electroshock.

3. Lobotomy, another effective form of treatment of the psychoses is directed toward affecting the autonomic nervous system. By this procedure pathways are cut which link the prefrontal cortex with the thalamus and lower centers, thereby isolating the autonomic cortex. Watts and Freeman[7] in describing

[6] Frostig, J. P., Van Harreveld, A., Reznick, S., Tyler, D. B., and Wiersma, C. A. G., *Arch. Neurol. and Psych.*, 1944, **51**, 232.

[7] Freeman, W., and Watts, J. W., *Tr. N. Y. Acad. Sci.*, 1944, **6**, 284.

the operation state that immediately there is a disappearance of nervous tension. Although memory is intact and conflicts still exist, they cause little concern. They report their patients are able to formulate ideas but lack the accompanying emotional drive that is necessary to put them into effect. As a result their productivity is usually markedly impaired.

Summary. By using small electrodes in electroshock treatment it was possible to localize the stimulation sufficiently to separate some of the many phenomena that occur with conventional electroshock therapy. The small amount of data thus far accumulated seems to indicate: (1) Memory loss and convulsion are probably not necessary to produce clinical improvement. (2) Stimulation of cortical autonomic centers seems to be the most important factor in producing clinical improvement in the affective disorders with electroshock.

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Diabetes Mellitus in Rabbits Injected with Dialuric Acid.*

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(Introduced by Elliott P. Joslin.)

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Since the discovery that alloxan produces diabetes when injected into animals[1-3] other chemically related substances have been studied for possible diabetogenic action. Until recently no chemical with such action has been found.

Koref, Vargos, Rodriguez and Telchi[4] reported the production of diabetes with alloxantin and confirmation of this work has already been published from this laboratory.[5] Recently, Bruckman and Wertheimer[6] have found that besides alloxantin methylalloxan, dialuric acid, methyl dialuric acid and dimethyl alloxantin produce diabetes when injected into rats. The present investigation reports the production of diabetes in the rabbit with dialuric acid and compares the diabetes so produced, clinically and histologically, with the diabetes produced with alloxan.

Experimental. Eight chinchilla male rabbits each weighing 1500-2000 g were injected intravenously with dialuric acid in doses of 150, 200 or 250 mg per kg. The rabbits were not fasted at any time during the experimental period and in all but one instance the injection was made with the animal under nembutal anesthesia. Anesthesia seemed advisable since the dialuric acid was injected as a hot solution, owing to its insolubility at lower temperatures.

The solution of dialuric acid was prepared as a 1.5% solution in nearly boiling distilled water. The solution was cooled to a temperature of 40°-50° C and injected immediately. It was found necessary to keep the solution at this temperature to avoid recrystallization of the dialuric acid which tended to occur at room temperature.

Blood samples were taken from the ear veins before and at frequent intervals following the injection of the dialuric acid.

* This investigation has been aided by a grant from the American Cyanamid Company, who also supplied the dialuric acid.

1 Bailey, C. C., and Bailey, O. T., *J. A. M. A.*, 1943, **122**, 1165.

2 Goldner, M. G., and Gomori, G., *Endocrinology*, 1943, **33**, 297.

3 Dunn, J. S., and McLetchie, N. G. B., *Lancet*, 1943, **2**, 384.

4 Koref, O., Vargos, L., Rodriquez, F. H., and Telchi, A., *Endocrinology*, 1944, **35**, 391.

5 Bailey, C. C., Bailey, O. T., and Leech, R. S., *Bull. New Eng. Med. Center*, 1945, **7**, 59.

6 Bruckmann, G., and Wertheimer, E., *Nature*, 1945, **155**, 267.