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Effect of N,N-Dibenzyl-β-Chloroethylamine Hydrochloride (Dibenamine) on Autonomic Functions and Catatonia in Schizophrenic Subjects.*

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The schizophrenic reaction, catatonic type,[1] (dementia praecox, catatonic[2]) is characterized by conspicuous abnormalities of motor behavior. Patients with this disorder frequently also show signs of imbalance of the autonomic nervous system. Pupillary changes, vasomotor disturbances, increased salivation, scanty or increased urine, constipation, and cardiovascular irregularities may occur.[3] Gellhorn concluded that studies of autonomic functions in schizophrenic patients demonstrate "not only a decreased reactivity of the sympathico-adrenal system, but also a relative preponderance of the vago-insulin system."[4] Nevertheless, mydriasis, delayed gastric and colonic emptying,[5] cold extremities, and hyperhidrosis indicate elements of increased sympathetic activity.

The object of this investigation was to study the effect of chemical blockade of sympathetic function in patients with schizophrenic reactions, catatonic type. The drug used was Dibenamine (N,N-dibenzyl-β-chloroethylamine hydrochloride),† a synthetic tertiary amine having the specific, powerful and prolonged action of blocking excitatory adrenergic activity.[6]

In October 1947, as a preliminary procedure, Dibenamine was given to 2 catatonic patients at the New Jersey State Hospital at Greystone Park. Definite changes in autonomic functions and transient improvement in the catatonia were observed. Controlled studies were therefore arranged. The present report concerns our investigation of a group of catatonic subjects in whom certain autonomic functions were evaluated and neurologic and psychiatric examinations were made before and after administration of saline, sodium amytal and Dibenamine infusions.

Methods and Materials. Nine subjects, diagnosed as having schizophrenic reactions, catatonic type, were selected from the general wards at the Veterans Administration Hospital, Lyons, N. J. Patients with marked impairment of spontaneous activity and poor responsiveness to stimulation were sought. The cases with the severest stigmata of catatonia were chosen. The ages of the subjects ranged from 22 to 38 years, and their psychoses had been present from 3 to 7 years. Subject 4 was the only one who showed any recent tendency to have spontaneous remissions. Most of the patients had received electric and/or insulin shock therapy, with which varying degrees of transient benefit had been noted. No shock treatment was given to any of the group for at least 10 weeks prior to the be-

* Published with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or the conclusions drawn by the authors.

1 Nomenclature of Psychiatric Disorders and Reactions, Vet. Adm. T.B. 10A-78, Oct. 1, 1947.

2 Hinsie, L. E., and Shatzky, J., Psychiatric Dictionary; London, New York, Toronto, Oxford University Press, 1940.

3 White, W. A., Outlines of Psychiatry, Washington, Nervous and Dental Disease Publishing Co., 1935.

4 Gellhorn, E., Autonomic Regulations, New York, Interscience Publishers, Inc., 1943.

5 Henry, G. W., *Am. J. Psychiat.*, 1928, **7**, 135.

† Dibenamine supplied through the courtesy of Dr. W. Gump, Givaudan-Delawanna, Inc., Delawanna, N. J.

6 Nickerson, M., and Goodman, L. S., *J. Pharm. and Exp. Therap.*, 1947, **89**, 167.

ginning of this project, and no treatment other than the drugs being tested was given until after this work was completed. All subjects had received the routine hospital studies at the time of admission. Recent additional tests, including chest x-ray, E.C.G., C.B.C. and urinalysis, were within normal limits.

Evaluation of the subjects at the time of administration of the drugs included determinations of blood pressure, pulse rate, skin temperature, sweat secretion, electrical skin resistance, and neurologic and psychiatric status.

Arterial blood pressure was measured in one arm by the standard auscultatory method. Radial pulse rate was counted for 15 seconds.

Skin temperature was measured using a Hardy Dermal Radiometer. Readings were taken from the forehead and from the palm and dorsum of the hand contralateral to the arm in which the infusion was given. Room temperature was also recorded.

Permanent records of palmar sweat secretion were made according to the technic described by Silverman and Powell.[7] Diluted tincture of ferric chloride was painted on the dried, free palm and allowed to evaporate. A print was obtained by holding the palm for 3 min. against a sheet of paper impregnated with tannic acid. Thus the secretory activity of each sweat gland was recorded by a dot of ferric tannate. The number, size and distribution of these dots could be noted readily, and the amount of sweating could be rated according to previously described standards.[8] A faint response (0) included prints varying from almost entirely blank to those showing a light grey shade with fine pinpoint dots. A moderate response (1+) showed thicker dots, darker in shade, arranged in a linear pattern. A strong response (2+) showed black speckles of varying sizes. An intense response (3+) showed blackening with blotches.

Electrical skin resistance was measured using a dermohmeter of the Jasper type.[9] The electrodes were pure silver discs, 1 cm in diameter. No electrolyte paste or jelly was used at either electrode. The resistance was measured between pads of the hallux and the index-finger of the same hand, giving a single reading per patient per examination. This thumb to finger resistance was quickly and simply obtained, and remained constant at an examination. It represents approximately double the value which is obtained if electrolyte paste or jelly is used to reduce the resistance at one electrode.

All neurologic examinations and evaluations of the signs of catatonia were made by the same observer and in a uniform manner. Twelve categories in which abnormalities are frequently found in catatonics had been previously selected. These categories were: posturing, facial immobility, facial grimacing, spontaneous activity, spontaneous speech, activity in response to request, speech in response to questions, strength of manual grip, passive resistance, waxy flexibility, response to pin-prick, and response to supraorbital pressure. In order that comparisons could be made, each subject was rated from 0 to 4+ in each of the 12 categories, according to the amount of deviation from the normal. The results of previous tests were not consulted at the time of subsequent examinations. Consistency of the evaluations was readily demonstrated.

Psychiatric examination consisted of observations and interviews lasting about 30 minutes per patient. All were done by the same examiner, who was already acquainted with the subjects and their histories. Detailed notes were kept.

The drugs employed were sterile sodium amytal, supplied in 0.5 g ampules, and sterile Dibenamine, supplied in ampules containing 500 mg of the drug in 10 cc acidified alcohol-propylene glycol. All drugs were administered intravenously in sterile, isotonic saline solution, supplied in 500 cc flasks, as described below.

Procedure. The investigation was carried out in an ordinary 12-bed hospital ward as-

[7] Silverman, J. J., and Powell, V. E., *Am. J. M. Sc.*, 1944, **208**, 297.

[8] Silverman, J. J., and Powell, V. E., *Psychosomatic Med.*, 1944, **6**, 244.

[9] Jasper, H., *J. Neurosurg.*, 1945, **2**, 257.

signed for the purpose. The subjects were kept lightly restrained in bed with their hands exposed for 2 hours preceding the testing, which was begun at about 9:00 a.m. Breakfast and lunch were withheld. After pre-injection observation (blood pressure, pulse rate, skin temperature, palmar sweat secretion, electrical skin resistance, neurologic and psychiatric status), intravenous infusions were started in all subjects, with 400 cc saline in the flasks. When the infusions were running well, 0.5 g of sodium amytal was added to the saline in each of 3 flasks, and mixed well. Similarly, Dibenamine in dosage of 5 mg per kg of body weight of the subject was added to the saline in each of 3 other flasks, and mixed well. The remaining 3 subjects received only saline. The infusion rate was adjusted to approximately 100 drops per minute, so that 1 to 1½ hours were taken for administration of the entire volume. In 4 subjects, whose reactions were inadequate after 350 cc of the dilute sodium amytal solution had been given, additional sodium amytal (up to 0.5 g) was slowly injected directly into the infusion tubing. At the end of each Dibenamine infusion, the tubing and vein were flushed by the addition of about 75 cc of saline to the flask. Immediately following the infusions the pre-injection tests and examinations were repeated. The subjects were kept in bed, but beginning that evening regular meals were served. After breakfast the next morning the tests and examinations were given for the third time, and those subjects who had received saline or amytal were allowed up ad lib. Those who had received Dibenamine were kept in bed until the orthostatic hypotension and tachycardia were gone (24 to 72 hours).

The first series of infusions was given March 9, 1948. Two weeks later the entire procedure was repeated, but the subjects were rotated with respect to the drug received. Two weeks after the second series of infusions, the third series was given, with the subjects again rotated. Thus, each patient received 3 infusions—one saline, one saline and sodium amytal, and one saline and Dibenamine (5 mg/kg body weight). (The only exception to this protocol was Subject 6, who was not given his third infusion, saline, because his severe feeding problem made it necessary to institute electric shock therapy.) The fourth and final series of infusions was given 2 weeks after the third. Three subjects who had previously responded comparatively poorly to Dibenamine were selected. This time they received Dibenamine in dosage of 7.5 mg per kg body weight (maximum dose was 500 mg), with the remainder of the procedure for them carried out as on the previous occasions.

Results. (A) *Blood Pressure* (*B.P.*): Pre-injection resting B.P. ranged from 124/80 to 96/68, with a mean of 115 ± 1.4/76 ± 1.2.‡ Neither saline nor sodium amytal resulted in significant B.P. changes, the post-injections means having been 109 ± 2.9/72 ± 1.5 and 110 ± 3.6/71 ± 3.1 respectively. The mean B.P. following the 12 Dibenamine infusions was 121 ± 3.3/67 ± 1.8. Although 4 of the Dibenamine infusions were followed by rises in systolic pressure averaging 15 mm each, the increase in the mean is not statistically significant. The mean change in the diastolic pressure was a significant decrease of 8.5 ± 1.0, representing the effect of blockade of sympathetic vasoconstrictor tone. Eighteen hours after Dibenamine administration the mean B.P. was 121 ± 2.7/68 ± 2.2, and cardiovascular effects of the drug were still in evidence. No testing for orthostatic hypotension was done immediately after the Dibenamine infusions. However, the following morning this phenomenon was noted in 3 of the 9 subjects who had received 5 mg/kg and in all 3 who had received 7.5 mg/kg. Orthostatic hypotension had disappeared from all subjects by the third post-injection day.

(B) *Pulse Rate* (*P.R.*): Pre-injection resting P.R. ranged from 60 to 96, with a mean of 73 ± 2.9/min. The saline and the sodium amytal infusions produced no significant alterations in the P.R. Following the 12 Dibenamine infusions the mean resting P.R. was 110 ± 6.1, a mean increase of 37 ± 6.8 over the pre-injection levels. This

‡ All means are given ± the standard error of the mean.

TABLE I.
Effect of Dibenamine on Blood Pressure and Pulse Rate in Catatonic and in Normotensive, Non-Psychotic Subjects.

	Catatonics	Non-psychotic normotensives[10]
Resting B.P.	115 ± 1.4	124 ± 2.2
	76 ± 1.2	73 ± 1.7
B.P. after Dibenamine	121 ± 3.3	122 ± 3.0
	67 ± 1.8	69 ± 1.9
Change in B.P.	+6 ± 3.1	—2 ± 2.6
	—8.5 ± 1.0	—4 ± 1.5
Resting P.R.	73 ± 2.9	78 ± 2.0
P.R. after Dibenamine	110 ± 6.1	84 ± 2.8
Change in P.R.	+37 ± 8.8	+6 ± 1.6

tachycardia lasted 18 to 36 hours. The morning after the infusions the mean P.R. was 96 ± 6.8, with 2 of the 9 subjects who had received 5 mg/kg and 2 of the 3 who had received 7.5 mg/kg still having resting rates over 100. All subjects had orthostatic tachycardia when tested 18 hours after the Dibenamine infusions. This lasted 24 to 72 hours.

It is of interest to compare the B.P. and P.R. effects of Dibenamine in this group of catatonic subjects with previously reported results in non-psychotic, normotensive general hospital patients.[10] (Table I.) The methods and circumstances of both studies were similar. The initial systolic pressure is significantly lower in the catatonics (difference in means = 9 ± 2.6), although there is no significant difference in diastolic pressures. B.P. studies in a larger series showed significantly lower systolic and diastolic pressures in schizophrenic patients compared with students.[11] Following Dibenamine the mean B.P. of the catatonic group is almost identical with that of the non-psychotics. However, although the initial P.R.s in the two groups did not differ significantly, the catatonics showed a very much faster P.R. following Dibenamine.

The response to Dibenamine of catatonic subjects differed from that of non-psychotic normotensives by showing a slight increase in systolic pressure and a large increase in P.R. These differences are suggestive of 2 effects of injected epinephrine which are not blocked by Dibenamine, namely the rise in cardiac output[12] and the tachycardia.[6,12,13] The presence or production of increased epinephrine in the catatonics might explain the observed differences. Further speculation will be deferred until additional studies are completed.

(C) *Skin Temperature.* Forehead, palm, hand dorsum and room temperatures were recorded. Room temperature varied between 20.0° and 22.4°. Although even this small amount of variation was undesirable, it did not appear to affect the skin temperature results significantly. Furthermore, since all three drugs were being administered to the groups of subjects at the same time, comparison of the mean changes of the groups is valid.

The mean pre-injection forehead temperature was 34.1 ± .2°, dorsum temperature was 27.4 ± .5°, and palm temperature was 27.4 ± .6°. No drug produced significant changes in forehead temperatures. Following saline infusions the hands were slightly cooler in all subjects. The mean change was −1.7 ± .5° for the dorsum and −2.5 ± .8° for the palm. This cooling probably represents the effect of the additional 1 to 1½ hours of exposure with relative immobility. After sodium amytal the mean dorsum temperature change was +3.2 ± 1.5° and the mean palm change was +3.0 ± 1.4°. These mean temperatures (increases) differ from those following saline (decreases) by 4.9 ± 1.6° and 5.5 ± 1.6°, both significant differences. This warming of the hands after sodium amytal was noted in 5 of the 6 subjects who were

[10] Haimovici, H., and Medinets, H. E., PROC. SOC. EXP. BIOL. AND MED., 1948, **67**, 163.

[11] Freeman, H., Hoskins, R. G., and Sleeper, F. H., *Arch. Neurol. and Psychiat.*, 1932, **27**, 333.

[12] Heeht, H. H., and Anderson, R. B., *Am. J. Med.*, 1947, **3**, 3.

[13] (a) Acheson, G. H., Farah, A., and French, G. N., *Fed. Proc.*, 1947, **6**, 305. (b) Youmans, W. B., and Rankin, V. M., PROC. SOC. EXP. BIOL. AND MED., 1947, **66**, 241.

neurologicly improved by the drug, and in 1 of the 3 who were not. Following Dibenamine the mean change in dorsum temperature was + 2.9 ± 1.3° and the mean change in palm temperature was + 3.6 ± 1.2°. These differ from the mean changes after saline by 4.6 ± 1.4° and 6.1 ± 1.4°, both significant differences. The increases in hand temperature after Dibenamine ranged up to 10.3°, and the greater changes were noted in the subjects who were more improved neurologicly by the drug. Eighteen hours after Dibenamine infusions the increase in hand temperature was still present, the mean changes for the dorsum and palm being +4.6 ± .7° and + 5.4 ± .8° respectively. Eighteen hours after the saline and the sodium amytal infusions the hand temperatures were not significantly different from pre-injection values.

(*D*) *Sweat Function*: Twenty-seven pre-injection palmar sweat prints were taken from 8 subjects. (No prints were obtained from Subject 6 because his pre-injection posturing included tightly clenched fists.) A faint response was found in 15 (55%) pre-injection prints, a moderate response in 6 (22%), a strong response in 2 (8%), and an intense response in 4 (15%). Individual variation between the days of examination was noted. However, 4 subjects usually produced almost entirely blank prints, whereas 2 others had hyperhidrosis consistently and 1 other had hyperhidrosis occasionally. Neither saline nor sodium amytal infusions produced significant changes in the sweating responses, but immediately following the Dibenamine infusions there were no longer any strong (2+) or intense (3+) responses. Of the 11 prints obtained after Dibenamine, 10 were faint (0) responses and 1 was a moderate (1+) response. This inhibition of excessive palmar sweating gradually disappeared. Eighteen hours after injection, Subject 3 again had an intense (3+) response and Subject 9 had a moderate (1+) response.

Palmar sweat prints obtained by the same technic and rated according to the same standards as the prints in this project were reported to have shown faint or moderate responses in 78% of a group of hospital personnel and strong or intense responses in 84% of the neuropsychiatric (mostly psychoneurotic) patients.

(*E*) *Electrical Skin Resistance* (*E.S.R.*): The mean pre-injection E.S.R. for all infusions in the 9 subjects was 192 ± 18 K.§ Three subjects, the same ones who had excessive sweating, showed E.S.R. values clearly abnormally low for the testing conditions. The mean pre-injection E.S.R. for these 3 was 105 ± 21 K, whereas for the 6 other subjects the mean was 238 ± 17 K. Five subjects showed pre-injection E.S.R. values which were constant for the several series of tests, but in the other 4 there were large spontaneous day to day variations. Neither saline nor sodium amytal infusions were followed by significant changes in the E.S.R. Immediately after the Dibenamine, the mean E.S.R. was 258 ± 25 K, an increase of 66 ± 30 K from the pre-injection mean; 18 hours post-injection the mean was 290 ± 17 K, an increase of 98 ± 24 K. The increases in E.S.R. after Dibenamine were noted to occur almost exclusively in those subjects whose initial resistances were low. Thus for 8 infusions in 6 subjects whose pre-injection values were under 200 K, the mean change immediately following Dibenamine was + 151 ± 40 K and 18 hours later it was + 195 ± 40 K.

The palmar sweat responses and the E.S.R. measurements made in this study and summarized above show a very high correlation. (Spearman method of rank: r = .48, t = 4.4, and p = less than .001.)

The initial observations were made with the subjects at basal conditions. The very low sweat responses with high E.S.Rs. found in 4 subjects in contrast with the hyperhidrosis and very low E.S.Rs. found in 3 others demonstrate the extremes of these functions which catatonic patients may show. Wide variation in the E.S.Rs. of catatonics may be found in the data of other reports,[14] although the average palm-to-palm E.S.R. of a group of

§ K. = 1000 ohms.

[14] (a) Richter, C. P., *Arch. Neurol. and Psychiat.*, 1928, **19**, 488. (b) Richter, C. P., *Arch. Neurol. and Psychiat.*, 1929, **21**, 363.

patients in catatonic stupor was found to be about the same as those of normals and of other groups of psychotic subjects.[15] A relation between a large amount of "free energy (or anxiety)" and low E.S.R., and between a small amount of free energy and high E.S.R. has been suggested.[16]

One may speculate regarding the mechanism by which Dibenamine inhibited excessive sweating and raised low E.S.Rs. in the subjects who showed these pre-injection abnormalities. The regions tested (palms and finger pads) have sweating responses which are of the emotional type, specific for conditions of mental stress.[17] Dibenamine therefore may have produced the observed changes indirectly, as a result of a central action in eliminating an "anxiety" factor. Against this explanation is the failure of sodium amytal to have produced a comparable autonomic effect. The second possibility is that Dibenamine acted on sympathetic ganglia or directly on the sweat glands. These would imply either that Dibenamine inhibited a cholinergic function,[18] or that the excessive sweating and low E.S.Rs. were exhibitions of adrenergic activity. There is no evidence to suggest that Dibenamine is anti-cholinergic. However, there is some reason to believe that certain sweating may have an adrenergic component.[19] It is also possible that Dibenamine decreased the sweating and increased the low E.S.Rs. by an action upon the hypothalamic sympathetic mechanism. Although there is no present direct evidence for this explanation, it is in accordance with other features of Dibenamine's central activity, which are described below.

(*F*) *Neurologic Signs and Signs of Catatonia.* Except for the physical signs of catatonia described below, no subject showed an abnormal neurologic status. Deep tendon reflexes ranged from hypo-active to hyper-active, with 3 tense subjects having occasional transient clonus. Pupils were equal bilaterally in all subjects, and one showed mydriasis. None of the drugs administered changed the general neurologic status significantly. However, transient clonus was not observed after sodium amytal or Dibenamine, and all subjects had miosis following Dibenamine.

As previously outlined, the signs of catatonia were observed in each subject and the amount of abnormality present in each of 12 categories was rated from 0 to 4+. It was therefore possible to record not only general impressions of improvement in the catatonia but also changes in each of the categories. In addition, the total number of points of abnormality shown by a subject at an examination may be considered his "catatonic rating" at that time, and used to rank the subject with regard to severity of the catatonic manifestations.

Pre-injection examinations revealed catatonic ratings for the individuals ranging from 13 to 40, with a mean of 26.5 $\pm$ 1.3. The following summarizes the pre-injection findings.

All subjects appeared to be content to lie lightly restrained in bed. Abnormal posturing was common, and was present to a marked degree in 3 subjects. Blankness of facial expression was the rule, although 2 subjects usually showed meaningless grimacing and 3 others grimaced occasionally. Spontaneous motor activity was rare in any of the group. No subject except No. 5 (on one occasion) evinced spontaneous speech during pre-injection testing. Subjects 4 and 5 were the only ones who would respond, even in monosyllables, when questioned prior to the injections. When requested or commanded to perform simple motor actions (lift arm, close eyes, open mouth), 4 subjects rarely or never complied, although 2 others were usually completely cooperative. No subject demonstrated more than feeble effort or strength of manual grip when requested, but considerable force was used by 3 subjects to resist certain pas-

[15] Syz, H., and Kinder, E., *Arch. Neurol. and Psychiat.*, 1928, **19**, 1026.

[16] (a) Solomon, A. P., and Fentress, T. L., *J. Nerv. and Ment. Dis.*, 1934, **80**, 163. (b) Darrow, C. W., and Solomon, A. P., *Arch. Neurol. and Psychiat.*, 1934, **32**, 273.

[17] Kuno, Y., *Lancet*, 1930, **1**, 912.

[18] (a) Feldberg, W., and Gaddum, J. H., *J. Physiol.*, 1934, **81**, 305. (b) Dale, H. H., and Feldberg, W., *J. Physiol.*, 1934, **82**, 121.

[19] Haimovici, H., PROC. SOC. EXP. BIOL. AND MED., 1948, **68**, 40.

sive movements. All but 3 subjects occasionally showed variable degrees of waxy flexibility, but none would hold an induced posture for more than several seconds. The responsiveness to pin-prick and to supra-orbital pressure was markedly diminished or absent in 4 subjects, and in 2 others it was increased to a startle reaction.

Immediately following the saline infusions no subject was significantly changed. The number of points change for each subject ranged from +3 to −3, with a mean of .3 ± .9 points improvement. Eighteen hours later the mean change was .4 ± 1.3 points improvement. Following amytal, 4 of the 9 subjects were improved 11 to 19 points each, and the mean change was 6.6 ± 2.7 points improvement. The most striking result of the amytal infusions was the production of fair to good verbal responsiveness in 4 subjects. There was also considerably less posturing and no grimacing. Spontaneous activity and spontaneous speech remained poor in all except No. 6, who developed marked resistance in addition. Most subjects were generally relaxed by the drug, and no improvement in strength occurred. Responses to noxious stimuli approached normal in 6 subjects, but were less than normal in 3. The improvement which the sodium amytal produced lasted up to 4 hours, except in Subject 6, who was still improved (7 points) the next day. Eighteen hours after sodium amytal infusions, the mean change from the pre-injection status was 1.1 ± 1.1 points improvement.

Following the 12 Dibenamine infusions, the 9 subjects showed improvements ranging from 0 to 19 points each, with the mean change being 9.2 ± 2.5 points improvement. Nine of the 12 infusions resulted in improvements of 8 points or more, and in these subjects the change in status was quite apparent. Posturing persisted in only one subject of the entire group, and grimacing in but one other. Spontaneous activity was clearly increased in 6 instances, with spontaneous speech appearing in 3 to a considerable degree. Five subjects responded well to requests for simple motor activity and 4 had good speech response. Strength of manual grip did not improve significantly. Although Subject 3 developed resistance to passive motions, all 6 subjects showing such resistance prior to drug administration were improved. Waxy flexibility decreased significantly in Subject 1. Three subjects developed more normal responses to pin-prick and to supra-orbital pressure. The improvement following Dibenamine gradually disappeared in most subjects over a period of 24 to 48 hours. Eighteen hours after the infusions, the mean change from the pre-injection status was 5.8 ± 1.7 points improvement. Speech function was the earliest to regress, disappearing a few hours after the infusion. (Subject 4 had a markedly atypical response to Dibenamine. His improvement began 5 minutes after the drug was started, and he remained improved for over three weeks. His pre-test history showed spontaneous remissions.)

Increasing the dosage of Dibenamine from 5 to 7.5 mg/kg of body weight was associated with an increase in the degree of immediate and 18 hour improvement.

Correlations were sought between initial neurologic status and initial abnormal autonomic functions, and between change in neurologic status and changes in autonomic functions. Because the series was small, statistically significant correlation is difficult. However, a significant coefficient of correlation was found between neurologic improvement and increase in hand temperature after Dibenamine. For the 12 infusions, $r = .5$ $t = 1.9$, and $p = .08$; and for 11 infusions (omitting Subject 4, whose response was atypical), $r = .74$, $t = 3.3$, and $p = .01$. Similar coefficients computed on the changes after sodium amytal are very low.

(*G*) *Psychiatric Examinations.* Without going into any details, the group of patients may be described as representative of the negative variety of schizophrenic reactions—catatonic type, moderately severe. There was no psychiatric change following saline, but sodium amytal brought about definite lessening of tensions. With the verbal mobilization that developed in 4 subjects after amytal, many schizophrenic (hebephrenic and para-

noid) symptoms previously not elicitable were observed. When the catatonia was dissolved, there was evidence of ego-centered and introspective concern, with little interest in the surroundings. At a later stage 4 subjects were moderately sleepy, and 1 was deeply so. Dibenamine, in contrast, produced definitely increased interest in surroundings, increased spontaneity, improved responsiveness to environmental stimuli, and no sleepiness. As with sodium amytal, every patient who had speech function after Dibenamine gave expression to hebephrenic or paranoid mental content.

The mechanism by which Dibenamine produced these changes in the catatonia may be considered. In non-psychotic individuals central effects have been observed after Dibenamine.[10,12] Drowsiness is common, and mental confusion with restlessness, or irritability, emotional lability, hallucinations, paramnesia or perseverations have been noted in some patients. Convulsions can be produced by rapid administration in animals[6] and were reported to have occurred in one patient.[12] Nickerson and Goodman state that the central stimulant action of Dibenamine is quite unrelated in time and mechanism to the adrenergic blocking activity, and that almost identical central effects can be produced by the hydrolysis product, N,N-dibenzylethanolamine, which has no adrenergic blocking action.[20] Investigation of this and other related compounds should be illuminating. Malononitrile, $CH_2(CN)_2$, has been reported to produce an effect on psychic functions in mental disorders and to stimulate nucleoprotein production in nerve cells.[21] Although flushing of the face resulted from malononitrile administration, there was no observed change in B.P. The cyanide radical can cause circulatory changes and has been shown to produce vasodilation, probably by paralysis of smooth muscle in vessel walls.[22] Catatonia has been observed to dissolve upon I.V. administration of 1/50 N. sodium cyanide solution.[23] While Dibenamine may have a direct effect upon nerve cell metabolism, it is not impossible that the improvement in the catatonia which followed its use also may be associated with alterations in cerebral circulation, particularly in the region of basal arterial supply. The correlation between neurologic change and change in skin temperature suggests at least parallel development of the increase in peripheral circulation and the improvement in the catatonia. The most recent study does not support the contention that the total cerebral blood flow in schizophrenics is abnormal.[24] The effect of Dibenamine on the circulation of blood in the brain of animals is being studied.

In this investigation, the responses to Dibenamine and the responses to sodium amytal were different. Only one of the 4 subjects who were greatly benefited by sodium amytal was among the 4 who were most improved by Dibenamine. Furthermore, the types of responses produced by the two drugs were characteristically dissimilar, the amytal changes being especially verbal and responsive and the Dibenamine changes being increased spontaneity and interest in surroundings. It would not appear that the mechanisms of action of these drugs are the same.

(*H*) *Toxic and Side Effects.* Few of the previously reported toxic effects of Dibenamine[10,12] were observed in these subjects. There were no instances of phlebothrombosis, although Subject 4 complained of pain along the vein throughout the infusion. Only one subject appeared to be nauseated or vomited (No. 3, who had brief retching after each of the 2 Dibenamine infusions given him. He was an intermittent soiler, and also showed loss of sphincter control following one administration of Dibenamine). Increased drowsiness was not produced. When Subject 2 exhibited masturbatory activity after Dibenamine (4th series of infusions), he and the 2 other patients who had received the

[20] Nickerson, M., and Goodman, L. S., *Fed. Proc.*, 1948, **7**, 397.

[21] Hyden, H., and Hartelius, H., *Acta Psychiat. et Neurol.*, 1948, **48**, 1.

[22] Sollmann, T., A Manual of Pharmacology, New York, W. B. Saunders, 1942.

[23] Lorenz, W. F., *Psychiat. Quart.*, 1930, **4**, 95.

[24] Kety, S. S., *et al.*, *Am. J. Psychiat.*, 1948, **104**, 765.

drug at the same time were found to have priapism. The subjects had not been examined for this in the previous tests.

Comments: There is psychiatric dissatisfaction with schizophrenia as a nosologic entity and particularly with the sub-classifications as they now stand. The stigmata characteristic of catatonia are physiologic and can be experimentally produced or abolished. When sodium amytal or Dibenamine dissolves the catatonia in patients with schizophrenic reactions, catatonic type, hebephrenia or paranoia appears. Catatonia, which is an abnormal physiologic state, is therefore actually at a different descriptive level from either hebephrenia or paranoia, which are psychopathic states. Further discussion of this matter is reserved for later publication.

There is considerable experimental and clinico-pathological evidence suggesting that the manifestations of catatonia are mediated by the hypothalamus[25] and/or the basal ganglia.[26] We will not review this material in the present paper. However, it can be pointed out that both motor and autonomic centers are located in this region of basal arterial supply, and that motor and autonomic disturbances frequently accompany clinical and experimental lesions in this area. Catatonia and epidemic encephalitis supply many examples of co-existence of such motor and autonomic abnormalities. The physiologic basis for the association of these abnormalities may be the common blood supply to the hypothalamus and the basal ganglia.

Summary: 1. Certain autonomic functions (B.P., P.R., skin temperature, palmar sweat response, electrical skin resistance), the signs of catatonia, and the psychiatric status of 9 patients with schizophrenic reactions, catatonic type, were evaluated before and after saline, sodium amytal, and Dibenamine infusions.

2. Pre-injection autonomic abnormalities were low systolic B.P., cool extremities, and either very low sweat responses with high E.S.Rs., or hyperhidrosis with very low E.S.Rs.

3. Saline produced no significant changes.

4. Sodium amytal infusions were followed by increased hand temperatures and improvement in the catatonia, especially in the verbal spheres. The subjects became relaxed, showed little interest in surroundings. In those 4 who developed sufficient speech function, hebephrenic or paranoid ideas were expressed. All changes were transient.

5. Dibenamine infusions were followed by a slight increase in systolic B.P. and a large increase in P.R., neither of which changes have been reported in non-psychotic subjects after Dibenamine. Excessive sweating was inhibited, and low E.S.Rs. were raised. The hands became warmer. Significant improvement in the signs of catatonia was noted in most subjects, especially (and in contrast to the effects of amytal) production of increased spontaneous activity and increased interest in surroundings. There was correlation between warming of the hands and the neurologic improvement. As with amytal, verbalization revealed hebephrenic and paranoid ideas. Toxic effects were infrequent and minor. All effects were transient, but of longer duration than with amytal.

6. The possible mechanisms by which Dibenamine inhibits sweating and by which it improves catatonia are discussed.

7. A difference in the descriptive level of catatonia from that of hebephrenia and paranoia is pointed out.

8. The common blood supply of the hypothalamus and the basal ganglia is suggested as a possible basis for the clinical association of certain motor and autonomic abnormalities.

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