The Mecholyl Test; Its Value In Depressions

Robert R. Schopbach
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ROBERT R. SCHOPBACH, M.D.*

In recent years a great deal of attention has been directed toward the hypothalamus and the reticular formation in relation to the psychologic functions of the organism. Disturbances in the functions of these areas are evidenced by altered activity of the autonomic nervous system and of the psyche. Attempts have been made primarily by Funkenstein\(^1,2\) and by Gelhorn\(^3\), to establish a predictable relationship between the more readily observed and measured alterations of autonomic system functions, and the more elusive variations of the psyche utilizing the Mecholyl test.

The hypothalamus may be roughly located between the mammillary nuclei, the optic chiasma, the anterior commissure, and the inferior surface of the thalamus. In this general area there are a number of cellular masses which are not clearly separable, but which have been roughly divided into so-called nuclei. The function of each of these nuclei is not clearly understood, but one of the most widely accepted statements is that the posterior nuclei appear to be directly connected with the activity of the sympathetic portion of the autonomic systems, whereas the anterior nuclei appear to be more connected with the parasympathetic division. These nuclei are inter-connected and also are connected both afferently and efferently with the cortex, thalamus, and reticular core of the central nervous system.

Consciousness seems to require activation of the cortex not only through the specific afferent sensory system but also through (1) the reticular substance and (2) the hypothalamus. These lower systems regulate the degree of receptivity of the cortex permitting it to become aware of stimuli which would otherwise be subliminal or filter out stimuli so that the cortex is not overwhelmed and confused by a flood of stimuli. Thus it is these systems which control what we perceive and not the cortical sensory areas as previously thought.

Emotional responses are similarly controlled by these systems. The general outline of this feed-back circuit is sensory cortex — frontal cortex — hypothalamus — reticular substance — cortex. If any portion of this circuit is impaired, the quality of the emotional response is also impaired.

The hypothalamus and reticular substance are also indispensable for the formation of conditioned responses in two respects. Firstly, they tend to determine the level of excitability of the cortex. Areas of increased responsivity then tend to gather unto themselves other temporally occurring stimuli. Thus the conditioning stimulus such as the sound of the bell, will attract the simultaneously received primary stimulus, the sight of food. Secondly, conditioning occurs only when some emotion — fear, pleasure, etc. — is involved. As shown above these systems definitely affect the level of emotional responsivity. Thus one of the main learning techniques is closely related to the reticular substance and the hypothalamus.

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Since hypothalamic activity has been shown capable of (1) altering perceptions, (2) modifying responses, (3) modifying emotional reactions, and (4) determining the rate of learning conditioned responses, it would appear likely that gross behavioral changes would occur from any alteration in hypothalamic activity.

Since the posterior hypothalamic nuclei seem to be so closely connected with the activation of the cortex and also with the activation of the sympathetic portions of the autonomic system, Funkenstein devised a test purported to measure the state of reactivity of that area. It has been well-established that when the pressure in the sino-aortic area is lowered through mechanical or chemical means, increased sympathetic discharges ensue which have a tendency to counteract the experimentally induced hypotension. These discharges appear to be mediated through the posterior hypothalamic nucleus as, when that nucleus is inactivated by barbiturates or more permanently by high frequency lesions, the prompt return of blood pressure to the normal level does not occur. When this nucleus is intact, not only does the blood pressure return to normal, but there are other signs such as changes in pupillary size indicative of increased sympathetic autonomic nervous system activity. Likewise, if this nucleus is further stimulated by the local application of strychnine, not only does the blood pressure return, but does so more promptly and even overshoots the resting mark for some period of time. Thus to the subcutaneous injection of 10 milligrams of methacholine, the normally active posterior hypothalamic nucleus is postulated to cause the blood pressure to return to normal in about 10 minutes with possibly a very slight amount of secondary increase. Should this nucleus be in a state of increased excitation the blood pressure would return sooner, and a greater degree of over-reaction would follow. Should the nucleus be underactive, the blood pressure would return to the resting level much more slowly. Of course there are all gradations in between these three characteristic responses and arbitrary boundaries have been drawn. One method has been to plot the change in the blood pressure in millimeters of mercury against the time in minutes for 25 minutes. Five millimeters change in blood pressure is equal to one centimeter, and one minute is equal to one centimeter. The area of change is then measured. Should there be an increase of greater than 6.4 square centimeters it is classified as type I or hyper-reactive. If the change varies between —6.39 and —35.49, it is type II or normal. Should the decrease be greater than —35.5 square centimeters it is then classified as type III or hypo-reactive.

Clinically Funkenstein reported a positive correlation between individuals with type III (hypo-reactive) responses, and the beneficial result of electro-shock therapy in relieving their symptoms whether the condition was schizophrenia or depression. Pasquarelli also reported a correlation between the type III responses and the presence of affect on one hand, and between the type III response and recovery from mental illness on the other hand. Neither of these correlations were as high as the one between the clinical estimate of affect and the recovery from illness. However Lotsof and Yobst and Sloane reported no correlation between the type of response to methacholine and improvement following ECT. It was the purpose of this investigation to determine whether any correlation could be seen between the blood
pressure reaction to methacholine and the clinical response to therapy and also what effect ECT had upon the methacholine reaction.

PROCEDURE

In this study the mecholyl test was administered to 20 newly admitted white patients (14 women and 6 men) between the ages of 28 and 69 who had the symptom of depression. In 14 this was associated with a neurosis; in the remaining 6 five other diagnoses were indicated. Each patient had a private room on the 24 bed "open" psychiatric floor in a 1,112 bed general hospital. Six full-time senior psychiatrists and 3 residents care for these 24 patients thus permitting the most intensive of therapy. There is a special occupational therapy unit on the floor and psychologic and social service assistance is constantly available. With such intensive therapy the average stay of a depressed patient is less than three weeks. The sight of others recovering and going home enhances this positively oriented atmosphere and, exerts an unmeasurable force toward recovery so that the patients' responses cannot be attributed to ECT alone.

The test was administered only by the author in order to avoid any variations due to technique or interpersonal relations. The patient was requested to remain quietly in his room after arising. Before breakfast was served the author visited him and requested he lie down until the blood pressure stabilized. Ten milligrams Mecholyl* was then injected subcutaneously and the blood pressure recorded for the next 25 minutes or longer. This was done a day or two after admission when the depression had been clearly recognized but no therapy had been yet begun. In seven cases the procedure was repeated after completion of their course of ECT to compare the responsivity before and after ECT.

The response to therapy was checked approximately one year after discharge and classified as follows:

1. Good recovery — depression relieved and patient essentially symptom free.

2. Recovered — relapsed — recovered. Patient did well during initial hospitalization, then had a return of his symptoms which responded either to psychotherapy or to further ECT until a good recovery was achieved.

3. Depression relieved — These were usually the psychoneurotics who had developed a depression in addition to their other symptoms. The therapy relieved the depression but the chronic neurosis remained symptomatic.

4. Slight improvement — The depression lessened so that patient could leave hospital but was still evident.

5. Essentially unchanged.

*The methacholine (Mecholyl) used in these experiments was kindly furnished by Merck, Sharp, & Dohme, West Point, N. Y.
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RESULTS

The two individuals who had a type I reaction to methocholine did rather poorly. This is not surprising as both were quite neurotic, passive, dependent personalities. However, one did gain considerable relief of her depression. The clinical responses of the remaining seven Type II, and eleven Type III, reactors showed no correlation whatsoever (chart I). One of the most prominent Type III reactors (—89 square centimeter) showed no change while two of the best recoveries occurred in Type II reactors (—9 and —22 square centimeter).

<table>
<thead>
<tr>
<th>Clinical response</th>
<th>No. Pts.</th>
<th>Type Mecholyl Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>5</td>
<td>0 1 4</td>
</tr>
<tr>
<td>Better, relapse, then final recovery</td>
<td>4</td>
<td>0 3 1</td>
</tr>
<tr>
<td>Depression relieved, other symptoms remain</td>
<td>4</td>
<td>1 1 2</td>
</tr>
<tr>
<td>Slight improvement only</td>
<td>4</td>
<td>1 1 2</td>
</tr>
<tr>
<td>Essentially unchanged</td>
<td>3</td>
<td>0 1 2</td>
</tr>
</tbody>
</table>

In those patients where the reaction was determined both before and after ECT the change in the area was calculated and charted against the degree of clinical response (chart II). In two cases there was essentially no change in the reaction although clinically the patients were considerably better. The patient showing the best clinical response went from —131 to —232 directly contrary to what would be expected from Gelhorn's thesis that ECT acts as a mass stimulus to the entire brain but that the sympathetic system's responses over-balance the parasympathetic ones. Were this true ECT should produce a hastening of the blood pressure's return to normal. However, the relative strengths and balances of individuals' autonomic systems varies widely. Richter observed that some persons flushed while others blanched during London air raids. Wolf observed similar variations in the gastrointestinal system.

<table>
<thead>
<tr>
<th>Change in area (sq. cms)</th>
<th>—101</th>
<th>—52</th>
<th>—4</th>
<th>+8</th>
<th>+28</th>
<th>+70</th>
<th>+95</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical improvement</td>
<td>+4</td>
<td>0</td>
<td>+3</td>
<td>+4</td>
<td>+3</td>
<td>+3</td>
<td>+3</td>
</tr>
</tbody>
</table>

SUMMARY

The Mecholyl test was administered to 20 acutely depressed persons. Except for noting that those who have a Type I (hyper-reactive) response did more poorly, no correlation of prognostic significance was found. The rate of return of blood pressure to the resting level was altered by ECT but in no predictable direction and this had no correlation with clinical improvement. ECT and depression affect too many portions of the nervous system to permit a test purportedly measuring only hypothalamic activity to be of prognostic significance.
Mecholy Test

REFERENCES


