THE JOURNAL OF NEUROLOGY AND PSYCHIATRY

FOUNDED BY S. A. K. WILSON

VOL. 3. [New Series]

JANUARY, 1940

No. 1

THE EMOTIONAL AND SOMATIC RESPONSE OF SCHIZOPHRENIC PATIENTS AND NORMAL CON- TROLS TO ADRENALIN AND DORYL

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(RECEIVED 12TH APRIL, 1939)

A CONSIDERABLE mass of experimental evidence has been accumulated in recent years indicating the great variability of symptomatology observed in schizophrenic patients (Freeman *et al.*, 1932, 1934, 1935 ; Hoskins *et al.*, 1933 ; Linton *et al.*, 1934 ; Desruelles *et al.*, 1934 ; Whitehorn, 1934 ; Gottlieb and Linder, 1935 ; Marquart, 1935 ; Petroff, 1934 ; Goldstein and Reichmann, 1914 ; Lowrey and Wright, 1920 ; Yoneyama, 1933 ; Gellhorn, 1938 ; McFarland and Goldstein, 1938). This variability serves to call attention to the fact that the term "schizophrenia" embraces a wide range of clinical syndromes. Hoskins *et al.* (1933), Freeman *et al.* (1933, 1934), and Linton *et al.* (1934) have demonstrated the altered activity of the peripheral autonomic nervous system in schizophrenic patients, with a failure to maintain the homeostatic mechanisms. On the other hand, Myerson *et al.* (1937, a, b, and c ; 1938) have employed schizophrenic patients to carry out an important series of tests to determine the pharmacological action of various drugs having an action similar to that of the autonomic nervous system. Their results would indicate that the peripheral activity of the autonomic nervous system as tested on schizophrenic patients was little different from that obtained by other investigators, using different controls (Starr, 1933 ; Starr *et al.*, 1933 ; Fraser, 1938). It has long been known that schizophrenic patients showed a physiological as well as a psychological dissociation. Bowman and Kasanin (1929) and later Whitehorn (1934) demonstrated that there was no correlation between the mood of the patient and the degree of fasting glycaemia. This finding was more or

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less at variance with Cannon's work with animals, which demonstrated that such reactions as rage and fear brought an increase in the output of adrenalin, a rise in blood sugar, and a glycosuria. Gildea *et al.* (1935) demonstrated that normal individuals under intense emotional stress developed a rise in blood sugar, again indicating a difference or variation from the observations made on schizophrenic patients, and tending to substantiate the work done on animals. Cori and Buchwald (1930) demonstrated that the vascular response in man is much more sensitive to adrenalin than in the common laboratory animal, indicating that there were probably both qualitative and quantitative differences between various autonomic mechanisms in man and in animals which made comparisons between them difficult.

Recently Lindemann and Finesinger (1938) used adrenalin and mecholyl to induce or reactivate the anxiety states of a group of psychoneurotic patients. They were more interested in the verbal report of the patient and his behaviour, following the use of these drugs, than in the evidence of peripheral activity, and give no series of normal controls receiving the same drugs. It is of considerable interest, however, to find that all of their patients except one had a typical anxiety attack induced by either adrenalin or mecholyl or by both drugs. This single exception is of particular interest as this patient seems to have been suffering from a schizophrenic-like mental illness. This raises two questions: How would a group of normal individuals respond to injections of these drugs, and how would a group of emotionally deteriorated schizophrenic patients respond to the same drugs? As has been indicated previously, this type of investigation has been carried out before, although the investigator's attention was primarily centred on the peripheral activity of the autonomic nervous system and not on the emotional response.

Method

Instead of dealing exclusively with the peripheral autonomic response of schizophrenic patients to various autonomic stimulants, we have attempted to correlate the patient's emotional response with the peripheral response, comparing it with a group of normal controls. The schizophrenic patients chosen for this investigation were co-operative individuals, capable of responding to direct questioning and having no gross physical abnormality. There were 10 patients selected (five men and five women). The average age of the group was 31 years. The average duration of the psychosis was 9 years. There was either marked poverty of affective response or an inappropriate affective response in each patient with evidence of emotional deterioration. Seven of the 10 had previously been given either insulin shock or convulsant drug therapy without improvement. There were six individuals in the normal control series (four men and two women), all recruited from a general surgical service. Two of the men were convalescing from an operation for hernia, and the remaining four patients were convalescing from chronic tuberculous lesions of bone, being in good physical condition otherwise and having no other demonstrable abnormality. The average age of the control group was 26 years.

None of the control group showed any abnormal mental symptoms and all were emotionally stable.

The investigation was carried out on both the schizophrenic and the normal control group in the morning. These patients were allowed no breakfast or sedatives, as it has been demonstrated that sedatives produce a definite alteration of glucose metabolism (Tod, 1935). The patients remained quietly in bed for at least 30 minutes before the tests were begun. Each patient was asked, "How do you feel?" If there were no complaints or symptoms of anxiety or apprehension, blood pressure and pulse rate were taken and a neurological examination was carried out, with special reference to the activity of the autonomic nervous system (e.g. sweating, pallor, flushing, salivation, lachrymation, peristalsis, or urgency). A sample of venous blood was taken from the patient and immediately following 1 c.cm. of normal saline solution was injected intramuscularly. At the end of 15 minutes the patient was asked, "How do you feel now?" and then, "Have you noticed any change?" If the patient made no spontaneous comment as regards his emotional reactions he was asked, "Have you felt nervous, apprehensive, or fearful?" Venous blood was again withdrawn 15 minutes after the saline injection, and another neurological examination carried out. The patient was then given either adrenalin or doryl (carbaminoylecholine chloride) intramuscularly. The former was given in doses of 0.5 to 1 c.cm. of a 1 to 1,000 solution and the latter in doses of 10 to 20 mgm. (1 to 2 c.cm.), and again venous blood was withdrawn (at 15 min. and 1 hour following), a neurological examination was carried out, and a record made of the patient's behaviour and spontaneous comments, as well as his answers to questions.

Results

The results of this investigation as regards blood-sugar determinations, pulse rate, blood pressure, and pulse pressure are recorded in the following tables. The figures represent the average of the maximum rise or fall of the particular item under investigation, giving a comparison of the reaction of the schizophrenic group with that of the control group. It might be stated that there was no significant somatic or psychic reaction in either group following the injection of normal saline.

TABLE 1.—ADRENALIN

INDICATOR	BLOOD SUGAR		PULSE RATE		BLOOD PRESSURE		PERCENTAGE RISE PULSE PRESSURE	
	0.5 c.c.	1 c.c.	0.5 c.c.	1 c.c.	0.5 c.c.	1 c.c.	0.5 c.c.	1 c.c.
Dose of adrenalin ..								
Schizophrenic (Range) ..	+23 (+1 to +53)	+66 (+46 to +118)	+20 (-4 to +34)	+21 (-8 to +52)	+14 (+8 to +20)	+23 (-10 to +52)	+40 (+17 to +72)	+122 (+70 to +186)
Normals (Range) ..	+43 (+16 to +71)	+47 (+6 to +92)	+12 (+4 to +20)	+16 (+12 to +20)	+15 (+10 to +20)	+29 (+25 to +30)	+128 (+82 to +175)	+92 (+73 to +114)

Table 1 shows the response of the schizophrenic and normal control groups to 0.5 c.cm. and 1 c.cm. of adrenalin given intramuscularly. The range of response is indicated by the figures in brackets, and as might be expected there was considerable individual reaction. There tends to be a somewhat wider range and more variability of response in the schizophrenic group than in the normal control group, although this difference is not invariably striking.

TABLE 2.—DORYL

INDICATOR	BLOOD SUGAR		PULSE RATE		BLOOD PRESSURE		PERCENTAGE RISE PULSE PRESSURE	
	1 c.c.	2 c.c.	1 c.c.	2 c.c.	1 c.c.	2 c.c.	1 c.c.	2 c.c.
Dose of Doryl ..								
Schizophrenic (Range) ..	-3 (-15 to +25)	-8 (-18 to 0)	-2 (-24 to +10)	+5 (-8 to +16)	-14 (-30 to +10)	-20 (-30 to +5)	-3 (-18 to +22)	-3 (-40 to +30)
Normals (Range) ..	-1 (-9 to -2)	-5 (-2 to +6)	-3 (-12 to +4)	-5 (-16 to +8)	-5 (-7 to +5)	-1 (-12 to +5)	0 (-4 to +9)	+1 (-11 to +9)

In spite of the fact that these indicators show so little reaction after doryl, the general peripheral action of the drug, as evidenced by flushing, sweating, lachrymation, increased peristalsis, and urgency of urination were all quite marked in both groups. If anything, the peripheral action of the drug was more noticeable and intense in the schizophrenic group.

The most significant feature of this investigation is the emotional reaction or lack of reaction. As previously stated, the schizophrenic group of patients in this series were selected primarily on the basis of their lack of affective response, or inappropriate affective reaction, of long standing, the average duration of psychosis being 9 years. The control group, on the other hand, were convalescent post-operative patients with no nervous or mental complaints and with quite an appropriate emotional response. Invariably and without exception each individual in the normal control group experienced some degree of anxiety, apprehension, or fear following the intramuscular injection of adrenalin. This occurred in those receiving 0.5 c.cm. as well as those receiving 1 c.cm. These members of the control group complained spontaneously of palpitation, a feeling of tension and substernal constriction, a vague and indefinite but very real anxiety, which lasted only for a few minutes and was followed by a feeling which most of them described as being "nervous, jumpy, and on edge." None of the control group had ever felt quite the same way before. Trembling and facial pallor were common reactions in this group. There was no aggressive behaviour exhibited by any member of the control group. In four of this group all subjective symptoms had subsided at the end of 1 hour. In two of the control group, symptoms of nervousness persisted for about 5 hours and culminated in a mild headache.

This general reaction in the control group following adrenalin is in striking contrast to the reaction of the schizophrenic group following the intramuscular injection of adrenalin. There was not a single schizophrenic in the entire group of 10 patients whose behaviour, spontaneous response, or verbal report on direct questioning indicated anything which could be interpreted as an anxiety reaction. There was no change in the individual patient's apathetic or inappropriate emotional response. There was no aggressive behaviour. A few of them laughed and talked to themselves or to imaginary companions, but invariably when questioned there was never any indication of apprehension, anxiety, or fear. In fact, the schizophrenic patients did not complain of palpitation, although it was quite obvious that their hearts were beating very forcibly and rapidly. The indicators of autonomic response as summarized in Table 1 show quite an adequate response in the schizophrenic group. Trembling and facial pallor were also observed in the schizophrenic group. This adequate peripheral response had no emotional counterpart such as was so plainly evident in the control group.

The normal control group showed no emotional reaction to intramuscular injections of doryl in either 10 or 20-mgm. doses. As previously stated, the peripheral response in each instance was not unusual. No aggressive behaviour was noted and no "panic" reaction as described by Lindemann and Finesinger (1938) was observed. The schizophrenic group likewise showed no evidence of emotional reaction to doryl in spite of an even more active peripheral autonomic response than was noted in the control group. Each patient remained placid and unperturbed. One schizophrenic patient stated that he had a pleasantly warm sensation over his body after receiving 20 mgm. of doryl. When questioned specifically not one of the schizophrenic patients admitted any anxiety or fear reaction at any time.

It is realized that the action of doryl on the cardiovascular mechanisms is less marked than the action of mecholyl used by Lindemann and Finesinger (1938) in their series. This may account for the fact that no anxiety reactions were experienced by either group, although under the circumstances one could not expect any more reaction in the schizophrenic group than was observed following adrenalin. It is, of course, realized that the complex emotional derangement observed in schizophrenia is not completely explained by the failure of this group to react emotionally to adrenalin. Other investigators have observed alterations in the peripheral autonomic response in schizophrenic patients, but have not stressed the failure of various autonomic stimulants to arouse in the schizophrenic those same emotions experienced by normal individuals. From the physiological side it has been demonstrated that the adaptive mechanisms of the schizophrenic to preserve the "steady state" (Cannon, 1935) are defective under stress. Bard and Rioch (1937) have demonstrated in animals that the cerebral cortex was not necessary for the regulation of emotional expression, and indicated the importance of the hypothalamus in preserving an appropriate emotional response. Haškovec (1925, 1929) has contributed to the literature in this respect as regards derangement of emotional expression observed in patients with lethargic encephalitis, tumours

of the hypothalamus, narcoleptic seizures, catatonic states, toxic conditions, drugs, etc. Recently Smyth and Stern (1938) have reported on the mental deterioration resulting from tumours arising primarily in the thalamus. Haškovec (1929) and Nathan (1931) are of the opinion that the cortex plays no essential part in the regulation of the individual's affective life, and believe that the nuclei in the walls of the third ventricle are of the utmost importance in the regulation of the individual's affective dispositions. Singer (1938) concludes that the presence of a psychosis always indicates a disturbance of central autonomic integration, although this would appear more speculative than based on sound experimental data. Papez (1937, 1939) takes a somewhat broader and less dogmatic view, recognizing the importance of the hypothalamic and paraventricular nuclei, but at the same time stressing the cortical connections of these various centres. It is not within the scope of this paper to discuss the anatomy and physiology of the thalamus or hypothalamic centres. The work of Head (1918, 1920), Head and Holmes (1911), Ranson (1937), and recently Fulton (1938), Walker (1938), Le Gros Clark *et al.* (1938), may be referred to, as well as the excellent summary articles by Papez (1937, 1939). The demonstration of a failure of large doses of adrenalin to arouse any evidence whatever of emotional response in a group of schizophrenic patients as compared with a group of normal controls would favour the opinion that the inappropriate emotional response in schizophrenic patients is at a physiological level as contrasted with the view held by many that a psychological explanation will account for the inappropriate emotional response observed in these patients. In view of the adequate peripheral autonomic response in the schizophrenic group, it would appear that the break in the chain of reactions was not at that point. Beyond these observations of the failure of the schizophrenic patients to respond with appropriate emotional response to adrenalin, we have no experimental evidence which localizes the actual site of the difficulty, and are aware of no other experimental work on human patients which demonstrates the part of the nervous system involved in this disorder. It might be suggested that the central autonomic connections were disturbed in schizophrenia. We present only indirect evidence of such disorder, which must await further direct confirmation.

Conclusions

Emotional and somatic reactions of schizophrenic patients and normal controls are compared following intramuscular injection of adrenalin and doryl.

No significant difference was noted in the somatic response of the two groups, although the schizophrenic group exhibited more variability of response to both adrenalin and doryl, tending to bear out the findings of others to the effect that the adaptive mechanisms of the schizophrenic to preserve the "steady state" are defective under stress.

Doryl injected intramuscularly produced an excellent peripheral autonomic

response in both the schizophrenic and normal groups, but no emotional disturbance (anxiety or fear) in either group.

The clear-cut and definite failure of adrenalin to arouse anxiety or fear response in the schizophrenic as compared with the normal control group is significant, and points to a disordered emotional mechanism at a physiological level. We present experimental data which only indirectly localize this break in the chain of physiological response, and all explanations are highly speculative.

No claim is made of the efficacy of using adrenalin to differentiate schizophrenics from other mental disorders by means of their emotional response, although the findings reported would suggest possibilities for investigation in an effort to understand better the central emotional mechanism.

We are indebted to Professor D. K. Henderson for placing the facilities of the Royal Edinburgh Hospital at our disposal, and also to Dr. Colin Campbell, Mr. Wm. C. Wilson, and Mr. C. F. W. Illingworth of the Surgical Department of the University of Edinburgh for securing a control group of patients.

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