PART III.

The Respiratory Regulation in Psychotic Subjects.

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THE preceding studies on the acid-base equilibrium in psychotics have made it evident that the failure to adjust must be attributed in the first instance to an inadequacy of the respiratory compensatory mechanism, and can be in no sense attributable to either a deficiency in the buffering power of the blood itself or to an increased organic acid production (acidosis). We have endeavoured to determine the excitability of the respiratory centre to the stimulus created by CO_2. For this purpose a number of psychotic patients were tested as to the excitability of the respiratory centre to air containing 2% CO_2 and the reaction compared with that obtaining in a number of normal subjects.

METHODS.

The estimation of the total ventilation when dealing with psychotic cases presented special difficulties. The simplest and most accurate method of recording the ventilation is that adopted by Haldane (1). He placed the subject in an air-tight box with the head only outside, an air-tight joint being made round the neck, and the respiratory changes of volume being recorded by a suitable apparatus connected with the box. Such a method is quite unsuitable for the majority of psychotic patients on account of the alarm occasioned by confining them in the narrow limits of the box, which results in a great disturbance of respiration. Any method depending on the collection of the expired air in a plethysmograph was found to be open to the grave objection that the filling of a sufficiently large plethysmograph could not be accomplished without an appreciable back-pressure on the lungs during expiration. The respiratory mechanism is extremely sensitive to air-pressure, and a type of forced breathing is engendered which vitiates an experiment intended to measure the slight changes produced by the chemical regulation of respiration. A further problem is raised by the difficulty of the attachment of the respiratory apparatus to the subject. Experience with the conventional mouthpiece in basal metabolism experiments has convinced all workers in this Laboratory that even with trained subjects there invariably ensues a type of over-ventilation which can easily be

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demonstrated by estimations of the CO_2 in the expired air in successive five-minute periods. During the first period a great washing-out of CO_2 occurs, and estimations of CO_2 in the alveolar air taken before and after a short period of breathing show that a degree of alkalæmia has been established. The use of a mask allowing nasal respiration obviates this source of error in the trained subject, but has a distinctly terrifying effect on many psychotics who, fearing suffocation, breathe as deeply as possible. It must also be premised that such a mask must be fitted with inlet and outlet tubes sufficiently large to allow of very free passage of air, together with far lighter valves than the type generally in use for metabolic experiments.

The ideal apparatus for recording variations in the total ventilation should offer no resistance to ventilation, and be not much greater in capacity than the tidal air volume of a single respiration. It is connected with the subject by an attachment that allows normal nasal breathing, and so comfortable as to produce no psychical effect on respiration. After many trials the apparatus described below was found to satisfy these requirements.

A very light and well-balanced aluminium volume recorder of about 6 litres capacity, floating in a water tank, was divided into two equal portions by an aluminium partition running along its length. The half A served for the expiratory air and the half B for the inspiratory (*vide* Fig. 1). The air-space of each half was connected by 1-in. tubing passing through the floor of the water tank, with the breathing attachment consisting of a glass and metal T-tube of 1 in. diameter (C) furnished with very light Chauveau valves set for inspiration and expiration respectively (D and E). Two second tubes, F and G, of the same diameter (1 in.), connected the air-spaces of the recorder with the outer atmosphere. In order to obtain a continuous record of respiration, it was necessary that when air was expired through E into the expiratory half of the recorder A the tube F connecting this half with the outside atmosphere should be closed, whilst the tube G, connecting the inspiratory half B with the atmosphere, remained open, thus allowing the recorder to rise during expiration and filling B with fresh air. During inspiration the reversed order was observed. Air was inspired from the half B, and the tube G communicating with the atmosphere was closed, the atmospheric tube F was opened, and whilst the recorder fell, it emptied the previously expired air into the room. In order to effect the automatic opening and shutting of the atmospheric tubes F and G during the two phases of respiration, free ends of these tubes were covered by the valve plates, H and I, of an electrically controlled valve. The two valve plates were pivotted on the arms of a lever, which was pressed down at

one end by the spiral spring S, so that the valve plate H was normally blocking the free end of the tube F on the expiratory side. The other side of the lever was furnished with a soft iron plate which could be pulled down when a current passed through the electro-magnet M, overcoming the resistance of the spring and thus opening F during inspiration and closing G. The inspiratory making and the expiratory breaking of the current to the magnet was effected by means of the tambour P connected by a small tube with the mid-valvular space of the T-tube C, the lever of which made the circuit to the magnet when the membrane of the tambour was depressed by the pull of inspiration, and broke it during expiration. To the free end of the upright of the T-tube was connected a Y-shaped glass tube about an inch long, and on each limb of the Y were affixed two bulbous tubes of soft rubber an inch in length which could be squeezed into either nostril, and accommodating themselves to the shape of the nostril, formed an air-tight joint with the nasal chamber. The weight of the T-piece was supported by a cushion. It was found that when the soft rubber end-pieces were coated with vaseline not the smallest discomfort was experienced, and after a short time their presence was unnoticed—in fact on many occasions a subject would fall asleep whilst breathing through them. The whole system offered no appreciable resistance, and the dead space in the T- and Y-tubes above the valves did not exceed 20 c.c. In order to introduce gaseous mixtures to the inspiratory chamber a box was fitted over the inspiratory valve I, with the lever moving up and down through a slit in the wall of the box lightly packed with cotton-wool. At one end of the box was a tube, X, connected with a large gasometer provided with an electrically driven stirring fan, and at the other end a tube of equal diameter, Z, was open to the atmosphere. When the patient was breathing atmospheric air alone he obtained this through Z. When he was being supplied with a gaseous mixture, this was furnished by pushing the mixture across the valve opening from X to Z, the gas being drawn in during inspiration through the tube G. To avoid psychical disturbances the gasometer was placed outside his field of vision. With such dilute mixtures as 2% CO_2, there is, of course, no subjective sensation. The recorder inscribed its movements on a smoked drum by means of the lever L, and at the end of an experiment the record was calibrated in the usual manner.

The Response of the Respiratory Centre to CO_2

For purposes of estimating the excitability of the respiratory centre to CO_2, the minimum percentage of CO_2 in the atmosphere

which would cause an easily demonstrable increase in the ventilation of normal subjects was determined. The standard mixture was an atmosphere containing 2% CO_2, though this is considerably above the *limen* of excitability of the respiratory centre. Of twelve normal cases examined all responded to a 2% CO_2 atmosphere by increased ventilation, the mean increase being about 20%. Fig. 2 gives a typical record. The curve is calibrated in intervals representing 100 c.c. by the abscissæ.

Twenty psychotic patients were examined. Six of these were certified cases of katatonic dementia præcox from Claybury Mental Hospital, and the remainder early unclassified cases from the Maudsley Hospital, in which anxiety and depressed states predominated. A case of dementia præcox gave a small increase of ventilation (9%) to the CO_2 mixture, and one of the Maudsley cases, a man recovering from an anxiety state, gave a normal response. None of the other psychotics showed any increase of ventilation with the 2% CO_2 mixture. Several were examined repeatedly both before and after meals. We have here a direct proof that the failure of the acid-base compensatory mechanism is associated with a depression of the excitability of the respiratory centre to CO_2.

The Response to the Ingestion of Sodium Bicarbonate.

A dose of 10 grm. of sodium bicarbonate was administered to a number of normal subjects and psychotics. This dose should raise the alkali reserve of the blood about 5% according to the formula of Palmer and Van Slyke (2, 3), when the effect on the alkali reserve $= \frac{38 \times \text{grm. } NaHCO_3}{\text{weight in kilos}}$ on the assumption of an equal

Table I.—*Showing the Response of a Normal Subject to a Single Dose of Bicarbonate.*

Normal (I) 10 grm. $NaHCO_3$ at 11 a.m.

Time.	% CO_2 in alveolar air.	Urine.			
		Volume c.c.	pH.	$NaHCO_3$, grm.	Chlorides, grm. NaCl.
11 a.m.	6·5	27	4·8	..	·431
11.15	6·4	21	5·0	..	·305
11.30	6·3	18	5·0	..	·291
11.45	6·6	24	8·5	·117	·279
12 noon	6·9	46	8·4	·425	·418
12.15 p.m.	6·8	26	8·4	·192	·243
12.30	6·5	21	8·4	·124	·216
12.45	6·5	13	8·4	·071	·121

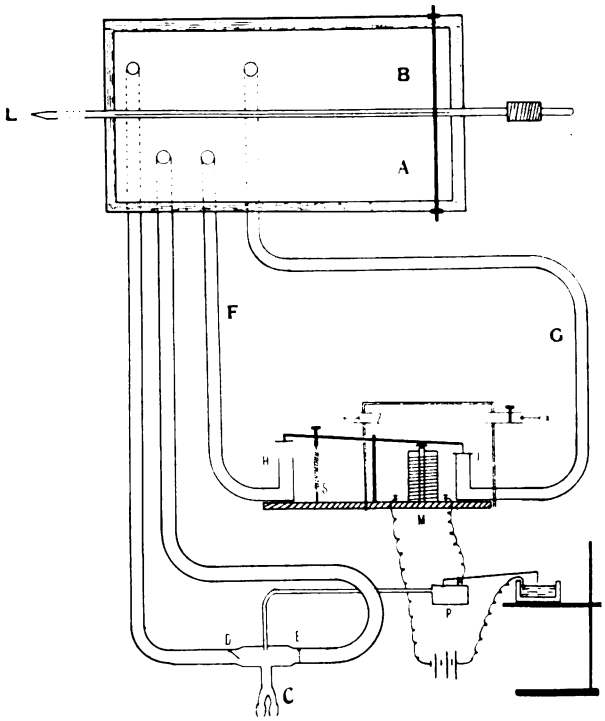

FIG. 1.—Diagrammatic representation of the electrically controlled plethysmograph. For description *vide* text.

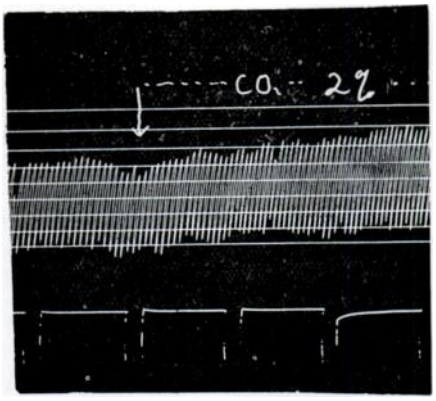

FIG. 2.—Typical record of normal ventilation response to 2% CO_2. Abscissæ represent 100 c.c. graduation.

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diffusion of $NaHCO_3$ through the body-fluids estimated as 700 c.c. fluid per kilo body-weight. All the normal and the psychotic cases responded to the bicarbonate with an increased urinary pH. Table I gives the response of a normal subject to a single dose. Table II shows the response of a normal subject to a repeated

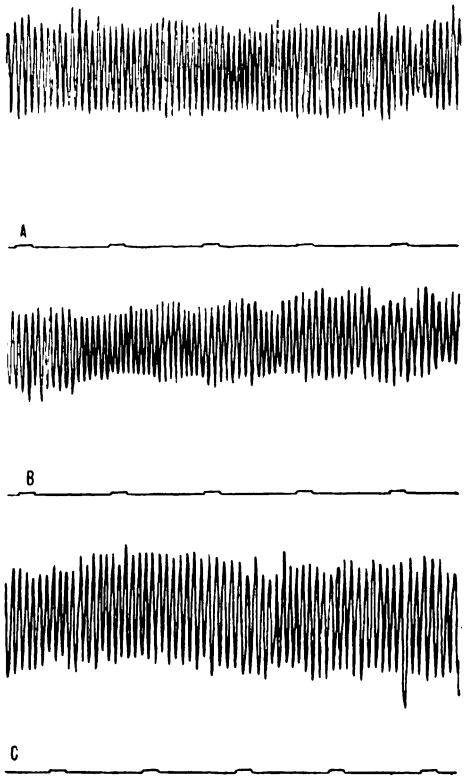

FIG. 3.—Showing ventilation following sodium bicarbonate ingestion in a normal subject. A, before; B, one hour after; C, two hours after.

dose of bicarbonate. Tables III and IV show the responses of two psychotic subjects to the same dose.

It will be noted that there is no significant difference between the urinary pH response of the normal and the psychotic subjects.

Turning to the respiratory response there is a marked difference. The initial alveolar air tension in the " acid " psychotics is, as might be expected, abnormally high. In both classes the ingestion of bicarbonate is followed by an increased alveolar CO_2 tension.

TABLE II.—*Showing the Response of the Normal Subject to a Repeated Dose of Bicarbonate.*

Normal (II) 10 grm. $NaHCO_3$ at 10.15 a.m., repeated after one hour at 11.15 a.m.

Time.	% CO_2 in alveolar air.	Urine.				
		Volume c.c.	pH.	$NaHCO_3$, grm.	Chlorides, grm. NaCl.	Phosphates, mgrm. P.
10.15 a.m.	5·4	11·5	4·8	..	·065	6·45
10.30	5·55	9·0	4·9	..	·081	6·5
10.45	5·52	11·5	5·2	..	·094	5·38
11.0	5·70	22	8·4	·145	·118	5·42
11.15	6·05	27	8·6	·281	·112	6·5
11.30	5·85	19	8·6	·281	·061	5·5
11.45	6·17	24	8·6	·403	·061	5·7
12 noon	6·40	31·5	8·6	·554	·069	8·2
12.15 p.m.	5·70	30	8·6	·516	·069	9·25
12.30	5·72	29	8·6	·513	·068	11·4
12.45	5·65	21	8·6	·371	·053	10·5

TABLE III.—*Showing the Response of the "Acid" Psychotic Subject to Sodium Bicarbonate.*

Case I (T.*) 10 grm. $NaHCO_3$ at 10.40 a.m.

Time.	% CO_2 in alveolar air.	Urine.				
		Volume c.c.	pH.	$NaHCO_3$, grm.	Chlorides, grm. NaCl.	Phosphates, mgrm. P.
10.40 a.m.	6·55	..	..	..	..	..
11.50	6·35	25	4·8	..	·140	5·05
11.10	6·85	21	6·8	..	·143	7·3
11.30	6·85	38	8·6	·33	·167	7·9
11.50	6·85	27	8·8	·36	·097	10·6
12.10 p.m.	6·85	26	8·8	·31	·094	14·7
12.30	6·9	18	8·8	·20	·065	11·2
12.50	7·3	16	8·8	·12	·061	12·0
1.0	7·4	..	..	..	..	..

* A man, æt. 44, who has suffered with an anxiety neurosis for many years which has recently led to an attack of melancholia during which he developed suicidal tendencies, and in which ideas of unworthiness and of the hopelessness of the future are predominant. He left the hospital where he was a voluntary boarder and has since committed suicide.

In the normal when the excretion of bicarbonate has brought the alkali reserve down to approach the resting value there ensues a corresponding drop in the alveolar CO_2, in the psychotic the alveolar CO_2 tension remains high. If the subject be connected with a plethysmograph we find, as illustrated in Fig. 3, that in the normal the respiratory centre responds to the increased pH tension

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TABLE IV.—*Showing the Response of the "Acid" Psychotic Subject to Sodium Bicarbonate.*

Case II (D. J—*) 10 grm. $NaHCO_3$ at 10.50 a.m.

Time.	% CO_2 in alveolar air.	Urine.				
		Volume c.c.	pH.	$NaHCO_3$, grm.	Chlorides, grm. NaCl.	Phosphates, mgrm. P.
10.40 a.m.	7·1	143	4·7	..	·970	84
10.50	7·1	..	..	..	..	..
11.0	7·55	21	4·8	..	·156	11·6
11.20	7·475	16	6·6	..	·096	7·4
11.40	7·45	30	7·6	·076	·156	11·7
12 noon	7·425	30	7·8	·09	·150	14·3
12.30 p.m.	7·525	28	7·2	..	·157	18·1
12.40	7·625	..	..	..	..	..
12.45	7·65	..	..	..	..	..

* A man, æt. 45, of cultured and highly æsthetic tastes, suffering from an anxiety neurosis due to conflict between financial stress and his artistic ideals. Obsessioned with regard to his general health. He showed considerable insight and improved under treatment.

of the blood by a preliminary drop in the ventilation, thus increasing the CO_2 tension to compensate the increase of the alkali reserve in accordance with the Hasselbalch formula. In terms of the actual ventilation (litres per minute) for the normal subject whose record appears in Fig. 3 the measurements of the curve give the following:

—	Rate of respiration.	Average respiration.
Before $NaHCO_3$ . . .	16 per min.	642 c.c., 10·28 litres per min.
1 hour after $NaHCO_3$ . .	15 ,, ,,	566 ,, 8·6 ,, ,,
1½ hours ,, ,, . . .	14 ,, ,,	656 ,, 9·1 ,, ,,
2 ,, ,, ,, . . .	14 ,, ,,	758 ,, 10·46 ,, ,,

When the alkali reserve has been brought to normal limits by the urinary excretion of bicarbonate the augmented CO_2 pressure stimulates the respiratory centre to get rid of it by hyperpnœa. In the psychotic there is at first a depression of the ventilation corresponding to that found in the normal subject, but the lowered excitability of the respiratory centre does not admit of its responding to the increased CO_2 pressure within the time-limits of the experiment once the alkali reserve has been lowered approximately to normal.

It appears, therefore, that whilst the respiratory centres of both normals and psychotics respond equally by decreased activity to a lowering of the pH of the blood, the respiratory centre of the psychotic is relatively inexcitable by CO_2.

Discussion.

The present observations on the activity of the respiratory centre represent the latest link in the chain of observations emanating from this Laboratory. All have as a common factor a disturbance of the acid-base equilibrium in the psychoses. Most of the evidence has been discussed at length in previous papers, and it is here only necessary to summarize the successive stages in attributing the primary cause of these disturbances to the depressed activity of the respiratory centre.

The earliest investigation of the activity of the vegetative nervous system in the psychoses, and a study of the carbohydrate metabolism in the psychotic as evidenced by the blood-sugar curve following ingestion of glucose were undertaken by Mann (4), and the results obtained were such as would be consistent with a lowered pH of the organism. Attention was next paid to the vasomotor responses to food ingestion, the reflex responses to heat and cold and postural stimuli, and Robertson (5, 6) found a complete inversion of the normal vasomotor response in most of the psychoses. In the light of our knowledge of the influence of ionic equilibrium on the responses of the vegetative nervous system, it appeared that a shift of the acid-base equilibrium to the acid side would again furnish a possible explanation of these abnormalities. It was therefore decided to investigate the response of the psychotic case to the disturbances of acid-base equilibrium caused by food ingestion and gastric secretion. Some preliminary work by Robertson (7) showed that the ingestion of food is not followed by the normal alkaline tide in 70% of the psychotic patients examined. In the two papers (8, 9) preceding this one in the present number of the *Journal of Mental Science*, and in a study to be published in the *Mott Memorial Volume* (10), Mann and his co-workers have furnished conclusive evidence that a failure of compensation of the acid-base equilibrium exists in the psychoses, and that this condition closely resembles that obtaining during sleep in the normal individual. Furthermore a study of the preceding evidence indicates that this failure in compensation must be ascribed to the CO_2 regulation, and not to a condition of acidosis. Evidence is adduced that the abnormality of CO_2 regulation is merely the expression of a lowered excitability of the respiratory centre to the stimulating effect of CO_2.

We have, then, proof that in the psychotic there exists a definite depressed excitability of the medullary centre for respiration. This may account for the abnormalities of carbohydrate metabolism, the inexcitability to insulin, and the inverted vasomotor reactions, and possibly as a consequence of this latter factor,

for certain anomalies of the bodily responses to the emotions. It is clear from our experiments that whilst the respiratory centre of the psychotic is not susceptible to the CO_2 stimulus, it reacts apparently in a normal fashion to the ingestion of bicarbonate in the early stages, though the secondary hyperpnœa by which the accumulated CO_2 is excreted would appear to be absent, judging from the results of alveolar air analysis.

On account of the conflicting views that obtain as to the mode of the chemical regulation of respiration, further consideration of this subject may be postponed whilst some investigations on the pH of the blood in psychoses are being pursued. The significance of the depressed excitability of the respiratory system will, however, decide the direction of further work. It may be that we are dealing with a sign of a general depression of the excitability of the nervous system as a whole due from congenital lack of excitability or toxic depression. Intoxication might be attributable to abnormal products of metabolism or to tissue acidification from deficient oxidation. The resultant disturbance of the acid-base may be of no significance other than this. On the other hand the permanent ionic disequilibrium consequent on a failure of respiratory compensation may in itself be responsible for a general disturbance of cerebral processes; as long ago as 1873 Obersteiner (11) suggested that sleep was due to accumulation of acid products of metabolism in the nerve-cells. It must be clearly understood that the alteration of blood and tissue pH due to failure of compensation is of an entirely different nature to the acidosis produced by organic acids, with an intact compensatory mechanism such as occurs in the diabetic up to the final stage when compensation breaks down.

There appears little ground for supposing that the depression of the respiratory mechanism is in any sense a *pari passu* manifestation of the general disorder of conduct that we term "insanity." Between an anxiety type such as Case 1 (p. 449) and the group of katatonic dementia præcox cases and the various excited and depressed melancholics investigated, there is no obvious common factor of conduct giving rise to the same type of bodily manifestation. Furthermore, if the inverted vasomotor phenomena recorded by Robertson be due to this disturbance of acid-base equilibrium, the inverted type persists independently of remissions and exacerbations of the disorders of conduct, and is spread over the whole class of cases that are actually or potentially certifiably insane. On the further investigation of this point all remains to be done—we have yet to trace the depression of the respiratory compensation through the phases of remission and exacerbation of conduct disorder that may occur in any one individual. We have

purposely avoided any attempt at the present stage of classifying our cases of psychosis, nor do the number of cases observed justify any expression of opinion as to the universality of the disturbance investigated in the multiple forms of disorder of conduct that are grouped together as psychoses. As the work here set forth is a preliminary account of a bodily disorder with disorder of conduct, it would be at the present stage of our inquiry undesirable to generalize.

Summary.

1. A new type of automatically controlled plethysmograph is described.

2. While normal cases respond to the inhalation of an atmosphere containing 2% CO_2 by increased respiratory ventilation, of the 20 psychotic cases examined only two showed any respiratory response to the CO_2 mixture.

3. After ingestion of 10 grm. sodium bicarbonate, both normal and psychotic patients respond by a decreased ventilation with an increase of the CO_2 percentage of the alveolar air. In both groups of cases there is a rise of the urinary pH and an excretion of sodium bicarbonate. When the greater part of the bicarbonate has been excreted a rise of the ventilation above that of the resting value occurs in normal subjects, and the CO_2 percentage of the alveolar air tends to fall to resting limits. In the psychotic patient there is no response to the increased CO_2 pressure during the period that it occurs in the normal subject.

4. The interpretation of this depression (obtaining in psychotics), of the respiratory compensation as a factor in the causation of an acid shift of the acid-base equilibrium is discussed.

We wish to express our thanks to Dr. Mapother, Medical Superintendent of the Maudsley Hospital; to Dr. Barham, Medical Superintendent of Claybury Mental Hospital; for giving us facilities to examine patients; to the staff of the Maudsley Hospital for volunteering to act as control subjects: and to Mr. E. Pemberton, Engineer of Hanwell Mental Hospital, for constructing the electrically controlled plethysmograph.

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