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DA COSTA'S SYNDROME (OR EFFORT SYNDROME)

THE MECHANISM OF THE SOMATIC MANIFESTATIONS *

BY

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Vasomotor Disturbances: 1. Tachycardia

It is this sign above all others which has drawn attention to the heart, yet it is one of the commonest psychosomatic effects, occurring in every one of us under the influence of sufficient emotion. It has been recorded by all observers, and in my own series of 200 cases the pulse rate averaged 82 beats per minute (48 to 136) during casual examination in the day-time, compared with 66 beats per minute (48 to 100) in 50 controls. During sleep, however, it is normal, averaging 60 to 65 in Hume's series (1918). It is customary to speak of the great lability of the pulse, which is said to accelerate unduly with change of posture, with effort, and with adrenaline. The evidence for this, however, is open to criticism.

Statements declaring that there is undue acceleration of the pulse rate on change of posture may be challenged directly, because the published figures do not show it, even those given by authors who make this very statement. Thus in 36 children with "effort syndrome" Bass and Wessler (1913) found the difference between the lying and standing pulse rates to average 7 beats per minute, which was the exact figure obtained by Lincoln (1928) in 320 controls aged between 3 and 13. In adult patients published figures are well within published control figures; they are hardly worth quoting, because little attention has been paid to the behaviour of the pulse on standing up. Douglas and I have found that the initial acceleration lasts for but nine to fifteen seconds in about two-thirds of patients and controls, and is followed by abrupt slowing. It is therefore necessary to count the pulse for the first ten seconds only, after the patient stands up, if the true speed at this time is wanted. In comparing patients with controls we took three readings: (1) during the first ten seconds as described; (2) during the second quarter-minute; (3) at the end of the first minute. The results are recorded in Table IX, and show no essential difference. It is con-

cluded that in the great majority of cases the reaction of the pulse rate to change of posture in children and adults with Da Costa's syndrome is normal; it is suggested that exceptions depend upon interference by an emotional mechanism, for in both patients and controls unusual acceleration with failure to slow down after the initial rise was apt to be accompanied by conspicuous palmar sweating.

Undue acceleration of the pulse during effort has been assumed by most authors, with the implication that the physiological reaction to effort is abnormal. Few have taken the trouble to test their assertions. Bass and Wessler (1913) found that the pulse rate rose 48 beats per minute after a standard amount of exertion in 36 children with Da Costa's syndrome, compared with 50 beats per minute in controls. Parkinson (1916) compared 20 patients with 20 healthy men, of whom 16 were in the football team, and found that the pulse rate rose 28 and 21 beats per minute respectively after standard effort. Meakins and Gunson (1917) obtained an average rise of 46 beats per minute in 39 patients, compared with one of 34 in 10 controls, after they had climbed 27 steps. Our test consisted in climbing 30 steps, and my results may therefore be compared with those of Meakins and Gunson. If the two are combined it is found that the average rise in 140 patients is 39.8, compared with 40.4 in 25 controls. My controls were ordinary healthy young men, not fully trained soldiers (Table X).

TABLE X

Author	Patients		Controls	
	No. of Cases	Pulse Rise immediately after Effort	No. of Cases	Pulse Rise immediately after Effort
Meakins and Gunson ..	39	46.0	10	34.0
Present series	101	37.4	15	44.6
Total	140	39.8	25	40.4

TABLE IX.—*Rise of Pulse Rate with Change of Posture*

	No. of Cases	Rise in First 10 Sec.	Rise in Second 1 Min.	Rise at End First Min.
Da Costa's syndrome {	20	21 (6-40)	7.8 (-4-20)	9 (0-40)
	20	24 (8-40)	9 (0-40)	8 (0-28)
	25			
Controls {	22	24 (6-40)	7.5 (0-24)	8 (0-24)
	40			

* The Second of three Goulstonian Lectures to the Royal College of Physicians of London, 1941. The first lecture was published in last week's issue.

According to Meakins and Gunson (1917) the pulse rate after effort returns to normal more slowly than in controls, and they showed a close correlation between the deceleration time and the final category of their patients. The effort-tolerance test is based on these findings. The deceleration time is recorded in relation to the final category in 164 of my patients in Table XI. The figures do not support the claims made for this test. It is true that a third of my whole series had a deceleration time longer than two minutes, and this is a higher proportion than is found in controls. But it does not follow that these patients have

TABLE XI

Deceleration Time	No. of Cases	Category Returned (%)		
		A 1 Full Duty	C Light Duty	E Totally Unfit
1 minute	72	33.3	41.6	25.0
2 to 3 minutes	53	28.3	32.0	39.6
Over 3 minutes	39	20.5	46.2	33.3

an abnormal reaction to effort itself, for no attempt has ever been made to control or to assess the degree of emotional reaction in these tests. It may be noted that when Meakins (Meakins and Wilson, 1918) attempted to measure the effect of emotion on the pulse rate he took good care to ensure that the patients were physically at rest. An unexpected pistol-shot or a sudden big flame had no effect on the pulse or respiration rates of 6 controls, but caused a rise in the pulse rate of 3 to 45 beats per minute in all 12 patients, and a rise of respiration rate of 1 to 24 per minute in two-thirds of them. Those with vigorous reactions had poor effort tolerance; those with slight reactions had relatively good effort tolerance. This work helps to show how necessary it is to allow for the effects of emotion in all tests on patients with Da Costa's syndrome. Sir Adolphe Abrahams informs me that effort-tolerance tests were hopelessly unreliable when performed on world-famous athletes during a contest, when the emotional factor was to the fore.

Cotton, Rapport, and Lewis (1917) have shown that if patients and controls are exercised to the breaking-point the final pulse rate is the same—about 155, the normals rising more than the patients. There is no evidence that this tachycardia is harmful, and, as Sir Adolphe Abrahams will testify, there have been a number of men in our unit who performed the heaviest of exercises perfectly and without symptoms, but whose pulse rates were unusually high and remained so for some time afterwards. These men felt and looked fit, and were placed in Category A 1. It must be appreciated that the pulse rate of normal controls during strenuous effort may rise to 190 per minute without causing distress (Gillespie, Gibson, and Murray, 1925). J. E. Lovelock tells me that his may reach 210 beats per minute.

The adrenaline test, introduced by Goetsch (1918) as a test for hyperthyroidism, consists in injecting 0.5 mg. of adrenaline subcutaneously and observing its effect on the pulse rate and blood pressure. It is positive if either rises 10 or more points. As a test for hyperthyroidism it was soon abandoned, because it was found to be positive in many other conditions, including "effort syndrome" (Peabody *et al.*, 1918, 1921; Kessel and Hyman, 1923). The implication that patients with Da Costa's syndrome are hypersensitive to sympathetic stimulation is not justified, for hypersensitivity to adrenaline can only be tested by intravenous administration, its effect when given subcutaneously or intramuscularly being influenced by its rate of absorption and by its rate of destruction in the tissues. Positive reactions in thyrotoxicosis may well be due to rapid absorption, for the increased blood flow in this condition is well known. A similar explanation may hold true for some cases of Da Costa's syndrome. Fraser and Wilson (1918) and Hume (1918) tested the effect of 0.1 mg. of adrenaline by intravenous injection. Their combined results show a rise of pulse rate of 28 in 22 cases of Da Costa's syndrome and of 28 in 9 controls. It is concluded that these patients are not hypersensitive to adrenaline as judged by the pulse rate. I believe this to be of fundamental importance, for it shows that the heart does not over-react to normal sympathetic stimulation—that it is not, in fact, irritable.

A possible cause of tachycardia is diminished vagal tone. This was investigated by Cotton, Rapport, and Lewis (1917). After the intravenous injection of 1 to 1.5 mg. (0.002 grain per stone of body weight) of atropine, the pulse rate rose 26 beats a minute in 7 patients and in 6 controls. Acceleration of the pulse rate on effort was increased by 29 beats a minute after atropine in both groups. They concluded that vagal tone was normal, for its release had the same quantitative effect in patients and controls. Their work was confirmed by Friedlander and Freyhof (1918), who used 2 mg. of atropine and found a rise of pulse rate of 30 beats a minute in 10 patients and of 28 in 10 controls. Sturgis, Wearn, and Tompkins (1919) obtained a rise of 30.4 beats a minute in 21 patients, against 21.8 in 10 controls, using 1.2 mg. of atropine subcutaneously. The degree of acceleration in their patients equalled that obtained in the other series quoted when the intravenous route was employed, and I therefore suggest that absorption may have been quicker in the "effort syndrome" cases.

2. Blood Pressure

At rest the blood pressure is normal (Cohn, 1919; Craig and White, 1934). During the first examination of the patient, when he is nervous, it is often elevated, averaging 145/85 in my series. That these high initial pressures do not imply incipient hypertension is proved by the follow-up study of Grant (1925) and by the cold pressor test of Hines (1940). Using the technique described by him, I found that 10% of 25 unselected cases gave a positive reaction, compared with 15% of controls (Hines); the average rise of blood pressure in the remaining 90% was 8/8.5, compared with 12.4/10.1 in Hines's controls. The lack of emotional response to this test was quite striking, and may be explained by its painless nature and by its complete dissociation from the constellation of ideas which commonly provoke an emotional reaction in these patients.

In normal subjects, during any kind of physical effort, the blood pressure rises slowly the first five or ten minutes, and then gradually falls away towards the resting level whether there is fatigue or not (Gillespie, Gibson, and Murray, 1925); immediately after effort there is an abrupt drop, followed quickly by a secondary rise which reaches a maximum in 10 to 90 seconds and then falls towards normal (Barringer, 1916, 1917): the greater the effort the higher the rise afterwards, and the more delayed its summit (Cotton, Rapport, and Lewis, 1917). Patients with "effort syndrome" are said to behave like normal subjects after greater effort (Cotton, Rapport, and Lewis, 1917; Mabon, 1919).

The effect of adrenaline depends upon the way it is given: if injected intravenously patients and controls react alike, the blood pressure rising 27 mm. Hg in 22 patients and 31 mm. Hg in 9 controls, combining the results of Fraser and Wilson (1918) and Hume (1918); if it is given intramuscularly or subcutaneously patients react more than the controls, as they do with reference to the pulse rate.

3. Dermatographism

Although it is often stated that dermatographism is common in "effort syndrome," there is no evidence to that effect. Cotton, Slade, and Lewis (1917) investigated the local vascular response to stroking the skin between the shoulder-blades with a blunt instrument in a group of 84 patients who happened to have "effort syndrome"; but they did not maintain that the reactions obtained were in any way abnormal, and they chose these cases only because there were no others. The simple red line occurred in 35 (with or without white borders), the flare or spread in 49; visible urticaria appeared in a quarter of them, and a fully developed wheal in 5%. Addis and Kerr (1919) found a well-defined red reaction in 36% of 413 recruits, 9% of

whom had "effort syndrome," but they did not state whether it was commoner in those with "effort syndrome" than in those without. The intensity and type of reaction depend upon the pressure exerted as well as upon the patient.

I stroked the skin between the shoulder-blades of 25 patients and 50 controls, using moderate pressure with a blunt-ended glass rod. The red reaction was obtained in all the patients: it was faint in 5, associated with a flare in 4, and with wheal formation in 1. The controls responded similarly, all but 3 showing a red reaction—6 with flares and 4 with wheals. I conclude that the capillary and arteriolar response to stroking the skin between the shoulder-blades in patients with Da Costa's syndrome is normal. It is mentioned because it is an example of a normal peripheral vascular reaction to a stimulus divorced from emotion.

4. Cold Blue Extremities

Cold blue hands occurred in 44.5% of my series. Despite the conclusion of Grace Briscoe (1918) and the remarks of Best and Taylor (1939), there can be little doubt that they are due to vascular spasm, being relieved by sympathectomy (White, 1935) and by heat (personal observations with skin-temperature thermometer). They are not constant, being often absent first thing in the morning, and being exaggerated by emotion (Mittelman and Wolff, 1939), by hyperventilation (Abramson and Ferris, 1940), and by cold.

5. Dizziness

This may occur spontaneously during or after effort, with sudden change of posture, or at any odd moment. It may be reproduced by asking the patient to stoop and then suddenly stand erect, by compression of the common carotid artery below the sinus, or by hyperventilation. As these three measures reduce the cerebral blood flow (Norcross, 1938), it is reasonable to suppose that spontaneous dizziness may be so caused. Any stimulus causing momentary fall of blood pressure or hyperventilation may be to blame; emotion is such a stimulus.

6. Syncope

Syncope unassociated with organic disease is of two types: that due to critical reduction of cerebral blood flow, as may follow a profound fall of blood pressure—the vasomotor type; and that in which no reduction can be demonstrated—the cerebral type (Lennox, Gibbs, and Gibbs, 1935). Syncope due to hypersensitivity of the carotid sinus (Weiss, etc., 1933, 1936; Ferris, etc., 1935, 1937) is usually vasomotor, but may be cerebral (Lennox, Gibbs, and Gibbs, 1935; Smith and Moersch, 1935; Robinson, 1939). Syncope following hyperventilation may be due to critical reduction of cerebral blood flow resulting from vasoconstriction (Forbes, Wolff, and Cobb, 1929; Norcross, 1938), or it may be of the cerebral type (cf. its effect on patients with petit mal and epilepsy).

In Da Costa's syndrome syncope is usually vasomotor (Cotton and Lewis, 1918; Brooks, 1924). Marked slowing of the pulse may or may not occur, and is unimportant. Adrenaline, not atropine, is curative. I have found no instance of hypersensitive carotid sinus among my patients; on the contrary, the reflex seemed to be depressed. There was no reaction in 65%; slowing was slight in 30%, moderate in 5%, and considerable in none. Spillane (1940) found no abnormal response in 90%. Douglas and I reproduced syncope in one patient by forced breathing. The pulse rate was 124 and the blood pressure 165/100 during the period of unconsciousness, so we concluded that syncope was due to cerebral vasoconstriction or that it was cerebral in type. As this patient showed hyperventilation on emotion on numerous occasions, we believe this to have been the mechanism of his frequent syncopal attacks.

Whatever the physiological mechanism of syncope, it usually represents an emotional reaction.

7. Headache

I investigated 21 cases of significant headache. They fell into two groups—throbbing and vague. There were 8 with throbbing headaches, the throb coinciding with the pulse rate. These were usually temporo-frontal, and could be initiated or aggravated by effort or by trinitrin. Undue pulsation of the cervical arteries was recorded in 3; the systolic blood pressure was between 150 and 190 in half of them; compression of the common carotid artery relieved all of them, usually only on the ipsilateral side; compression of both temporal arteries helped in 2 out of 3 in which it was tried; bilateral jugular compression relieved 6, but had no effect on the other 2. Change of posture had a variable result—3 being aggravated, 3 being relieved, and 2 remaining unchanged. This type resembles the histamine headache (Pickering and Hess, 1933) and the headaches of fever (Sutherland and Wolff, 1938), alcohol (Thomas, 1937), and other cerebral vasodilators. The essential mechanism depends upon increased pulsation of the intracranial vessels (Pickering and Hess, 1933; Pickering, 1939; Clark, Hough, and Wolff, 1936). Relief is obtained by any measure which lowers the amplitude of excursion of the offending arteries.

In the other 13 cases the headaches were vague, and obeyed no rules. Their nature remains obscure, but they are not unlike the other vague aches and pains to which these subjects are notoriously prone.

Sweating

Very little detailed attention has been paid to sweating in Da Costa's syndrome. Cotton, Slade, and Lewis (1917) compared the reactions of 8 patients and 6 controls to pilocarpine nitrate. When 1/5 grain was administered subcutaneously the response was the same in both groups. With 1/10 grain the patients reacted a little more than the controls, but the difference was not enough to be significant.

Of the utmost importance is the distribution of the sweating, for in most cases it is confined to the palms of the hands, the soles of the feet, and the axillae. The studies of Kuno (1934), List and Peet (1938a, 1938b), and others have demonstrated that this form of sweating requires an emotional stimulus. As pointed out by Darwin (1872), it is all the more remarkable because the hands are cold; but this seems strange only to those who associate sweating with heat. Thermal sweating and that induced by the cholinergic drugs have an entirely different distribution. In the main, sweating provoked by effort is thermal, but an emotional response may occur at the onset or in anticipation of effort.

Not only does the distribution of sweating in Da Costa's syndrome necessitate an emotional stimulus, but this stimulus is witnessed again and again. Typical situations include waiting for the doctor, inspection by an officer, waking from a nightmare, an anxiety attack, a fainting attack, standing behind a fluoroscopic screen, etc. Undue sweating in hot weather is rare and the effect of effort variable.

I was not surprised, therefore, to find no hypersensitivity to the cholinergic drugs. Fifteen patients and 5 controls were given 6 mg. of acetyl-beta-methylcholine (methyl) subcutaneously, the sweat reaction being observed with the aid of an iodine and castor-oil paint on which was dusted powdered starch (Minor, quoted by List and Peet, 1938a). An arterial tourniquet was placed round one arm so that an emotional sweat reaction in the palm could be detected. The degree of sweating was assessed by giving marks of 1, 2, 3, 4, and 5 for fine stippling, coarse stippling, semi-coalescence, coalescence, and trickling, respectively, and

subtracting the figure before the injection of mecholyl from that achieved after it. Five sites were selected for observation—the brow, chest, axilla, free palm, and obstructed palm. The average results are recorded in Table XII.

TABLE XII.—*Sweat Response to Acetyl-beta-methylcholine*

Cases	Brow	Chest	Axilla	Free Palm	Obstructed Palm
15 patients	1.6	1.2	0.8	0.3	0.06
5 controls	3.2	1.8	1.8	0.6	0.40

Further controls were not considered necessary because even if the next 5 did not sweat at all the reaction in the patients would still be less than in the controls. The findings are all the more impressive because the patients chosen were those with conspicuous sweating. Five other patients and 3 controls were tested with carbo-amino-acetylcholine (doryl), with similar results. It is concluded that patients with Da Costa's syndrome are not hypersensitive to cholinergic drugs.

I have checked the fact that palmar sweating is due to central stimulation by placing an arterial tourniquet round one arm and noting that sweating continues to the same degree in the obstructed palm as in the free.

Fatigue

This aspect of Da Costa's syndrome has not yet been properly investigated. Providing there is an adequate supply of fuel, oxygen, and water, and proper means of disposal of carbon dioxide and heat, the normal dog is virtually tireless (Dill, Edwards, and Talbott, 1932). The fasting blood sugar, the blood sugar at the end of effort sufficient to induce fatigue, and glucose-tolerance curves are normal in Da Costa's syndrome (McCullagh, 1934; and personal observations); there is no evidence of oxygen want, as discussed under "Breathlessness," or of dehydration; heat and carbon dioxide appear to be eliminated satisfactorily. Obvious causes of fatigue do not apply, and case histories suggest an entirely different mechanism. One patient described how he felt when a bomb dropped near him in France: he was panic-stricken, and the onset of gross fatigue was immediate and abrupt, so that he could not withdraw the bolt of his rifle, and could only crawl along with the greatest difficulty. Only a nervous mechanism could have acted so quickly.

The relation of the autonomic nervous system to skeletal muscle action is interesting. Sympathetic stimulation increases the power of voluntary muscle and reduces fatigue independent of its parallel action in mobilizing sugar (Kuntz and Kerper, 1924; Gruber, 1924); ephedrine reduces fatigue in myasthenia gravis. Injected cholinergic drugs produce a sensation of fatigue and weakness similar to that experienced by the patients; prostigmin, which inactivates cholinesterase, thereby preventing destruction of acetylcholine, is the best remedy for the fatigue of myasthenia gravis. The full significance of such facts has yet to be learned, as has the mechanism of paralysis by fright.

Suprarenal cortical extract should prove a useful ally of psychotherapy in treating fatigue. It practically doubles the effort capacity of treadmill-running normal dogs (Eagle, Britton, and Kline, 1932), increases the effort capacity of normal human beings by 50 to 500% as measured on the ergometer (Hartman, Greene, Bowen, and Thorn, 1932), quiets and improves experimental neurosis in sheep (Liddell, Anderson, Kotyuka, and Hartman, 1935), and relieves depression and reduces fatigue in psychoneurotics, including patients with "effort syndrome" (Hartman, Beck, and Thorn, 1933; Huddleson and McFarland, 1939; Schaefer and Strickroot, 1936).

Respiratory Manifestations

There can be no doubt that these patients experience a true sensation of breathlessness in circumstances which would not affect a normal person. Hurried, irregular, and shallow breathing is common in the more nervous patients, apart from effort; frequent deep sighs occur in many; in a few there is true hyperventilation, usually the result of emotion.

Breathlessness is not due to diminished vital capacity (Levine and Wilson, 1919; Adam and Sturgis, 1919) or to slowing of the circulation time (Spillane, 1940); it is not associated with excess of carbon dioxide in the alveolar air (Drury, 1920) or with excess of carbon dioxide in the blood as judged by the carbon-dioxide-combining power of the plasma, which is normal (Adams and Sturgis, 1919; Wilson, Levine, and Edgar, 1919; van Slyke, 1921), or with excess of other acid metabolites on the same grounds. On the contrary, the alveolar carbon dioxide tension is reduced; there is intolerance to carbon dioxide in the inspired air, and intolerance to accumulation of carbon dioxide when the breath is held (Drury, 1920). In my series of 200 cases the average breath-holding time was 21 seconds: it was over 30 seconds in 24%; 11 to 30 seconds in 46.6%; and 2 to 10 seconds in 29.3%. Normal subjects have no difficulty in holding their breath for at least 30 seconds (Drury, 1920; White, 1920; and 50 controls of my own). Further, after forced breathing for 45 seconds the breath-holding time remained about the same in those with low figures; indeed, many of these patients hyperventilated after forced breathing. In normal subjects rapid deep breathing for two minutes is followed by apnoea for periods up to two minutes (Haldane and Poulton, 1908); maximum hyperventilation for 45 seconds is followed by apnoea for 15 to 35 seconds (average 24 seconds) in 90 to 95% (Henderson, 1908). With the help of Drs. Douglas and Daniell, I have observed the effect of forced breathing on 100 patients with Da Costa's syndrome. Hyperventilation was carried out for 2 to 10 minutes, in the first group of 50 and for 45 seconds in the second group of 50, but as the results were similar they have been combined. Apnoea lasting 5 to 60 seconds (average 24 seconds) occurred in 65, there was quiet breathing in 5, and hyperventilation continued for one to three minutes in 30. Dividing the cases into those with considerable breathlessness and those without, it was found that 25 out of 37 breathless patients hyperventilated after forced breathing, compared with 5 out of 63 in whom breathlessness was unimportant. Although minute-volumes were not measured, other classical symptoms of hyperventilation (dizziness, paraesthesia, shakiness, etc.) were nearly always produced, showing that enough carbon dioxide was washed out to induce tissue alkalosis. All those who hyperventilated after forced breathing said that they felt breathless, the sensation being indistinguishable from their spontaneous breathlessness. The evidence indicates that these patients may feel breathless when the carbon dioxide content of the arterial blood is lowered to a degree which causes apnoea for 20 to 30 seconds in normal persons.

It follows that if the stimulation to the respiratory centre is chemical the changes must be local. For example, local vasoconstriction, which would be increased by forced breathing, might lead to local oxygen want and to accumulation of lactic acid, so that the respiratory centre would respond to an abnormally low concentration of carbon dioxide. Such a mechanism would resemble that of the dyspnoeic phase of Cheyne-Stokes breathing. In the latter, however, hyperventilation causes apnoea by burning the lactic acid and reducing the carbon dioxide tension, whereas in the cases under consideration the hypothesis is that hyperventilation, by causing undue cerebral vaso-

constriction, increases local oxygen want, encourages further accumulation of lactic acid, and induces the respiratory centre to respond to even lower concentrations of carbon dioxide. I have tested the theory in two ways. (1) Since theophylline-ethylenediamine (aminophylline, euphylline, cardophylline, etc.) abolishes Cheyne-Stokes breathing, it should have some effect on such a mechanism as that described. If its action is to stimulate the respiratory centre directly, then the breath-holding time should be diminished and post-hyperventilation dyspnoea increased; if its action is by way of cerebral vasodilatation so that lactic acid is burned by increased oxygen supply to the respiratory centre, then the breath-holding time should be increased and post-hyperventilation dyspnoea abolished or diminished. Accordingly, I gave 0.24 gramme of this substance intravenously to 5 patients immediately before repeating their respiratory tests, but it influenced neither the breath-holding time nor, so far as could be judged clinically, post-hyperventilation dyspnoea. (2) If cerebral vasoconstriction has anything to do with the breathlessness, the latter should be influenced by cerebral vasodilators; but 10 mg. of acetyl-beta-methylcholine injected subcutaneously into five patients neither improved the breath-holding time nor reduced post-hyperventilation dyspnoea. These findings therefore do not support the hypothesis.

A much more probable explanation is that the stimulus is emotional. The effect of fear on respiration has been described by Darwin (1872), Henderson (1908), Cannon (1929), Finesinger (1939), and many others. Spirometric tracings from patients with Da Costa's syndrome often show irregularity of rate, depth, and level (Christie, 1935) similar to tracings obtained from cases of anxiety neurosis and other psychoneuroses (Nielsen and Roth, 1929; Christie, 1935). That inability to hold the breath may be hysterical or due to lack of determination is suggested by the observation that very few of these patients have dyspnoea or show any kind of distress when they reach the breaking-point—in contrast to controls. Post-hyperventilation dyspnoea may also be hysterical, for Fraser and Sargant (1938) found that hyperventilation tends to induce a hypnotic state, especially in suggestible individuals; and my colleague Dr. Gillespie successfully treated two trial cases of this sort by means of hypnotic suggestion. After treatment post-hyperventilation dyspnoea no longer occurred, and breathlessness on effort was much diminished.

Whatever the true explanation, the fact that hyperventilation makes many of these patients breathless is important, because it means that whenever breathlessness is induced another mechanism is ready to increase and prolong it. The whole subject is being investigated more thoroughly by my colleague Dr. Maxwell Jones.

The Hyperventilation Theory

Collip and Backus (1920) first suggested that certain symptoms provoked by effort (e.g., cramp in runners and swimmers) might be due to ventilation in excess of that required. Spontaneous hyperventilation tetany following effort was described in five cases by Goldman (1922) and in one case by Lawrence and McCance (1930), and was mentioned by Barnes and Greaves (1936); but it was Soley and Shock (1938) who first claimed that hyperventilation was responsible for the symptoms of "effort syndrome." They described a typical case, complicated by spontaneous attacks of hyperventilation. They reproduced the symptoms in this case and in six others by forced breathing. Biochemical studies revealed a rise in the pH of the blood, a fall of the plasma carbon dioxide, and a corresponding fall of the plasma bicarbonate. Their theory is unjustified on their evidence, for the same symptoms and the same biochemical findings may be induced by forced breathing in

controls, and they made no attempt to correlate these phenomena with effort. This is essential, of course, but especially so because forced breathing before effort increases the capacity for effort in controls (Douglas and Haldane, 1909a, 1909b).

The chief symptoms of hyperventilation are dizziness, paraesthesia, shakiness, a dazed mental state, and "tonic paralysis" (Henderson, 1908). The tonic paralysis was not recognized as tetany until 1920 (Collip and Backus, 1920; Grant and Goldman, 1920). They are closely correlated with tissue alkalosis, carbon dioxide wash-out resulting in an immediate fall of plasma bicarbonate so that the correct pH level of the blood is maintained. As the amount of alkali excreted in the urine is not sufficient to account for the fall in plasma bicarbonate, it is thought that alkali passes out of the blood into the tissues. Spontaneous attacks are cured by tetany, which neutralizes tissue alkalosis by acid products of metabolism (Barnes and Greaves, 1936; Fraser and Sargant, 1938).

Certain observations may support the theory of Soley and Shock. Spontaneous hyperventilation tetany occurs typically in psychoneurotic subjects (Goldman, 1922; Fraser and Sargant, 1938; Fowweather, Davidson, and Ellis, 1940); it is usually initiated by emotion (Henderson, 1908), palpitations (Maytum, 1933), pain (Rosett, 1924), anxiety or sinking feelings (Fraser and Sargant, 1938), and may be aggravated by heat (Landis *et al.*, 1926); it may be associated with cardiovascular neurosis (Kerr, Dalton, and Gliebe, 1937; Maytum and Willius, 1934) or with acute infections of the upper respiratory tract (Goldman, 1922). Many of the symptoms of Da Costa's syndrome are reproduced by hyperventilation, and although Guttman and Jones (1940) object that palpitations and pain are very rarely reproduced, I do not entirely agree; for Douglas and I induced pain in 15 out of 38 patients in whom it occurred, and palpitations initiated spontaneous hyperventilation in all cases seen by Maytum (1933) at the Mayo Clinic, and so occupy a peculiar relation to it; further, when breathlessness is the chief symptom, forced breathing induces a sensation of breathlessness in the majority, and hyperventilation replaces apnoea at the end of the experiment. Many of the signs of Da Costa's syndrome are also produced by hyperventilation: tachycardia (Henderson, 1908; Henderson *et al.*, 1918; Hill and Flack, 1910); fall of blood pressure (Dale and Evans, 1922; Vincent and Thompson, 1928; McDowall, 1930); flushing or pallor (Collip and Backus, 1920); tremor (Henderson, 1908); increased muscle tone (Henderson, 1908); increased tendon jerks (Rosett, 1924); profuse sweating in a few (Collip and Backus, 1920); mild leucocytosis (Collip and Backus, 1920); and increased susceptibility to pain, tenderness, and tickling (Rosett, 1924). The objection that the fast breathing of patients with Da Costa's syndrome (average 27 per minute, compared with 16 per minute in controls: Drury, 1920) is too shallow to cause hyperventilation is not valid, for with rapid shallow breathing the minute-volume may vary between 3 and 24.6 litres (Mudd, 1925), and tetany may occur (Barker and Sprunt, 1922; Harrop and Loeb, 1923).

Against all this evidence, which is merely suggestive, are the facts that tissue alkalosis predisposes to greater effort (Douglas and Haldane, 1909a, 1909b), that ventilation in excess of the body's needs has not been demonstrated during effort, that the plasma bicarbonate is not reduced (Adams and Sturgis, 1919; Wilson, Levine, and Edgar, 1919), and that the urine is nearly always acid.

If there was excess ventilation during effort, sufficient to cause symptoms from tissue alkalosis, the plasma CO_2 , and consequently the plasma bicarbonate, would be lowered, and this would be reflected in the urine by a rise in the urinary pH, which is one of the most constant

and conspicuous changes in all patients and controls during hyperventilation. Accordingly, I tested the effect of effort on the pH of the urine in 17 patients and 13 controls; the graphs shown in the accompanying figure demonstrate normal development of an acid urine during effort, but they

some, and when present must aggravate certain of the symptoms. In any case, spontaneous hyperventilation is not a diagnosis, but, apart from rare organic causes, merely one mechanism by which psychosomatic manifestations are produced. It is commonest in the hysteric.

Graphs showing normal development of acid urine during effort, and a tendency to hyperventilation after effort.

do show a tendency to hyperventilation after effort. Dr. Archer has kindly confirmed these results for me by measuring total urinary acidity and urinary ammonia: both rose during effort. It follows that symptoms during effort cannot be due to tissue alkalosis. Symptoms after effort may or may not be due to hyperventilation.

According to Hill and Flack (1910) hyperventilation may cause distress by interfering with the circulation. They suggested that very deep inspirations might cause cardiac tamponade by pulling the pericardium taut. The result of this would be elevation of the venous pressure, diminished circulation through the lungs, relative anoxaemia, and carbon dioxide retention. The theory was based on their observation that normal subjects could hold their breaths for six minutes after breathing oxygen moderately deeply, but only for a minute or two after extreme hyperventilation. Henderson, Prince, and Haggard (1918) believed that this interference with the circulation might explain the absence of apnoea after hyperventilation in 5 to 10% of controls. That this mechanism does not operate in the post-hyperventilation dyspnoea seen in the breathless type of Da Costa's syndrome is easily proved. I made direct and continuous measurements of the venous pressure during and after hyperventilation in 5 such cases, but no obstruction to the cardiac inflow could be detected. Further, tachycardia is not a special feature of those with pronounced respiratory symptoms, but rather are there two types of case—those with "respiratory neurosis" and relatively normal cardiovascular behaviour, and those with "cardiovascular neurosis" and a relatively normal respiratory mechanism: the former complain chiefly of breathlessness, the latter of palpitations. The majority are, of course, mixed to a greater or less degree.

The total evidence indicates that hyperventilation cannot be held responsible for the symptoms and signs of Da Costa's syndrome, neither by causing tissue alkalosis nor by interfering with the circulation; but it does occur in

Hyperadrenalism

In a series of articles Crile (1931, 1932, 1934a, 1934b) claims that "neurocirculatory asthenia" results from hyperadrenalism, a condition parallel to hyperthyroidism. He thinks that cerebral association mechanisms are overactive, so that weak stimuli, which would not affect a normal individual, are sufficient to produce an emotional response in these persons. On each occasion the adrenal-sympathetic system is stimulated, the symptoms of effort syndrome being produced. These symptoms become associated with the stimuli in the cortex of the brain, activate the thalamus as conditioned stimuli, and so complete the vicious circle. He says that sensations from viscera usually cause the feeling which is termed "nervousness," and that the anticipation of feeling these disagreeable sensations is the common cause of the anxiety neurosis which may be present. In order to break the vicious circle Crile has evolved the operation of suprarenal denervation. He claims by this means to have cured 61% and improved 33% of 114 cases of "neurocirculatory asthenia." One of his cases has been reported separately (Anderson, 1936).

I selected a patient for suprarenal denervation—a man who had been discharged from the Army and who had returned at my request as a civilian. He was 24 years old, and gave the following history:

His parents were strong and healthy, and appeared to be normal enough when I interviewed them. Four years previously he had been brought to the edge of a nervous breakdown by repeated painful manipulation of his hands following injury to the tendons. He recovered, however, and did good work as a wood machinist until October, 1939, when documents showed that he lost his job through trade stagnation and reduction of staff. He volunteered for service in October, and in January, 1940, fell ill with influenza, after which he complained of fatigue, tremor, dizziness, breathlessness, palpitations, flushes, headaches, occasional loss of consciousness, sighing respiration, cramps, sweats, and left breast

pain. We were unable to find any cause for his condition, and he seemed very anxious to get well. Although he had been told by several doctors that his heart was diseased, he accepted our reassurance and explanation to the contrary. Examination revealed no organic disease, but there were tremor, profuse sweating of the palms and axillae, overaction of the heart, tachycardia, objective breathlessness, obvious nervousness, and shakiness. The blood pressure was 165/100 to 210/115; the pulse rate 68 to 152. While in hospital he was observed to have spontaneous attacks in which all his symptoms and signs were exaggerated.

Suprarenal denervation was kindly performed by Mr. Boyd, to his technical satisfaction, in August, 1940. The patient made an uninterrupted recovery, and during his stay in hospital appeared much improved; during air raids he showed no alarm, and said he was anxious to enter the Air Force and train as an air gunner. It was not thought advisable to make repeated examinations at that time, but he was asked to return to the hospital, and was seen by me in January, 1941.

He said he was much better, was tired of being a civilian, and wanted to know if he could now join the Air Force. A few questions revealed that he had done no work, and that on the only occasion when he had attempted it he "came over queer," just like he used to, and had to sit down. He expressed considerable anxiety about lower abdominal pain and scar tenderness. He wore a home-knitted woollen garment to protect his flanks from the cold.

Despite his protestations to the contrary, he looked as nervous and shaky as before. Tremor, sweating, overaction of the heart, and tachycardia were unchanged; the pulse rate was 100, the blood pressure 175/105. The only alteration was the change in his focus of attention: whereas he used to be concerned about his heart and lungs, he was now worried about his lower abdomen.

The lack of any sign of objective improvement in this case is not encouraging.

While the experiments of Cannon (1928) make it highly probable that the adrenal glands play their part in the mechanism of psychosomatic phenomena, there is no evidence that they hold a more important position.

(Lecture III will appear next week with a complete list of references.)

RAPID IDENTIFICATION OF CL. WELCHII BY THE NAGLER REACTION

BY

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The usual criterion for the rapid identification of *Clostridium welchii*, apart from its morphology and colony form, is the production of a stormy clot in litmus milk. However, this reaction may be falsely negative, for some strains of *Cl. welchii* are non-clotters, and with others the test fails because the inocula employed are too small. For example, in a test of 58 strains the seeding of a whole colony was insufficient to establish the growth of 32 of them in litmus milk; even the cultures that grew were slow to form a clot, 1 reacting in one day, 17 in two days, and 8 in three days. The reaction may also be positive in the absence of *Cl. welchii*, especially with mixtures of aerobes and anaerobes. Nagler's (1939) reaction—the production by *welchii* toxin of turbidity and sometimes a fine curdiness in human serum—constitutes a possible diagnostic test for *Cl. welchii*. The reaction, being inhibited by *welchii* antitoxin, has the great advantage of being serologically specific.* It has been found valuable in

routine diagnostic bacteriology of war wounds infected with *Cl. welchii*.

The reaction of a typical *Cl. welchii* and the technique finally adopted to elicit it are as follows. To one of two sterile 6-mm. (Wassermann) tubes is added 0.3 c.cm. of a mixture of equal volumes of human serum and Fildes's peptic blood digest broth; to the other tube, a control, 0.3 c.cm. of a similar mixture containing in addition 10% of concentrated *welchii* antitoxin. These test and control mixtures are conveniently made in bulk and kept at 2° C. Each tube is inoculated either with a drop of culture or with half the suspected *welchii* colony, and is observed after sixteen, forty, and sixty-four hours' anaerobic incubation at 37° C. If the reaction is positive the serum becomes turbid, and in strong reactions there appears a fine yellowish curd, which tends to float on the surface of the fluid. On spinning, three zones are seen—a compact deposit of bacilli, a more or less compact scum of fat-like material, and an intermediate fluid that is either turbid or clear, apparently depending on the packing of the fatty material in the top layer. When only a small amount of toxin is produced spinning does not cause the formation of a scum, but the fluid above the bacterial deposit is turbid. Reactions are recorded ++ or + according to whether or not a well-defined top layer is formed. The control tube shows turbidity due to bacteria only, which on spinning form a compact deposit at the bottom of a column of clear fluid.

In the hope of simplifying the technique several methods of eliciting the reaction with living cultures have been tested by both quantitative and qualitative methods. In the first the test fluids were inoculated with graded inocula of *Cl. welchii*, viable-counted by the method of Miles and Misra (1938). In the second—"the colony test"—the test fluids were sown with single colonies varying from 0.3 to 1.7 mm. on sixteen-hour blood-agar plates. A 0.9-mm. colony was found to contain 4,000,000 living organisms, so that these inocula were of the order of a million living bacilli. All tests were made with appropriate antitoxin-containing controls. The single-colony inoculum was adopted as representing most nearly the conditions of routine bacteriological testing.

Reagents and Conditions of the Test

Human Serum.—Different serum samples vary in sensitivity even when they are from one person. For example, the minimal inocula of a standard culture giving a positive reaction with three specimens of serum from one person were 400, 3,000, and 200,000 viable bacilli. However, all sera tested have been sensitive enough for use with single-colony inocula. Nagler recommends inactivation, but this is not necessary; indeed, in 5 of 12 colony tests inactivated serum proved slightly less sensitive than fresh serum. Macfarlane *et al.* (1941) and Nagler (1941) find that a suspension of hen-egg yolk in saline is more sensitive than human serum to toxin. Yolk saline, even when mixed with Fildes's broth, proved in 7 of 16 colony tests to be a poor growth-promoter of *Cl. welchii*, and the Nagler reactions with living cultures were consequently much feebler than those with the broth-serum mixture.

Antitoxin.—Concentrated gas-gangrene antitoxin (*perfringens*), with a minimum of 730 units per c.cm., prepared by the Lister Institute, was used throughout the tests.

Broth.—Nagler (1939) found that some strains of *Cl. welchii* grow only when broth is added to human serum. Comparative tests were made on serum mixed with nutrient broth (tryptic digest of ox heart) alone, and enriched with Fildes's extract or with 2% glucose. The superiority of Fildes's broth over nutrient broth for promoting growth is evident in Table I. This was confirmed in colony tests of 15 strains, when nutrient broth failed to promote

* Seiffert (1939) has described a similar flocculation in human serum to which *welchii* toxin has been added. This may be the same phenomenon, but since Seiffert specifically states that his reaction is not inhibited by antitoxin it must be assumed that the phenomenon is different. Nagler's name has accordingly been applied to the test investigated in this paper.