SPONTANEOUS HYPERVENTILATION TETANY

BY

F. S. FOWWEATHER, M.D., M.R.C.P., F.I.C.

C. L. DAVIDSON, M.B., M.R.C.P.

AND

L. ELLIS, B.Sc., Ph.D.

(From the Department of Chemical Pathology, University of Leeds and the General Infirmary at Leeds)

Tetany as a sequel to overbreathing has been known for some time. The first observations appear to have been made by Haldane and Poulton (1908), who in experiments involving forced breathing noticed that the subjects of the experiments developed tingling in the hands and feet, and certain other symptoms. It was Grant and Goldman (1920), however, who first completely identified with tetany the condition following forced respiration. Shortly afterwards the occurrence of clinical cases of hyperventilation tetany was reported by Barker and Sprunt (1922) and by Goldman (1922).

The causes of overbreathing which may give rise to tetany are numerous. They include certain cerebral conditions which presumably operate by some effect on the respiratory centre, exercise, pain, and nausea. The great majority of cases, however, have little or no recognizable organic background, but occur in those suffering from anxiety states, hysteria, or psychoneuroses, and the patients are for the most part young women.

Diagnosis in most cases is not difficult; there may be a history of disturbance of respiration, or increased rate or depth of respiration may be obvious on examination. Many authors stress the value of making the patient overbreathe and so inducing an attack. This is useful not only as a diagnostic procedure but also in demonstrating to him how, by voluntary effort to check overbreathing, he may ward off attacks. Kerr, Dalton, and Gliebe (1937), Rossier (1939), and others believe that not only typical tetany but many other clinical manifestations may be the result of hyperventilation in patients suffering from anxiety states. They describe cases, and depend largely on a hyperventilation exercise for diagnosis, as they claim that such an exercise causes the patient to reproduce the symptoms complained of.

We have observed five cases of spontaneous hyperventilation tetany. In each of them the serum calcium was determined as a routine measure, and in four the serum inorganic phosphorus also. In three of the latter the phosphorus was in the neighbourhood of 1 mg. per 100 c.cm. of serum. We believe this figure to be much lower than previously reported in this type of case. Moreover, the results in these three cases are so definitely below the normal range as to be of valuable diagnostic significance, and phosphorus determinations should therefore prove a useful addition to the methods of diagnosis already referred to. It is important to note that the specimens of blood for analysis were taken from the patients *immediately after* an attack of tetany.

Illustrative Cases

Case 1.—A nurse aged 19 was first seen on account of pains in the joints that did not respond to salicylates. The blood picture showed no anaemia, but there was a relative lympho-

cytosis. The serum gave a positive agglutination to *Br. abortus* in a dilution of 1 in 200. The spleen was not palpable. The pains continued for many weeks. On three or four occasions she had attacks starting with pain in the left side of the chest, followed by periods of deep sighing respirations lasting about half an hour, and on two occasions by tetanic spasms. One attack followed a hot bath: the patient felt breathless and began to breathe rapidly and deeply. Cramp-like pains developed in about ten minutes, and finally a typical tetanic spasm of the hands occurred. This gradually passed away, the whole attack lasting twenty to thirty minutes. Blood was taken at the end of the attack, and the serum contained 11 mg. of calcium and 1.3 mg. of inorganic phosphorus per 100 c.cm. A week later, when all such symptoms were absent, the serum contained 10.6 mg. of calcium and 3.8 mg. of inorganic phosphorus.

Case 2.—A nurse aged 21 came under observation when suffering from a cold in the head of a rather persistent kind. During the illness she had attacks of a type similar to those experienced by the previous patient; they started with pain in the chest, followed by deep sighing respirations and then by typical tetanic spasms. Just after one attack the serum contained 11 mg. of calcium and 1 mg. of phosphorus. Some time afterwards, when the patient was quite free from symptoms, the calcium was 10.6 mg. and the phosphorus 3.6 mg.

Case 3.—A married woman aged 24 complained of loss of weight, palpitation, and nervousness. There was a history of fainting attacks occurring at intervals during the previous two years, and in the past fourteen months she had had attacks beginning with stiffness of the left side, constriction of the throat, and difficulty in breathing, followed by tremors and tetanic spasms of the hands and feet. These attacks lasted about twenty minutes. She had an enlarged thyroid and was considered to be suffering from thyrotoxicosis secondary to diffuse simple goitre. There was a remarkable family history: her mother and three brothers had enlarged thyroids and a sister had undergone thyroidectomy. She was treated by x rays and later admitted as an in-patient. In hospital a typical attack of tetany occurred in the early morning. She believed it was caused by the screaming of another patient in the ward, and said that such attacks were more likely to occur when she was upset. Since then she has had two minor and less typical attacks; after one of these the serum calcium was 11.2 mg. and the phosphorus 2.1 mg. At a time when she was free from attacks the calcium was 10.4 mg. and the phosphorus 4 mg., and on another occasion the calcium was 10.7 mg. and the phosphorus 3.6 mg.

Case 4.—A married woman aged 23 was described by the house-physician as "a woman of healthy appearance and many complaints." She was an only child. She had had spasmodic dysmenorrhoea before and after marriage and after pregnancy. Attacks of sickness and dizziness had occurred over many years, and three years before admission she had a "nervous breakdown." During the past nine months she had had fainting attacks, with spasms of arms and hands and sometimes cramps in the feet. Examination revealed no abnormal physical signs. While in hospital she had two or three attacks of fainting, one of them followed by well-

marked tetanic spasm, which was immediately relieved by intravenous calcium gluconate. Another attack began with fainting, and on recovery the patient found it difficult to get her breath; her arms and trunk felt numb, stiff, and quite powerless. At the end of this attack the serum contained 11.1 mg. of calcium.

Case 5.—An unmarried female typist aged 29 was admitted with over four years' history of attacks of unconsciousness. These are said to last for three hours. She always falls on the back of her head, but is never seriously hurt; the tongue is never bitten and there is no incontinence. She has also experienced another kind of attack, which invariably follows exercise but occurs sometimes when she is at rest. She breathes deeply, sobs, and develops a tremor; her limbs feel cold, her hands and legs become stiff, and her thumbs are drawn into her palms. Following these attacks, which last about fifteen minutes, she experiences a tingling sensation all over her body and face. In this case the serum calcium was 12.8 mg. and the phosphorus 1 mg.

Precipitating Factors

In the first three of these cases attacks of tetany occurred during the course of another illness, which may well have been a contributing factor in the production of the tetany or a precipitating cause of the attacks. Hyperventilation is not an uncommon response to pain, and pains in the joints were the outstanding complaint in Case 1. It is also interesting to note that one attack followed a hot bath, which is a well-known cause of hyperpnoea. In Case 2 the feeling of difficulty in breathing consequent on the cold in the head would act as a stimulus to increased respiratory effort, leading to hyperventilation. In Case 3 the increased respiration rate due to thyrotoxicosis was probably a factor, reinforced at times when the patient was "upset" by the hyperventilation which commonly results from mental distress in many individuals. In Cases 4 and 5 spasmodic attacks were the major complaint. Both patients were obviously of neurotic type—one "full of complaints," the other giving a history of fairly typical hysterical fits.

It has been noticed in some of the reported cases that tetany has been initiated very easily by overbreathing and that occasionally the overbreathing is barely noticeable. Barnes and Greaves (1936) consider that the period of overbreathing required to produce tetany in all cases occurring clinically is greatly reduced compared with that required in normal people. This, however, is not true. In Case 2 of Kerr, Dalton, and Gliebe's series, for example, the period of overbreathing before tetanic spasms occurred was twenty-three minutes. Schultzer and Lebel (1939), while recognizing that patients of the "nervous" type are often oversensitive to hyperventilation, divide clinical cases of spontaneous hyperventilation tetany into two types—namely, those who behave like normal individuals to hyperventilation, requiring vigorous forced breathing usually for a period of fifteen or more minutes before tetany supervenes, and those who get tetany after comparatively mild hyperventilation. They describe one case of each type.

We have no doubt that variations in sensitivity to hyperventilation do exist, and these variations are probably important factors in determining the liability to tetanic attacks and the ease with which they are produced. But we are not inclined to agree with the division of cases into two clear-cut groups from this point of view. One factor involved in this sensitivity will be the condition of the patient before obvious hyperventilation occurs. In certain individuals hyperventilation is a frequent and unconscious response to relatively mild emotional stimuli, change of mood, pain, fatigue, etc. Such persons are often in a state of hyperventilation which may not easily be recognized, but which may have already initiated the process that ultimately causes tetany, so that relatively

little further hyperventilation is needed to complete the process. Schultzer and Lebel suggest that the "oversensitive" patient described by them was constantly in a state of latent tetany and thus would require little further stimulus to evoke a frank attack.

Probably the most important factor in the production of spontaneous hyperventilation tetany is the type of reaction to a variety of stimuli. Some persons may hyperventilate very little or not at all to the usual stimuli and thus will have scarcely any liability to attacks of tetany; at the other extreme are those who hyperventilate readily on the slightest provocation. Our own cases illustrate two grades of response—the first to definite physical stimuli, and the second to stimuli which are apparently temperamental or emotional in origin.

Calcium and Phosphorus Levels

The serum calcium in four of our cases was at a high normal level, while in the fifth it definitely exceeded the normal. In the three cases in which blood was examined in periods when the patients were free from attacks the figures were below those obtained just after an attack. Some authors find a slight rise in serum calcium in this type of case. Others say that the calcium is either normal or slightly raised, while others find it unchanged.

As already noted, the serum inorganic phosphorus in three of our cases was in the neighbourhood of 1 mg., while in the remaining case in which the determination was made it was 2.1 mg. In the three cases in which the serum phosphorus was determined in attack-free periods the figures obtained were between 3 and 4 mg.; one of these was the case showing 2.1 mg. immediately after an attack. Many authors omit any mention of the serum inorganic phosphorus in their cases. Where mention is made the figure is generally found to be between 2 and 3 mg. Barnes and Greaves, however, obtained figures exceeding 3 mg., and their values before and during tetany were approximately the same. (The majority of figures for normal adults lie between 3 and 4 mg.)

Where blood has been analysed in reported cases the specimens have been taken *during* the tetanic attack, and quite often during the early part of it. The fact that in our cases the specimens have been taken *immediately after* an attack accounts, we think, for the greater departures from the normal that we have observed. In this connexion the work of Haldane, Wigglesworth, and Woodrow (1924) appears to be of considerable importance. One of them kept up forced breathing for periods varying from one to one and a half hours on four occasions. Carpal spasm was present throughout most of these periods, and Chvostek's and Trousseau's signs throughout the whole of them. On every occasion the inorganic phosphorus of the blood fell below 1.25 mg. per 100 c.cm. In addition to the fall in blood phosphorus there was also a marked drop in urinary phosphate excretion: the curves for blood and urine phosphorus were parallel. The very low phosphorus excretion continued beyond the end of the period of forced breathing, and the lowest blood phosphorus was obtained in the latter half of this period. The blood phosphorus figure soon after the end of the period was not ascertained, but from the form of the urine curve it seems very probable that such a figure would also be low, corresponding closely to that found immediately after periods of clinical tetany. No mention of the blood calcium is made by Haldane *et al.*, but it seems quite probable that the maximum change here is also near the end of the period. If so, it would explain our own findings and the variable results reported by other authors, since there has apparently been no uniformity in the time at which blood has been taken by them with reference to the tetanic attacks.

As already pointed out the very low phosphorus figures we have obtained should prove useful evidence in diagnosis, particularly in otherwise difficult cases; where the actual phosphorus figure is only moderately reduced a comparison between it and the figure obtained in attack-free periods should serve a similar purpose. The low figures are also of some importance in demonstrating another similarity between spontaneous hyperventilation tetany and experimental tetany produced by deliberate overbreathing.

Alkalosis and Anoxia

Tetany following hyperventilation is generally believed to be due to an alkalosis resulting from the washing out of carbon dioxide from the blood brought about by overbreathing; there is thus a disturbance of the ratio $\text{H}_2\text{CO}_3:\text{NaHCO}_3$, on which the acid-base equilibrium of the blood largely depends. In an attempt to bring tetany due to alkalosis into line with low-calcium tetany it has been claimed that the alkalosis, although leaving the total calcium of the blood unaltered, causes the ionized fraction of it to be reduced. Thus all forms of tetany are explained as the result of a fall in the ionized calcium of the blood. There is, however, opposition to the view that in hyperventilation tetany a reduction of ionized calcium occurs. McCance and Watchorn (1937), for example, found that in a normal person and in a patient subject to spontaneous attacks the "ultrafilterable" calcium of the blood was slightly increased during attacks of tetany induced by voluntary overbreathing. Schultzer and Lebel determined the ionized calcium of the blood in the cases already referred to, and found it practically unaltered during the attacks. Moreover, in one of these cases they increased the ionized calcium by injecting 10 c.cm. of a 10% calcium chloride solution intravenously, and then got the patient to overbreathe. Tetany set in just as on previous occasions, and during the attack both the total and the ionized calcium were higher than when no calcium chloride had been given. A review of all the evidence leads to the conclusion that reduction of the ionized calcium of the blood during hyperventilation tetany has not been proved.

In addition to alkalosis, anoxia is also believed by some to be a factor of importance. Kerr, Dalton, and Gliebe quote evidence to show that alkalization of capillaries by local application will cause constriction, while carbon dioxide will dilate the capillary bed; and Rossier draws attention to the change in the dissociation curve of oxyhaemoglobin in alkalosis, which has the effect of making oxygen more tightly bound to haemoglobin and therefore less readily given up to the tissues.

Not all observers, however, accept alkalosis as the basis of the spontaneous tetanic attack; some believe it to be due to the direct effect of hyperventilation on the central nervous system. We consider the marked similarities in the chemical findings in spontaneous hyperventilation tetany and in tetany experimentally induced by voluntary overbreathing, in which there is little doubt that alkalosis is produced, to be against this view. The repeated observations that spontaneous attacks can quickly be terminated by causing the patient to breathe air enriched with carbon dioxide show that carbon dioxide deficit is an essential factor in the production of the attack; and carbon dioxide deficit is a sufficient cause of alkalosis.

Yet when alkalosis is admitted there is controversy as to whether it acts on the central nervous system or more directly on the tissues. It is well known that changes in the ratio $\text{H}_2\text{CO}_3:\text{NaHCO}_3$ in the blood are met by attempts at adjustment. Adjustment for reduction of blood CO_2 requires reduction of NaHCO_3 to maintain the ratio at a constant level. Such reduction is seen in the

elimination of some NaHCO_3 through the kidneys, but this process is not fast enough to prevent some of the NaHCO_3 from being deposited in the tissues. The fall in blood phosphate simultaneously with a great diminution of phosphate excretion in the urine during periods of hyperpnoea shows that phosphate also must pass into the tissues. It is therefore reasonable to assume that a tissue alkalosis exists which alone, or in combination with the anoxia already referred to, is responsible for the tetanic symptoms. Another consideration which favours this view is the fact that some, at any rate, of the blood changes resulting from overventilation are found to be greatest at the end of the tetanic attack. This we have shown to be the case with regard to the inorganic phosphorus, and probably of the calcium also. Yet it is seen when attacks have terminated spontaneously. If the tetany were caused by the effect of changes in the blood acting on the central nervous system it is rather difficult to understand why that action should cease when the changes are at their maximum. The difficulty disappears, however, if we assume that tissue alkalosis is the chief factor involved; for the alkalosis which causes the tetany is neutralized by its result—namely, acid metabolites produced as an outcome of the muscular spasms. The attack is thus brought to an end while the blood changes are still in evidence; reversal of the blood changes then follows.

Probable Explanation of Hyperventilation Tetany

The most probable explanation of spontaneous hyperventilation tetany therefore appears to us to be as follows:

As a result of certain stimuli—physical in some cases, emotional in others—some individuals respond by overbreathing. If this is sufficient to cause a reduction of the concentration of carbon dioxide in the blood alkalosis will follow, and this in its turn may be sufficient to cause an attack of tetany. The attack is mainly due to tissue alkalosis and comes to an end spontaneously, largely as a result of the tendency to tissue acidosis consequent on the muscular activity of the tetany itself. Cessation of overbreathing also occurs, and quickly assists in the return to normal conditions. The principal factor involved is the tendency to overbreathe. This tendency appears to be greatest in those of emotionally unstable temperament, sufferers from anxiety neuroses, etc. In these and others the tendency may be influenced by physical factors. Other factors which probably play some part are the state of the acid-base equilibrium when the overbreathing takes place and the susceptibility of the subject to alkalosis and its effects.

We should here like to make some reference to conditions other than tetany which have been associated with hyperventilation. Many of these are referred to by Kerr, Dalton, and Gliebe. Sargent (1940) has drawn attention to the part played by hyperventilation in conditions mostly described under the terms "neurocirculatory asthenia" and "effort syndrome." While it is possible that there may be other causes of the symptoms complained of in these conditions, there is clear evidence that carbon dioxide deficit is the determining factor in those cases associated with spontaneous hyperventilation. Soley and Shock (1938) investigated seven cases of effort syndrome, and showed that respiratory alkalosis was responsible for the symptoms of this condition.

It seems clear, therefore, that alkalosis resulting from spontaneous hyperventilation may cause either tetany or the conditions just referred to, but what determines the actual clinical manifestations in any given case is not apparent. Certain facts, however, seem to be of importance. First, effort syndrome and related conditions, without tetany, are rarely, if ever, seen as a result of voluntary overbreathing in normal individuals. Secondly,

in spontaneous tetany resulting from hyperventilation, and to a much less extent in the tetany induced by voluntary overbreathing in normal people, many of the symptoms associated with effort syndrome, etc.—breathlessness, dizziness, faintness, palpitation, tremor—are also present, but tend to be overshadowed by the tetanic spasms. Thirdly, in most cases of spontaneous hyperventilation tetany and in all reported cases of effort syndrome, etc., there is a background of anxiety, emotional stress, or other psychological disturbance.

Conclusions

Two conclusions of importance appear to follow. The first is that the clinical manifestations which may arise from hyperventilation cover a much wider field than is comprised by the term "tetany"; there is much justification for the use of the recently introduced term "hyperventilation syndrome" to include all these manifestations. Of this syndrome tetany is only a component, though the most striking one, particularly when the syndrome appears in normal persons. The second conclusion is that the altered reaction to overbreathing of certain patients as compared with normal individuals is due to the altered psychological state.

This altered reaction might be accounted for in various ways. Thus the changes brought about by overbreathing might fall short of what is required to produce tetanic spasms, so that attention is concentrated on the other components of the syndrome which appear. In the case of effort syndrome which Soley and Shock describe at length voluntary overbreathing caused the appearance of frank tetany immediately following the development of the symptoms originally complained of. A similar result was found in some of Kerr, Dalton, and Glibe's cases. In others, however, tetany failed to appear at all. These might be explained on the assumption that tetanic spasm is inhibited or suppressed while other components develop more or less completely. In more general terms, it may be assumed that there is an alteration of sensitivity of various tissues to the effects of alkalosis, so that, while in normal individuals and in many patients the principal manifestations are shown in the voluntary musculature, in some patients they are shown in the circulatory system, in others in the respiratory system, and so on.

We have not so far had the opportunity of investigating cases showing the hyperventilation syndrome without tetany, and we do not know if these cases produce the same changes in the blood phosphorus and calcium as in those we have reported. Information on this point, however, would be of interest, and, if these changes do occur, of value in diagnosis. Effort syndrome, for example, is, according to Soley and Shock, probably the commonest source of error in the differential diagnosis of organic cardiac disease. Additional help in the diagnosis of this and related conditions would therefore be welcome.

Summary

Five cases of spontaneous hyperventilation tetany, all occurring in young women, are described. In three the tetanic attacks occurred during the course of another illness, while spasmodic attacks were the major complaint in the remaining two.

In blood specimens taken immediately after a tetanic attack the calcium was found to be at a high normal level in four cases and above normal limits in the fifth. In the three cases in which blood calcium was determined in symptom-free periods it was definitely lower than just after the tetanic attack. The inorganic phosphorus of the blood immediately following an attack was in the neighbourhood of 1 mg. in three cases and 2.1 mg. in the other case in which it was determined. In the three cases in which it was determined in symptom-free periods the figures were between 3 and 4 mg.

This great fall in blood phosphorus has not previously been reported in clinical cases, but has been seen in experimental tetany induced by voluntary overbreathing.

The causes of spontaneous hyperventilation tetany have been discussed. Attention has been drawn to the tendency to hyperventilate in persons suffering from anxiety states, and to the tissue alkalosis which results from hyperventilation and which is considered to be the principal factor in bringing on the tetanic attack.

Reference is made to other clinical manifestations associated with hyperventilation, especially effort syndrome and related conditions.

REFERENCES

- Barker, L. F., and Sprunt, T. P. (1922). *Endocrinology*, **6**, 1.
 Barnes, C. G., and Greaves, R. I. N. (1936). *Quart. J. Med.*, n.s. **5**, 341.
 Goldman, A. (1922). *J. Amer. med. Ass.*, **78**, 1193.
 Grant, S. B., and Goldman, A. (1920). *Amer. J. Physiol.*, **52**, 209.
 Haldane, J. B. S., Wigglesworth, V. B., and Woodrow, C. E. (1924). *Proc. roy. Soc. B*, **96**, 1.
 Haldane, J. S., and Poulton, E. P. (1908). *J. Physiol.*, **37**, 390.
 Kerr, W. J., Dalton, J. W., and Glibe, P. A. (1937). *Ann. intern. Med.*, **11**, 961.
 McCance, R. A., and Watchorn, E. (1937). *Lancet*, **1**, 200.
 Rossier, P. H. (1939). *Schweiz. med. Wschr.*, **69**, 357.
 Sargant, W. (1940). *Lancet*, **1**, 314.
 Schultzer, P., and Lebel, H. (1939). *Acta med. scand.*, **101**, 303.
 Soley, M. H., and Shock, N. W. (1938). *Amer. J. med. Sci.*, **196**, 840.

THE INSULIN TREATMENT OF PULMONARY TUBERCULOSIS

BY

GEORGE DAY, M.D.

Physician, Vale Royal Abbey

In the days before there were such things as artificial pneumothoraces and thoracoplasties a great deal of attention was paid to the dietetic treatment of pulmonary tuberculosis. Patients were encouraged to eat heavily at meals and to drink lots of milk in their spare time in the belief that increase in body weight promoted healing. With the advent of surgical procedures dietetic treatment tended to be overlooked or, at any rate, to be pushed into the background. It became the fashion to feed patients on an ordinary full and attractive diet and to regard increase in body weight as an encouraging sign of improvement in local lesions, the credit being given to whatever adjuvant treatment was being employed. Indeed, in one of the latest publications on the subject (Pearson and Day, 1937) the authors had not emerged from this way of thinking, in spite of evidence to the contrary that was accumulating. They advocated an ordinary full diet such as might be given to a boat-race crew in training, although two cases were recorded in which insulin and a high carbohydrate diet had been employed with most promising results. It was the account given by Himsworth (1938) of the gratifying manner in which the diabetic consumptive responded to a high carbohydrate diet together with insulin in excess of his diabetic requirement that encouraged us to try exactly the same regime on consumptives who had not got diabetes. During the past three years we have been feeding an increasing number of our patients on a high carbohydrate diet and rendering their blood sugar low by repeated hyperinsulation. The results suggest the need for a further reshuffling of the cart and horse. Improvement in healing may after all sometimes be the result of regained body weight and not the cause. It certainly appears that improvement can be brought about by forced and "unnatural" feeding.

Technique

The patient receives five injections of insulin, each of 10 to 15 units, during the twenty-four hours. Three of them are given half an hour before the main meals—breakfast, lunch, and dinner—the other two in the middle