injection, as a test for the immunity produced. It will be seen that only 3 out of 13 guinea-pigs receiving toxoid without alum survived 1/50 of a test dose of toxin, and out of 4 none survived 1/10 of a test dose. Of the guinea-

TABLE III.—Showing the number of guinea-pigs surviving different doses of tetanus toxin given two to three weeks after the second of two doses (given at four weeks' interval) of 0.1 c.cm. tetanus toxoid diluted to 5 c.cm. with saline or with alum.

Toxin in terms of test doses.	Number of survivals out of total tested.		
	Diluent Saline.	0.01% alum.	0.1% alum.
0.01	2 out of 4	—	—
0.02	3 out of 13	2 out of 2	2 out of 2
0.05	—	1 out of 2	2 out of 2
0.1	0 out of 4	3 out of 4	2 out of 2
0.2	—	—	2 out of 2
1.0	—	2 out of 2	2 out of 3
10.0	—	2 out of 2	2 out of 2
100.0 (over 70,000 M.L.D.)	—	0 out of 1	4 out of 4

pigs given alum-toxoid, nearly all survived the injection of toxin, and 4 out of 4 survived 100 test doses.

Tetanus alum-toxoid has proved of great service in the immunization against tetanus of horses used for the production of therapeutic serum. The majority of horses given one injection of toxoid with alum have over 1 unit (U.S.A.) per c.cm. of serum four weeks later. Those given toxoid without alum rarely have over 0.001 unit. A comparison between the results with and without alum is given in Table IV. In a further series of 17 horses

TABLE IV.—Showing the antitoxic value of horses four weeks after a single injection with 10 or 50 c.cm. tetanus toxoid with varying doses of alum.

Toxoid.	Percentage of Alum.	Number of horses with antitoxic value of (per c.cm.)			
		0.0002 unit.	0.0002-0.01 unit.	0.01-1 unit.	1-30 units.
50 c.cm.	0.5-2.0	0	1	8	23
10 c.cm.	0.5-2.0	0	1	5	4
50 c.cm.	0-0.1	8	4	0	0
10 c.cm.	0-0.1	2	0	0	0

receiving toxoid without alum, 1 had 0.01 unit, and the others less than this amount; of 156 horses with alum, 124 gave over 1 unit; of these 86 had over 3 units, 20 over 10 units, and 1 had 25 units per c.cm. of serum as a result of a single injection. All the horses were tested before injection, and were proved to contain no normal tetanus antitoxin.

In the hyperimmunization of horses the addition of alum to tetanus toxin has doubled the value of the antitoxin produced. Glenny, Pope, Waddington, and Wallace (1925) showed that if horses were rested for a month or more after a primary stimulus before tetanus immunization was continued, much stronger antitoxin was produced. Ramon and Descombey (1930) have recently confirmed this. Horses with a primary stimulus of alum-toxoid that have been rested at least a month before the commencement of their main tetanus immunization produced an average of 800 (U.S.A.) units per c.cm.

A somewhat similar but smaller effect than that produced by alum has been obtained by Ramon (1926) by the addition of tapioca to toxoid. Ramon, observing that horses developing abscesses at the site of injection yielded serum of higher antitoxic value, tried various substances that would produce sterile abscesses, and eventually chose tapioca as the most suitable. It appears probable that in both cases increased antigenic response is due to delayed absorption. Alum was first tried by us in 1925,

when we wished to determine the effect of delaying absorption by presenting toxoid in a relatively insoluble form. My colleague Mr. Pope suggested the alum precipitate as a suitable product. Recent work has shown that the original idea is probably correct. Dr. Buttle, continuing this work, has found that several substances which produce relatively insoluble precipitates of toxoid also increase antigenic efficiency. Other work, not yet published, has established that toxoid, injected as a primary stimulus, is excreted with extreme rapidity, and that within a few days of injection not 1 per cent. remains in the animal body. The increase in efficiency of alum toxoid is therefore probably caused by its slow rate of absorption, so that antigenic stimulation is maintained for many days. The addition of alum to toxin has also been used with success in the immunization of horses against the toxins of scarlet fever, *B. welchii*, and dysentery.

Summary.

The immunity produced by the precipitate, formed by the addition of alum to tetanus and diphtheria toxoids, is greater than that produced by toxoid alone. The increase in certain experimental conditions has reached even a thousandfold.

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TETANY AFTER EXERCISE:

A CLINICAL AND CHEMICAL STUDY OF A CASE.

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TETANY after exercise is extremely rare. In a series of clinical cases of tetany due to overbreathing Goldman¹ refers to some students who developed tetany after a fight, but they were not personally observed by him. The only other example in the literature is that recorded by Collier²; the underlying cause in this case was never investigated. Recently we have had the opportunity of studying such a case in detail, and have clearly established the etiology of the tetany, which has proved to be alkalaemia following functional overbreathing.

History.—The patient, a girl aged 16 years and 9 months, was referred to us for examination by Dr. C. Attenborough of Camberley. Tetany first came on two and a half years ago after a lacrosse match at school; since then she had shown definite signs of tetany about six times at irregular intervals. The attacks began, as a rule, about ten minutes after games, such as tennis or lacrosse, and lasted half an hour. She never suffered during the holidays, even after vigorous exercise. Quite recently she had three seizures following the sudden death of her head mistress, which was a great mental shock. Once lately she had tetany after quite a gentle walk, and once actually in bed about noon, half an hour after Dr. Attenborough had called to see her. Calcium lactate (5 grains) and parathyroid (1/40 grain) had been given by the mouth by Dr. Attenborough, who thought that this had once been beneficial, but was recently much less so. The girl's general health has always been satisfactory, and she is described at school as "clever, good at games, and very highly strung."

Previous history disclosed nothing of etiological importance. She was breast-fed for two months, and then given Savory and Moore's food. Inquiry and physical examination revealed no evidence of rickets. Her only illnesses were chicken-pox and German measles. Menstruation began at the age of 13½, and has been regular. There have never been any of the gastro-intestinal disturbances which are associated with some types of tetany.

The family history contained nothing of importance. An elder brother had had asthma. Two younger brothers were healthy.

Physical Examination.—Nothing abnormal was found. Her pulse was rapid (100), but her heart was normal. Her hands tended to be—and were—rather cold. She was liable to chilblains on her fingers. Her teeth were somewhat soft, and required constant attention.

Experimental Investigation.

As the patient did not always develop tetany after exercise we were fortunate in being able to produce and study it on the morning when she came up from school to the hospital for examination. She was made to exercise vigorously on a stair for fifteen minutes until she was fairly exhausted. She then lay down on a couch, where she remained until she left the hospital. We noticed at once that her respiration rate did not slow down normally after exercise, and, indeed, she continued overbreathing for the next half-hour. Three minutes after she stopped running her pulse rate was 148, and her respirations 52 per minute. The latter were extremely deep as well as rapid; in fact, she seemed to be breathing as deeply and rapidly as she could. At the end of nine minutes* she announced that one of her attacks was coming on, as she could feel the usual tingling in her fingers and a tightness round the waist. In fifteen minutes tetany was fully established; her hands were fixed in the typical position and Chvostek's sign was present. The feet and ankles were slightly, but less, stiff. Knee-jerks were extremely active. The respiration rate remained between 40 and 50 per minute for thirty-two minutes, when she suddenly became apnoeic for about two minutes and the spasms rapidly relaxed. In forty minutes her hands were quite free. Her pulse rate was then 96, and her respirations 22 per minute and very shallow. By sixty-five minutes everything seemed perfectly normal, and she got up none the worse.

Chemical Investigations.

Samples of venous blood were obtained without constriction under paraffin before exercise and fifteen minutes after, when tetany had been fully established for five

	Before Exercise.	During Tetany.	Methods Used.
	Milligrams.	Milligrams.	
Serum:			
Calcium	11.7	11.8	Kramer-Tisdall. ³
Plasma:			
Inorganic phos- phorus	3.6	2.54	Briggs. ³
Magnesium	2.24	2.19	Hammett and Adams. ⁴
Sugar	104.0	102.0	MacLean. ³
Chlorides	575.0	555.0	Whitehorn. ³
Alkali reserve: CO ₂ ...	51 vols.	55 vols.	Van Slyke. ³
pH	7.37	7.42	Quinhydrone electrode.

	Before Exercise.	85 Minutes after Exercise.	Methods Used.
Urine:			
pH	6.9	8.4	B.D.H. capillator.
Ammonia	traces	0	Aeration.
Acetone	0	trace	Rothera.

Duplicate estimations were made in all tests.

minutes. Urine was obtained before and again eighty-five minutes after exercise, the latter specimen by catheter as she was unable to pass any urine at this time. The volume of the catheter specimen was only 60 c.cm. The results are embodied in the above table with the changes shown in italics. The alveolar CO₂ was estimated at intervals, but the results were not embodied in the table, as we do not feel that they are very reliable, partly because the subject was not previously trained, and partly because the respirations during overbreathing were so rapid and

uncontrolled. Before exercise a figure of 4.62 per cent. was obtained; three minutes after, 3.05 per cent.; and fifty minutes after, 3.8 per cent.

Discussion.

It was clear from these observations that our case fell into the class of tetany due to alkalaemia from over-ventilation. Tonic rigidity of the hands after overbreathing was first described in 1909 by Vernon,⁵ and has since been experimentally investigated by Collip and Backus,⁶ Grant and Goldman,⁷ and Haldane and others.⁸ A series of clinical cases has been placed on record by Goldman¹ and Adlersberg and Porges.⁹

It is obvious from the high normal level of the serum calcium that calcium deficiency was not a causal factor. It is possible that the rather high calcium value was due to the parathyroid therapy which had been stopped only four days previously.

The urinary findings are diagnostic. Ammonia disappeared from the urine; traces of acetone were excreted; and the pH changed to the maximum possible alkalinity. These changes have all been produced experimentally again and again, and leave no ambiguity. Diuresis is not unusual experimentally, but we did not obtain it.

The blood chemistry merits a little more discussion. Falls in blood phosphate of magnitudes equivalent to ours have been repeatedly obtained by Haldane and others. The majority of the experimental workers have obtained small rises in the serum calcium,^{7, 10, 11} but this has not been universal, even after very prolonged overbreathing. The rise in the pH of the blood in this case is of the same order as obtained by Grant and Goldman,⁷ but in one respect our results differ from those of the experimental workers. We obtained no fall in the alkali reserve; in fact, a small rise was observed. The fall usually obtained is explained as part of the buffering adjustment made by the body to maintain the normal pH of the blood. In our case this must have been entirely absent, and yet the change in pH was smaller than many other observers have obtained. We can offer no satisfactory explanation why our results should differ in this one respect from those of other workers, unless it be that our result was obtained with blood collected only fifteen minutes after exercise. The reduction of plasma bicarbonate of some 10 volumes per cent., recorded by other workers, has been after longer periods of overbreathing, usually thirty minutes or more.

The underlying cause of the hyperventilation we regard as "functional." The patient has never been troubled at home, but only at school, and, until recently, after definite matches into which the nervous strain of competition has entered. She has, moreover, been worse lately—since the shock caused by the sudden death of her head mistress. We classify her case, therefore, with those due to alkalaemia from over-ventilation recorded by Goldman¹ and Adlersberg and Porges⁹ in hysterical and post-epileptic subjects.

Summary.

A case of tetany after exercise has been investigated and found to be due not to the exercise *per se*, but to an alkalaemia caused by prolonged (presumably functional) overbreathing after the exercise was completed.

Our thanks are due to the excellent co-operation of the patient in a rather arduous investigation, and to Mr. Mann of the Maudsley Hospital for estimations of the blood pH.

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* All the times recorded are after the cessation of exercise.