THE DIAGNOSIS OF LATENT TETANY WITH OBSERVATIONS ON THE EFFECT OF CALCIFEROL

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The object of this publication is to call attention to some pitfalls in the diagnosis of latent tetany and to show that the usual diagnostic methods are inadequate. A more detailed account of a new hyperventilation test which was mentioned in a preliminary communication (O'Donovan, 1945) is included.

The 34 patients studied were adults and adolescents, and almost all had chronic latent tetany. This may be important, as most writers on the subject deal with children and with acute or transient tetany. All the patients in this series had hypocalcaemia—i.e., less than 9 mg. per 100 ml. of serum calcium. With the method used (Clark and Collip, 1925) the normal serum calcium varied from 9.5 to 11.5 mg. per 100 ml., but it is fairly reasonable to presume that figures between 9 and 9.5 mg. are not definitely abnormal. Hypocalcaemia is here assumed to be synonymous with latent tetany, as none of the patients had renal disease or any gross abnormality of their serum protein. If the methods of diagnosis of latent tetany in hypocalcaemia are reliable they should also be reliable in other causes of latent tetany.

It will be noted from the Table that the number of observations exceeds the number of individual patients, since patients were usually seen at intervals of six to twelve

Tests for Latent Tetany on Hypocalcaemic Patients not Receiving Calciferol

	No. of Patients	No. of Observations	No. of Positive Reactions	Positive	Negative
Chvostek's sign ..	30	85	23	27%	73%
Trousseau's sign ..	32	89	59	66%	34%
Combined test ..	13	27	23	85%	15%
Trousseau's sign and the combined test where necessary	32	58	55	95%	5%

months. Only one observation was recorded when a patient was studied daily for some days and there was no gross change in serum calcium or signs of latent tetany.

The patients' hypocalcaemia was due to surgical hypoparathyroidism (14 cases), apparent idiopathic hypoparathyroidism (2 cases), or calcium deficiency (18 cases). The last-named were mostly cases of idiopathic steatorrhoea, although dietary deficiency may have influenced some. When patients were given calciferol (50,000 to 100,000 units daily) the calcium intake was kept at an approximately normal level by instructing them to take half a pint of milk daily in addition to the usual diet.

Signs of Latent Tetany without Calciferol Therapy

Erb's sign of electrical excitability is not considered here, as it is not a feasible procedure in ordinary clinical examinations. It is unreliable in minor degrees of latent tetany in which an improved method of diagnosis is needed. It is also not so objective and clear-cut as some descriptions would lead us to believe.

Chvostek's sign is so unreliable that its sole merit is its convenience. In only 27% of observations (see Table)

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was it found positive. If it has any value it is in recent or acute tetany, as it was observed to be strongly positive in 9 out of 11 cases of hypoparathyroidism within three days after thyroidectomy. It is considered that when the tap on the facial nerve causes contraction around the mouth, nose, and eyes (+ 3 response) there is very satisfactory evidence of latent tetany and biochemical investigation is indicated. A negative or trace reaction involving the upper lip is of no significance, and should not exclude the other clinical tests for tetany.

Trousseau's Sign

This was found positive in 66% of observations (see Table). It is very dependable, as it is rarely positive in normal subjects. It is, however, sometimes positive in people of a hysterical type or in workers whose hands are held in a semi-tetanic position for some hours daily—e.g., seamstresses, cobblers, and glove or leather stitchers. Another source of error may be avoided if the test is always done on the arm that is more often used, as it is rarely positive on that side only (O'Donovan, 1945).

The technique of Trousseau's sign is seldom described adequately. The tourniquet should be applied at greater than systolic blood pressure so that the radial pulse is obliterated. This should be checked during the test. The tourniquet should be applied without painful nipping of the skin, and a sphygmomanometer is therefore advisable. For a very obese or heavy muscular arm a pressure pad may be applied on the brachial vessels and nerves. The presence of carpal spasm should be checked by feeling the muscles, as an experienced patient may voluntarily assume the position. If no cramp appears after four minutes the test may safely be considered negative.

The Hyperventilation Test

Various attempts have been made to utilize the response to hyperventilation as a diagnostic aid in latent tetany. Most authors mention the induction of tetany by hyperventilation, stating the time but not the rate. Lachmann (1941) in a detailed study of the subject considered hyperventilation a reliable means of revealing latent tetany, even more reliable than Trousseau's phenomenon, but his report did not mention controls. My first attempt (O'Donovan, 1943, 1945) to use hyperventilation consisted in getting the subject to breathe at the rate of 55 to 60 a minute for three minutes. If no tetanic manifestation appeared by then latent tetany was ruled out. In 72 normal adult controls it was observed that only 9 developed carpal cramp at or before three minutes.

This procedure has little practical value, as patients are likely to develop disturbing generalized signs and symptoms after hyperventilation for two or more minutes. Usually it is also found positive only when the tourniquet test is already positive, therefore no further information is gained. In only 7 out of 64 instances of hypocalcaemia did it indicate latent tetany when the tourniquet test was negative. Details are given in the previous publications (O'Donovan, 1943, 1945).

The Combined Test

Hyperventilation was found to be more practical in application if it was used only when the tourniquet test was negative and if begun immediately after release of the tourniquet. It can then very readily produce an isolated cramp in the ischaemic hand. The combination of the two procedures is referred to as the combined test, and the details are as follows.

The tourniquet is applied as described above for four minutes, and if no definite carpal cramp appears it is removed and the subject is asked to breathe in and out deeply at 55–60 respirations a minute. He should be sitting upright, with the hands

placed loosely on the knees. The rate may be controlled by using rhythmic pressure on a shoulder with one hand while beating the time with the other. Respirations should flow evenly from expiration into inspiration without pause and should not be unduly forcible. The hyperventilation should be started within 15 seconds after releasing the tourniquet, and the procedure should therefore be explained to the patient before the tourniquet is released. Hyperventilation is stopped at 75 seconds or sooner if carpal cramp appears. In cases of latent tetany the hand previously under the tourniquet becomes spastic before 75 seconds, while there are few or no generalized symptoms of tetany. Rarely the opposite hand becomes cramped also, but not so intensively.

The standard of 75 seconds' hyperventilation is an approximation based upon 68 observations on adults and adolescents of all ages, including 25 female medical students. The same standard is used for both sexes, except that men are asked to hyperventilate more actively. Female medical students are always more sensitive subjects for the demonstration of latent tetany, partly because they tend to carry out the test with excessive enthusiasm and partly because young educated adults are more emotional than the average hospital patient. Hence some normal individuals of this type may reveal tetany even in 60 secs. This variation in the normal control is a disadvantage which is inherent in all tests for mild degrees of latent tetany, and the important characteristic of any test is that it should be positive in a high percentage of hypocalcaemic patients and in only a very small percentage of normal subjects. A positive test then indicates the necessity for a more detailed investigation of the possible causes of tetany.

Four out of the 68 controls developed cramp before or at 75 sec., whilst in 27 observations on 13 patients there were 23 positive reactions. In 58 observations based on Trousseau's sign, and the combined test where necessary, failure to diagnose latent tetany occurred in only three (95% positive) (see Table).

Evaluation of the Combined Test

The combined test is a useful procedure to demonstrate the phenomenon of carpal spasm to applied physiology classes. It shows that tetany is often a summation of factors which increase the sensitivity of the nervous system. In this case alkalosis and the hyperexcitability in the arm are augmenting one another. The test is of some practical value in checking the efficacy of treatment in chronic hypocalcaemic patients who have hypoparathyroidism or steatorrhoea, as it obviates repeated blood analysis. In the individual patient on routine examination the error of variable degrees of hyperventilation is negligible, so that one can very readily detect a sudden drop in serum calcium. Finally, by improving bedside diagnosis the test should aid in the diagnosis of various diseases associated with latent tetany.

The combined test is an improvement on the simple hyperventilation test because it reduces the period of hyperventilation, eliminates the possibility of an unpleasant generalized tetany, and is more sensitive than either the tourniquet test or the hyperventilation test alone. It also reduces the frequency of the necessity to hyperventilate.

The disadvantages include its failure in cases of respiratory disease such as asthma and emphysema, recurrent laryngeal-nerve paralysis after thyroidectomy, and abdominal tumours which prevent the proper movement of the diaphragm. The scope of the test in pregnancy has not yet been investigated. Lastly, in any serious physical or mental disability and in children under 10 years it would be difficult to obtain the necessary co-operation. These points are serious deficiencies in the routine use of the test. There were 4 patients in a total of 34 who were unable

to hyperventilate. In two of these Trousseau's sign was already positive, and therefore hyperventilation was not necessary.

Influence of Calciferol

In the initial phase of this investigation it was observed that when hypocalcaemic patients were taking calciferol (50,000 to 150,000 units daily) the tests for latent tetany were

FIG. 1

FIG. 2

frequently negative although the serum calcium was still subnormal. Fig. 1 shows that this inhibitory action of calciferol on latent tetany cannot be entirely attributed to its effect on the serum calcium level. The data in Fig. 1 were obtained by use of Trousseau's sign followed by hyperventilation when Trousseau's sign was negative. As already stated, in 58 observations on hypocalcaemic patients,

not taking calciferol, latent tetany was demonstrated in all but three instances. In 27 observations on patients who, notwithstanding calciferol treatment, still had hypocalcaemia the state of latent tetany was demonstrated in only five instances. Calciferol seems to have this effect irrespective of whether the patients have hypoparathyroidism or calcium deficiency. Study of individual patients clearly reveals the effect of calciferol (see Fig. 2).

Discussion

What should be the clinician's criterion of dosage when treating chronic hypocalcaemia with calciferol? The drug appears to influence latent tetany both by raising the serum calcium and by some other independent effect. The doses required to inhibit the signs of latent tetany in the average case of hypoparathyroidism on ordinary diet is between 50,000 and 150,000 units daily. The dose necessary to keep the serum calcium within normal limits may be considerably larger. It would appear more reasonable to base the therapeutic dosage on a biological test than on a purely chemical estimation. The higher dosage necessary to keep the serum calcium around 10 mg. per 100 ml. may not only be unnecessary but may have a deleterious effect on the patient. It seems well established both in animals and in man that the toxic manifestations of vitamin D are not necessarily accompanied by hypercalcaemia (Reed, Struck, and Steck, 1939); while Eaton (1946) reported a hypoparathyroid patient taking calciferol who notwithstanding a normal serum calcium developed metastatic calcification.

The patients considered here, whose dosage and treatment were based on the signs of latent tetany, have so far shown no ill effect of low blood calcium such as lens opacities. The period of observation, however, is not long enough to permit conclusions.

It is difficult to explain the inhibitory action of calciferol on latent tetany that is not due to increased serum calcium. A relative increase in ionized calcium is at least a theoretical possibility. Unfortunately, complete data on serum protein are not available, but in a small number of cases studied there was no appreciable change. Feeny, Sandiland, and Franklin (1947) found no change in the serum protein fractions, except a slight alteration of globulin fractions, in cases of lupus vulgaris receiving large doses of calciferol. Ingram, Anning, and Dawson (1948) recently reported that the high dosage of calciferol used in treatment of lupus vulgaris did not alter the ionized calcium fraction but significantly increased a diffusible calcium complex. It is unlikely that this alteration would have any bearing on the inhibition of latent tetany as described above.

Summary

The clinical tests for detection of latent tetany in adults and adolescents were investigated, using hypocalcaemia as an index of latent tetany. Almost all the patients observed had chronic latent tetany. It was concluded that the well-known tests are unreliable. The tourniquet test was negative in 34% of 89 observations on 32 patients and Chvostek's sign was negative in 73% of observations.

A new test combining the tourniquet test and hyperventilation is described. It is used when the tourniquet test is negative, and is more reliable than either of the two procedures used separately. Of 58 observations on 32 patients 95% were positive. Two other patients whose tourniquet test was negative were physically unable to hyperventilate.

Calciferol has an inhibitory effect on the signs of latent tetany which is independent of the increase in serum calcium. In 22 of 27 observations on patients who had received a total of more than 500,000 units the signs of latent tetany were negated although the serum calcium was still less than 9 mg.

per 100 ml. Calciferol therefore inhibits latent tetany in two ways. The significance of this observation in the treatment of chronic latent tetany is discussed.

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PATHOGENIC STAPHYLOCOCCI

DETECTION OF α -LYSIN PRODUCTION ON RABBIT- AND SHEEP-BLOOD-AGAR PLATES

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The coagulase reaction is the simplest and perhaps the most important test for pathogenicity of the staphylococcus. However, the agreement between pathogenicity and this reaction, although close, is not absolute (Christie, North, and Parkin, 1946), and it is sometimes desirable to use confirmatory tests. This is especially the case when detecting carriers of pathogenic staphylococci. Christie and his co-workers (1946), having examined a very large number of strains, conclude that the production of α -lysin is the property most closely associated with pathogenicity. This conclusion is shared by Schwabacher *et al.* (1945).

Until recently it was commonly believed that the lysis of a blood-agar plate was an unreliable guide to pathogenicity. The relatively tedious detection of α -lysin in supernatants from broth cultures is still often recommended (Knott, 1947). However, several workers have used sheep-blood-agar plates successfully for this purpose. The changes produced by α - and β -lysins on this medium can usually be distinguished with ease (Naidu, 1934; Bryce and Rountree, 1936; Kojima and Kodama, 1939; Christie and North, 1941). Christie, North, and Parkin (1946), using spot inoculation of strains on sheep-blood-agar plates, observed that with nearly all haemolytic strains there was no difficulty in deciding whether they produced α - or β -lysin. However, with strains producing only a trace of lysis on blood agar it was difficult to decide whether this was due to α -lysin or to something else. Williams and Harper (1947) describe a sheep-blood-plate method similar to that of Christie and his co-workers, except that a control plate containing incorporated α -antitoxin is included with each batch of tests, which are incubated in an atmosphere containing 30% CO₂. They found that the method, although reliable, failed to detect about 2% of α -toxigenic strains (positive by broth method) and that β -lysin, when produced, could mask the α -lysin. They recommend that all apparently negative and all evidently β -toxigenic strains should be tested in a tube before being classed as non- α -toxigenic.

The rabbit-blood-plate method of α -lysin detection described here is simple to perform and gives results which are easily interpreted. Other lysins do not interfere with the test.