THE SERUM CALCIUM IN WHOOPING COUGH

BY

Archd. W. Mc. Crorie, M.B.Ch.B.

December 1929.

THE SERUM CALCIUM IN WHOOPING COUGH.

INTRODUCTION.

Whooping cough is a specific infectious disease characterized by catarrh of the respiratory tract and by paroxysms of coughing terminating in a "whoop". In addition to the local manifestations there is some degree of toxaemia, and the nervous system is profoundly affected.(1) There is little doubt that the vagus and recurrent laryngeal nerves are particularly irritated by the toxin, and this alone may be sufficient to account for the paroxysm and the subsequent vomiting. Some believe that the cause of the whoop is the action of toxins on the spinal cord and that this causes a reflex action which is transmitted through the vagus to the lungs and larynx. It has also been stated that the whoop is due to the enlarged bronchial glands, (which are characteristic of the disease) pressing on the vagus and recurrent laryngeal nerves.

In some cases the nervous irritability is so marked that a touch or the turning of the patient in bed will excite the whoop. Convulsions are frequently observed in whooping cough, more commonly in severe cases of the disease, but in a few instances even in mild cases, and frequently even a slight stimulus will induce one. These convulsions were attributed,

by the older writers to asphyxia, cerebral haemorrhage, meningitis, and encephalitis, but Ker states that definite pathological lesions have rarely been found in these cases.

From the above it will be seen that in most cases of whooping cough there is a marked hyperexcitability of the nervous system, which is due probably to the action of toxins produced by the organism which causes the disease. It is an established fact that in many cases of irritability of the nervous system there is a definite upset in the calcium metabolism, and it was decided therefore to estimate the serum calcium in a series of cases of whooping cough - a disease which on account of its nervous manifestations might be expected to furnish instructive and interesting data in this direction.

ORIGIN AND CHEMISTRY OF SERUM CALCIUM.

Calcium, in the human body, is derived chiefly from milk, green vegetables, animal tissues and blood. It is absorbed in the form of soluble calcium phosphate, and is excreted mainly in the faeces and to a slight extent in the urine. In health it has been shown that calcium is present in the blood in very constant amounts, the normal serum calcium in health being 10 millegrammes per 100 cubic centimeters and anything below 9 mg.

per 100 cc. or above 11 mg. per 100 cc. is abnormal. A serum content so constant as this points to some mechanism which regulates the absorption, elimination and deposition of calcium, and this constancy suggests that calcium plays an important part in the life of the individual. It is thus assumed that the calcium of the blood can be taken as an index of the calcium in the body in general.

We will now consider briefly the state in which calcium exists in the blood. (2) According to Howland tricalcium phosphate $Ca_3 (PO_4)_2$ is present in the serum, but it is relatively insoluble, giving rise to free calcium ions. Under the influence of the carbonic acid of the plasma it is converted into the more soluble calcium bicarbonate $Ca (H CO_3)_2$ and calcium hydrogen phosphate $Ca H P O_4$ in accordance with the equation:-

$$Ca_3 (PO_4)_2 + 2 H_2 CO_3 \rightleftharpoons 2 Ca H PO_4 + Ca (H CO_3)_2$$

$$\rightleftharpoons 2 Ca^{++} + 2 H P O_4^{--} + Ca^{++} + 2 H C O_3^{-}$$

It is obvious that the amount of these soluble calcium salts present in the blood and consequently the amount of calcium in the active ionic form, will depend on the carbonic acid tension. If for any reason the carbonic acid tension is reduced the equations will act from right to left and some of the insoluble tricalcium phosphate is reprecipitated. Furthermore, in such

an equilibrium, as is represented by these equations, a change in the concentration of any one ion will at once produce changes in the concentration of the other ions. The chemical conclusions from this statement may be summarised thus:-

$$\frac{(Ca^{++}) \times (HCO_3^-) \times (HPO_4^-)}{(H^+)} = K \text{ (constant)}$$

A reduction in the carbonic acid tension of the blood and so in the hydrogen ion concentration will lower the denominator in this equation, and therefore an equivalent diminution in the numerator will occur, i.e. the concentration of calcium bicarbonate or phosphate ions must correspondingly fall. Alkalaemia will therefore tend to lower the blood calcium and acidaemia will tend to raise it. Further, if a fall in the blood calcium occurs primarily one would expect to find a raised HCO_3^- or HPO_4^- content or a diminished hydrogen ion concentration.

The amount of the total calcium in the serum is used as an indication of the calcium supply in the living body. All of this calcium, however, is not in the same state of chemical combination. The quantity that is in an ionised state has been variously estimated as only 20 to 25 per cent of the total.[3] Salvesen and Linder[4] suggest that part is in

combination with protein, and this part will not only be in an un-ionised form but in an non diffusible form, and therefore not easily available for utilisation by the tissues. The diffusible calcium is not easily estimated with accuracy but from observations by many workers it would appear to constitute 50 to 60 per cent of the total.(5)

Since this diffusible calcium is alone available for producing specific or ionic calcium effects, it is obvious that the figure for the total calcium of the serum may not give a true indication of the available calcium. From the work of Vines(6) it would appear that about 4 mg. of calcium per 100 c.cs. that was in a non diffusible form in the whole blood, is converted into a diffusible form, during the process of clotting. If this is confirmed, the figure of the total serum calcium is still further from being a true indication of the available calcium.

In considering the significance of departures from the normal values for the calcium content of the serum it is important therefore to remember that they may affect (a) the non-diffusible fraction combined with protein, (b) the diffusible and easily ionised fraction, or (c) the ionised fraction. It is possible that even when normal values for the total calcium are obtained, the available calcium may be present in deficient amounts.

It appears that the corpuscles contain little or no calcium, and that true plasma contains 10 to 20 per cent more calcium than does the serum but this does not prevent the serum calcium being taken as a guide to the calcium metabolism; figures for serum are more reliable than those of whole blood owing to the variability of corpuscle volume.

Another very important factor in the calcium metabolism is the secretion of the parathyroid glands. It has been shown by the works of Collip and others that this secretion regulates the calcium level in the blood or perhaps maintains the correct balance between the various ions in the blood. Collip has prepared a hormone from the parathyroid glands which when injected into dogs after thyro-parathyroidectomy prevents tetany and raises the blood calcium. In normal animals this hormone has been found to raise the blood calcium as much as 100 per cent above normal. Stewart and Percival (7) have shown by animal experiments that parathormone does not increase the blood calcium by increasing the absorption from the intestine, nor does it diminish calcium excretion and thus increase calcium retention. It must therefore act by withdrawing calcium from the tissues and eventually from the bones. It is therefore of no use where it is desired to increase calcium absorption.

The process of calcium absorption will now be considered. Calcium is absorbed by the small intestine but only when the reaction of the contents is slightly acid. Therefore if for any reason the reaction is persistently alkaline, calcium will be absorbed in deficient quantity or not at all. It is important that the amounts of calcium and phosphorus in the diet should be insufficient quantity and properly balanced, since excessive amounts of phosphorus tend to impair the absorption of calcium. Certain fats must be present in the dietary; a child fed on a low fat diet shows a negative calcium balance. The absorption of calcium from the bowel can be increased by the oral administration of Vitamine D. in the form of cod-liver oil or irradiated ergosterol and also by artificial ultra-violet therapy. The presence of Vitamin D. is probably the most important factor of all.

The chief functions of calcium in the body are:-

1. It is necessary for the clotting of blood.
2. It is essential for controlling the excitability of nerves, when Ca (and Mg) are diminished the K and Na ions overact and cause this excitability.
3. It is necessary for the contraction of the heart muscle and has a stimulating action on the peripheral circulation.
4. It helps in maintaining the ionic balance

$$\frac{Na \quad K}{Ca \quad Mg} = \text{constant.}$$

5. It is necessary for the ossification of bone.
6. It has an effect on the phosphorus ions, in that they appear to be inter-dependent.
7. It favours the passage of water from the tissues into the blood.

As we have already stated, the normal serum calcium is 9 - 11 mg. per 100 cc. and this is at present the most reliable index we have to the calcium metabolism of the body. It has been shown by several workers that in certain diseases there are marked variations from the normal. In infantile tetany the serum calcium may fall as low as 3.7 mg per cent, (8) and it is also reduced in rickets, in certain forms of nephritis and in certain skin diseases. It is increased in osteitis fibrosa and in neuralgia. (9) It would seem that hypocalcaemia is a more serious condition than hypercalcaemia, as the former is accompanied by the more severe constitutional symptoms, although extreme hypercalcaemia has caused death in experimental animals.

It will be seen from the above that the study of the calcium metabolism is a wide and important one and that there are still some aspects of it which are not yet fully understood.

DESCRIPTION OF METHOD USED FOR ESTIMATING THE SERUM CALCIUM.

There have been several methods brought forward in the last ten years for estimating the amount of calcium in the blood, some using whole blood, some plasma and some serum. The following is a description of the method used in this series of cases. It is a modification of the method of Kramer and Tisdall by Clark and Collip.(10)

The principle of this method consists in precipitating the calcium as oxalate, and the precipitate after washing and dissolving in sulphuric acid is titrated with permanganate.

Two cubic centimeters of serum are measured into a 15 c.c. graduated centrifuge tube containing 2 c.c. of distilled water, to this 1 c.c. of a 4% solution of ammonium oxalate is added and mixed by tapping the lower end of the tube, this is allowed to stand for at least 30 minutes. The mixture is then centrifuged for 5 minutes until the precipitate is well packed in the bottom of the tube, the supernatant fluid is decanted, and the tube inverted on filter paper where it remains draining for 5 minutes. The mouth of the tube is wiped with a fine cloth and the sides washed down with 3 c.c. of a 2% ammonia solution,

directed in a fine stream from a wash bottle. The tube is again centrifuged and drained as before. Two c.c. of N. $H_2 SO_4$ are blown on to the precipitate from a pipette in order to break it up and facilitate solution. The tube is placed in a boiling bath for about one minute, until all the precipitate has dissolved. The oxalic acid is titrated with $\frac{N}{100}$ potassium permanganate solution until a definite pink colour, which must persist for at least one minute appears. During the titration the tube is kept in a bath of water maintained at a constant temperature of 70° - 70° C. A microburette graduated in 0.02 cc. is used for the titration.

Calculation. The number of c.c. of permanganate used, multiplied by ten, will equal the number of mg. of calcium per 100 c.c. of serum. The amount of $\frac{N}{100}$ permanganate needed to impart a definite pink colour to 2 c.c. of fluid must be determined and subtracted from the quantity of permanganate used in the final titration.

Reagents. The permanganate is kept as $\frac{N}{10}$ solution and freshly made up to $\frac{N}{100}$ each time it is used. It is then standardised against an $\frac{N}{100}$ sodium oxalate (Sorensen) solution, before being used for the blood calcium estimation. All glass apparatus was washed first with acid and then with distilled

water. The centrifuge tubes were cleaned with sulphuric acid bichromate mixture and washed with distilled water each time before they were used.

SERUM CALCIUM IN SOME CONTROL CASES.

In order to test the accuracy of the method and to become accustomed to it, various blood calcium estimations were made in normal individuals. During the first 50 estimations in whooping cough one or two blood calcium estimations were made in control cases. These controls are of interest as they were cases of bronchopneumonia (acute and convalescent) of the same age group (6 months to 6 years) as the whooping cough cases and many of the latter were complicated by bronchopneumonia.

RESULTS IN 20 CASES OF BRONCHOPNEUMONIA.

Case.	Sex.	Age.	Acute.	Convalescent.	Serum Calcium in mg per 100 c.c.
1	F	3	"		9.1
2	M	4	"		10.8
3	M	2	"		10.3
4	M	1 3/12	"		10.8
5	M	1	"		9.7
6	M	4	"		9.0
7	M	9/12	"		10.5
8	F	2 9/12		"	9.8
9	M	9/12		"	8.7
10	F	10/12		"	8.5
1	M	5		"	9.5
2	F	5		"	9.4
3	F	1 8/12		"	12.0
4	F	1 5/12		"	10.5
5	F	9/12		"	8.8
6	M	1 4/12		"	10.8
7	F	7/12		"	10.5
8	F	2		"	10.5
9	M	4		"	11.4
20	M	3		"	9.0

The average serum calcium in twenty cases of bronchopneumonia is 9.9 mg per 100 c.c. which is within normal limits.

THE SERUM CALCIUM IN 110 CASES OF WHOOPING COUGH.

An attempt was at first made to note every spasm in the 24 hours, but this was soon found to be impossible in a busy whooping cough ward. In the following tables of results the spasms are classified as mild, moderate and severe.

Mild means that the spasms were infrequent and never very distressing.

Moderate tends towards the mild type, perhaps severe for a day or two but soon becoming mild.

Severe is the full-blown distressing whoop, frequent and severe over a considerable period.

This estimate of the spasm was carefully considered by the ward sister from the time of admission, and her estimation was taken in all cases. It may thus be considered constant, and more accurate than a record of the number of spasms estimated by several people during the twenty-four hours.

The duration of the disease at the time when the serum calcium was estimated cannot be considered accurate in every case. It is taken in most instances from the history supplied

by the parent, and may be regarded as dating from the time that the first whoop was heard. This factor has a certain amount of interest, as will be seen later.

RESULTS IN 110 CASES OF WHOOPING COUGH.

Sex.	Age.	Duration in days.	Estimate of spasms.	Serum calcium in mg. per 100 c.c.
F	3 6/12	30	Severe	7.3
F	6	8	Mild	8.2
F	1	12	Mild	10.4
M	2	6	Moderate	8.8
M	2	11	Moderate	7.9
F	10/12	5	Mild	10.5
F	1 5/12	16	Moderate	7.2
M	1 4/12	14	Severe	5.6
F	5	9	Mild	10.5
M	1 4/12	7	Severe	8.5
F	6/12	6	Severe	8.6
F	9/12	-	Moderate	8.4
M	1 2/12	-	Severe	9.2

Case.	Sex.	Age.	Duration in days.	Estimate of spasms.	Serum calcium in mg. per 100 c.c.
4	M	4	6	Mild	9.9
5	M	1 11/12	7	Severe	8.5
6	M	4	18	Mild	9.0
7	F	1 7/12	-	Moderate	7.5
8	M	1 6/12	-	Moderate	9.6
9	M	4	7	Mild	10.2
20	M	8/12	10	Severe	7.1
1	F	3/12	22	Mild	9.0
2	F	11/12	-	Mild	10.5
3	F	2 9/12	9	Mild	9.4
4	F	5	15	Severe	10.6
5	M	6/12	13	Mild	9.4
6	F	2	12	Severe	9.4
7	M	11/12	3	Severe	8.3
8	M	10/12	19	Severe	7.2

Case.	Sex.	Age.	Duration in days.	Estimate of spasms.	Serum calcium in mg. per 100 c.c.
29	F	2	10	Moderate	8.8
30	F	2	21	Severe	8.9
1	M	$\frac{10}{12}$	10	Moderate	7.2
2	M	1 $\frac{9}{12}$	17	Mild	10.5
3	F	1 $\frac{9}{12}$	21	Moderate	9.7
4	M	$\frac{5}{12}$	32	Severe	7.4
5	M	$\frac{4}{12}$	17	Severe	8.2
6	F	4	5	Severe	9.9
7	M	1 $\frac{5}{12}$	-	Severe	6.9
8	F	5	-	Severe	8.5
9	M	1 $\frac{10}{12}$	18	Mild	9.0
40	M	5	20	Moderate	9.7
1	F	6	10	Severe	9.0
2	M	2 $\frac{6}{12}$	17	Severe	7.8

Case.	Sex.	Age.	Duration in days.	Estimate of spasms.	Serum calcium in mg. per 100 c.c.
43	F	6	20	Severe	9.0
4	F	2 $\frac{11}{12}$	21	Severe	9.9
5	F	7	27	Severe	9.0
6	F	4	22	Severe	10.0
7	M	2	6	Severe	8.5
8	M	1 $\frac{3}{12}$	6	Severe	8.1
9	F	1 $\frac{1}{12}$	17	Moderate	8.0
50	F	$\frac{9}{12}$	19	Mild	8.4
1	M	5	7	Severe	9.1
2	F	$\frac{8}{12}$	10	Moderate	9.0
3	M	1 $\frac{6}{12}$	14	Moderate	9.4
4	F	4	28	Moderate	9.6
5	M	4	12	Moderate	10.5
6	M	1 $\frac{2}{12}$	18	Severe with convulsions	6.3

Case.	Sex.	Age.	Duration in days.	Estimate of spasms.	Serum calcium in mg. per 100 c.c.
57	M	1 2/12	18	Severe	8.5
8	F	1 4/12	5	Severe	8.1
9	F	11/12	8	Moderate	8.6
60	M	1 5/12	17	Severe	8.5
1	M	6/12	18	Severe	6.9
2	M	8/12	10	Severe	8.0
3	F	8/12	27	Severe	7.4
4	F	1 9/12	11	Severe	9.3
5	F	1 4/12	13	Moderate	9.6
6	M	4/12	13	Moderate	8.9
7	M	3 6/12	14	Severe	9.6
8	M	1 3/12	28	Mild	10.2
9	M	1	22	Severe with convulsions	6.4
0	F	2	9	Mild	9.6

Case.	Sex.	Age.	Duration in days.	Estimate of spasms.	Serum calcium in mg per 100 c.c.
71	F	3 6/12	23	Mild	10.0
2	M	1 6/12	32	Mild	9.0
3	M	1	34	Severe	7.3
4	F	5	7	Severe	10.3
5	M	3	9	Moderate	9.0
6	M	10/12	28	Moderate	8.7
7	F	11/12	9	Moderate	9.1
8	M	5 6/12	30	Severe	8.7
9	M	1 7/12	12	Severe	8.8
0	M	7/12	18	Severe with convulsions	6.5
1	F	1 4/12	15	Mild	9.9
2	M	4	13	Moderate	9.0
3	F	6/12	12	Severe	7.6
4	M	4	12	Severe	10.1

Case.	Sex.	Age.	Duration in days.	Estimate of spasms.	Serum calcium in mg. per 100 c.c.
85	M	$\frac{7}{12}$	15	Severe	8.7
6	M	3	13	Mild	9.9
7	F	3	19	Severe	8.8
8	M	6	7	Severe	10.6
9	F	$1\frac{2}{12}$	5	Moderate	9.0
90	M	$\frac{10}{12}$	4	Moderate	9.1
1	M	$\frac{7}{12}$	8	Severe with convulsions	7.1
2	M	6	6	Severe	8.9
3	F	$1\frac{1}{12}$	12	Mild	10.0
4	M	1	21	Moderate	9.4
5	M	$1\frac{6}{12}$	10	Severe	8.5
6	F	$1\frac{6}{12}$	11	Mild	9.7
7	M	$1\frac{8}{12}$	9	Moderate	7.9
8	F	$2\frac{2}{12}$	-	Moderate	10.2

Case.	Sex.	Age.	Duration in days.	Estimate of spasms.	Serum calcium in mg. per 100 c.c.
99	M	1 5/12	-	Mild	9.5
100	F	8/12	7	Severe with convulsions	6.5
1	F	10/12	16	Moderate	9.2
2	F	10/12	8	Moderate	8.0
3	M	9/12	16	Severe	7.5
4	M	9/12	8	Severe with convulsions	7.3
5	F	7/12	9	Moderate	9.8
6	F	1	10	Mild	10.2
7	M	2 4/12	20	Severe with convulsions	7.7
8	M	11/12	8	Mild	10.5
9	F	2	16	Mild	9.0
110	F	1 6/12	13	Moderate	9.1

SUMMARY OF RESULTS.

1. The average serum calcium in 110 cases of whooping cough was found to be 8.7 mg. per 100 c.c.

2. The average serum calcium in 26 mild cases of whooping cough was 9.6 mg. per 100 c.c.

3. The average serum calcium in 53 severe cases of whooping was 8.2 mg. per 100 c.c.

4. The average serum calcium in 12 severe cases between the ages of 4 - 6 years was 9.5 mg. per 100 c.c.

5. The average serum calcium in 28 severe cases below the age of 1½ years was 7.5 mg. per 100 c.c.

6. The average serum calcium in 7 cases of whooping cough complicated by convulsions was 6.8 mg. per 100 c.c.

EXTRACTS FROM THE LITERATURE ON BLOOD CHEMISTRY IN WHOOPING COUGH.

I can find no references to the serum calcium in whooping cough in the literature of this country, but in America some work has been done on the blood chemistry in this disease.

Regan and Tolstoonhov (11) state that they determined the calcium content of the plasma in 46 cases of whooping cough by the method of Clark. Slight variations from the normal were noted in some cases but the majority of the analyses gave results within the normal range, the average in 17 cases being 10.7 mg per 100 c.c. They found, however, that the hydrogen ion concentration of the blood was low in many cases, the lowest results being found in the most severe cases and in the full paroxysmal stage. They also found in many cases a lowering of the inorganic phosphorus content of the plasma. They found normal values for urea, uric acid, creatinin, and sugar.

In another article (12) the same authors state - "In cases of pertussis studied, the calcium determinations carried out in 58 specimens of serum gave figures showing some varia-

tions but averaging before treatment 10.5 mg. in 34 analyses. In only 8 or 23% was there more than one mg. less than the normal value given by Howland and Kramer (10.5 - 11) and only two of the 8 cases were below the normal range according to de Wesselow's figure (9 - 11). This variation of one mg. in a few cases is not significant as an alteration because of possible error in determinations. Therefore we do not consider the calcium content altered in any constant way in pertussis, although it is possible that slight changes may occur as the result of shifting of calcium in connection with the characteristic phosphorus and P/K alterations."

On the other hand Powers (13) found that the serum calciam in five cases of pertussis with convulsions was 4.9 mg, 7.6 mg, 7.9 mg, 8.9 mg, and 7.9 mg. per 100 c.c. He thinks that these were probably all cases of latent tetany, and concludes "the calcium content of the blood and the electrical reactions of all infants with whooping cough should be determined if possible and therapusis guided by the evidence for or against latent tetany."

Sheffield (14) states - "I wish to direct particular attention to the marked antispasmodic value of calcium and sodium hypophosphites in mitigating and often arresting the "whoop" in pertussis". He goes on to state that he thinks

that the parathyroids may be damaged as a result of the harassing cough in the earliest stages of pertussis and this damage would presumably cause an upset in the calcium metabolism.

Smith (15) has published results showing that the exposure of children who have whopping cough to Röntgen rays has a marked effect in reducing the frequency and severity of the spasms. He believes that this is due to a diminution in size of the peribronchial glands, which are enlarged in pertussis. Others believe that the benefit is due to an increase in the serum calcium, but calcium estimations were not made in Smith's cases.

To summarise these extracts we see that Regan and Tolshoonhov found variations in the serum calcium in some cases but do not consider it important. Powers found the calcium content markedly diminished in cases with convulsions. Sheffield found great benefit from calcium therapy which would seem to indicate a lowering of the serum calcium. The beneficial effects of Röntgen rays may be due to an increase in the serum calcium.

It is obvious therefore that the investigation of the calcium metabolism in whooping cough may be of considerable importance.

SUMMARY AND COMMENT OF RESULTS IN 110 CASES OF WHOOPING COUGH.

From my own results it is evident that the average figure for the serum calcium is less than normal, namely 8.7 mg. per 100 c.c. this being .3 mg. less than de Wesselow's lower figure and 1.8 mg. less than that of Howland and Kramer. From a study of the results, however, it will be seen that the serum calcium is not by any means lowered in every case.

In the mild cases the average calcium content was within normal limits, the average in 26 such cases being 9.6 mg. This result I think is what one might expect. In these cases there was no marked hyperexcitability of the nervous system, and as far as the serum calcium content is related to this we would expect little or no alteration.

In the severe cases the serum calcium was below normal limits. In 53 cases age $\frac{6}{12}$ - 6 yrs. it was 8.2 mg. while in 28 cases aged $\frac{6}{12}$ - $\frac{18}{12}$ it was as low as 7.5 mg. In these cases there is extreme hyperexcitability of the nervous system, the slightest stimulus being sufficient to produce a paroxysm.

As hyperexcitability of the nervous system and a low serum calcium are closely related, the results appear to be what one might expect. Before attempting to explain the low calcium content in severe cases the following points must be made clear.

It is well known that whooping cough is generally divided into two stages. First the invasion or catarrhal stage which lasts from 8 - 14 days, although in severe cases, according to Ker, (16) it may last only a few days. The second, or paroxysmal stage, lasts on an average six weeks and is usually most severe in the second and third weeks.

It must be understood that none of the calcium estimations in this series took place in the catarrhal stage, all took place after the child had been heard to whoop. The earliest estimation took place 3 days after the child had been heard to whoop, this was case No.27 and here the serum calcium was 8.7 mg. In two cases 5 days after the whoop, case No.36, was 9.9 mg. and case No.58 was 8.1 mg. In case No.1, 30 days after the first whoop the serum calcium was 7.3 mg. and in case No.73, 34 days after the whoop it was 7.3 mg. We thus cannot say at what stage the lowering of the serum calcium takes place in severe cases, but as will be seen from the above it may be very early in the paroxysmal stage and may continue low until near

the end of this stage.

Can we account for a low serum calcium in severe cases of whooping cough?

According to Sheffield (14) the parathyroids may be damaged by the harassing cough in the earlier stages of pertussis, but as we have shown above the first stage in severe cases may be very short and the serum calcium low in the earliest part of the second stage, then there is hardly time for the parathyroids to be damaged, so this does not seem a suitable explanation.

It has been stated previously that calcium is absorbed only when the reaction of the small intestine is slightly acid. There is every reason to believe that in many cases of whooping cough the digestion is extremely weak owing to the vomiting, and this vomiting may get rid of most of the gastric H.~~ce~~ Cl, the small intestine remain alkaline and thus calcium is not absorbed.

Regan and Tolstoonhov (11 & 12) have found a low inorganic phosphorus content of the blood in whooping cough. It has been demonstrated by several workers that the blood calcium and phosphorus are both low in certain types of rickets, and that the calcium and phosphorous metabolism appears to be inter-

dependent. The explanation in rickets is believed to be an alkaline reaction small intestine and the absence of Vitamine D. It is possible that this happens in whooping cough.

In an article on calcium retention Oscar Loew (17) states - "It is therefore a logical inference that the losses of calcium are smaller (or the calcium retention is greater) when the degree of blood alkalinity is high." Then as Regan and Tolstoonhov (11 & 12) have stated, there is a low hydrogen ion concentration (an acidosis) in whooping cough. We would expect an increased loss of calcium and therefore a low blood calcium in this disease.

Included in the severe cases there is a group of 12 children between the ages of 4 and 6 years, in whom the average serum calcium was 9.5 mg. I think the explanation for this is that the older the child is the more able is he to mobilise his calcium reserves, and the acidosis will favour this. Thus, although there will be an increased excretion of calcium, the serum calcium will be kept normal. It is possible in these cases that although the serum calcium is normal the available calcium is deficient.

There remain to be considered the 7 cases of whooping cough complicated by convulsions. In this group the average serum calcium was 6.8 mg, and the average age was 12 months.

I will give a short history of each of these cases.

Case 56. T.H. male aged $\frac{10}{12}$ admitted on 26.1.29. Past History negative.

On admission - a well nourished baby. Sharply ill. Febrile. Pulse and colour poor. Frequent spasmodic cough and whoop. No evidence of rickets. Signs of bronchopneumonia in both lungs. Stools green. Serum calcium 6.3 mg. Convulsed on 30 and 31/1/29. Died 2/2/29.

Case 69. A.M. male. 1 year. Admitted on 14/2/29. First heard to whoop on 31/1/29. History of convulsions prior to admission. On admission - a fairly well nourished baby. Febrile, Acutely ill. Colour and pulse poor. Signs of bronchopneumonia in both lungs. Generalised convulsions of 15, 21 and 22/2/29. Serum calcium 6.4 mg. 22/2/29. Given calcium-sodium lactate by mouth gr. 5 t. i.d. No further convulsions until 26/2/29 when serum calcium was 7.3 mg. Convulsed again on 29/2/29 and died.

Case 80. J.A. Male. Aged 7/12. Admitted on 21/2/29 as Diphtheritic croup. Well nourished, spasmodic cough. Cultures negative for B. diphtheriae. A febrile. Heard to whoop on 2/3/29. Convulsed on 3 & 5/3/29. Febrile. Signs of broncho-pneumonia now present. Convulsed on 14/3/29. Serum calcium 6.5 mg. On calcium-sodium lactate by mouth. gr. X t. i.d. Continued to convulse and died 22/3/29.

Case 91. P.B. Male, aged 7/12. Admitted 6/4/29. Illness of three weeks' duration, cough, sickness and convulsions, heard to whoop on 1/4/29. On admission febrile. Colour and pulse poor. Bronchopneumonia present. 8/4/29 convulsed. Serum calcium 7.1 mg. Given .5 collosol calcium intra-venously. Continued to convulse and died 10/4/29.

Case 100. K. McL. F. aged 8/12. Has been ill since 16/5/29, cough followed by sickness and convulsions. Admitted on 19/5/29. A fairly well nourished infant. Acutely ill. Colour and pulse poor. Convulsing on admission. Signs of broncho-pneumonia in both lungs. Severe spasmodic cough and whoop. 21/5/29 serum calcium 6.5 mg. Died 22/5/29.

Case 104. J.K. Male. 9/12. Admitted on 20/5/29, history of cough, whoop and convulsions. On admission a well nourished infant. Acutely ill. Bronchopneumonia present. Convulsed 21 & 24/5/29. On 1/6/29 his condition had improved and serum calcium was 7.3 mg. Dismissed well on 27/7/29.

Case 107. M.D. Male, aged 2½ years. On admission a well nourished child. Severe spasmodic cough and whoop. Bronchopneumonia present in both lungs. Convulsed on 23/6/29, serum calcium 7.7 mg. 26/6/29 convulsed. Lumbar puncture 15 c.c. clear fluid obtained. Fluid normal. Died same day.

The period at which the occurrence of convulsions is most common is during the first two years of life. The factors contributing to the increased incidence at this period are -

(1) Convulsions in the new born due to asphyxia or injuries at birth.

(2) The occurrence of "idiopathetic" convulsions in the first few months and

(3) The effect of rickets as a predisposing cause from roughly the six month to the end of the second year.

Ker (18) states that fits are sometimes seen in comparatively mild cases of whooping cough and that any small irritation is often sufficient to produce them in children who suffer from the nervous excitability so characteristic of the disease. He regards them as due to the toxins of the disease, and post mortem has never found any gross lesions in these cases. In his opinion convulsions are most frequently found in cases complicated by bronchopneumonia.

According to Neuburger (19) the convulsions in whooping cough are due to small air emboli in the brain from disrupted pulmonary capillaries.

Powers (13) thinks that they are manifestations of latent tetany.

On the other hand Blüchdom (20) states that the absence of

any benefit from large doses of calcium in whooping cough with convulsions shows that the symptoms are not due to spasmophilia.

Holt and Howland (21) have observed that the subjects of convulsions in whooping cough are usually rachitic infants.

It will be seen from the histories of the severe cases with convulsions in this series that:-

(a) All were well nourished infants.

(b) None had obvious signs of rickets.

(c) All had bronchopneumonia.

(d) All except one died.

(e) All except one were within the age period ($\frac{6}{12}$ - 2 yrs.) when rickets and infantile tetany are commonest.

(f) The serum calcium was low in all cases.

Two were given oral calcium and one intravenous calcium but in spite of this they died. The electrical reactions were not done in any of these cases. In only one case was the cerebro-spinal fluid examined and here was found to be normal.

Bronchopneumonia, although present in all cases with convulsions, cannot be the cause of the low serum calcium, since

the serum calcium was found to be normal in the series of control cases.

I think the extremely low serum calcium is sufficient to account for the convulsions in all of these cases. Whether this was due to latent tetany or not, I am not prepared to say.

CALCIUM THERAPY IN WHOOPING COUGH.

I do not intend to discuss the question of calcium therapy in whooping cough at any great length. Some thirty cases were given calcium-sodium lactate gr.5 twice daily over a period of two weeks. Three cases showed a definite improvement. But in the others there was absolutely no diminution in either spasms or sickness.

For various reasons frequent serum calcium estimations could not be made and without this the results of calcium administration are, in my opinion of no value. It is possible that the calcium was not absorbed, or that better results would have been obtained if vitamine D. or ultra-violet radiation had been administered at the same time.

The frequent sickness and spasms which may be excited by the swallowing of drugs, and the weak digestion, makes the oral administration of calcium difficult, and I do not think this method can ever be satisfactory in whooping cough. Some form of hypoderimic administration would be much more dependable and should be attempted.

CONCLUSIONS.

1. That there is an alteration of the calcium metabolism in whooping cough, the average serum calcium being diminished.

2. That, generally, the more severe and frequent the spasms the lower is the serum calcium.

3. That cases up to 2 years of age are the most constantly and markedly affected.

4. That the serum calcium is normal in the older cases (4 - 6 years) of this series and that this is due to the fact that the older children can utilise their "calcium reserves", this being brought about by the acidosis.

5. That the serum calcium is low in all cases complicated by convulsions, and that this low calcium content is sufficient to account for the convulsions in whooping cough.

6. That the low serum calcium is not the sole cause of the spasms since the older severe cases had calcium contents within normal limits.

7. That the oral administration of calcium alone is useless in whooping cough.

BIBLIOGRAPHY.

(1) Ker's Infectious Diseases. 3rd. Edition. p.490. (Oxford Medical Publications).

(2) Applied Physiology by Samson Wright. Page 132. (Oxford Medical Publications).

(3) Neuhausen and Marshall. Jour. Biol. Chem. 1922. L III p. 365.

(4) Salvesen and Linder. Jour. Biol. Chem. 1923. L VIII. p. 617 & 635.

(5) Cushny. Jour. Physiol. 1920 L III. p.391.

(6) Vines. Jour. Physiol. 1921. L V. p.86, 287.

(7) Stewart. B.M.J. Oct.29, 1927. p. 782.

(8) Kramer, Tisdall and Howland. Amer. Jour. Dis. Child. 1921. XXII. 560.

(9) Herzfeld and Lowboski. Deut. Med. Work. 1923. p. 603.

(10) Clark and Collip. Jour. Biol. Chem. 1925. LXIII. p. 461.

(11) Regan and Tolstoonhov. Jour. Amer. Medical Assoc. Vol. 86 page 181. Jan. 1926.

(12) Regan and Tolstoonhov. Jour. Amer. Medical Assoc. Vol. 86, page 1116. April 10th. 1926.

(13) Powers. Amer. Jour. Dis. Child. Vol.30. Page 633. Nov. 1925.

(14) Herman B. Sheffield, New York, Diseases of Children, page 433.

(15) Smith, L.W. Jour. Amer. Med. Assoc. Vol.85 171 July 1925.

(16) Ker's Infectious Diseases, 3rd. Ed. page 492. Oxford Medical Publications.

(17) Loew. Brit. Med. Jour. page 894. May 26, 1928.

(18) Ker's Infectious Diseases, 3rd. Ed. pages 498 - 499.

(19) Neuburger, Klin. Woch. Berlin. 4 Jan. 1925. page 113.

(20) Bluchdom Zeilschrift fur Kinderhulkunke, Berlin. 1920. 26 page 251.

(21) Holt and Howland, Diseases of infancy and childhood. New York. Appleton. 1923.