CHANGES IN THE BLOOD CHEMISTRY IN CONGENITAL HYPERTROPHIC PYLORIC STENOSIS AND THEIR CLINICAL SIGNIFICANCE.

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A fairly extensive literature is accumulating regarding the clinical symptoms and chemical findings in cases of high intestinal obstruction, and particularly when the obstruction is situated at the pylorus. Hartmann and Smyth¹ have recently published an exhaustive report of a series of investigations in infants suffering from vomiting due to various causes. More observations, however, have been made in the adult, but the bulk of the published work is a record of the study of the condition as experimentally produced in animals.

In 1918, McCann² showed that the plasma CO_2 combining power of the blood was greatly increased after experimental obstruction of the pylorus. Two years later, McCallum³ and his co-workers demonstrated the same phenomenon and indicated its association with a fall in the chloride content of the blood. This they explained as being due to loss of chloride by the vomiting of the gastric juice which in turn led to an increase of the plasma CO_2 to make good the deficiency of acid radicles. These same investigators found that the onset of tetany, which invariably occurred, could be prevented by intravenous administration of sodium chloride. Hastings, Murray and Murray⁴, Haden and Orr⁵ and Gamble⁶ have also published papers throwing further light on the condition. Brown, Eusterman, Hartmann and Rowntree⁷ described similar chemical findings in duodenal obstruction in the adult and Ellis⁸ demonstrated the presence of alkalemia in two cases of intestinal obstruction. An identical picture was shown to be present in cases of duodenal ulcer after intensive alkali treatment especially in the presence of impaired renal function (Hardt and Rivers⁹).

In the present communication we wish to record the observations both clinical and chemical made during a study of congenital hypertrophic pyloric stenosis extending over the past four years. It is obvious that because of the age of the patients and the severity of the condition, the investigations had of necessity to be less complete than desired. In all over fifty cases were studied but we propose to give only such details as are relevant for correlating the various findings.

Before we proceed to analyse our results, it will be of advantage to give a brief resumé of these findings which, on the whole, are in accord with those of other workers. A most striking and probably the only important clinical manifestation of the presence of an alkalosis in these cases is the depressed breathing. This may be evidenced in one or more of the following three ways. First, there may be a shallow type of respiration, so shallow in fact that even with the bell of the stethoscope placed in front of the nose and mouth, it is

often very difficult to hear the respirations. Secondly, the rate is frequently diminished, often to six or eight times per minute, and thirdly, there are well-marked and often alarming periods of apnoea followed by three or four shallow respirations producing a typical Biot type of respiration. Most often, all three manifestations are present at the same time. At this point we would mention that we believe this condition to be present at some time in practically every case of pyloric stenosis in infancy. Coupled with this respiratory depression there exists a general lethargy, giving one the impression that the infant is under the influence of a hypnotic drug. In one instance, a baby was brought to hospital because the mother had noticed undue quietness. Recognition of the depressed breathing raised the suspicion of pyloric stenosis although the infant had not vomited on any single occasion. On examination typical gastric peristalsis was evident together with a palpable pyloric tumor. The diagnosis of pyloric stenosis was ultimately confirmed post mortem by the presence of a hypertrophied pylorus.

The biochemical examination of the blood shows usually a decrease in chlorides and an increase in the total CO_2 content and, less frequently, in the non-protein nitrogen. As a rule, these three findings are present together but the variations from the normal in each are not necessarily of the same degree. Table I gives some results which will serve to indicate this variation. In several cases, the fixed base of the serum was also determined (Table 2), and it will be seen that it is usually within normal limits (149—162 mM per litre) although occasionally it is slightly reduced.

TABLE I
GENERAL BIOCHEMICAL FINDINGS IN THE BLOOD IN PYLORIC STENOSIS.

Name	Age in weeks	Total CO_2		Chlorine (Cl)		Non- protein nitrogen mgm. per cent.	Excess non-prot. nitrogen (mM. per litre)	$\text{CO}_2 + \text{Cl}$	$\text{CO}_2 + \text{Cl}$	Respir. rate (per min.)
		Vol. per cent.	mM. per litre	mgm. per cent.	mM. per litre			(mM. per litre)	+ excess N.P.N. (mM. per litre)	
R. C. ...	8	140.5	63	140	40	46	2	103	105	18
N. R. ...	4	140.0	63	180	51	80	8	114	122	16
A. M. ...	8	83.1	37	210	60	32	—	97	97	40
W. G. ...	6	85.0	39	190	54	35	—	93	93	24
M. M. ...	12	62.5	28	330	94	60	5	122	127	40
M. A. ...	8	125.6	56	110	31	145	20	87	107	—
A. W. ...	7	110.2	50	170	49	63	5	99	104	26
E. M. ...	8	100.5	45	160	46	86	9	91	100	12
J. K. ...	6	91.8	41	160	46	50	3	87	90	24
J. McK. ...	8	112.0	50	220	63	32	—	113	113	—
A. C. ...	3	113.0	50	240	69	34	—	119	119	10
G. H. ...	7	95.8	43	190	54	75	7	97	104	14
W. A. ...	3	103.7	46	300	86	38	—	132	132	—
W. A. ...	4	148.0	66	130	37	183	27	103	130	—

TABLE 2.
SHOWING RELATIONSHIP BETWEEN CO₂, CHLORIDE AND FIXED BASE.

Name	J.McK.	J.P.	T.S.	G.C.	W.B.	A.B.	M.McP.	D.F.	R.S.	E.F.
CO ₂ (mM. per litre) ...	51	53	56	21	50	54	28	49	45	46
Cl (mM. per litre) ...	63	54	—	70	—	34	83	—	—	60
Fixed base (mM. per l.) ...	144	151	150	160	159	152	154	153	143	161

CHART I.
Showing Relationship between Respiratory Rate and Total CO₂ Content of Blood.

Relationship of the total CO₂ Content and Respiration. One of the most striking correlations among our findings is that between the total CO₂ content of the blood and the respiratory rate. This is all the more striking when one remembers that it is the total respiratory exchange and not merely the rate of breathing which is of significance. Further, it is not the total CO₂ but rather the ratio of the free and combined CO₂, which is the regulating factor in respiration. In Chart I are plotted individual observations of the total CO₂ content of the blood against the respiratory rate at the time of withdrawal of the blood. The slower the respiratory rate, the greater is the increase in CO₂. There are certain anomalous findings on the chart but when one remembers the possibility

Relationship of the CO₂ Content and Vomiting. The relationship between the total CO₂ content of the blood and the severity of the vomiting is not close. It is, however, admittedly difficult to gauge the amount of vomitus and, what is even more important, the character of the vomitus, for example, the amount of chlorine present. An attempt has been made in Table 5 to correlate these two factors but we feel that too much stress should not be laid on it. When the records of individual patients are examined, it is found that, occasionally, the total CO₂ content of the blood may remain high despite the fact that there had been no vomiting for several days prior to its estimation. This might be explained by the length of time which it takes for the blood to return to its normal composition. But in one patient, vomiting can have played absolutely no part in producing the increase in the CO₂. This was the case already referred to, who, although suffering from pyloric stenosis, did not vomit either previous to admission or during a four weeks' stay in hospital. The total CO₂ content of the blood reached the value of 102 vol. per cent., and the CO₂ dissociation curve showed clearly its increased capacity of holding CO₂.

TABLE 5.

SHOWING CORRELATION BETWEEN CO₂ CONTENT, CHLORIDE CONTENT, AND VOMITING IN CASES OF PYLORIC STENOSIS

Severity of vomiting				Nil	Slight	Moderate	Severe
Total CO ₂ vol. % (average)	...	...	...	102.9*	77.2	97.6	103.2
Cl mgrm. % (average)	...	...	...	—	260	250	180

* Only two cases.

In patients suffering from vomiting, and even from severe vomiting, due to causes other than pyloric stenosis, one rarely if ever finds the CO₂ content raised. It must be remembered, however, that it is not the mere presence of vomiting but rather the nature and amount of the material vomited which is of significance. One nevertheless feels justified in concluding from a study of this series of pyloric stenosis that the severity of the vomiting is no measure of the metabolic disturbance as evidenced by the increase in the total CO₂ content of the blood.

The total CO₂ content of the blood and the general nutrition. An association between the fall of the CO₂ to normal and the increase in the weight of the infant is illustrated in Chart II. This correlation holds good only for the same individual and therefore an isolated observation on the CO₂ content cannot be taken as a prognostic sign. A great increase in the CO₂ content does not necessarily mean a worse prognosis than a moderate rise. Furthermore, there does not seem to be any relationship between the level of the CO₂ and the length of time the vomiting has existed.

The association between the fall in CO₂ and the improvement in general nutrition was recognized to be simply the result of concomitant events and not dependent on cause and effect. Nevertheless, an attempt was made in a few

instances to influence the CO_2 content of the blood and determine whether such change resulted in clinical improvement. In one case, by means of transfusion, the CO_2 value was reduced from 98 vol. per cent. before transfusion to 70.2 vol. per cent. five minutes after transfusion. The donor's blood, of which 110 c.cm. were given along with 40 c.cm. normal saline, contained 62.1 vol. per cent. CO_2 . Assuming the volume of the infant's blood to be 200 c.cm. (weight of infant 3.1 kilos) then 75.5 vol. per cent. represents the value one would calculate from a mixture of the two bloods and the saline. There was no apparent change in

CHART II.

To show increase in Weight and Fall in total CO_2 content of Blood in case of infant J.B.

the clinical condition of the infant and this lowering of the CO_2 content was not permanent, as within four days it had risen again to 97.8 vol. per cent. In another case, the infant's blood was withdrawn twenty hours after transfusion but the CO_2 content was practically unaltered from the pre-transfusion value. In two cases calcium chloride was given. In one the CO_2 content was reduced from 110 vol. per cent. to 62.3 vol. per cent. although the clinical condition was unchanged, while in the other, the CO_2 content was unaffected.

The CO_2 content of the blood and its reaction. The question arises whether the increase in the CO_2 content is indicative of a non-gaseous alkalosis or of a gaseous acidosis. The CO_2 dissociation curve of the blood shows a shift

to the left, *i.e.*, the capacity to hold CO_2 is increased, a finding equally characteristic of either of the above two conditions. It is obvious that if the depressed breathing is primary, the condition is one of gaseous acidosis such as occurs in subnormal activity of respiratory function. If, however, the increase in CO_2 content is the cause of the diminished respiratory exchange, the condition must be one of non-gaseous alkalosis. Ellis⁸ has given details of the findings in two cases of high intestinal obstruction in both of whom there was an alkalemia, as indicated by the pH of the blood. In a few instances in our series, the pH of the blood has been determined. The figures obtained are found in Table 6. It will be seen that if any change from the normal does occur, it is toward the alkaline side. In contrast with this finding, it is interesting to note the pH figure in the case of J.L. suffering from encephalitis. Here, although the respiratory rate was only eight per minute, the total CO_2 content was 67 vol. per cent. and the pH 7.25. This slightly increased CO_2 value and the pH on the acid side of normality indicate a gaseous acidosis. One can, therefore, conclude that in pyloric stenosis, the disturbance of the acid base balance is toward the alkaline side and that the change in the respiratory volume is secondary.

TABLE 6.
pH FINDINGS AND THE RELATIONSHIP TO CO_2 CONTENT OF BLOOD.

Name	Diagnosis	Respiratory rate (per min.)	Total CO_2 (vol. %)	pH
J.C.	Pyloric stenosis	?	140.0	7.76
R.R.	" " " " " " " "	15	110.0	7.33
W.B.	" " " " " " " "	?	73.2	7.35
McL.	" " " " " " " "	?	53.4	7.39
M.R.	" " " " " " " "	24	110.0	7.52
J.L.	Encephalitis lethargica... ..	8	67.0	7.25

The presence of such a degree of alkalosis as suggested by the high CO_2 values would lead one to expect the frequent occurrence of tetany. Signs of increased muscular irritability, as a matter of fact, have been reported frequently in high intestinal obstruction in the adult, as well as that produced experimentally in dogs. Convulsions, although said to be common by some observers, are in our experience rare in pyloric stenosis of infancy. In only two cases was there any such history obtained. In one of these laryngismus was an associated symptom. In no case tested was the neuro-muscular excitability increased as one might have expected. The reason for this absence of the signs of tetany may in part be due to the increased blood calcium content which we have found as high as 14 mgrm. per cent.

The cause of the alkalosis presumably is the increased amount of available base resulting from a deficiency of chlorine. It becomes necessary for the CO_2 content to rise in order to combine with this base.

Fig. I (a) adapted from Gamble's paper shows that CO_2 is one of the acid radicles combined with fixed base, the others being Cl , HPO_4 , SO_4 , organic acid and protein. Of all these acid radicles, CO_2 is the most mobile and elastic, being very easily retained or dispensed with by the activity of the respiratory centre. In Fig. I (b) is represented the state of affairs found in pyloric stenosis. It will be seen that the excess of CO_2 makes up for the deficit of Cl . The results recorded in Table I indicate that this balancing of diminished Cl by increase of CO_2 although generally complete is not necessarily the rule. Unfortunately, we have not obtained complete data in any one case. The figures for fixed base indicate that it is practically unchanged. Our data for acid radicles other than

Cl and CO_2 are scanty. In two cases we found values for inorganic phosphorus of 10.5 and 11.6 mgm. per cent. respectively. Atchley and Benedict¹⁰ maintain that they can demonstrate an increase in the phosphate, sulphate and protein of the blood sufficient to account for the diminution in the $(\text{Cl} + \text{CO}_2)$ value. Gamble⁶ postulates an increase in organic acid. The ketone content of the blood has not been estimated in this series but frequently we have noted a fair degree of ketonuria. This may be consequent on the inanition (starvation), or due to alkalemia or to both factors, and it is quite probable that these ketone acids take part to a certain extent in the compensation for the diminished $\text{Cl} + \text{CO}_2$ content.

The behaviour of the chlorides:—The fall in the blood chloride is one of the most constant changes in the biochemical findings. The reduction seems to

bear some relationship to the severity of the vomiting (Table 5), even although this relationship is masked by the inability to determine the actual amount of vomitus and its chloride content. The urine contains but a trace of chlorine, which is to be expected if chlorine is a threshold substance. Following the intravenous injection of a solution of normal saline practically all the water is excreted whereas approximately 80 per cent. of the chlorine is retained. In infants suffering from vomiting from other causes, only about 10 per cent. is retained. These results are shown in Table 7. In the two infants who were vomiting from causes other than pyloric stenosis, the amount of Cl retained was 11.8 and 7.0 per cent. respectively. In the cases of pyloric stenosis, 80.7 and 81.8 per cent. were retained. After operation in one case only 2 per cent. was retained which indicates that the condition was relieved. This retention of Cl in the examples of pyloric stenosis indicates definitely a chlorine hunger of the tissues. Hartmann and Smyth¹ maintain that severe vomiting may also lead to a depletion of the blood chloride. While it is true that the chloride may be somewhat reduced, it appears evident that the metabolism of chlorine in non-obstructive cases presents a different picture from that in pyloric stenosis.

TABLE 7.

CHLORIDE CONTENT OF URINE AND PERCENTAGE ABSORPTION OF CHLORIDE IN CASES OF PYLORIC STENOSIS AND NON-OBSTRUCTIVE VOMITING.

Name	Volume of urine	Amount of saline injected (cc.)	Chloride in urine		Percentage of chloride retained	Remarks
			Per cent.	Total		
W.B.	91	—	0.585	0.532	—	Feeding case. Vomiting +
	205	100	0.647	1.326	11.8	
R.W.	370	—	0.303	1.120	—	Meningitis. Vomiting +
	450	80	0.420	1.890	7.0	
J.R.	265	—	0.048	0.128	—	Pyloric stenosis.
	330	60	0.07	0.232	80.7	
C.C.	232	—	nil	nil	—	Pyloric stenosis (before operation) (After operation).
	350	100	0.047	0.164	81.8	
	784	—	0.738	5.786	—	
	920	100	0.725	6.670	2.0	

DISCUSSION.

Several views have been put forward as to the cause of the biochemical picture in high intestinal obstruction. That most commonly held is the one suggested by MacCallum² and elaborated by Gamble³ and his colleagues. They believe the primary factor to be the loss of chlorine, base, and water by vomiting. This impoverishment of body chlorine is compensated for by the retention of

CO₂ with consequent production of an alkalosis. Haden and Orr⁵, however, previously pointed out that a similar condition could be produced by experimental pyloric obstruction in rabbits, animals which do not vomit. But Gamble and McIver¹¹ were able to show that in rabbits there followed a very marked dilatation of the stomach into which the chloride was secreted and virtually lost to the body despite the absence of vomiting. This view certainly seems to explain all the experimental findings in animals. Ellis records the case of a patient suffering from carcinomatous obstruction of the pylorus with symptoms of tetany and biochemical evidence of a severe alkalæmia. There was no free hydrochloric acid in the gastric juice. The vomiting was severe, entailing in all probability a great loss of neutral chlorides. An explanation to fit this case is found in the fact that the reserve of fixed base is greater than that of chlorine so that the former is maintained at a more or less normal level in the blood while the chlorine content falls despite the fact that equivalent amounts of base and chlorine are lost in the vomitus.

In the analysis of the results in this series there is undoubtedly some relationship between the depletion of the blood chloride and the severity of the vomiting, and this in spite of the difficulty in estimating the latter factor and the great variation which is bound to exist in the chloride content of the tissues of different individuals. There is, however, one case in our series which does not permit of explanation on the basis of this hypothesis. This is the case of the infant referred to previously who did not vomit. He was admitted to the ward at the age of four weeks with the diagnosis of mental deficiency and pyloric stenosis. Visible peristalsis was readily demonstrated and there was a tumour palpable in the region of the pylorus. This infant was in the ward for four weeks and finally succumbed to a secondary infection. At the post-mortem examination, typical hypertrophic pyloric stenosis was revealed. During his residence in hospital he took his feeds well but never once vomited. He was not constipated. He presented the typical clinical picture of a severe alkalosis and the total CO₂ content of the blood was 102 vol. per cent. The respiratory rate averaged about 12 per minute. Unfortunately the blood chlorides were not estimated. It is difficult to understand how the depletion of the chloride resulted in this particular instance. It is highly improbable that the chlorine lost to the body during the four weeks' stay in hospital could have been lost *via* the gastric secretions. We have no information regarding the renal efficiency in this case.

Another hypothesis which has been advanced is that the condition is in part due to renal inefficiency. The chief evidence in favour of this view is the presence of an increased non-protein nitrogen content of the blood. At first this increase was attributed to increased destruction of tissue proteins as a result of toxæmia (Cooke, Rodenbaugh and Whipple¹²). Brown, Eusterman, Hartmann and Rowntree⁷ suggested that the increase in the blood uræa is the result of inefficient renal activity and concluded that the tetany-like symptoms are really uræmic in nature. In their paper they give details of the macroscopic and microscopic appearances of toxic nephritis occurring in six cases of fatal pyloro-duodenal obstruction. Ellis supported this view by his finding of a

low percentage excretion of urea despite a high blood urea, and by the fact that an alkalosis can be produced by administration of alkali only when the renal function is impaired. In one of the two cases reported by him there was pyæmia involving the kidney and in both there was noted the excretion of an acid urine ($\text{pH}=5.6$) associated with an over-alkaline plasma.

Hartmann and Smyth¹ have given figures which lead them to believe that the increase in N.P.N. is for the purpose of maintaining the normal osmolar concentration. They calculated the molecular value of the excess N.P.N. on the assumption that it is all urea and that two molecules of urea constitute one milli-equivalent. In Table 1 we have attempted to do the same and the findings occasionally lend some support to their view. Especially is this the case in the patient W.A. whose blood was analysed on two separate occasions. On the second occasion there was a more marked diminution in chloride with an increase in the CO_2 which did not compensate for the extra chloride deficiency. On calculating the value for the excess N.P.N. it is found that the deficiency is almost exactly balanced by the rise in N.P.N. Many of the other results, however, fail to support the view. Thus in the blood of A.M. or W.G. the decrease in the combined CO_2 plus Cl value is not associated with any increase in the non-protein nitrogen. Two possible explanations of these discrepancies suggest themselves, first in the excessive formation of ketone bodies and second, an increase in the base binding power of the proteins. Atchley and Benedict¹⁰ have shown that owing to anhydræmia, the serum protein is increased in amount. Its base-binding power depends in addition on the pH of the medium. The more alkaline the plasma the greater is the capacity of the protein to hold base.

A third view was put forward in a series of papers by Haden and Orr⁵. They suggested that the chlorine was fixed in the tissues by some toxin and supported this view by the beneficial results obtained from the administration of chlorides. This can be equally well explained on Gamble's theory which Haden and Orr¹⁴ in a recent paper apparently accept. Drake and Tisdall¹³ have obtained similar results to those found in experimental obstruction by the injection of histamine. They found that there was no relationship between the decreased Cl content and the degree of intoxication which was, however, closely related to the concentration of non-protein nitrogen. Further they concluded that the decreased Cl content was not due to loss in the gastric secretions since apomorphine which led to a greater loss of Cl in the vomitus did not induce any diminution in the plasma Cl. Our results do not throw any light on this point.

CONCLUSIONS.

1. Pyloric stenosis in infancy is associated with an alkalosis presumably produced by a loss of the acid radicle chlorine from the body. The loss of chlorine is roughly related to the severity of the vomiting. The total CO_2 content varies inversely with the blood chlorides. The fixed base as a rule is unaltered or at the most only slightly diminished.

2. The rise in CO_2 is evidenced by a depression of the breathing (Biot type of respiration), which affords a ready method of its clinical recognition.

3. Certain cases occur which do not permit of the explanation of loss of chlorine by vomiting. It would appear that in such cases another factor, possibly impairment of renal function is present.

4. The conclusion that the rise in the non-protein nitrogen occurs in order to restore the osmolar concentration of the blood is not always justified.

We desire to express our thanks to the Medical Research Council for their help in this work.

Analytical methods used:—Blood—Total CO_2 —Haldane¹⁵: Chloride—Whitehorn¹⁶: Non-protein Nitrogen—Folin-Wu method: Fixed Base—Stadie and Ross¹⁷: Calcium—Kramer and Tisdall's method: Phosphorus—Tisdall's method: pH—Dale and Evans¹⁸. Urine chloride—Volhard's method.

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