INTESTINAL INTOXICATION IN INFANTS

THE IMPORTANCE OF IMPAIRED RENAL FUNCTION *

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Preceding the development of toxic symptoms in intestinal intoxication¹ there is pronounced diarrhea, vomiting and diminished ingestion of fluid, the relative importance of which varies in different cases. In the acute stage of the symptoms the excretion of urine is greatly diminished, and at this time the urine contains albumin and abundant casts.

During the past year investigation of cases of intestinal intoxication has furnished evidence which emphasizes the importance of the loss of fluid and the impaired secretion of urine. In this communication it is proposed to present such evidence and to discuss its significance with special reference to the symptomatology.

I. NONPROTEIN NITROGEN AND UREA OF THE BLOOD

*Technic.*²—The nonprotein nitrogen was determined by the method of Gettler and Baker³ except that the final determination was by aeration instead of by distillation. Fiftieth-normal acid and hundredth-normal alkali were used with methyl red as indicator. It was found that the presence of mercury used

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1. It is realized that the use of the term "intestinal intoxication" is open to objections. This term is not applied to the complex described by Finkelstein as "alimentäre intoxicikation" but is used merely to designate the series of toxic symptoms which frequently occur in association with profound nutritional disorders in infants.

The term "diarrhea with toxic symptoms" is cumbersome and is not more exact, for there is not always a direct relation between the severity of the diarrhea and the degree of toxemia. Indeed, there are cases with symptoms indistinguishable from those of intestinal intoxication in which there is no diarrhea at all.

2. All blood for analysis was withdrawn from the superior longitudinal sinus by means of a syringe and the type of needle described in a previous communication. The blood was always taken at least three hours after the last meal.

3. Gettler, A. O., and Baker, W.: Jour. Biol. Chem., 1916, **25**, 211.

in the precipitation of the protein interfered with the aeration of ammonia, probably through the formation of a stable ammonia-mercury compound which was not broken up by alkali. At Dr. Gettler's suggestion potassium hydrogen sulphid was used to precipitate the mercury, and by this means the obstacle was overcome. A very strong pump was used for aeration and blank determinations demonstrated that aeration for one half hour was sufficient. This was shown, (1) by determinations of pure ammonium sulphate or urea, and (2) by distilling mixtures which had been aerated from ten to thirty minutes to determine whether all ammonia had been removed.

As a rule 3 c.c. of blood were used. In some cases in which the nonprotein nitrogen was increased, the determination was made with only 2 c.c. In the earlier cases all determinations were made in duplicate. These were always within the limits of experimental error, and owing to the limited amount of blood one can take from infants, duplicates were omitted in the later cases. The purity of all reagents was checked by blank determinations. Whenever ammonia was present the amount was regularly deducted.

Urea was determined by the urease method of Van Slyke and Cullen.⁴ The enzyme was tested for ureolytic power and also to exclude the presence of ammonia. Fiftieth-normal acid and hundredth-normal alkali were used with methyl red as indicator.

Normal Infants.—Determinations were made on thirty normal infants. Such infants were of practically normal weight, had normal appetite and bowel movements and were apparently well. The values for urea and nonprotein nitrogen are shown in Table 1.

In such infants the nonprotein nitrogen ranged from 23 to 39.1 mg. per 100 c.c. of blood. These figures are considerably higher than those obtained by Minsk and Sauer,⁵ who used Folin's method. The difference is probably due to the difference in methods, as the values for normal adults obtained by Gettler and Baker are higher than those given by Folin's method.

The urea nitrogen was from 4.9 to 14.6 mg. per 100 c.c. of blood. In only a few cases was the urea nitrogen approximately one half of the nonprotein nitrogen, which is generally the case in adults and is what Minsk and Sauer⁵ found in their patients. The difference in these results and those of Minsk and Sauer is due mainly to the fact that the values for nonprotein nitrogen were greater than theirs and not to the difference in the amounts of urea nitrogen.

As shown in Table 1, the amount of urea nitrogen varies greatly in different infants. A careful analysis of the food and the method of feeding fails to reveal an adequate cause for this variation. It seems possible that such variation may be due to the different rate of urea elimination by the kidney in accordance with Ambard's hypothesis.

Infants with Intestinal Intoxication.—Forty-six patients with intestinal intoxication were studied. Thirty-six had acidosis and thirty-three of these showed an increase in the nonprotein nitrogen of the blood. There were, therefore, only three patients with acidosis without

4. Van Slyke, D. D., and Cullen, G. E.: Jour. Am. Med. Assn., 1914 **62**, 1558.

5. Minsk, L. D., and Sauer, L. W.: AM. JOUR. DIS. CHILD., 1917, **13**, 397.

TABLE 1.—THE NONPROTEIN NITROGEN AND UREA NITROGEN IN THE BLOOD OF NORMAL INFANTS *

Number	Age, Months	Weight		Carbon Dioxid Tension Alveolar Air, Mm.	Nonprotein Nitrogen, Mg. per 100 C.c. of Blood	Urea Nitrogen, Mg. per 100 C.c. of Blood
		Lb.	Oz.			
1	1¼	9	4	38.2	33.35	8.6
2	1½	9	1	36.6	35.1	7.4
3	1¾	9	2	41.2	30.15	18.8
4	2¼	10	1	39.1	34.0	12.9
5	2½	10	4	42.4	35.2	10.8
6	3	11	4	40.6	37.6	4.9
7	3¼	11	4	37.6	39.1	7.7
8	3¾	11	8	35.9	36.2	13.3
9	3¾	11	4	38.7	38.0	11.8
10	4	12		41.2	39.1	10.9
11	4½	12	4	40.1	35.2	12.2
12	4½	11	12	36.1	35.4	12.3
13	4¾	13	12	40.0	39.0	11.3
14	5¼	14	1	39.1	27.6	8.3
15	5½	13	4	36.8	29.8	11.2
16	5¾	12	15	40.1	38.2	7.1
17	5¾	14	14	44.6	26.6	8.3
18	6	15	8	37.8	27.4	14.6
19	6½	15	14	43.2	34.3	13.9
20	7	18	4	35.8	31.1	7.9
21	7¼	17	2	39.2	38.0	11.8
22	7½	16	12	40.3	24.2	11.7
23	7½	17	4	41.2	23.0	7.8
24	8¼	17	12	36.7	31.6	10.7
25	9	18		38.9	27.5	4.9
26	9½	18	14	37.6	25.0	10.2
27	10	17	14	42.3	38.4	11.3
28	11	21	11	36.4	34.3	10.1
29	11¾	20	4	40.1	31.2	7.2
30	12	21	4	37.5	28.0	9.3

* The air was collected by the Plesch-Higgins method as modified by Howland and Marriott. The air analyses were made in the Haldane apparatus.

an increase of the nonprotein nitrogen. In only one of these patients was more than one determination made. There were four cases without acidosis but with an increased nonprotein nitrogen and four cases with neither acidosis nor increased nonprotein nitrogen. Thirty-seven of the forty-six cases showed a decided increase in the nonprotein nitrogen of the blood.

Twenty-three of the cases with acidosis are shown in Table 2. These were selected for presentation as they were the ones most completely observed, and, moreover, they are representative of the entire series. Of these cases there was only one with no increase in the nonprotein nitrogen (Case 18). In the remainder the nonprotein nitrogen ranged from 57 to 232 mg. per 100 c.c. of blood, the urea nitrogen from 20.1 mg. to 108.2 mg. per 100 c.c. of blood. Comparison with the results from normal infants (Table 1) shows that in intestinal intoxication the urea and nonprotein nitrogen are much increased.

Minsk and Sauer⁵ determined the nonprotein and urea nitrogen in six cases of intestinal intoxication; in three there was a distinct increase. The greatest nonprotein nitrogen in their cases was 67.6 mg. nitrogen per 100 c.c. of blood, which was much lower than in most of my cases. The urea nitrogen in their cases constituted a larger percentage of the nonprotein nitrogen than in my cases, but the actual values for urea nitrogen obtained by them were less.

Discussion.—It is therefore apparent that infants suffering from intestinal intoxication show a marked increase of nonprotein nitrogen and urea in the blood. The nonprotein nitrogen of the blood consists of urea, uric acid, creatin, creatinin, ammonia, amino-acids and probably other substances of unknown nature. As shown in Table 2, the increase in nonprotein nitrogen is due in part only to urea, which comprises less than 50 per cent. of the total nonprotein nitrogen. Determinations of the amounts of uric acid, creatinin, ammonia and amino-acids in this series of cases would have been of interest and perhaps of practical importance, but they were not made, as more blood would have been required than we felt justified in taking. Determinations of these substances, however, have been made in individual cases and are being concluded at the time of preparing this article.

In three cases of the present series uric acid and creatinin were determined and a decided increase found. The results were as follows:

Case	Nonprotein N, Mg. per 100 C.c. Blood	Urea N. Mg. per 100 C.c. Blood	Uric Acid. Mg. per 100 C.c. Blood	Creatinin, Mg. per 100 C.c. Blood
21	189.0	71.9	18	3.0
22	140.0	59.7	21	2.1
23	159.6	63.2	10	2.9

TABLE 2.—THE NONPROTEIN NITROGEN AND UREA NITROGEN IN THE BLOOD OF INFANTS WITH INTESTINAL INTOXICATION *

Number	Date	Age, Months	Weight		Carbon Dioxid Tension of Alveolar Air, Mm.	C.c. of CO ₂ , Reduced to 0,760 Mm., Bound as Bicarbonate by 100 C.c. of Blood Plasma (Van Slyke)	Nonprotein Nitrogen, Mg. per 100 C.c. of Blood	Urea Nitrogen, Mg. per 100 C.c. of Blood
1	1/12	3	Lb.	Oz.	22.0	40.0†	140.0	62.3
	1/14‡		8	15	42.0	92.0	98.0	
	1/18				33.0		29.0	11.1
	1/24					65.0	28.0	
2	1/15	5	10		19.0~		58.0	20.1
	1/16				20.0	36.0	123.0	
3	2/ 2	5½	12	4	14.7§	26.0	140.0	
	2/ 5				17.4§		193.2	
	2/ 6					34.0	184.8	
4	3/ 2	4	6	6	31.37§		137.0	
	3/ 3				21.0	42.0	193.0	
5	3/ 5	3	8	8	17.0		150.0	84.0
	3/ 6					38.0	169.0	75.6
6	3/10	5½	5	9	34.2§		83.0	39.0
	3/12					40.0	73.0	
	3/13				22.0		97.0	
7	3/19	4	13	6	35.1§		78.6	25.2
	3/20				17.2§			
	3/21					88.0		
	3/26‡				36.4§	100.0	57.0	15.9
8	4/18	9	17		28.4§		142.0	72.1
	4/19‡				56.0	97.0	127.0	64.3
	4/26					69.0	95.0	
9		6	11	4	21.5§	40.0	84.0	39.7
10		11½	12		17.0		61.9	
11		13	15	3	23.4§	25.1	124.0	44.8
12		6	12	8	25.0		133.0	39.1
13	5/16	5	11	12	23.0		134.4	
	5/17‡				37.5§	76.0	176.9	76.58
14		8½	14	3	17.0		232.0	108.2
15		5	10	4	23.6§		179.0	68.4
16		7	13	1	26.1§		58.8	27.6
17		8½	14	2	16.0	34.0	143.0	78.7
18		9½	13	4	16.0		36.0	13.2
19	11/11	7	11	6	21.3§		176.0	89.0
	11/18‡				38.0		160.0	
	11/24						28.0	7.0
20	5/20	9	14	8	14.4§	23.2	211.0	96.1
	5/25‡				44.3§		50.1	13.4
21	5/23	9	14	4	24.6§		189.0	71.9
	5/27‡				39.6§		34.0	14.0
22	6/ 1	10	15	6	23.0		140.0	59.7
23		13	19		25.0		159.6	63.2

* This table includes only part of the cases, as forty-four cases of intestinal intoxication were investigated. The results were so uniform that it seemed superfluous to tabulate all cases. Some of the additional cases will be cited in the text.

† These values are cited merely in general confirmation of the alveolar air analyses. They cannot be compared accurately with the figures for alveolar air, since the values for the carbon dioxide of alveolar air represent venous blood while the plasma analyses are probably more nearly representative of arterial blood. In a late series of cases, to be reported shortly, this discrepancy has been eliminated.

‡ After treatment. The treatment comprised the administration of 2 to 7 gm. of sodium bicarbonate by subcutaneous or intravenous injection and giving large amounts of water by mouth, or salt solution subcutaneously or intravenously.

§ Air collected by the method of Plesch-Higgins as adapted to infants by Howland and Marriott and analyzed in the Haldane apparatus. The remaining figures represent alveolar air collected in the same way but determined by the colorimetric method of Marriott.

TABLE 3.—THE CORPUSCULAR VOLUME AND TOTAL SOLIDS OF THE BLOOD; THE SPECIFIC GRAVITY AND TOTAL NITROGEN OF THE BLOOD
SERUM OF NORMAL INFANTS *

Number	Total Solids of the Blood, per Cent.	Corpuscular Volume of the Blood, per Cent.	Specific Gravity of the Blood Serum	Total Nitrogen of the Blood Serum, Gm. per 100 C.c.	Ratio of Nonprotein Nitrogen of Blood to Total Nitrogen of the Blood Serum N.P.N. : T.N.
1		35.2	1.021	1.123	1 : 34
2		34.3	1.026	1.088	1 : 31
3		38.9	1.024	1.101	1 : 27
4		42.0	1.023	0.9876	1 : 29
5		38.0	1.021	1.043	1 : 30
6		32.5	1.020	1.181	1 : 32
7		35.5	1.022	1.198	1 : 31
8		34.0	1.020	1.11	1 : 31
9		33.0	1.025	1.02	1 : 27
10		29.0	1.024	0.983	1 : 25
11		34.0	1.025	1.13	1 : 32
12		31.0	1.023	0.987	1 : 28
13	18.6	45.0	1.022	1.061	1 : 27
14	17.9	39.0	1.020	1.113	1 : 40
15		32.0	1.021	0.997	1 : 33
16	17.5	33.0	1.022	1.043	1 : 28
17	17.1	29.8	1.024	1.121	1 : 41
18		32.0	1.026	1.069	1 : 40
19	17.7	36.0	1.020	1.00	1 : 29
20		37.0	1.026	0.983	1 : 32
21		33.0	1.025	1.18	1 : 31
22	18.4	38.0	1.020	1.108	1 : 46
23	17.3	31.0	1.024	1.16	1 : 50
24	18.2	39.0	1.023	0.977	1 : 30
25	17.2	32.9	1.021	1.111	1 : 40
26		34.0	1.020	1.023	1 : 41
27		32.0	1.021	1.101	1 : 29
28	17.4	34.0	1.022	1.097	1 : 32
29		35.0	1.023	1.114	1 : 36
30	18.5	39.8	1.025	1.01	1 : 36

* The figures in this table were obtained from the same infants as those in Table 1 and are numbered the same. To avoid needless repetition the age, weight, etc., are not given in the foregoing table as they are shown in Table 1.

The substances comprising the nonprotein nitrogen are normally excreted in the urine, and an accumulation in the blood usually signifies an impairment of renal function. While this interpretation is generally accepted, yet in connection with infantile diarrhea another possibility must be considered. The loss of water through the bowels in diarrhea is one of the most prominent clinical features of the disease and the question naturally arises whether this loss of water could be responsible for the high nonprotein nitrogen in the blood. If the blood became more concentrated through loss of water, it seems possible that there could be a relative increase of nonprotein nitrogen due to this cause. Such an increase, however, would be merely apparent.

To obtain evidence bearing on this possibility, determinations of the blood concentration were made.

II. THE CONCENTRATION OF THE BLOOD

1. *Corpuscular Volume*.—This was determined in the special pipet of Gettler and Baker³ and in the manner described by them.

The corpuscular volume of normal infants ranges from 31 to 42 volumes per cent. (Table 3). Gettler and Baker found in normal adults that the corpuscular volume ranged from 33 to 50 volumes per cent., which values are considerably higher than those in normal infants.

In cases of intestinal intoxication the values were from 32 to 49 volumes per cent. (Table 4). Comparison of Tables 3 and 4 shows that in cases of intestinal intoxication the average corpuscular volume is higher, and in a number of the individual cases this increase is marked. The corpuscular volume, however, is not regularly increased in the cases of intoxication, and in a number of instances, despite the increase in nonprotein nitrogen, the corpuscular volume was within normal limits. Of most significance was the fact that there was no direct ratio between the corpuscular volume and the nonprotein nitrogen. For example, Case 5 showed a corpuscular volume of 38 and a nonprotein nitrogen of 150 mg. per 100 c.c. of blood, and later a corpuscular volume of 30 and a nonprotein nitrogen of 169. In both instances the corpuscular volume is within normal limits while the nonprotein nitrogen is greatly increased. Moreover, the second determination showed a lower corpuscular volume in the presence of a slightly increased nonprotein nitrogen. The same evidence is shown in several of the tabulated cases.

These determinations show that there is no constant decrease of the blood plasma in relation to corpuscles and that according to these results the high nonprotein nitrogen in cases of intestinal intoxication cannot be explained on the basis of increased blood concentration.

This argument would be valid only if, in intestinal intoxication, there was no increased destruction of red cells and if the red cells were

TABLE 4.—THE CORPUSCULAR VOLUME AND TOTAL SOLIDS OF THE BLOOD; THE SPECIFIC GRAVITY AND TOTAL NITROGEN OF THE BLOOD SERUM OF INFANTS WITH INTESTINAL INTOXICATION *

Number	Date	Total Solids of the Blood, per Cent.	Corpuscular Volume of the Blood, per Cent.	Specific Gravity of the Blood Serum	Total Nitrogen of the Blood Serum, Gm. per 100 C.c.	Ratio of the Nonprotein Nitrogen of the Blood to the Total Nitrogen of the Blood Serum N.P.N. : T.N.
1	1/12		36.0	1.0279	1.397	1 : 10
	1/14		37.0	1.025	1.36	1 : 14
	1/18		32.0	1.023	1.11	1 : 38†
2	1/15		39.5	1.026	—	
	1/16	21.8	—	1.027	1.55	1 : 13
3	2/ 2		47.0	1.029	1.36	1 : 10
	2/ 6	20.4	34.0	1.029	1.219	1 : 6
4	3/ 2		32.0	—	—	
	3/ 3	20.9	31.0	1.030	1.368	1 : 7
5	3/ 5	20.6	38.0	1.031	—	
	3/ 6	19.7	30.0	1.027	1.112	1 : 7
6	3/10	21.1	—	1.026	1.114	1 : 13
	3/12	20.0	—	—	0.914	1 : 12
	3/13		37.0	1.030	1.28	1 : 13
7	3/19		49.0	1.030	1.176	1 : 15
	3/21		39.0	—	—	
	3/26	20.8	35.0	1.024	0.985	1 : 17
8	4/18	21.6	37.0	1.032	1.513	1 : 11
	4/19	21.1	42.0	1.030	1.42	1 : 11
	4/26	19.3	27.0	1.026	0.942	1 : 10
9			—	—	—	
10			35.0	1.024	1.057	1 : 17
11			39.0	1.030	—	
12		20.8	49.0	1.028	1.218	1 : 9
13	5/16	21.3	42.0	1.029	1.358	1 : 10
	5/17		37.0	1.026	1.204	1 : 7
14		21.1	49.0		1.36	1 : 6
15				1.030	1.302	1 : 7
16		17.4		1.023	0.980	1 : 17
17			47.0	1.029		
18			29.0	1.026		
19	11/11	19.9	39.6	1.030	1.3	1 : 7
	11/18		38.4		1.23	1 : 8
	11/24	18.9†	34.0	1.027	1.09	1 : 39†
20	5/20	21.7	39.8	1.031	1.365	1 : 6
	5/25	19.1†	37.0	1.025	1.071	1 : 22†
21	5/23	21.6	45.0	1.029	1.361	1 : 7
	5/27	18.5†	38.9	1.023	1.14	1 : 33†
22			49.9	1.030	1.298	1 : 9
23			46.2	1.031	1.321	1 : 8

* The figures in this table were obtained from the same infants as those in Table 2 and are numbered the same. To avoid needless repetition the age, weight, etc., are not given in the above table as they are in Table 2. See footnotes * and † Table 2.

† After treatment.

of normal size. Obviously, a marked destruction of red cells would decrease the corpuscular volume while an increase or decrease in the size of the cells would be of marked influence. Whether there is an increased blood destruction in intestinal intoxication is impossible to say, but there is no evidence to support such a view. Fresh blood preparations have been examined in a number of cases and these showed no apparent change in the size of the red cells.

2. Specific Gravity of the Blood Serum.—The specific gravity was determined by weighing the blood serum in small Nicholl pycnometers with a capacity of from 0.4 to 1.5 gm. of water. All determinations were at 22 C.

The specific gravity of the blood serum of normal infants varies from 1.020 to 1.025 (Table 3). These values are lower than those in normal adults, which, according to Gettler and Baker,⁸ are from 1.026 to 1.030. In cases of intoxication the specific gravity was from 1.026 to 1.031, which is greater than that of normal infants. This increase, however, is too slight to account for the increase in nonprotein nitrogen merely on the basis of increased blood concentration.

Assuming that the normal specific gravity of the blood serum of infants is 1.020, this signifies that each 100 c.c. of blood serum contains 2 gm. of dissolved solids. An increase of the specific gravity to 1.031, which was the maximum found in cases of intoxication, would indicate an increase of 1.1 gm. of solids per 100 c.c. This would merely signify that the serum contained a trifle more than one and one-half times as much solids as normal. In the cases of intestinal intoxication, we find that the nonprotein nitrogen is often five times as great as normal, and if this increase were merely a matter of increased blood concentration, all solids should be equally affected and the specific gravity should be as great as 1.100. In no instance was the specific gravity increased to any degree comparable to the increase in nonprotein nitrogen. Moreover, a comparison of the nonprotein nitrogen and specific gravity in cases of intoxication shows that there is no direct ratio and that in several instances there was a great increase in the nonprotein nitrogen, with a specific gravity within the limits of normal. Moreover, the mere increase in nonprotein nitrogen would cause an increase in the specific gravity of the serum aside from any increase in concentration due to loss of fluid from the blood.

3. Total Nitrogen of the Blood Serum.—One half to 1 c.c. of blood serum was digested in a small Kjeldahl flask with 2 c.c. of sulphuric acid, about 0.5 gm. of potassium sulphate and a small crystal of copper sulphate. The determination was made by aeration into twentieth-normal acid and titration with twentieth-normal sodium hydroxid, using congo red as indicator.

If the increase of nonprotein nitrogen in the blood of infants suffering from intestinal intoxication is due merely to increased concentra-

tion of the blood, there should be a similar increase in the other substances comprising the total nitrogen of the blood. That such is not the case is readily seen by referring to Tables 3 and 4.⁶ While there is a greater total nitrogen of the blood serum in cases of intoxication, this increase is in no way comparable to the increase of nonprotein nitrogen, and in several cases the increase in total nitrogen can be explained almost entirely by the increase in nonprotein nitrogen. This is shown best by comparing the nonprotein nitrogen:total nitrogen ratio in the normal cases with those of intoxication.

4. *Total Solids of the Blood.*—The total solids were determined by weighing a few drops of blood on blotting paper previously weighed, drying at 110 C. and again weighing.

As shown in Table 3, the total solids in normal infants ranged from 17.1 to 18.6 per cent. In cases of intoxication (Table 4) the values were from 19.6 to 21.8 per cent. These figures agree closely with those recently published by Courtney and Fales⁷ and have the same significance as those for corpuscular volume, total nitrogen and specific gravity.

TABLE 5.—SHOWING THE RETENTION OF NONPROTEIN NITROGEN AND UREA AFTER THE BLOOD CONCENTRATION BECAME NORMAL

Date	Weight, Pounds	Nonprotein Nitrogen, Mg. per 100 C.c. of Blood	Urea Nitrogen, Mg. per 100 C.c. of Blood	Specific Gravity of Blood Serum	Total Nitrogen in Blood Serum, Gm. per 100 C.c.	Corpuscular Volume, per Cent.
11/11	11½	176	89	1.030	1.301	39.6
11/18	11	160	..		1.23	38.4
11/20	11½	120	50	1.026	1.18	34.5
11/22	11¾	100	..	1.025	1.12	
11/24	11¾	28	7	1.024	1.09	34.0

Baby G. (Case 19) was admitted Nov. 11, 1916, with a history of severe diarrhea and vomiting for four days. The infant was greatly emaciated and the fontanel was sunken. The mental condition was dull. Hyperpnea was marked and the carbon dioxide tension of the alveolar air was 19 mm.

Seven and a half grams of sodium bicarbonate were given by intravenous injection. The carbon dioxide tension of the alveolar air became normal and the hyperpnea ceased. Large amounts of water were given by mouth and by subcutaneous injection (physiologic sodium chloride solution).

Discussion.—It is of interest that the corpuscular volume of the blood, the total solids of the blood, the total nitrogen and specific gravity of the blood serum are all much lower in normal infants than in

6. In adults Gettler and Baker (Footnote 3) found that the total nitrogen of the blood serum was from 1.2 to 1.4 gm. per 100 c.c. These values are much greater than those from normal infants.

7. Courtney, A. M., and Fales, H. L.: AM. JOUR. DIS. CHILD., 1917, **14**, 202.

adults. This is probably in correspondence with the fact that the tissues of the infant contain a higher percentage of water and that the water metabolism is more active in infants than in adults.

The data furnished by the total nitrogen, specific gravity, corpuscular volume and total solids indicate that in intestinal intoxication there is often an increase in blood concentration. This increase in concentration, however, is insufficient to account for the increase in nonprotein nitrogen found in these cases.

Further evidence bearing on this question is the observation that a number of patients begin to retain fluid for some time before the non-protein nitrogen falls to normal. The nonprotein nitrogen remains high after the corpuscular volume of the blood and total nitrogen and specific gravity of the serum reach normal. This would indicate that the high nonprotein nitrogen was not due merely to the increased blood concentration. The results from a case of this kind are shown in Table 5.

On the basis of the evidence given it seems that the increased non-protein nitrogen which occurs in cases of intestinal intoxication is due to defective elimination of the nitrogenous waste products by the kidney.

III. TESTS OF RENAL FUNCTION. PHENOLSULPHONEPHTHALEIN ELIMINATION: AMBARD'S COEFFICIENT OF UREA EXCRETION

Phenolsulphonephthalein Elimination: Technic.—The infant was put on a metabolism frame three hours after the last feeding and was given 120 c.c. of slightly sweetened water. Three mg. of phenolsulphonephthalein were given intramuscularly and the urine collected for two hours. One half of the urine was used to determine the phthalein in a Rowntree and Geraghty modification of the Autenreith-Königsberger colorimeter; the other half was used for estimation of urea, ammonia and total nitrogen.

Tests were made on thirty normal infants from 3 months to 1 year of age. The phenolsulphonephthalein elimination ranged from 58 to 94 per cent. during two hours, the water elimination from 56 to 100 c.c. (47.5 to 83.5 per cent.). (Table 6.)

The results from 16 infants with intoxication are shown in Table 7. The phenolsulphonephthalein elimination was from 4 to 38 per cent., the water elimination from 23 to 48 c.c. (19 to 40 per cent.). The interpretation of these results in terms of renal permeability cannot be made with any degree of assurance, owing to the greatly diminished secretion of urine. During the acute stage of intestinal intoxication the infant may pass no urine for hours and the twenty-four hour elimination may total only a few cubic centimeters. For this reason, in the cases of intestinal intoxication used for the phenolsulphonephthalein test the patients had recovered from the acute stage and had commenced

TABLE 6.—THE ELIMINATION OF WATER AND PHENOLSULPHONEPHTHALEIN; AMBARD'S COEFFICIENT OF UREA EXCRETION. NORMAL INFANTS

Number	Age, Months	Weight, Pounds	Water Elimination after Ingestion of 120 C.c. of Water, 2 Hour Period		Phenol-sulphone-phthalein Output, 2 Hour Period, per Cent.	Ambard's Coefficient of Urea Excretion, 2 Hour Period, Ur $\sqrt{D \frac{V_c}{V_5}}$
			C.c.	per Cent.		
1	8	11½	66	55.0	80	0.072
2	3½	10½	80	67.5	64	0.061
3	4	12½	90	75.0	68	0.096
4	4	11¾	58	47.5	96	0.084
5	5	18	74	61.5	58	0.10
6	5½	13½	94	78.0	73	0.071
7	6	14½	59	49.0	67	0.05
8	6	15	67	56.0	74	0.11
9	6½	14¾	66	71.5	88	0.065
10	7	16½	73	61.0	71	0.093
11	7	16	81	62.5	81	0.061
12	7½	15½	59	49.0	61	0.01
13	8	16¾	62	52.0	70	0.072
14	8	17½	56	47.5	59	0.076
15	10½	18	79	66.0	86	0.068
16	11	19½	100	83.5	94	0.05
17	12	20¾	77	64.0	87	0.078
18	13	21	67	56.0	75	0.087
19	13	20½	99	82.5	71	0.061
20	13½	21¼	78	65.0	78	0.072

to pass moderate amounts of urine. No test was included during which less than 20 c.c. of urine was voided. Despite the selection of cases and the fact that 120 c.c. of water were ingested at the time of the test, the water output was greatly diminished. As shown by Tables 6 and 7, the phenolsulphonephthalein elimination was greatly diminished in cases of intoxication. Owing to the decreased secretion of urine the low phenolsulphonephthalein output cannot be attributed to an anatomic kidney lesion.

Ambard's Coefficient of Urea Excretion.—According to Ambard⁸

8. Ambard, L.: *Physiologie normale et pathologique des reins*, Paris, 1914; Ambard, L., and Weill, A.: *Jour. de physiol. et de pathol. gén.*, 1912, **32**, 217. This subject has also been considered in detail by McLean, F. C., and Selling, L.: *Jour. Biol. Chem.*, 1914, **19**, 31; McLean, F. C.: *Jour. Exper. Med.*, 1915, **22**, 212; Addis, T., and Watanabe, C. K.: *Jour. Biol. Chem.*, 1916, **24**, 203, and Lewis, D. S.: *Arch. Int. Med.*, 1917, **19**, 1.

TABLE 7.—THE ELIMINATION OF WATER AND PHENOLSULPHONEPHTHALEIN;
AMBARD'S COEFFICIENT OF UREA EXCRETION. INFANTS
WITH INTESTINAL INTOXICATION *

Number	Age, Months	Weight, Pounds	Water Elimination after Ingestion of 120 C.c. of Water, 2 Hour Period		Phenol- sulphone- phthalein Output, 2 Hour Period, per Cent.	Ambard's Coefficient of Urea Excretion, 2 Hour Period, Ur $\sqrt{D \frac{V_c}{V_b}}$
			C.c.	per Cent.		
1	3	8¾	26	13.0	22.0	0.23
2	4½	9¾	31	26.0	18.0	0.31
3	5	9	40	33.0	29.0	0.21
4	5¾	10	25	31.0	34.0	0.19
5	6¾	9¾	48	40.0	34.0	0.22
6	7½	12¾	35	29.0	17.0	0.36
7	7¾	11¾	29	24.0	20.0	0.27
8	8	13½	31	26.0	23.0	0.29
9	8½	12¾	23	19.0	15.5	0.27
10	9	14	47	40.0	38.0	0.10
11	9	13½	36	30.0	27.0	0.17
12	10½	12¾	28	23.0	14.0	0.37
13	10¾	13¾	30	25.0	30.0	0.20
14	11	14	37	31.0	29.0	0.27
15	11½	12¾	44	37.0	39.0	0.18
16	11¾	15½	33	27.5	20.0	0.3

* During the acute stage of intestinal intoxication so little urine is secreted that tests of renal function are impossible. The figures shown were derived from a study of patients who had begun to improve and who excreted more than 20 c.c. of urine during the two-hour period.

and his co-workers there is a definite ratio between the urea in the circulating blood and that excreted in the urine per unit of time. The formula used to derive the coefficient is obtained from Ambard's third law and is as follows:

$$K = \frac{Ur}{\sqrt{D \frac{70 \sqrt{C}}{P \sqrt{25}}}}$$

K=Coefficient of urea excretion.

Ur=Urea per liter of blood.

D=Output of urea for twenty-four hours calculated from the amount excreted during the period of observation.

P=Weight of patient in kilograms.

C=Grams of urea per liter of urine.

70=Standard weight.

25=Normal amount of urea per liter of urine.

Our observations were made during two-hour periods at the same time the phenolsulphonephthalein tests were made. The analytical methods were those previously described.

In applying Ambard's formula to infants it is obvious that certain changes must be made. In the formula the standard weight of 70 kg. is used. This is, of course, relative to adults. It is practically impossible to introduce a standard weight for young infants owing to the fact that the weight changes are so rapid. The use of the average weights for different ages would not be strictly accurate, since the weights of normal infants of the same ages may vary within several pounds, which makes a considerable error when one considers such differences in relation to total weight. A further difficulty arises from the circumstance that infants with nutritional disorders show great fluctuations in weight within short periods of time. Actual calculations in normal cases show that the coefficient is more constant if the factor 70/P or any equivalent is eliminated.

For adults the standard value of 25 gm. of urea per liter of urine is used. Our determinations on thirty normal infants under 1 year of age gave figures which ranged from 4.2 to 6.37 gm. of urea per liter. On the basis of these figures the standard value of 5 was substituted for 25 in the formula. As used by us the formula was as follows:

$$K = \frac{Ur}{\sqrt{D \frac{\sqrt{C}}{\sqrt{5}}}}$$

In adults it has been found that the normal coefficient ranges from 0.6 to 0.9 and that defective kidney function causes the constant to increase. In normal infants the constant, as calculated by the formula we used, ranges from 0.05 to 0.11 (Table 6). The coefficient, therefore, has a tendency to be higher in infants than in adults, and in several of our normal cases values above 0.09 were obtained which in adults would signify impairment of renal function.

In cases of intoxication the constant ranged from 0.13 to 0.39, thus indicating a considerable degree of impairment of renal function (Table 7).

In general, these results are roughly parallel to the phenolsulphonephthalein elimination and are open to the same criticism in reference to the excretion of water. All that these tests signify is that in intestinal intoxication the power of elimination by the urine is greatly impaired.

IV. THE CAUSE OF DEFICIENT ELIMINATION BY THE KIDNEYS

In consideration of the greatly diminished excretion of urine during the acute stage of intestinal intoxication it seems only natural to expect that substances normally excreted in the urine would be retained. This would certainly occur unless there were some other channel through which the waste products could be eliminated. Despite the self evidence of this proposition it is a question of some importance whether the retention is entirely a matter of lessened water excretion, or whether it is dependent on a kidney lesion.

The occurrence of albumin and casts in the urine of infants affected with severe diarrhea has long been recognized and is mentioned in practically every treatise on this disease. The subject was considered in detail by Pick,⁹ in 1905, who gave an exhaustive review of the literature. He noted that the toxic symptoms in severe diarrhea are not unlike those of uremia, and suggested the possibility that in some cases the symptoms may be of uremic origin.

Neuman,¹⁰ in 1907, found that in general there was a close parallel between the presence and degree of albuminuria and cylindruria and the severity of the toxic symptoms. He concluded, however, that the renal lesions were probably secondary and not of etiologic importance.

In all of the cases in this series the urine contained albumin and casts during the acute stage of the disease. With improvement in the symptoms, albumin and casts soon disappeared. The degree of albuminuria, however, was rarely great and not often of sufficient amount to give a reading in the Esbach tube. In most instances the number of casts seemed much greater than one would expect from the amount of albumin present. The period at which the albuminuria and cylindruria were most marked coincided with the period when the urine was very scanty, so that the number of casts, at least, would appear much greater than it actually was.

A detailed consideration of the significance of albumin and casts in the urine is beyond the scope of this paper. Certainly their presence is abnormal, but whether their occurrence indicates a kidney lesion capable of causing retention of nitrogenous waste products is impossible to determine. It does seem clearly established, however, that the occurrence of albuminuria and cylindruria does not necessarily indicate a kidney lesion which is demonstrable by our present histologic methods. If definite anatomic lesions are the sole criteria of kidney disease, we should not be warranted in assuming that a kidney lesion was present solely on the basis of albuminuria and cylindruria.

9. Pick, J.: *Arch. f. Kinderh.*, 1905, **40**, 291.

10. Neuman, G.: *Jahrb. f. Kinderh.*, 1907, **66**, 633.

Neuman¹⁰ found slight parenchymatous renal lesions in one of his cases. In another, the kidneys were practically normal. Pick,⁹ however, found distinct anatomic lesions in several cases. Definite renal lesions in infants dying of intestinal intoxication were described by Hoffsten,¹¹ Epstein,¹² Bernhard and Felsenthal,¹³ Czerny and Moser,¹⁴ Jehle¹⁵ and others.

In nine of the cases presented in this paper necropsies were performed and the results are shown in Table 8. In two cases, 14 and H., there was distinct parenchymatous nephritis, severe in one (14) and moderate in the other (H.). In both of these cases the tubules contained many necrotic cells which were often massed to form distinct foci. These foci stained a deep blue with hematoxylin, which suggested the deposition of calcium salts. The lesions in these cases resembled closely those seen in poisoning with mercuric chlorid. Three cases, 10, 5 and O'D., showed no definite renal changes at all. The remaining four cases showed slight or moderate parenchymatous changes in the tubular epithelium and hemorrhage into the tubules. Dr. Charles Norris, who kindly examined the sections, stated that the hemorrhage was possibly agonal and in consequence may have borne no direct relation to the disease. This is suggested strongly by the fact that the urine of none of these patients contained blood, which should have been true had the hemorrhage existed for some time before death.

Unfortunately, there is no evidence available which indicates the degree of kidney damage necessary to cause retention. On the basis, however, of the lesions present in nephritis in adults with nonprotein nitrogen retention it would seem that in only two of our cases was the kidney lesion sufficient to account for the high nonprotein nitrogen. Lesions of similar grade to those found in the other cases are often found in the absence of any chemical evidence of defective renal function.

It seems apparent, therefore, that the impairment of renal function in intestinal intoxication cannot be due in the majority of cases to a definite kidney lesion, but must depend on some other cause. It seems most probable that the cause lies in the depleted water supply of the body.

It is well established that water is the most efficient diuretic, and without an adequate supply secretion of urine is impossible. In intestinal intoxication the water supply of the body is usually depleted by the great loss of water in the stools. Many of the patients refuse to

11. Hoffsten: *Virchow-Hirsch Jahresb.*, 1888, **11**, 478.

12. Epstein: *Festschrift Edw. Henoch*, Berlin, 1890.

13. Bernhard and Felsenthal: *Arch. f. Kinderh.*, 1894, **17**, 222.

14. Czerny and Moser: *Jahrb. f. Kinderh.*, 1894, **38**, 430.

15. Jehle: *Jahrb. f. Kinderh.*, 1907, **65**, 40, Part 1.

TABLE 8.—EVIDENCES OF RENAL INVOLVEMENT IN NINE CASES OF INTESTINAL INTOXICATION

Patient	Nonprotein Nitrogen, Mg. per 100 C.c. of Blood	Albumin in Urine	Casts in Urine	Evidence of Renal Lesions	
				Macroscopic	Microscopic
10*	61.9	+ Trace	Few hyaline many granular	Moderate congestion; no swelling of cortex; markings distinct	No significant lesions
13*	134.4	Heavy trace	Many hyaline granular and epithelial	Cortex pale, slightly swollen; markings slightly obscured	Many tubules contain red blood cells; tubular epithelium shows parenchymatous degeneration; apparent increase in nuclei in malpighian corpuscles, possibly due to shrinkage
14*	232.0	1 Gm. per liter by Esbach	Many granular and epithelial	Kidneys pale; greatly enlarged; edematous; cortex much swollen and markings obscured	Marked swelling and necrosis of tubular epithelium; foci of necrotic cells in tubules of cortex; coagulated material in glomeruli; apparent increase in number of cells in malpighian tufts; definite acute parenchymatous nephritis
6*	83.0	Trace	Many hyaline few granular	Kidneys slightly enlarged; cortex slightly swollen	Moderate swelling and parenchymatous degeneration of tubular epithelium; nuclei slightly pale
5*	150.0	Trace	Many hyaline few granular	Slight congestion	No significant lesions
P	113.4	Trace	Few hyaline many granular	Kidneys pale; slightly enlarged; cortex slightly swollen; slight edema	Many tubules contain red blood cells; parenchymatous degeneration of tubular epithelium
H	65.8	Moderate 1.5 Gm. per liter by Esbach	Many hyaline and granular	Kidneys pale; slight swelling of cortex	Marked hemorrhage into tubules of pyramids; hemorrhage into glomeruli; necrosis of tubular epithelium with the formation of a few necrotic foci in tubules; acute parenchymatous nephritis
V	90.3	Trace	Many hyaline few granular	Slight enlargement of kidneys; marked congestion	Hemorrhage into tubules; tubular epithelium shows moderate parenchymatous degeneration
O'D	68.0	Trace	Many hyaline few granular	Slight congestion	No significant lesions

* These figures refer to the same patients as those in Tables 2 and 4.

† A few red blood cells in urine.

ingest even water and vomit water or food, so that there is but little fluid available to replace even the normal loss of water in the excretions. It seems probable, therefore, that the deficient elimination by the kidney is purely functional and is due to the fact that there is no water available for the formation of urine.

The fact that the increased concentration of the blood is insufficient to account for the high nonprotein nitrogen is in no way antagonistic to this idea. There are a number of factors which tend to keep normal the water composition of the blood.

Bang¹⁶ found that when dogs are deprived of water the blood shows increased nonprotein nitrogen. The nonprotein nitrogen became normal when water was given in sufficient amounts. Bang gave no evidence bearing on the blood concentration. It seems quite possible that the high nonprotein nitrogen was due to defective elimination owing to lack of water.

The clinical importance of the great loss of water in intestinal intoxication is too well known to require special consideration. It is a matter of considerable difficulty to give these infants sufficient water to replace that lost in the excretions. In six cases of intoxication in which it was possible to give sufficient water approximately to replace that lost the excretion of urine was apparently normal and there was no significant increase in the nonprotein nitrogen of the blood. Of the same significance is the fact that in no case was there any material reduction in the nonprotein nitrogen of the blood before the normal excretion of urine was reestablished.

From the evidence at our disposal it seems probable that the deficient kidney elimination in intestinal intoxication is dependent, to a great degree at least, on the negative water balance. Whether insufficient water in the blood and tissues is directly and entirely responsible for the diminished secretion of urine offers considerable field for discussion. There are a number of factors capable of affecting kidney function which may be of influence. It has been demonstrated by Starling¹⁷ that the colloids of normal blood exert an osmotic pressure of 25 to 30 mm. of mercury and under these conditions the arterial pressure in the kidney glomeruli must be greater than 30 mm. of mercury to insure the formation of urine. A greater concentration of colloids would require a greater arterial pressure in the kidney for glomerular filtration to occur.

In intestinal intoxication it seems possible that the blood colloids may be increased to such degree that they exert an osmotic pressure greater than the pressure in the glomerular capillaries. If this were

16. Bang, I.: *Biochem. Ztschr.*, 1915, **72**, 119.

17. Starling: *Jour. Physiol.*, 1899, **24**, 317.

true the formation of urine would be prevented. Moreover, the total blood volume is probably reduced in cases of intestinal intoxication, which would diminish the blood flow through the kidney and consequently reduce the secretion of urine. Such conditions, however, would arise in great part, if not entirely, from the water deficit and at present have not been accurately determined.¹⁸

V. THE ACIDOSIS OF INTESTINAL INTOXICATION

Howland and Marriott¹⁹ showed that acidosis is a frequent occurrence in severe diarrhea in infants. The frequency and degree of acidosis in cases of intestinal intoxication has been discussed also by Schloss and Stetson.²⁰

According to our present conception, acidosis is best defined as a reduction in the alkaline reserve of the blood. Our knowledge of the significance of the alkaline reserve and the factors which influence it is based on the work of Henderson²¹ and Henderson and Palmer,²² and has been discussed by Lundsgaard,²³ Peabody,²⁴ Hasselbalch and Gammeltoft,²⁵ Barcroft,²⁶ Howland and Marriott,²⁷ Van Slyke and Cullen²⁸ and others.

On the basis of this definition it is theoretically possible for acidosis to be due to several causes. In acidosis occurring with diarrhea Howland and Marriott¹⁹ found no evidence that abnormal acids were formed. They found no significant increase in the acetone bodies in the blood, which demonstrated that the acidosis was not due to increased formation or diminished oxidation of these substances.

18. There is no means of ascertaining the blood pressure in the kidney of human beings. In dogs it is assumed to be 20 per cent. less than the carotid blood pressure, but Cushny states that such assumption is little more than a guess (*The Secretion of Urine*, London, 1917). MacKenzie (*Brit. Jour. Child. Dis.*, 1912, **9**, 343) says that the anuria in severe diarrhea of infants is due to lowered blood pressure, although he gives no evidence to support this view. Hill (*Arch. Pediat.*, 1913, **30**, 588) has reported blood pressure determinations (femoral artery) in eighteen cases of severe diarrhea. His results show no reduction in blood pressure when compared with the values for normal infants obtained by Morse and Wyman (*AM. JOUR. DIS. CHILD.*, 1914, **8**, 270) and others.

19. Howland, J., and Marriott, W. McK.: *AM. JOUR. DIS. CHILD.*, 1916, **11**, 309.

20. Schloss, O. M., and Stetson, R. E.: *AM. JOUR. DIS. CHILD.*, 1917, **13**, 218.

21. Henderson, L. J.: *Am. Jour. Physiol.*, 1908, **21**, 427; *Ergebn. d. Physiol.*, 1909, **8**, 254; *Jour. Biol. Chem.*, 1911, **9**, 403.

22. Henderson, L. J., and Palmer, W. W.: *Jour. Biol. Chem.*, 1912-1913, **8**, 393; 1913, **14**, 81; 1914, **17**, 305.

23. Lundsgaard, C.: *Biochem. Ztschr.*, 1912, **41**, 149.

24. Peabody, F. W.: *Arch. Int. Med.*, 1914, **14**, 236.

25. Hasselbalch, K. A., and Gammeltoft, S. A.: *Biochem. Ztschr.*, 1915, p. 205.

26. Barcroft, J.: *The Respiratory Function of the Blood*, Cambridge, 1914.

27. Howland, J., and Marriott, W. McK.: *Bull. Johns Hopkins Hosp.*, 1916, **27**, 63.

28. Van Slyke, D. D., and Cullen, G. E.: *Jour. Biol. Chem.*, 1917, **30**, 289.

There is no evidence that the acidosis is caused by abnormal loss of alkali, for, as pointed out by Howland and Marriott, the analyses of diarrheal stools by Holt, Courtney and Fales show actually a loss of more acid than base. Nor can there be any significant loss of alkali in the urine, for both the hydrogen-ion concentration and the titrable acidity are increased.

Howland and Marriott concluded that the acidosis of diarrhea was probably dependent on defective elimination of acid by the kidney and suggested the possibility that it was due, in part, at least, to the failure of the kidney to eliminate acid sodium phosphate. Recently, they have found that there is a considerable increase in the inorganic phosphorus in the blood, which is in accord with this view.²⁹

The evidence derived from my own cases is entirely in accord with the view that the acidosis of intestinal intoxication is due to faulty elimination by the kidney. The blood has been examined for acetone bodies in six cases with severe acidosis, and in no case was the amount greater than could be accounted for by starvation. The greatest value was 37 mg. of total acetone bodies, determined as acetone, in 100 c.c. of blood.

In a great number of cases of relatively severe acidosis in intestinal intoxication, a single dose of sodium bicarbonate is sufficient permanently to correct the acidosis. It would seem most unlikely that this could occur if abnormal acids were being formed in large amounts. As an example the following protocol is given:

Protocol 1.—The patient, a boy, aged 6 months, was admitted Jan. 15, 1916. For two days before admission he had vomited almost every feeding and had many loose yellow stools. For twelve hours he had marked muscular twitchings, was semistuporous and refused all food. On admission the infant was somnolent, had distinct hyperpnea and seemed very ill.

Date	Carbon Dioxid Tension, Alveolar Air, Mm.	C.c. of CO ₂ , Reduced to 0, 760 Mm., Bound as Bicarbonate by 100 C.c. of Blood Plasma (Van Slyke)
1/15	22	34.6
	3 gm. sodium bicarbonate by intravenous injection	
1/16	40	80.0
1/18	39	72.0
1/20	41	69.0
1/25	37	68.0

The hyperpnea disappeared entirely after the bicarbonate and the stupor lessened but did not disappear. The diarrhea continued until January 20, and during this period the infant was toxic and very ill. Improvement began January 20 and January 25 the infant was practically free from symptoms. A single dose of alkali was therefore sufficient to eliminate entirely a marked degree of acidosis.

29. Personal communication, Dr. John Howland, Dec. 11, 1917.

It might be suggested that in cases of this type the acid formation had perhaps occurred at a time before the patient came under observation and had ceased, so that the single dose of alkali was sufficient, merely because no acid formation was in progress at that time. Such objection, however, would be invalid in the cases in which the acidosis developed under observation. Five cases of this type have been studied, an example of which is given in illustration:

Protocol 2.—Case 22, boy, aged 10 months. The baby had from eight to ten loose stools daily for five days; the day before admission he refused all food and became somnolent. On admission he showed evidence of moderate fluid loss and his expression was dull. There was no hyperpnea. The development of acidosis is shown by the following data. On November 19 hyperpnea was noted.

Date	Carbon Dioxid Tension, Alveolar Air, Mm.	C.c. of CO ₂ , Reduced to 0, 760 Mm., Bound as Bicarbonate by 100 C.c. of Blood Plasma (Van Slyke)
11/14/16	36.0	64.0
11/16	36.0	65.1
11/17	30.0	
11/18	27.0	
11/19	23.0	38.0
3.7 gm. sodium bicarbonate by intravenous injection		
11/20	40.0	87.0
11/21	42.0	
11/23	37.5	
11/25	37.5	80.0
Death		

In this case the acidosis developed under observation and was corrected by the administration of sodium bicarbonate. The hyperpnea disappeared; the other evidences of intoxication were influenced but little, and the infant died without further evidence of acidosis.

These observations are entirely in accord with the view that the acidosis is due to the failure of the kidney properly to fulfil its function of preserving the alkali reserve of the blood and contrary to its dependence on the formation of abnormal acids.

Evidence has been given which demonstrates that there is an accumulation of waste products in the blood due to defective secretion of urine. It seems only reasonable to suppose that the acidosis is of similar origin.

Six patients with intestinal intoxication have been observed to whom it was possible to supply approximately as much water as was lost. None of these patients showed a marked diminution in the excretion of urine and none developed acidosis.

In five cases the acidosis developed under observation. In three the output of urine was carefully observed, and in each instance the

acidosis was preceded by a diminished excretion of urine and the chemical evidence of impaired renal function. This occurrence is illustrated by the accompanying curve.

It would seem, therefore, that the acidosis of intestinal intoxication is probably due to defective kidney function.

Baby Y., aged 9 months. For three days previous to admission he appeared ill and passed from three to four loose green stools a day. During this period he vomited four times. On admission he was fairly nourished, the fontanel was not depressed and the skin was fairly moist and elastic. The infant was somnolent but could be roused easily. Until November 7 the food consisted of 3 ounces each of protein milk and barley gruel, given every four hours. In addition, large amounts of water were given. The stools were watery and from five to seven were passed in twenty-four hours. Vomiting became severe on November 8 and the food was changed to barley gruel. In the chart ----- with the figures at the left = urine in c.c. during a two-hour period after ingestion of 120 c.c. of water; ————— = nonprotein nitrogen of the blood in milligrams per 100 c.c.; with the figures at the left = carbon dioxid tension, in millimeters, of the alveolar air.

VI. THE SYMPTOMS OF INTESTINAL INTOXICATION

To determine definitely at present the origin of the symptoms of intestinal intoxication is obviously impossible, but there are facts bearing on this question which seem of sufficient importance to mention.

In a number of cases the acidosis bears a definite relation to the symptoms. This is quite evident when the symptoms disappear promptly after the correction of the acidosis by alkali. In some of the cases there is but little improvement in the symptoms after acidosis is eliminated. Hyperpnea, if present, always disappears, but at times the patient remains semistuporous and the prostration and other manifestations remain unchanged. Although in such cases the symptoms cannot be due directly to acidosis, yet it seems possible that the lack of alkaline reserve had caused injury to the tissue which is not repaired by the mere correction of the existing acidosis. Even granting the correctness of this assumption, there are cases of intestinal intoxication in which the symptoms are marked and yet acidosis is absent. The symptoms in these cases, except that hyperpnea is absent, seem identical with those of cases in which acidosis is present. This is also true of those cases in which the symptoms improve after the administration of alkali but return within a short time despite the fact that there is no recurrence of acidosis.

The improvement which occurs after the administration of sodium bicarbonate is probably not always due entirely to the alkali. Part is due to the water, and moreover, in the regular treatment of these cases, large amounts of water are given independently of alkali.

While there seems no question that acidosis is an important cause of the symptoms of intestinal intoxication, yet it is by no means the whole cause.

There is no evidence to indicate that the retained nitrogenous waste products are responsible for the symptoms. It is generally believed that in uremia, even with considerable nonprotein nitrogen retention, these substances are not responsible for the toxic symptoms. Recently, Hewlett, Gilbert and Wickett³⁰ were able to cause toxic symptoms in normal adults by feeding large amounts of urea. The symptoms, however, were slight in comparison to the degree of urea retention in the blood and as compared with what is often observed in uremia. These experiments show that large amounts of retained urea can be toxic, yet they do not demonstrate that the amount of urea retained in intestinal intoxication can be the cause of the toxemia.

There is a close analogy between intestinal intoxication and uremia. Indeed, all of the evidence points directly to the fact that their nature

30. Hewlett, A. W., Gilbert, Q. O., and Wickett, A. D.: *Arch. Int. Med.*, 1916, **18**, 636.

is essentially the same. In uremia the kidney fails to fulfil its proper function, due to an anatomic lesion. In intestinal intoxication the same result is brought about through loss of fluid. Waste products normally excreted by the kidneys are retained because there is insufficient water for diuresis.

Similar to uremia, based on symptomatology, there are two groups of cases of intestinal intoxication. In one group convulsions, involuntary muscular movements, muscular twitching and coma are present. The onset is usually acute and the infant is not greatly emaciated. Diarrhea may be slight and is absent in some cases. Food or water is usually refused and is vomited if taken.

In the second group the onset is less acute, but occurs following vomiting and diarrhea of some days' duration. Convulsions rarely occur and the infant is somnolent or semistuporous instead of comatose. Wasting is very marked and the patient presents the shrunken appearance which is so characteristic of great loss of fluid.

In both uremia and intestinal intoxication acidosis is a frequent occurrence.

Aside from the question of acidosis, intestinal intoxication similar to uremia appears to be some form of poisoning. Whether this poison is a product which the kidney has failed to excrete, whether it arises from disordered metabolism or is elaborated by bacterial growth in the intestinal tract, is one of the fundamental problems with which we are confronted.

SUMMARY

In intestinal intoxication there is a marked increase in the non-protein nitrogen and urea of the blood. This increase is not due directly to increased concentration of the blood from loss of water. The high nonprotein nitrogen and urea are due to defective kidney elimination.

The renal lesions in intestinal intoxication are not sufficient to account for the impaired elimination by the kidney. It is probably due to the fact that lack of water restricts the formation of urine. This condition is probably due to the following factors which may act singly or in combination: 1. The loss of water in the stools is so great that it is impossible for the infant to ingest sufficient fluid to replace the loss. 2. The patient refuses to ingest fluid or vomits practically all that is taken. As a result the tissues become dehydrated. The retention of nitrogenous waste products and the failure of the kidney to do its part in preserving the acid-base equilibrium results from the deficient secretion of urine. The oliguria may be due to the fact that the dehydrated tissues hold as much water as possible so that none is available for the formation of urine. Other factors, dependent mainly

on the loss of water, which may play a rôle are: 1, an increase in the concentration of blood colloids to such degree that their osmotic pressure is greater than the arterial pressure in the kidney; 2, a diminution in the total blood volume leading to decreased blood flow through the kidney.

The symptoms of intestinal intoxication are essentially those of uremia. The two conditions are similar in all essentials. In one, defective kidney function is due to an organic lesion; in the other it results from the negative water balance and consequent oliguria.

Acidosis plays a definite part in the symptomatology of intestinal intoxication, but the essential cause is probably some unknown toxic agency.

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