

## BODY FLUID CHANGES DUE TO CONTINUED LOSS OF THE EXTERNAL SECRETION OF THE PANCREAS.

BY JAMES L. GAMBLE, M.D., AND MONROE A. McIVER, M.D.

WITH THE ASSISTANCE OF PAULINE MARSH AND DOROTHY SLOAN.

(From the Departments of Pediatrics and of Surgery, Harvard Medical School, Boston.)

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The body fluid changes caused by continued loss of gastric secretions have been fairly well defined by the experimental work of a number of investigators (1-3). The outstanding alterations are dehydration of the interstitial body fluids and of the blood plasma, and alkalosis. These changes are referable to a continued withdrawal of fixed base and of chloride ion from the blood plasma. The data in the preceding paper demonstrate that the digestive secretions entering the duodenum also contain these plasma substances in appreciable amounts. Presumably loss of these secretions, in the absence of adequate replacement of the materials contained, will cause disturbances of body fluid volume and structure. The data to be presented in this paper describe an experimental attempt to define the body fluid changes developing as a result of continued loss of the external secretion of the pancreas.

The general effects accompanying complete loss of pancreatic juice were first observed by Pawlow (4). He found that dogs with pancreatic fistulæ die unless certain measures are taken. To quote from his description of an experiment: "3 to 4 weeks after the operation, the animal previously well to all appearances, became suddenly ill. Food was almost at once refused and a rapidly increasing disability supervened . . . followed after 2 or 3 days by death. . . . There remained but one supposition, *viz.*, that the animals, in the escape of pancreatic juice, lost something essential to the normal processes of life." Pawlow made the significant observation that this train of events could be prevented by placing sodium bicarbonate in the food, and also noted that the survival period was much longer on a diet of bread and milk than when meat alone was given. Elman and McCaughan (5) have recently withdrawn and collected the external secretion of the pancreas by an ingenious method involving cannulation of the

duct. The survival period of their animals (dogs) was very much shorter than observed by Pawlow, probably because of the development of persistent vomiting, an event which, according to Pawlow's experiments and our own, does not occur when the external secretion is withdrawn by means of a fistula.

The findings to be here described were obtained from two experiments with dogs. In the first experiment a Pawlow fistula was constructed using the accessory pancreatic duct. The external secretion lost was therefore only a part of the total production. The diet was bread and milk until the 37th day of the experiment when it was changed to meat. Except for a gradual decline in weight, this animal remained in good condition for 38 days. Symptoms of muscular weakness, apathy, and loss of appetite then developed progressively until the animal was *in extremis* on the 42nd day after operation. In the animal used in the second experiment the main and accessory pancreatic ducts were found united before entering the duodenum so that all of the external secretion was drained from an external fistula of the Pawlow type. The diet given was exclusively meat. The survival period was very much shorter than in Experiment I. The animal was active and apparently in good condition for 10 days and then became progressively weaker and more apathetic, and took little or no food or water. 15 days after operation the animal was in serious condition, showing symptoms of marked prostration; extremities cold, pulse rapid, respiration increased in depth and frequency, and blood pressure so low that it was impossible to obtain a blood sample until the femoral artery had been exposed under novocaine anesthesia. At what seemed to be almost the end of the survival period each of these animals was given large amounts of salt solution by subcutaneous injection and intravenous injections of sodium bicarbonate solution. The surgical part of these experiments was carried out under ether anesthesia, and with aseptic technic. The animals were then placed in comfortable cages and distilled water provided for drinking. When the end of the survival period was evidently near, they were killed by etherization.

#### *Chemical Methods Used.*

Plasma bicarbonate was determined by the method of Van Slyke (8) and fixed base by the method of Fiske (9). An unpublished method by Fiske was used

in measuring plasma chlorides. Sodium and potassium in urine and in the horse meat used as food were determined together by the electrolytic method of Stoddard (10) and potassium was separately measured by the method of Fiske (11).

The data obtained from these two experiments are presented in Tables I and II and those from Experiment II which describe the acid-base changes found in the blood plasma are repeated graphically in Fig. 1. As may be seen in the tables the earliest change noted is

TABLE I.  
*Data from Experiment I.*

The value  $R'$  represents the remainder of the acid equivalence of total fixed base after subtracting  $\text{HCO}_3' + \text{Cl}'$ .

Day after operation	Body weight	Food	Blood plasma			
			B'	$\text{HCO}_3'$	$\text{Cl}'$	$R'$
	<i>kg.</i>		<i>cc. 0.1 N per 100 cc.</i>	<i>cc. 0.1 N per 100 cc.</i>	<i>cc. 0.1 N per 100 cc.</i>	<i>cc. 0.1 N per 100 cc.</i>
16	17.6	Bread and milk	175	26	110	39
22	17.8	" " "	175	30	106	39
32	17.2	" " "		24	101	
36	17.2	" " "		24	104	
37	16.8	Meat				
39	16.3	"		21		
41	15.3	"	161	13	105	43
42		"	146		101	
43	15.3	"	139	11	99	29
44*	15.3	Bread and milk				
45**	15.1	" " "	155	21	103	31

\* 1000 cc. 0.9 per cent NaCl solution injected into peritoneal cavity. 100 cc. 2 per cent  $\text{NaHCO}_3$  solution given intravenously.

\*\* 5 gm.  $\text{NaHCO}_3$  given in milk.

decline of body weight. This begins directly following establishment of the fistula and proceeds gradually until the sudden development of anorexia, when it is greatly accelerated. The data on this point are complete only in Experiment II. The plasma factors studied were found not to be appreciably altered during approximately the first two-thirds of the experimental periods. Then, and corresponding with the sudden appearance of the symptoms described above, extensive change in plasma factors developed rapidly.

Except as regards the concentrations of bicarbonate and of chloride ion, these changes resemble closely those produced by continued loss

TABLE II.  
Data from Experiment II.

The value  $R'$  represents the remainder of the acid equivalence of total fixed base,  $B'$ , after subtracting  $HCO_3' + Cl'$ .

Day after operation	Body weight	Meat intake	Water intake	Blood		Blood plasma							
				Hematocrit	Red count	Protein	N.F.N.	Urea	B'	HCO <sub>3</sub> '	Cl'	R'	
	kg.	gm.	cc.	per cent		per cent	mg. per 100 cc.	mg. per 100 cc.	cc. 0.1 N 100 cc.	cc. 0.1 N 100 cc.	cc. 0.1 N 100 cc.	cc. 0.1 N 100 cc.	
Operation		0				9.4							44
1	20.4	0	460										
2	20.0	624	1440										
3	20.2	567	1120										
4	20.2	454	800										
5	20.0	340	640							25			
6	19.7	1247	1280										
7	19.7	623	1120										
8	19.5	567	960	36	5,300,000				175	22	101		52
9	18.8	737	960										
10	18.7	680	960	41	6,910,000	9.4			161	19	98		44
11	18.2	680	960										
12	17.5	170	0	44	6,570,000	11.6			158	12	96		50
13 a.m.	16.8	170	0	47	6,480,000	12.0			160	12	93		55
p.m.							220	187		12	94		
*14 a.m.	15.8	0	20	44	6,820,000	12.1			159		93		
p.m.				47	7,890,000	11.1	315		161	7	87		67
**15 a.m.	16.1	0	20	47	7,880,000	9.8	290		166	7	103		56
p.m.				43	7,100,000	8.8	325	285	167	17	104		46

\* 2000 cc. 0.9 per cent NaCl solution injected into peritoneal cavity.  
\*\* 400 cc. 2 per cent NaHCO<sub>3</sub> solution injected into femoral vein.

of stomach secretions. Dehydration of the plasma is indicated by the increase of plasma protein, the rise in red count, and the hematocrit readings (see Table II). Elman and McCaughan (5) in their much

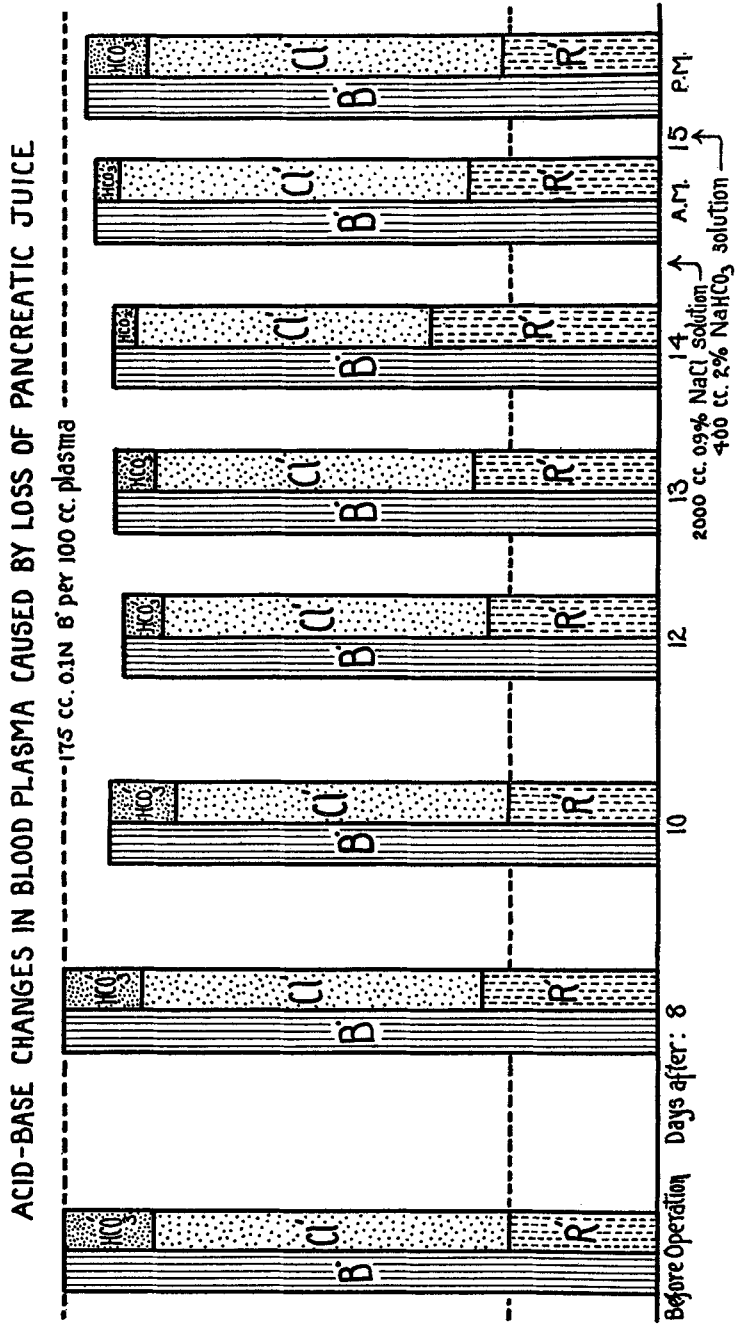


FIG. 1. From data in Table II.

more extensive series of experiments report dehydration of the blood as an outstanding finding. The few measurements of non-protein nitrogen and of urea nitrogen obtained in Experiment II near the end of the survival period show a very large accumulation of protein end-products in the plasma.

A chief purpose of these experiments was to define the changes in the acid-base structure of the plasma caused by loss of a digestive secretion containing much more of fixed base than of chloride ion. Since, when stomach secretions are lost, the relatively much larger withdrawal of chloride ion causes an extension of bicarbonate, it might be expected that loss of pancreatic juice would produce a reduction of bicarbonate.<sup>1</sup> This change was actually found in these two experiments and its relationship to changes in other acid-base factors in the plasma is easily apparent in the diagrams constructed from the measurements obtained in Experiment II (Fig. 1). There occurs a decrease in the concentration of fixed base and an increase in the sum of the acid factors other than the bicarbonate ion and chloride ion (the value  $R'$  in the diagrams), just as has been found to occur when stomach secretions are lost. These two changes will cause a reduction of bicarbonate unless accompanied by an equivalent or more than equivalent decrease of chloride ion concentration. This latter event occurs when stomach secretions are lost and explains the bicarbonate increase. When pancreatic juice is lost there is also, according to the data here presented, a decline in chloride ion concentration but not of sufficient extent to prevent a large reduction of bicarbonate. It is of interest to note that, had the chloride ion concentration been sustained at its initial level, bicarbonate would have been entirely obliterated. These points of agreement and of contrast between acid-base changes caused by loss of stomach secretions and by loss of

<sup>1</sup> The sum of the acid factors in the plasma is kept equal with the sum of the base factors by adjustment of the bicarbonate ion concentration, change in any factor causing change in bicarbonate in the direction which will maintain acid-base equivalence. In the diagrams in Figs. 1 and 2, equivalence is represented by the equal height of the two columns measuring the sum of acid and of base factors respectively, and the extent of change in bicarbonate necessary to maintain equivalence in the presence of change found in other factors is clearly described.

pancreatic juice, may be readily seen by comparing the diagrams in Fig. 2, constructed from data by Gamble and Ross (3) with those in Fig. 1. These data then demonstrate the expected finding that the continued loss in pancreatic juice of fixed base in excess of chloride ion causes a reduction of plasma bicarbonate. Elman and McCaughan (5) report that in their experiments a rise in plasma pH was noted. This would of course indicate a bicarbonate ion concen-

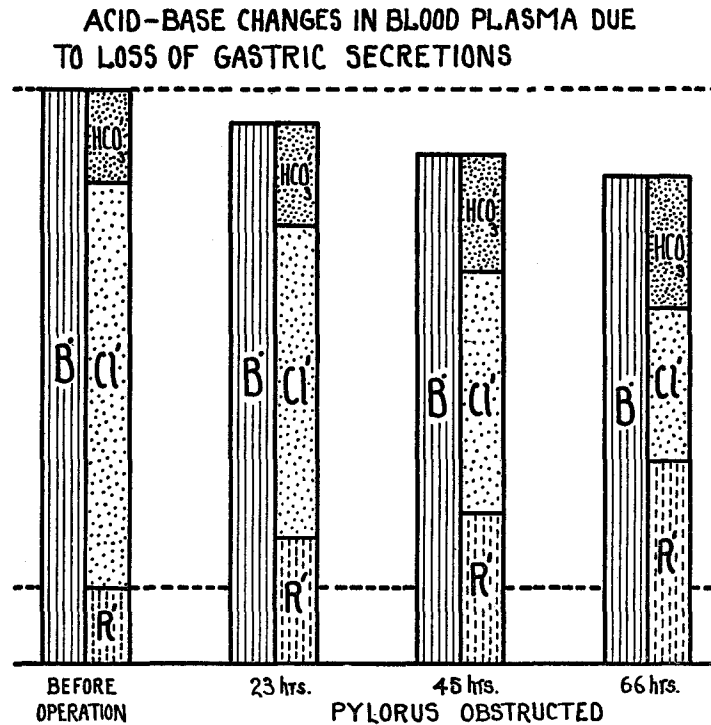


FIG. 2. From data published by Gamble and Ross (3).

tration higher than usual. They state, however, that vomiting was a regular and prominent circumstance during the last several days of the survival period, so that unquestionably there was some loss of stomach secretions as well as of pancreatic juice, an event which, as has just been noted, tends to cause extension of the plasma bicarbonate. Evidently the gist of these findings is that loss of the external secretion of the pancreas produces extensive dehydration

of the plasma and interstitial body fluids and a reduction of plasma bicarbonate in contrast with dehydration and bicarbonate extension caused by loss of stomach secretions.

Dehydration can probably be correctly regarded as the result of a loss of fixed base (3). The fixed base lost in digestive secretions is almost entirely sodium. That a large deficit of fixed base does occur from loss of stomach secretions following pyloric obstruction is easily demonstrable. This may not be directly assumed, however, as a result of withdrawal of pancreatic juice under the experimental circumstances here present for the reason that food was given from which replacement of sodium and of chloride ion can presumably to a certain extent be obtained. Pawlow's observation that ingestion of sodium bicarbonate will greatly, and a milk diet considerably, prolong the survival period obviously suits the conception of a sodium deficit. Meat, the greater part of the fixed base content of which is potassium, which cannot be used to an appreciable extent in the plasma, should be an unsuitable food. The meat given the animals in our experiments was boiled horse meat without added salt. On analysis of several samples it was found to contain per 100 gm.: K, 90 cc. 0.1 N; Na, 11 cc. 0.1 N; and Cl, 17 cc. 0.1 N. From these data and the amounts of meat eaten by the animal in Experiment II during the 11 days preceding the appearance of symptoms and extensive changes in the blood plasma, it may be computed that the average daily intake of sodium was 65 cc. 0.1 N. We have unfortunately no measurements of the daily loss of pancreatic juice from this animal. On this point, however, the extensive data of Elman and McCaughan (5) are available. In a series of twelve experiments they found an average daily production of 250 cc. of pancreatic juice. All of their animals were smaller than the animal used in our Experiment II. This average daily quantity of juice would contain, according to the analyses in the preceding paper, about 370 cc. 0.1 N sodium. If all of the sodium in the ingested meat (65 cc. 0.1 N per day) is assumed to have been absorbed, the estimated daily deficit of sodium from the outset of the experiment is thus approximately 300 cc. 0.1 N. If the loss of this amount of sodium was accompanied by the water which contained it in the interstitial body fluids, dehydration of this animal may be

taken as having proceeded at the rate of about 200 cc. per day.<sup>2</sup> This is admittedly an extremely rough estimation of the probable sodium and corresponding water loss for this animal. It may be noted however that the actual loss of body weight during the first 10 days of the experimental period was approximately 2000 gm. As further evidence of sodium poverty a sample of urine obtained by catheter on the 12th day of this experiment was found to contain relatively minute amounts of sodium and of chloride, as may be seen from the following values per 100 cc. of urine: K', 171 cc. 0.1 N; Na', 1.6 cc. 0.1 N; Cl', 1.3 cc. 0.1 N; PO<sub>4</sub>'', 87 cc. 0.1 N.

The experiment of attempting to prevent the appearance of symptoms by early and continued replacement of sodium was not undertaken, our chief purpose being to define the plasma changes. Attempt was however made to repair these changes, at what was apparently almost the end of the survival period, by administration of sodium chloride and sodium bicarbonate solutions. Although in both instances the condition was hopelessly advanced, repair was to a certain extent accomplished and striking though temporary improvement in behavior of the animal was observed. The dog used in Experiment I was, on the 43rd day, extremely sick, showing marked muscular weakness and apathy. Within an hour after administration of 1000 cc. of salt solution by clysis and 100 cc. of 2 per cent sodium bicarbonate solution by intravenous injection, the apathy and muscular weakness disappeared to a remarkable degree. On the following day 5 gm. of sodium bicarbonate were given in milk by stomach tube and a bread and milk diet was substituted for meat. The next morning as may be seen in Table I, there was substantial replacement of plasma base and the bicarbonate concentration was almost doubled. In Experiment II, the animal was almost *in extremis* when the administration of

<sup>2</sup> The concentration of sodium in the interstitial fluids is for this rough calculation taken as 150 cc. 0.1 N per 100 cc., which is the usual value found in the blood plasma of the dog. The similarity of the inorganic composition of interstitial fluids and blood plasma, except for relatively slight differences referable, in terms of the Donnan law, to unequal concentrations of protein, is indicated by recent studies of the composition of transudates and cerebrospinal fluid (6, 7). For discussion of the limitation of dehydration to interstitial fluids and blood plasma, the reader is referred to papers cited above (3).

repair materials was undertaken. On the afternoon of the 14th day there was marked prostration and respirations were of the type characteristic of severe acidosis. Salt solution, 2000 cc. of 0.9 per cent, warmed to body temperature, was injected into the peritoneal cavity. The animal survived the night and the next morning 400 cc. of 2 per cent sodium bicarbonate solution was injected into the femoral vein. By afternoon there was definite improvement in the physical behavior of the animal. The alterations of plasma factors produced by these solutions are shown in Table II and also by means of diagrams in Fig. 1. It is of interest to note that the sodium chloride solution produced an increase of fixed base and to a somewhat larger extent of chloride ion, but did not alter bicarbonate. Following the injection of bicarbonate solution there was extension of plasma bicarbonate due, curiously, to recession of  $R'$ , there being only slight further increase of fixed base.

#### SUMMARY.

From the data given above the following explanation of the effects of continued loss of the external secretion of the pancreas may be offered. The underlying event is a steadily increasing deficit of sodium and of chloride ion due to the large requirement for these electrolytes in the construction of pancreatic juice. In consequence there is continued loss of water, chiefly from the body fluids in which sodium and chloride ion are large factors of total ionic content, *viz.*, interstitial fluids and the blood plasma. During about two-thirds of the survival period the volume and composition of the blood plasma remain approximately normal, the losses of water, sodium, and chloride ion being replaced at the expense of interstitial fluids. Reduction of the volume of these fluids is indicated by loss of body weight beginning directly after establishment of the pancreatic fistula. Ultimately reduction of plasma volume begins and, as it progresses, serious symptoms develop and death occurs unless water, sodium, and chloride ion are abundantly replaced. Owing to the relatively greater loss of sodium than of chloride ion in pancreatic juice, reduction of bicarbonate ion concentration in the plasma tends to occur. The death of the organism may be simply and reasonably explained as the result of progressive impairment of the function of the blood by the physical changes,

dehydration and acidosis, produced in the plasma by the continued loss of sodium and of chloride ion in the pancreatic juice.

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