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THE USE OF FLUIDS IN THE TREATMENT OF HYPEREMESIS GRAVIDARUM*

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QUITE recently there have appeared in this Journal two papers[11, 13] dealing with the treatment of pernicious vomiting of pregnancy, the one advocating, at least in certain cases, the use of sodium chloride as "specific neutralizing antitoxic protective" substance, and the other advocating the use of insulin together with glucose. The publication in so short a time of two methods of treatment apparently so different and each reporting a successful therapy, can only mean that even yet the fundamentals of treatment of pernicious vomiting are not understood. In our opinion, in both papers there is a misinterpretation of data.

In order to make clear our position, it is necessary to review briefly the steps which have led to our treatment of hyperemesis gravidarum and describe the routine procedure which has given excellent results in this hospital during the last four years.

The theory of carbohydrate deficiency or glycogen deficiency of the liver as the etiologic cause of the nausea and vomiting of pregnancy was first stated by Duncan and Harding in 1918[1] and published in extenso by Harding in 1921.[2] (Titus, Hoffmann and Givens[3] independently published a similar theory.) It postulated either an absolute or relative lack of glycogen reserve in the maternal liver. It

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allowed a correlation of the fatty degenerated liver found at autopsy in this condition with physiologic fatty infiltration due to hunger, as noted by Mottram,[4] and thus brought in the factor of starvation as one, if not the main, contributory cause of the clinical entity. It is important to note that at no time was the ketonuria, which usually accompanies pernicious vomiting of pregnancy, ever thought to be more than secondary to a lack of carbohydrate and never of itself the cause of the vomiting. Nevertheless, as both the vomiting and the ketonuria were believed to be dependent upon the common origin of lack of carbohydrate, the determination, either qualitatively or quantitatively, of acetone bodies in the urine became an indication of the clinical condition. This fact was later borne out by the work of Harding and Potter.[5] It thus became logical to treat such cases with carbohydrate in an attempt to supply any deficiency, and a scheme of treatment was elaborated by Harding and Watson.[6] Mild cases were treated with small meals, consisting mainly of carbohydrate, throughout the day; more severe cases, where it was impossible to supply food by mouth, were treated by the use of glucose solutions rectally, interstitially, or intravenously, as the case demanded.

From the investigation of a number of cases treated in this manner, it soon became evident that the best laboratory guide for treatment was the observation of the daily excretion of urine. Cases which responded successfully to the therapy showed, coincident with improvement in clinical condition, a greatly increased volume of urine with a lowered specific gravity. The investigation of Harding and Drew[7] on the N.P.N. and uric acid content of blood in vomiting of pregnancy led to the conclusion that the raised values, often found in these patients, were due to dehydration; for, consequent on the production of diuresis, the high values for these substances became normal. The value of this particular piece of evidence has become somewhat weakened by the later discoveries of Harding, Allin, Eagles, and Van Wyck;[8] but further evidence that dehydration plays a marked part in pernicious vomiting of pregnancy has been found in the behavior of the serum proteins during treatment.[9] So important do we consider the factor of dehydration, that any patient admitted for vomiting of pregnancy to the wards of the Toronto General Hospital is at once treated, as a matter of routine, with 1000 c.c. of 5 per cent glucose solution in 1 per cent saline given intravenously each day until a diuresis is obtained. By "diuresis" is meant that the twenty-four-hour output of urine shall reach at least 1000 c.c. and shall have a specific gravity of 1010 or less. During this period of treatment the patient is isolated from the remainder of the ward and no visitors allowed. At the same time rectal enemata of 200 c.c. of 10 per cent glucose in normal saline are given three times daily and at bedtime 30 to 60 grains of sodium bromide are given in each enema for

the first day or so. No attempt is made to feed solids by mouth, but fluids are urged even if the patient is vomiting freely, and she is encouraged and allowed to drink any liquid she may fancy except tea, coffee, milk, or cocoa. This treatment usually results, within three or four days, in such marked improvement that the patient is able to take food. It is not continued for a period longer than six days without clinical improvement. In the event of failure under these conditions therapeutic abortion is performed. The treatment may thus briefly be described as rest in bed with isolation, and the forcing of fluids by all routes. The use of glucose, though important, thus has become secondary to the use of fluids in treating a severe case of pernicious vomiting of pregnancy. The later improvements in treatment were described by Harding.[10]

The first paper referred to is that of Haden and Guffey,[11] who came across a case of pernicious vomiting of pregnancy in which an examination of the blood revealed a slightly raised N.P.N., urea N and uric acid, but more significant, according to their own interpretation, a lowered chloride content and a raised CO_2 combining power. Led by the studies of the chemistry of high intestinal obstruction made by Haden and Orr,[12] these authors postulated an analogous condition of "toxemia" and treated their case accordingly. Their patient was admitted May 10, suffering from severe vomiting of pregnancy. On May 11 and 12 they gave 1500 and 500 c.c. respectively of 3 per cent sodium chloride subcutaneously; on May 13, 400 c.c. of normal saline. The amount of fluid given on May 13 and 14 was not recorded, but 1 gram of sodium chloride was given on each day. The patient continued vomiting until May 14, when, according to the report, there was a striking response to the therapy. The blood findings dated May 13 showed normal figures, although perhaps the chlorides might be considered as still slightly low. The urine volumes of May 10, 11, and 12 were not noted. Presumably the amount was small, and we, ourselves, know how difficult it is to obtain complete twenty-four-hour specimens of urine from such patients. For absolute accuracy it demands a special nurse and constant attention. On May 13, however, the urine volume was stated as 1180 c.c.; the specific gravity was not given, but we feel sure from the evidence before us that the urine volume on that day was very much larger and more easily collected than on the previous days, and that Haden and Guffey had reached that stage in therapy which we designate as "diuresis" and which we always find is accompanied by clinical improvement. Our interpretation of the case cited by these authors is that they successfully overcame the dehydration of the patient quite independently of the supply of sodium chloride. This assumes that the cure was not brought about by death of the fetus, an explanation Haden and Guffey are loth to accept. Our position is much strengthened by previous

observations of the chloride content of blood in pernicious vomiting of pregnancy given by Harding and Drew, a paper which Haden and Guffey entirely overlooked. There we found many times a lowered chloride content of the blood, often below threshold value, which rose to a normal figure at the time of diuresis. Our interpretation was that the lowered chloride of the blood was due to the consequent dehydration. It is true that the general case of pernicious vomiting of pregnancy does not show such a lowered content of the blood as was found by Haden and Guffey. The lowest figure observed by Harding and Drew was 330 mg. Quite recently, however, we have been able to observe another case of pernicious vomiting with a low chloride content and raised CO_2 combining power, analogous to that of Haden and Guffey, although there was no raised N.P.N. or urea.

CASE 1.—Mrs. P-l-k., age thirty years, para v; two months pregnant. She had been vomiting for six days, her eyes were sunken, her skin dry, and there was evidence of jaundice. She complained of epigastric pain; her pulse was 134, and temperature 100 to 102° F. The urine was highly colored, and of small volume. The blood showed slightly raised uric acid with the NaCl content 290 mg. and CO_2 combining power 63.1. For the first two days the patient was treated in the usual way with intravenous glucose, glucose enemata, and urging of fluids. There was an immediate clinical improvement, and on March 21, the third day of treatment, the blood chloride had risen to 412 with a CO_2 combining power of 66.4. During those two days sodium chloride had been given in the enemata and the intravenous glucose to the extent of 6.5 gm. On March 21 and 22 the treatment was continued as on the two previous days, except that the sodium chloride was excluded from the intravenous glucose and the enemata. The patient continued to improve, but the chloride content of the blood sank from 412 to 375 mg., the CO_2 combining power remaining approximately the same. By this time the patient was able to take a little milk and water and a small carbohydrate meal. Sodium chloride was now supplied with the meals to the extent of 6 gm. a day. The patient continued to improve, and on March 25 the blood chloride was 455 with a CO_2 combining power of 63.6. The patient made steady improvement, and on March 27 the sodium chloride was 511 mg. and the CO_2 combining power had dropped sharply to 48. The case, therefore, is similar to that observed by Haden and Guffey and was treated successfully without the use of hypertonic saline, and the chloride content of the blood rose or fell in accordance with the intake of salt. The CO_2 combining power did not drop until the chloride of the blood was well above the threshold value. Small amounts of chloride appeared in the urine on March 23, 24, 25, and 26, indicating a lowered threshold, but chloride equilibrium was not established until March 27 at a time when the CO_2 combining power had fallen to what would be a more normal figure for the condition of pregnancy. The details of the case are shown in Table I. Whatever may be the exact significance of a lowered chloride content of the blood in vomiting of pregnancy, it certainly does not demand the use of hypertonic saline in order to restore chemical equilibrium, and the clinical condition of hyperemesis gravidarum is in no way dependent upon that particular balance of ions.

The second paper is that of Thalhimer,[13] advocating the use of insulin and glucose for the treatment of excessive vomiting of pregnancy. This paper is one of a series published by the same author, in which reports are given of ten cases of hyperemesis gravidarum with

successful results. The author's advocacy of this method of treatment would appear to depend upon two claims. The first, that in this condition we are dealing with a true acidosis brought about by the production of acetone bodies, and the second, that the use of insulin considerably shortens the time of treatment and is thus advantageous. Thalhimer's interest in the treatment of this condition was apparently stimulated by his success in the treatment of some cases of postoperative vomiting,[14] where often there may occur a true acidosis with a lowered CO_2 combining power and an increased hydrogen-ion concentration. The usual case of pernicious vomiting of pregnancy, however, does not show any degree of acidosis which we should consider as significant. Judged by the CO_2 combining power of the plasma there is a slight degree of acidosis. (We are using this term in a

TABLE II

CASE	CO_2 COMBINING POWER	
	Admittance	Recovery
P-n-t	–	48.5
H-l	39.5	54.8
D-l-r	48.4	
N-k	–	49.0
P-l-k	63.1	50.9
H-y	42.6	53.9
D-l-g	–	57.4
M-r-s	40.6	–
R-b-n	51.3	50.3

very general way; the finding of a low CO_2 combining power of plasma does not necessarily indicate a true acidosis.) Losee and Van Slyke,[15] examining a series of cases of pernicious vomiting of pregnancy, found only a slight diminution of the CO_2 combining power when compared with normal pregnancy, and it must be remembered that a normal pregnancy even in its early stages shows a lowering of that figure. Thalhimer is aware of this for he makes reference to some work of Williamson,[16] yet apparently he ignores the conclusion to be drawn, for he states "the figure for a normal alkali reserve being 60." The CO_2 combining powers found in cases of pernicious vomiting should be compared with a figure of 50 instead of 60. Harding and Potter in their series of cases of pernicious vomiting were able to find only one case in which the alveoli CO_2 tension was significantly low (Case C-k).

In Table II will be found the CO_2 combining powers of some recent cases under observation in the Toronto General Hospital before, and after treatment. It will be seen that, compared with the value for a normal pregnancy, the CO_2 combining power of the plasma is not significantly low. Moreover, Harding and Potter showed that although large amounts of ketone bodies might be produced, the concentration of these substances in the blood did not rise to the high level com-

TABLE I

SHOWING DETAILS OF TREATMENT, URINE, AND BLOOD ANALYSES IN CASE P-L-K

DATE 1925	MEDICATION OR DIET	INTAKE			CLINICAL CONDITION	URINE					BLOOD				
		CARB.	SALT	WATER		24 HR. VOL.	SP. GR.	ACETONE	NaCl	NOTES	N.P.N.	UREA N	NaCl	SERUM PROTEIN	CO_2 COMBINING POWER
		gm.	gm.	c.c.		c.c.			gm.		mg. per 100 c.c. whole blood			per cent	vol. per cent
Mar. 19	1000 c.c. 5% glucose intravenous Nutrient enemata of 10% glucose in saline	68	4.5	–	Tongue coated and dry, with sordes. Face drawn and anxious. Skin dry. Slight jaundice and epigastric tenderness. Anorexia; complaining of severe thirst. Pulse 134; temp. 100°-102°; resp. 24.	–	1026	++	nil	Bile ++ Albumin neg. Sugar neg.	29.9	14.5	290	–	63.1
Mar. 20	Same as Mar. 19 + weak tea with sugar	156	6.5	2970	Patient resting more comfortably. Beginning to retain some fluids by mouth. Vomiting infrequently. Pulse 120; temp. 99.2°; resp. 22.	140	1020	+	nil	" "					

Mar. 21	Same as Mar. 20 but no NaCl	140	0	2880	General condition much improved. Skin moist. Pulse 120; temp. 99.4°; resp. 22.	1100	1009	–	nil	" "	30	9.8	412	6.18	66.4
Mar. 22	Same as Mar. 21	135	0	2800	Further improvement. Pulse 124; temp. 99.4°; resp. 22.	1460	1008	–	nil	" "					
Mar. 23	Enemata discontinued Milk and water and small carb. meals	–	2	2420	Retaining meals with only occasional vomiting. Feeling much better and stronger. Pulse 120; temp. 98.2°; resp. 22.	1110	1010	–	1.22	" "	24.6	10.1	375	7.53	64.8
Mar. 24	Intravenous discontinued. Meals as before and broth	–	6	2480	Still improving with no further vomiting.	780	1012	–	1.63	Bile +					
Mar. 25		–	6	2820		1140	1012	–	1.84	Bile trace	31.0	8.7	455	6.81	63.6
Mar. 26	Light meals	–	6	2730		850	1010	–	1.70	Bile					
Mar. 27	Light meals	–	6	2180		1780	1009	–	5.34	Bile absent	21.0	9.5	511	6.29	48.2

parable with that found in diabetes, and showed evidence of uncompensated acidosis.

The vomiting of pregnancy is thus usually not characterized by acidosis, although there is always a ketonuria arising, undoubtedly in part, from the starvation accompanying the condition. Without considering whether an uncompensated acidosis per se can produce the symptom of vomiting, there is no doubt that a simple ketonuria does not give rise to this effect. In a recent publication Harding, Allin, Eagles, and Van Wyck[8] described the action of high fat ketonuria-producing diets in pregnancy. These diets produced no symptoms of nausea or vomiting, although in some cases the ketonuria was marked. Moreover, we have given these same high fat diets to one or two patients who had just recovered from pernicious vomiting, under the treatment described, without reproducing the symptoms.

The use of insulin in order to abolish ketonuria is thus clearly unnecessary. Its use in skillful hands may be harmless, but we do not believe it to be a valuable adjuvant to treatment. While this is true, we should not like, however, to deny that there may be an occasional case of vomiting of pregnancy in which the production of acetone bodies becomes so great, or their elimination becomes so impaired that a condition of true uncompensated acidosis may occur and the patient pass into coma. Here the use of insulin would be clinically justified. We should clearly recognize, however, that the insulin is used to combat the coma or impending coma, and not pernicious vomiting of pregnancy per se. The level of CO_2 combining power is, however, no index of the severity of the clinical condition. Thus, our most serious cases were undoubtedly D-l-r and P-l-k where the values were 48.4 and 63.1. It would be justified also were we able to prove in this class of patient an inability to utilize carbohydrate based upon a lack of insulin. Such an inability is very improbable. It is impossible, of course, to utilize the glucose tolerance test in this connection, but we ourselves, and Titus and Givens,[17] have determined blood sugars, only to find normal figures. The utilization of glucose given intravenously is normal. Such an injection should, of course, be given slowly, and Thalhimer's remarks and directions on this point are excellent. Most physicians are afraid to give daily intravenous glucose solutions, yet their use is attended with no untoward results, provided proper care is taken in the sterilization of the solutions, and the temperature and rate of administration are carefully controlled. Although we have thus stated our belief that glucose is utilized by this class of patient, we do, however, think the effect of continued dehydration upon glucose tolerance worthy of further investigation.

The second claim of Thalhimer's for the use of insulin would appear to rest on a comparison of his own results with those given by Harding and Potter. The cases cited by Harding and Potter were those in-

vestigated early in the history of this work, and where an intravenous or an interstitial glucose solution was only given occasionally. Even so, a study of the protocols reveals that the majority of cases were able to tolerate light carbohydrate meals on the third or fourth day. As stated in the forepart of this paper we then became impressed with the importance of dehydration, even when, from a clinical viewpoint, it did not appear to be very great. We have examined our more recent records and find that in uncomplicated cases the patients are able to take small meals in from three to six days. The average for fourteen cases is 4.1 days from admittance to cessation of vomiting and the taking of food.

A study of the cases cited by Thalhimer shows that he has carried out a very similar form of treatment, plus the use of insulin. By use of intravenously given fluids Thalhimer has overcome the dehydration of his patients and brought about the improvement in their condition.

CONCLUSION

The successful treatment of hyperemesis gravidarum depends upon the use of fluids.

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