CONCLUSIONS

1. The problematic relationship between mild and profound toxemias of pregnancy warrants a study of the former in order to gain information regarding the latter.

2. The development of a course of treatment, the success of which seemed to depend on the use of carbohydrates in large amounts, led to the assumption that a deficiency in carbohydrates has an important bearing on the origin of toxemia of pregnancy.

3. Carbohydrate deficiency during pregnancy is of twofold origin; (1) a relative deficiency due to an unexpected demand for glycogen on the part of the fetus and the uterus, and (2) an actual deficiency, augmented in the presence of nausea and vomiting, from lessened carbohydrate intake.

4. Carbohydrate deficiency in the maternal organism causes a glycogen depletion of the liver, because this is the organ in which carbohydrates are stored for use as needed.

5. There is experimental evidence to show that liver function is impaired and the body flooded with toxins after carbohydrate starvation.

6. Pathologic changes in the liver lobules which are similar to those of fatal toxemias of pregnancy can be produced experimentally by the use of certain chemical poisons. These changes can be made to disappear rapidly by the ingestion of carbohydrates.

7. Mild cases of nausea and vomiting may be controlled by so regulating the diet that there is a preponderance of carbohydrates, and an avoidance of more than short intervals of fasting by the taking of food more frequently than under ordinary circumstances. This increased carbohydrate intake should be augmented by giving the patient from 8 to 16 ounces of 10 per cent. glucose and 2 per cent. sodium bicarbonate solution daily by mouth. This may be given in 1 or 2 ounce doses.

More severe cases require more rigid attention. After an initial period of rest, gastric lavage and the introduction of saline cathartics through the stomach tube, small amounts of liquid food are allowed alternately with from 1 to 2 ounces of the glucose and soda solution, described above, every two hours. By mouth or by bowel it should be possible to give the patient 1 quart of this solution daily.

In the seriously toxic patients the treatment is pushed even more vigorously with the addition of intravenous injection of from 15 to 25 gm. of glucose in from 250 to 300 c.c. of water. This is given from one to three or more times daily, according to the needs and response of the patient. The injections should be made in close accordance with the directions in the body of this paper. Other treatment is carried out along much the same lines as that for the second group.

8. Not only is intravenous injection of glucose solution a valuable therapeutic measure, but the rate of its absorption and storage by the liver is an index of liver efficiency which is of prognostic value. More rapid storage than normal is favorable because it indicates that the liver, depleted as it has been of glycogen, is nevertheless still able to restore itself. Storage which is slower than normal offers an unfavorable prognosis, since this is evidence that liver efficiency is impaired. Our clinical evidence regarding these views is still too limited to permit a definite conclusion, but our experience thus far has been entirely confirmatory.

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THE THERAPEUTIC USE OF CARBON DIOXID AFTER ANESTHESIA AND OPERATION *

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There is ample experimental evidence that inhalation of carbon dioxid, properly diluted with air or oxygen, should be a therapeutic agent of great potency. In fact, however, aside from the indirect use of this gas in the rebreathing methods of anesthesia, particularly with nitrous oxid, inhalation of carbon dioxid is not used in surgery. Likewise in internal medicine it is not employed, except perhaps in the Nauheim bath treatment of cardiac conditions; and here there is no agreement as to whether or not the inhalation is a factor.

This lack of use is the more striking when we note the present deficiency in therapeutic agents to stimulate breathing, and the great need for one; for carbon dioxid is Nature's own stimulant to the respiratory center.[1]

On the circulation its influence is equally important—particularly on the venous return to the right heart. It is the insufficiency of this return which chiefly gives to postoperative depression its similarity to the effects of hemorrhage. Thus, recovery of the circulation and a rapid return of a normal arterial pressure are the results to be expected from the restoration to the blood and tissues of the carbon dioxid lost during anesthesia and operation.[2] At least, this is the result which we have obtained.

The reason for the neglect of carbon dioxid is not far to seek. It lies in the fact that without a reliable method and apparatus, or without the acquisition of great skill and tact in a practically unexplored field, the administration of carbon dioxid might be dangerous. Indeed, if insufficiently diluted with air or oxygen, it would be quickly fatal. Doubtless, in the not distant future it will seem almost incredible that progress should have been halted for a long period for want of an apparatus for controlled gas administration. In fact, however, only recently, after ten years of effort in the laboratory where two of us work, has an apparatus

* In the text of this paper we deal only with such degrees of functional depression as commonly occur after anesthesia and operation. Mention should, however, be made here of work done by us during the winter of 1917-1918 which, although itself negative in result, was nevertheless an essential preliminary to this. It was a study of accident cases brought in by the ambulance. It revealed not a single case of "shock," other than hemorrhage or concussion, during ten weeks at a very large and active hospital in a field where such cases would be expected. Apparently this ignis fatuus of physiology is the product—at least in discoverable amounts—only of the battle field and the operating room, arising doubtless on the one from unrelieved pain, hemorrhage or cold, and in the other largely from some element in anesthesia. Our work had the approval of the Surgeon-General of the Army and was carried out at Bellevue Hospital, New York. We take this occasion to express our thanks to the directors of that hospital, to Dr. Charles Norris and Dr. Adrian V. S. Lambert, and to Col. F. F. Russell of the Surgeon-General's Office.

1. Henderson, Yandell: Bull. Johns Hopkins Hosp. **21**: 235, 1910.
2. Henderson, Yandell: Am. J. Physiol. **27**: 152, 1910. Henderson, Yandell, and Harvey, S. C.: Ibid. **46**: 533 (Aug.) 1918. Henderson, Yandell; Prince, A. L., and Haggard, H. W.: Observations on Surgical Shock, J. A. M. A. **69**: 965 (Sept. 22) 1917. Henderson, Yandell, and Haggard, H. W.: J. Pharmacol. & Exper. Therap. **11**: 189 (April) 1918. Henderson, Yandell; Prince, A. L., and Haggard, H. W.: Ibid. **11**: 203 (April) 1918. Haggard, H. W.: Low Levels of Alkaline Reserve under Surgical Conditions, Tr. Sect. Surg., Gen. & Abd., A. M. A., 1918, p. 139.

at all suited to clinical use become available; and yet it is very simple. It needs only a single operator; but he must be an expert in the vital signs of anesthesia and of the powerful functional effects of carbon dioxid, and he must at all times be keenly observant of the patient under treatment.

The first apparatus which we employed was, on the contrary, quite complicated, requiring the constant attention of three or four operators. It involved an air blower, electric motor, tank of carbon dioxid, gas meters, and accessory devices,[3] and was unsuited, therefore, to general clinical use. It had, however, the experimental advantage that with it any volume of air of any desired percentage of carbon dioxid could be delivered into the mask from which the patient inhaled.

With this apparatus we were enabled, through the courtesy of Drs. John F. Erdmann and Thomas H. Russell, to make, at the Post-Graduate Hospital, New York, what we believe are practically the pioneer observations (excepting those of Cotton [4] and of Levy [5]) on the effects of administration of carbon dioxid after ether anesthesia and major surgical operations.

Obviously, in order to show the effects of inhalation of carbon dioxid it was essential that we should first establish, as a standard of comparison, how patients usually behave. In this there is considerable difficulty; for, as we found and as indeed every one knows, there are the widest variations according to the length of anesthesia, its depth, preliminary medication, the character of the patient, and the severity of the operation. Below is presented the abbreviated protocol of a case fairly typical of conditions which are, however, frequent:

PROTOCOL OF CONTROL CASE IN WHICH NO CARBON DIOXID WAS ADMINISTERED

W. M., man, aged 34; double hernia; ether administration, sixty minutes.

Time Minutes	Arterial Pressure Mm. of Mercury	
..	132	Before operation
0	...	In bed, after operation
5	120	Gasps and apneas; cyanotic
25	...	Vomiting
30	108	Depressed respiration; cold, cyanotic, pallid skin
55	102	No improvement
65	...	Vomiting
80	110	Signs of returning consciousness

It is here to be seen that, after the patient was back in bed, arterial pressure continued to fall for an hour—to a level 30 mm. below normal. Respiration during this time was notably depressed. The elimination of ether was correspondingly slow.

EFFECTS PRODUCED BY THE INHALATION OF CARBON DIOXID

While other control cases, after operations for appendicitis, hernia, gallstones, etc., showed these features in more or less marked degree, this case, in our observations, is by no means an unusual or extreme illustration of postoperative depression. Using it as a rough standard of comparison, we give the protocols of four cases illustrative of the effects observed under inhalations of carbon dioxid.

PROTOCOLS OF CASES IN WHICH CARBON DIOXID WAS GIVEN

As it seemed that the benefits hoped for from inhalation of carbon dioxid might possibly involve also grave danger during the inhalation—an anticipation which fortunately was not verified—every precaution was taken to minimize the risk. In all cases the mask was held by one of us (R. C. C.), who has had an extensive experience as an anesthetist, and particularly in the administration of nitrous oxid and rebreathing. At least one other of us kept an uninterrupted watch on the patient, while one kept his eyes on the gages and meters of the apparatus and his hands on its cocks and switches. In this work we are indebted to Dr. W. H. Taliaferro for assistance.

CASE 1.—S. S., man, aged 46; double hernia; ether administration, seventy minutes; postoperative administration of carbon dioxid.

Time Minutes	Arterial Pressure Mm. of Mercury	
..	136	Before anesthesia
0	120	In bed, after operation
1	...	Inhalation of 10 per cent. CO_2 begun
2	...	Marked respiratory augmentation
3	136	Breathing 35 liters of air per minute
4	160	Inhalation reduced to 6 per cent. CO_2 Warm, pink skin; Sweating
31	...	CO_2 stopped; patient fully conscious, but emotionally unbalanced; crying; wanted to get out of bed
33	132	
	136	Four days later

No nausea, vomiting or gas pains; an uneventful recovery.

CASE 2.—R., woman, aged 20; appendicitis and adhesions; prolonged illness; patient weak; ether administration, forty minutes; postoperative administration of carbon dioxid.

Time Minutes	Arterial Pressure Mm. of Mercury	
..	100	Before anesthesia
0	96	In bed, after operation; 10 per cent. CO_2 started
2	110	
4	130	Breathing 40 liters per minute; CO_2 reduced to 8 per cent.
18	...	Struggling; breathing 40 liters per minute
19	122	Conscious; CO_2 stopped
24	122	
	104	Three days later

No nausea, vomiting or gas pains; water given as asked for; an uneventful recovery.

CASE 3.—L. S., man, aged 26; appendicitis and adhesions; ether administration, sixty minutes.

Time Minutes	Arterial Pressure Mm. of Mercury	
..	115	Before anesthesia
0	108	In bed after operation
5	102	Cyanotic
8	96	Inhalation of 8 per cent. CO_2 begun
15	112	No respiratory augmentation
18	...	Respiration augmented
19	...	Fine pink skin color
21	118	Breathing 35 liters per minute; talks rationally
43	116	CO_2 stopped
45	112	
	115	Three days later

No nausea, vomiting, or gas pains; allowed to drink water freely; an uneventful recovery.

CASE 4.—A. S., woman, aged 32; exploratory laparotomy and removal of appendix and gallstones; ether administration, fifty minutes; uneventful recovery.

Time Minutes	Arterial Pressure Mm. of Mercury	
..	118	Before anesthesia
0	116	In bed, after operation
1	...	Inhalation of 8 per cent. CO_2 begun
2	...	Slight increase of respiration; color pale
6	...	Increased respiration
11	126	Breathing 30 liters per minute; pink skin
20	134	Struggling; responds to verbal suggestions
28	136	Answers questions rationally
31	134	CO_2 stopped
32	...	Vomited a little yellow fluid
180	118	
	120	Four days later

No subsequent nausea, vomiting or gas pains; bowels easily stimulated to function; uneventful recovery.

3. Parts of a Connell nitrous oxid-oxygen apparatus were used, for the loan of which and for assistance in assembling the whole apparatus we are indebted to Mr. C. A. Mandolini of the Scientific Apparatus Company, New York City.
4. Cotton, F. J.: Acapnia: Its Surgical Importance, Boston M. & S. J. 167: 432, 1912.
5. Levy, Ettore: The Clinical Use of Carbon Dioxid with Oxygen, J. A. M. A. 58: 773 (March 16) 1912.

In these four cases, typical of a total of seventeen so treated, certain points deserve notice:

Within a few minutes after the initiation of the inhalation of carbon dioxid, there was a great augmentation of respiration. Knowing the volume of air delivered to the mask by our apparatus, we could estimate quite accurately the volume of the patient's breathing. A normal well-developed adult at rest in bed breathes from 6 to 8 liters of air a minute. In our control cases, observed without treatment, the volume of breathing was estimated often at less than half as much: hence the common cyanosis. Under the inhalation of carbon dioxid, the volume of breathing was increased to amounts from 35 to 70 liters per minute, volumes corresponding to those which the subjects would have breathed under vigorous physical exertion.

The greater part of the ether was thus rapidly ventilated out of the blood. In from fifteen to twenty-five minutes the patient was conscious, although prone to emotional disturbances, sometimes of anger, but oftener of hilarity. Frequently the patient fell asleep fifteen or twenty minutes after the termination of the inhalation. Presumably there was a slight secondary rise of ether in the blood due to continued diffusion from the muscles, adipose tissue, etc.

Immediately after the operation, the arterial pressure was usually from 5 to 15 mm. below normal, with a tendency to fall further. Under inhalation of carbon dioxid it rose rapidly, sometimes 30 or 40 mm. within four or five minutes; and at the end of the first ten or fifteen minutes it was often 10 or even 20 mm. above normal. It then tended gradually downward again, although remaining above the normal level. After the termination of the inhalation it returned in a few minutes to a practically normal value. It never fell appreciably thereafter.

To the observer, the return of a normal pink skin color [6] was one of the most striking effects of the inhalation of carbon dioxid, indicating a return of the normal capillary circulation, a feature of fundamental importance in the recovery from postoperative circulatory depression.

As the patients came off the operating table, they showed invariably the inadequately filled veins which indicate a reduced venous return to the right heart. To combat this condition effectively is, in our opinion, to solve practically the whole problem of the treatment of postoperative circulatory depression. Under inhalation of carbon dioxid, the veins became filled to an extent even exceeding that seen after vigorous physical exertion. We limited the strength of the carbon dioxid administered by this sign, in order not to overload the right heart with blood.

Although vomiting was not entirely absent, it was much less than in untreated patients. The patients were allowed to drink water freely. The inhalations seemed to diminish greatly the usual postanesthetic thirst.

We anticipated from previous experimental observations on animals that one of the benefits to be derived from inhalations of carbon dioxid would be found in the restoration of normal tonus in the stomach and intestine, and thus in the prevention of gas pains and constipation.[7] While no patient developed gas pains, and all recovered normal bowel movements easily, our total of only seventeen cases treated is not sufficient to warrant a definite conclusion on this point.

BLOOD ALKALI

We turn now to a matter of profound theoretical significance. It is well established that under anesthesia and operation there is frequently a considerable reduction in the alkali of the blood as measured by its carbon dioxid combining power.[8] But the cause, the nature and the significance of this reduction are not established.

Recent work by Henderson and Haggard [9] has demonstrated experimentally that a reduction of blood alkali may be induced by two distinct processes: (*a*) The entrance of acids into the blood may partially neutralize the alkali. This is the acidotic process. Or (*b*) excessive breathing with blowing off of the carbon dioxid of the blood, reinforced perhaps by diminished carbon dioxid formation in the tissues under anesthesia, leaves the blood abnormally alkaline. In compensation, alkali passes out of the blood, partly perhaps into the urine, but chiefly presumably into the tissues. This is the acapnial process.

To distinguish between these two—superficially similar but fundamentally unlike—conditions of low blood alkali or, as we term it, hypocapnia, experiments on animals have afforded a simple and conclusive test. It consists in the inhalation of 6 or 8 per cent. carbon dioxid. If the condition is of acidotic origin the extreme acidosis, due to the summation of carbonic acid and fixed acids, aggravates the symptoms, and, if pushed, may kill the subjects in half an hour. On the other hand, if the low blood alkali is of acapnial causation, the increase of carbonic acid in the blood induces a compensatory process by which alkali is recalled, presumably from the tissues, into the blood in normal, or even supernormal, amounts. During the period of inhalation of carbon dioxid and high hydrogen ion concentration, recovery of the circulation, respiration and intestinal motility occurs.

With this distinction in mind it was only after very cautious preliminary tests on patients (of which we have omitted an account) that we ventured to push the inhalations with the intensity indicated in the cases reported. As none suffered any ill effect, but all the patients were rapidly restored to a condition of approximate functional normality, their low blood alkali, so far as it occurred, was clearly not of acidotic, but rather of acapnial origin.

To clinch this point we report observations which we were enabled to make at the New Jersey State Hospital for the Insane, Trenton, through the courtesy of Dr. Henry A. Cotton, medical director, and Dr. John W. Draper, of New York, attending surgeon:

CASE 5.—M. F., female, underwent operation for developmental reconstruction, involving the removal of 150 cm. of terminal ileum, about one third of the colon, and a number of mesenteric glands. Ether was administered for 120 minutes. Immediately after the patient was returned to bed, carbon dioxid inhalation was begun and continued for half an hour with the simplified apparatus. Samples of blood were drawn from an arm vein (*a*) before anesthesia, (*b*) at the end of operation, and (*c*) after termination of the carbon dioxid inhalation. They were equilibrated with air containing 5.6 per cent. of carbon dioxid at room temperature, and were analyzed for their carbon dioxid content, that is, the alkali in use.

Analytic results: $a = 53$; $b = 48$; $c = 58$ per cent. carbon dioxid by volume.

6. Bryant, John, and Henderson, Yandell: Closed Ether and a Color Sign, J. A. M. A. **65**: 1 (July 3) 1915.
7. Henderson, Yandell: Am. J. Physiol. **24**: 66, 1909. Cotton (Footnote 4).
8. Morriss, W. H.: The Prophylaxis of Anesthesia Acidosis, J. A. M. A. **68**: 1391 (May 12) 1917. Reimann, S. R., and Bloom, G. H.: J. Biol. Chem. **36**: 211 (Oct.) 1918.
9. Henderson, Yandell and Haggard H. W.: J. Biol. Chem. **33**: 333, 345, 355, 365 (Feb.) 1918; **39**: 163 (Aug.) 1919.

Case 6.—M. A., female, was operated on as in the previous case. Ether was administered for 120 minutes.

Blood samples: $a=56$; $b=42$; $c=57$ per cent. carbon dioxid by volume.

Case 7.—S. McK., female, had a 5.6 kg. abdominal fibroid tumor and 12 liters of ascitic fluid removed. Ether was administered for fifty-five minutes. The arterial pressure before operation was 154 mm.; after removal of the tumor, 100; after carbon dioxid inhalation, 160.

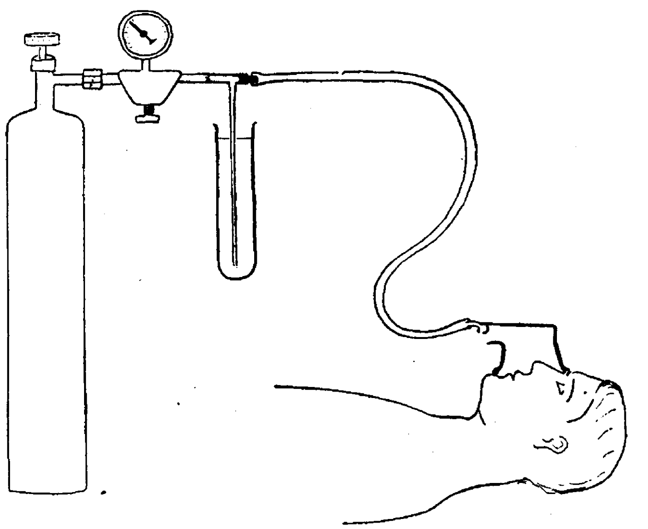
Blood samples: $a=56$; $b=48$; $c=64$ per cent. carbon dioxid by volume.

Case 8.—M. M., female, was operated on for appendicitis. Ether was administered for fifty-five minutes.

Blood samples: $a=59$; $b=52$; $c=61$ per cent. carbon dioxid by volume.

THE APPARATUS

The simplified apparatus used in the last series of observations is shown in the accompanying illustration. It involves a tank of carbon dioxid of the best beverage quality, and a reducing valve. From the valve the gas passes to a T-tube, one limb of which leads to a capillary tube 1.8 mm. in diameter and 10 mm. long, and the other limb to a glass tube projecting down into a vessel of water. The latter serves both as a gage and as an escape valve, preventing any excessive pressure on the capillary. Under the maximum pressure possible, not more than 8 liters of gas pass through the capillary, which in turn is connected to the mask by a 5 or 6 mm. rubber tube.



Simplified apparatus.

The construction of the mask is simple, but involves the idea of preventing any possibility of accumulation of gas in the mask, with consequent excess administration. It depends on the subject's own breathing to draw the gas in and to mix it with air. These purposes are achieved by delivering the gas through a number of small openings just outside the open end of a short, large tube (from 2 to 3 cm. in diameter) connected with the mask. During expiration, or apnea, the gas merely wastes into the outside air; during inspiration it mixes with the inspired air. The operator controls the administration according to the reactions of the patient. With this apparatus the patient receives approximately one half of the gas which the apparatus measures off per minute. The percentage of carbon dioxid in the inspired air depends on the volume of breathing, and the administration must be controlled accordingly.

These investigations are being actively continued at St. Bartholomew's Hospital for Diseases of the Alimentary Canal, New York, where every facility has been provided for the further development of the carbon dioxid therapy.

CONCLUSIONS

The observations here reported indicate that the inhalation of carbon dioxid, properly diluted with air, is a highly beneficial and, with care, a safe treatment after anesthesia and operation.

The beneficial effects observed are: (*a*) an augmentation of breathing which rapidly ventilates the anesthetic out of the blood; (*b*) a powerful stimulant effect on the circulation, particularly on the venous return, and a rapid restoration of arterial pressure, without subsequent relapse or unfavorable consequences; (*c*) marked decrease of postoperative nausea, vomiting and thirst, and (*d*) a possible restoration of intestinal tonus.

TETANY IN A CASE OF SPRUE *

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Early in 1919, Bassett-Smith [1] reported a case of sprue in which tetany developed shortly before the death of the patient. The author stated that his was the first published account of this complication of the disease. As no similar reports have been found in the literature since that time, it was considered that this case might be of interest both on account of its rarity and because of certain significant features bearing on the question of the etiology of tetany.

REPORT OF CASE

History.—R. W. C., an American medical missionary, aged 41, entered the private ward of the Presbyterian Hospital, Sept. 20, 1919, complaining of abdominal pain and diarrhea. As in all previous visits, he was cared for by Dr. David Bovaird. The patient had had measles and scarlet fever as a child; dengue in 1909, and bacillary dysentery in 1912. Since 1907, when the patient arrived in the Philippine Islands, small ulcers had been continuously present in his mouth, and he had been bothered by diarrhea of a greater or less degree. In 1914, his condition became very much aggravated. The tongue became red, swollen and tender, and the small white ulcers along its margin merged. Moderate abdominal tenderness with slight distention accompanied a troublesome diarrhea. The stools were large, white, semifluid and frothy, with an offensive odor. He suffered from hemorrhoids, and fissures appeared in the margin of the anus. In the six months preceding his first entrance to the Presbyterian Hospital, the patient lost 40 pounds.

First Admission.—The patient was admitted, July 24, 1914, and discharged, Aug. 17, 1914. The lips were cyanotic; there were white spots on the tongue; on the buccal mucous membrane were two shallow ulcerations with a narrow zone of inflammation around them. There was a systolic murmur at the apex and the base; the abdomen was tender and tympanitic. The systolic blood pressure was 114; the diastolic, 70. Blood examination revealed: hemoglobin, 88 per cent.; red blood cells, 4,800,000; white blood cells, 9,200; polymorphonuclears, 56 per cent.; lymphocytes, 39 per cent.; eosinophils, 5 per cent. The stool contained no ova or parasites; the Cammidge test was positive; amylase was diminished. The diagnosis was "sprue." Under a regulated dietary regimen of fruit and proteins, the patient

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1. Bassett-Smith, P. W.: Lancet 1: 178 (Feb. 1) 1919.