ON STARVATION AND OBESITY, WITH SPECIAL REFERENCE TO ACIDOSIS.

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Assuming that excreted "acetone bodies" are chiefly derived from incompletely oxidized fat, and assuming that some persons show a pronounced tendency to store up fat and become "stout," while others living under substantially identical conditions reveal no such tendency we may ask: Which, if either, of these two classes of individuals can better withstand starvation without excreting the above mentioned products of incomplete fat oxidation? Most physiologists or experts in metabolism work, if required to formulate an answer to the above, not altogether hypothetical question, would probably support the view that since fat persons tend to store fat more readily than lean ones, they probably tend to utilize it less readily, and that they therefore should be more subject to acidosis when compelled to live on their own tissue materials. Although much has been written on acidosis and still more on the metabolism of fasting there is as yet hardly any experimental work available on the basis of which any positive answer can be given to the question raised. Indeed it is only within the last few years (since the introduction of Shaffer's method for determining β-oxybutyric acid) that any satisfactory experimental material on this point could have been acquired. Brugsch's[1] investigation on the professional faster, Succi, is occasionally quoted as evidence showing that the acidosis in fasting is determined by the available fat deposits. Brugsch merely showed that the faster, Succi, who was not very emaciated at the end of his thirty day fast, continued to eliminate acetone bodies to the end of the

[1] T. Brugsch: *Ztschr. f. exper. Path. u. Therap.*, i, p. 419, 1905.

fast, while an extraordinarily emaciated hospital patient who had no visible body fat did not have any acidosis. Brugsch's results simply confirm the accepted view that the acetone bodies are derived from fat; they show nothing more, nor did Brugsch draw the conclusion ascribed to him by Sassa,[2] namely, that the extent of the fat deposit is the chief factor determining the degree of acidosis obtained in fasting. On the basis of results obtained from phlorhizinized dogs, Sassa does conclude that the extent of the fat deposits is the most important factor in the production of acidosis. Sassa's results, though interesting, have little bearing on the question of fasting acidosis in the human subject, first because of the use of phlorhizin, and secondly because there is no reason to believe that acidosis in animals is quantitatively comparable with that obtained in man. In fact the common laboratory animals (including the pig) develop very little if any acidosis during fasts of moderate duration (three to five days).

Clinically as well as from the standpoint of metabolism it is important to know whether persons with a pronounced tendency to obesity are less capable of drawing on their own fat deposits without developing acidosis than are persons without such a tendency.

In this paper we wish to report on the fasting metabolism of two extraordinarily fat women, both essentially normal except with reference to their obesity. Our analyses include practically all the determinable urinary constituents (except the metals), but our chief interest concerns the acetone bodies, and it hardly seems worth while to report all the other findings.

Our first subject (Mrs. M.), age 48, height 124 cm. (4 ft. 1 in.), entered the Massachusetts General Hospital for the relief of a large hernia which had formed in the scar of a former abdominal operation. As the surgeons advised that her weight be reduced by at least thirty-five pounds before operative procedures were instituted, the patient was transferred to the medical service and thus came under our observation.

The woman stated that she "came of a fat family," her father, mother, and brothers having all been extremely obese. She had remained quite thin as a girl, but after her marriage, at the

[2] R. Sassa: *Biochem. Ztschr.*, lix, p. 372, 1914.

age of twenty-eight, she gained rapidly in weight and had been very heavy ever since.

Our original intention was to subject her to a series of fasts of a week or more and to keep her during the interims on diets low in nitrogen and of insufficient fuel value. On account of the acidosis and the pronounced subjective symptoms (headache,

TABLE I.

Mrs. M. Urine.

DAY	ACETONE	DIACETIC ACID	β-OXYBUTYRIC ACID	NH_3N	TITRATED ACIDITY	ACETONE IN EXPIRED AIR PER HR.	REMARKS
	gm.	*gm.*	*gm.*	*gm.*	*cc.*	*mg.*	
1	0.04	0.27	0	0.41	230	0	Feeling well.
2	0.08	1.42	2.90	0.73	250	5.2	Slight headache.
3	0.10	1.57	17.94	1.87	508	24	Severe headache.
4	0.88	2.46	18.47	2.50	695	49.5	Headache, nausea, and dizziness.
15	0	0	0	0.31	180	0	Feeling well.
16	0.02	0	0	0.37	290	0	" "
17	0.03	1.17	0.17	0.53	335	30	" "
18	0.35	1.16	5.44	1.01	595	32	Slight headache, nausea.
19	0.40	1.15	13.54	1.50	655	45	Headache, nausea, and dizziness.
24	0	0	0	0.50	145	0	Feeling well.
25	0	0	0	0.37	160	0	" "
26	0.04	0.37	0.18	0.51	210	66	" "
27	0.20	1.36	17.34	0.81	300	24	Headache, nausea.

The subjective symptoms disappeared as if by magic as soon as the patient began to partake of food. A single piece of toast with a cup of coffee at once restored the patient and kept her perfectly cheerful for several hours.

nausea, and dizziness) accompanying the fasts, particularly the first one, it was deemed advisable to shorten the starvation periods.

The figures for the acetone bodies as well as for the ammonia and the acidity of the urine obtained during three successive fasting periods are given in Table I. The days are numbered so as to show the duration of the intervening feeding periods.

The elimination of the acetone bodies and the ammonia rises during the first four day fasting period to higher figures than

any heretofore recorded in connection with starvation. 10 to 12 grams of β-oxybutyric acid and not over 2 grams of ammonia nitrogen seem to represent the maximum starvation figures recorded in the literature, whereas Mrs. M. eliminated over 18 grams of β-oxybutyric acid and no less than 2.5 grams of ammonia nitrogen during her fourth day of starvation. The unusually high degree of acidosis, and the accompanying subjective symptoms thus observed in this very fat woman, seemed to indicate that persons suffering from obesity are indeed more subject to acidosis when fasting than are persons who do not carry an excessive amount of adipose tissues.

After an eleven day period on a diet which proved sufficient to cause a disappearance of the acetone bodies (in the course of three or four days), the second fast began and was continued for five days. A striking difference between the acidosis figures of this period and those of the first is to be noted. The acidosis did not begin until the third day of this fast, and the patient felt well until the fourth day, when 5.4 grams of oxybutyric acid and 1 gram of ammonia nitrogen were eliminated. On the next day (the fifth) all the subjective symptoms were severe, though the analytical results do not indicate an excessive acidosis (13.5 grams of β-oxybutyric acid and 1.5 grams NH_3N).

During the third and last fasting experiment with this patient, which began five days later, the onset of acidosis is even slower than during the second period. Indeed, the results of the three fasting periods suggest with regard to the complete oxidation of body fat in starvation that the human organism is capable of at least a certain amount of adaptation and that it is this individual factor rather than the tendency to obesity or the extent of the fat deposits in the body which chiefly determines the onset and the degree of acidosis.

In order to avoid misapprehension, attention must be called to the high β-oxybutyric acid value (17.3 gm.) and the low ammonia nitrogen (0.8 gm.) excreted on the last day of the third fasting period. The results are altogether anomalous, and it looks as if the patient had been given some alkali, a suspicion which we were, however, unable to confirm. The analyses were repeated and were found to be correct as given in the table.

If the preceding subject was fat, our next one, Mrs. B., was a veritable pork barrel. Mrs. B. entered the Massachusetts

General Hospital for the relief of a small infected abrasion of the skin on the left leg. After three or four days' treatment the lesions began to heal rapidly and gave no more trouble; and as the patient found her movements much hampered by her immense burden of fat, she readily agreed to undergo several short periods of starvation. She was 44 years old, her height

TABLE II.*

Mrs. B. Urine.

DAY	ACETONE	DIACETIC ACID	β-OXYBUTYRIC ACID	AMMONIA N	TITRATED ACIDITY	ACETONE IN EXPIRED AIR PER HR.	REMARKS
	gm.	*gm.*	*gm.*	*gm.*	*cc.*	*mg.*	
1	0	0	0	0.51	340	0	Feeling well.
2	0	0	0	0.53	365	12.6	Feeling well, but hungry.
3	0.28	0.70	0.89	0.58	330	35	Feeling well.
4	0.61	1.74	2.84	0.86	390	48	
9	0	0	0	0.52	230	0	Feeling well.
10	0	0	0	0.56	310	0	" "
11		0	0	0.68	300	16	" "
12	0.40	0.90	2.03	0.87	300	37	" "
13	0.57	2.20	7.12	1.22	295	60	Very hungry.
27	0	0	0	0.75	240	0	Feeling well.
28	0	0	0	0.45	300	0	" "
29	0	0	0	0.54	300	Trace	" "
30	0.07	0.18	0	0.57	290	28	" "
31	0.11	0.40	2.9	0.81	300	30	" "
32	1.00	1.28	7.2	1.00	380	48	Very hungry.

* The daily ration of Mrs. B. for three days preceding the first fasting period, and in the intervals between the first, second, and third fasts consisted of 200 gm. of bread, three eggs, 25 gm. of butter, and 100 gm. of boiled cabbage or spinach. No salt was allowed. Our first patient, Mrs. M., was given a somewhat similar diet. In her case, however, the food was not weighed. During the fasting periods distilled water only was taken.

was 133.5 cm. (5 ft. 4.5 in.), and she weighed 178 kilos when admitted to the hospital.

Table II contains the analytical figures bearing on the acidosis that developed in the course of three fasting experiments. On comparing these figures with those in Table I it will be seen that Mrs. B., notwithstanding her extraordinary obesity, developed nowhere near the degree of acidosis that we encountered in Mrs. M. At the end of the first four day fast the latter excreted 18.5 grams of β-oxybutyric acid in twenty-four hours, while Mrs.

B. excreted only 2.8 grams. On the fifth day of the second period the figures were 13.5 grams and 7.1 grams, respectively, and in the third period (fifth day) 13.5 as against 2.9.

In view of these results we are inclined to conclude that obesity cannot be regarded as a predisposing factor in the development of acidosis.

By comparison of the three fasting periods in Table II it will be seen that the adaptation to fasting observed in connection with the first patient is again quite unmistakable, notwithstanding the fact that the acidosis developed during the initial period was very slight indeed. We therefore concluded that one of the effects of repeated fastings is habituation to the complete oxidation of mobilized body fat, and a consequent retardation of the development of acidosis. It would, of course, have been very interesting and instructive if each of these two series of experiments could have included a great many more fasting periods, but the first patient had to be operated on, and both women were impatient to get back to their families.

The results obtained suggest, however, that one perfectly safe, rapid, and effective method of reducing the weight of very obese persons is by a series of repeated fasts of increasing duration, using the ammonia or β-oxybutyric acid elimination as a guide to the length of each fast. Qualitative tests or quantitative determinations of the acetone or the diacetic acid or both are of comparatively little value as measures of the acidosis, because whatever there is of acid intoxication must be chiefly due to the β-oxybutyric acid, and there is apparently no quantitative relationship between this acid and the other two acetone bodies.

Tables I and II also contain figures for the acetone of the expired air. The acetone of the breath has figured extensively in clinical literature on acidosis, one statement frequently encountered being that the expert clinician can detect the acetone smell as soon as he enters the room of a child or diabetic patient who has acidosis. From our quantitative figures it can be seen that the total amount of acetone eliminated through the lungs in the course of an hour always fell below 50 mg. 50 mg. per hour would amount to 1.2 grams for a full twenty-four hour day. Such an amount of acetone, and indeed several times

as much, can be scattered on the floor of a closed closet, and within an hour the odor will have disappeared.

Method used for the determination of the acetone in the breath. The patient was made to breathe through a rubber mouth-piece, such as is used in respiration work, the nose being closed by means of a nose-clip. The mouth-piece was connected with a respiration valve to which in turn was attached a wide absorption tube (inside diameter 25 mm.). The lower end of this tube was perforated by several holes (about 2 mm. in diameter), and reached to the bottom of a cylinder (60 mm. in diameter), containing 75 cc. of a 0.5 per cent solution of sodium bisulphite. The breathing

TABLE III.

Mrs. M. Urine.

DAY	VOLUME	TOTAL N	CREATININE N	CREATINE N	URIC ACID N	HIPPURIC ACID N	NaCl	WEIGHT
	cc.	*gm.*	*gm.*	*gm.*	*gm.*	*gm.*	*gm.*	*kg.*
1	495	6.8	0.33	0.0	0.09	0.04	0.67	108.2
2	550	6.8	0.33	0.06	0.08	0.03	0.40	
3	1130	8.7	0.35	0.12	0.08	0.03	0.32	
4	1140	9.4	0.35	0.18	0.12	0.03	0.31	104.7
15	340	3.1	0.30	0.0	0.07	0.04	0.14	104.0
16	345	3.1	0.33	0.0	0.07	0.02	0.16	
17	420	4.3	0.33	0.03	0.07	0.02	0.17	
18	580	5.5	0.33	0.03	0.07	0.02	0.16	
19	750	5.2	0.33	0.01	0.07	0.02	0.15	100.9
24	450	5.5	0.33	0.05	0.09	0.05	0.18	100.5
25	400	4.0	0.33	0.03	0.08	0.03	0.20	
26	370	4.7	0.31	0.02	0.08	0.02	0.17	
27	560	4.5	0.33	0.02	0.07	0.02	0.19	98.9

through this absorption apparatus was continued for one to two minutes.[3] The solution was then made up to a definite volume and the acetone was determined in an aliquot part by our turbidity method.

In Tables III and IV are given a few additional analytical data which it has seemed best to put on record.

Creatinine and creatine. The creatinine figures are given partly as an index of the degree of completeness of the urine

[3] Both of our patients had been used many times in respiration experiments in connection with the determination of basal metabolism and had been trained to maintain their normal respiration rate when breathing through the apparatus.

collection, although the quantitative collection of urine from fasting women is a relatively simple matter, since defecation occurs so seldom in this condition. Except during the first period with our second patient the creatinine elimination remained very constant.

The creatinine figures indicate one other point which is not without interest. Our second patient has been presented as being, if anything, fatter than the first, their weights being 178 and 108 kilos, respectively, at the beginning of the first fast;

TABLE IV.

Mrs. B. Urine.

DAY	VOLUME	TOTAL N	CREATININE N	CREATINE N	URIC ACID N	NaCl	WEIGHT
	cc.	*gm.*	*gm.*	*gm.*	*gm.*	*gm.*	*kg.*
1	540	9.1	0.74	0.10	0.10	0.54	178
2	600	10.1	0.74	0.10	0.12	0.54	
3	420	8.0	0.60	0.12	0.13	0.38	
4	500	8.0	0.49	0.25	0.12	0.38	175
9	400	5.2	0.65	0	0.14	0.30	174.4
10	310	5.5	0.66	0	0.14	0.21	
11	400	7.1	0.66	Trace	0.13	0.26	
12	390	6.7	0.66	0	0.12	0.21	
13	520	8.3	0.64	0	0.12	0.26	170.5
27	320	5.8	0.65	0	0.12	0.14	168.2
28	460	6.2	0.65	0	0.12	0.12	
29	355	7.0	0.65	Trace	0.12	0.14	
30	420	6.3	0.65	0	0.11	0.14	
31	390	6.7	0.72	0	0.11	0.14	
32	480	6.8	0.72	0	0.12	0.14	164.6

judging by the weights, appearance, and body measurements that seemed to be true.

From the acidosis standpoint, both patients were certainly extremely obese, without regard to which may have carried the greater amount of inert fat per unit of fat-free living tissue. The creatinine figures indicate perhaps that the less heavy woman, Mrs. M., was the more obese of the two, since she excreted only half as much creatinine per day as Mrs. B., yet weighed considerably more than half as much as the latter. The "creatinine coefficient" is, however, very variable in women, and it is doubt-

ful how much significance can be attached to the creatinine elimination as an index of obesity. The muscular tonus of Mrs. M. was probably greater than in Mrs. B. Except when fasting the former was very active and carried her weight well, while the latter declined to take any exercise whatever.

We have included our creatine figures in the tables, although we do not care to discuss them at the present time. Every precaution was taken to remove the acetone and diacetic acid before making the creatinine determinations. The figures given for the creatine nitrogen are, therefore, of some interest in connection with the conclusion of Graham and Poulton, that the so called creatine in urine of fasting subjects represents nothing else than errors in the determination of the preformed creatinine, and that no creatine is obtained if the diacetic acid is destroyed before determining the preformed creatinine.

Total nitrogen and uric acid. The total nitrogen elimination is strikingly low in both subjects. The current opinion that fasting adults reach an approximately common and relatively high level of nitrogen elimination (10 to 14 grams) after three to five days of fasting, and this independently of their previous diet, is probably not correct. In this connection we might cite the figures which one of us obtained several years ago from a man who began to fast at the end of a two week feeding experiment on an almost protein-free ("starch and cream") diet.

	1st day	2d day	3d day	4th day	5th day
	gm.	*gm.*	*gm.*	*gm.*	*gm.*
Nitrogen	4.4	6.5	10.8	11.0	12.2
Uric acid N	0.15	0.21	0.22	0.21	0.23

This subject was neither fat nor unusually emaciated and was confined to his bed during the starvation period. His daily creatinine N elimination was 0.33 gram; *i. e.*, exactly the same as that given by Mrs. M.

Two conclusions with reference to the nitrogen elimination suggest themselves: first, that the obese destroy less body protein during moderate periods of starvation than others; and, secondly, that with repeated fastings their adaptation to the complete utilization of body fat, which was indicated by a re-

tarded and diminished excretion of acetone bodies, is also accompanied by a sparing of the body protein. The latter conclusion may be regarded as a verification of a similar deduction arrived at by Howe and Hawk[4] in their experiments on dogs.

The uric acid output is also remarkably small in our obese women as compared with the uric acid values obtained from the man. Opinions differ as to whether the uric acid elimination in man is or is not completely independent of the total nitrogen elimination. Since the metabolism of glandular organs plays a much greater rôle in the production of purines than in the setting free of creatinine there is no reason why the total protein metabolism might not affect the total purine production more than it affects the production of creatinine, and our results indicate that such is the case.

SUMMARY.

Obesity is not a predisposing or contributing factor in the onset or intensity of the acidosis of starvation.

The total acetone excretion with the breath in starvation is quantitatively insignificant (at most 1 gram per day), and the notion, current among clinicians that they can smell acetone "all over the room" when a case of acidosis is present, is erroneous.

By repeated fasts of moderate duration the obese acquire an increased ability to starve without the production of acetone bodies.

The obese lose less body protein than others in the course of moderate periods of starvation (four to six days), and on repeating the fasts the losses of body protein become still smaller.

Successive moderate periods of starvation constitute a perfectly safe, harmless, and effective method for reducing the weight of those suffering from obesity.

[4] P. E. Howe and P. B. Hawk: *Jour. Am. Chem Soc.*, xxxiii, p. 253, 1911.