tributed in milk, eggs, liver, kidney, vegetables and fruit, it is not abundantly distributed. The work done has shown that in the cooking of vegetables more than 50 per cent of the B_1 vitamin present may be lost. It is not destroyed by heat, but it is destroyed by going into solution in the water that is thrown away. When one stops to consider that the diet is made up of from 30 to 50 per cent of food that contains no vitamin B_1 and from food cooked in water that is thrown away, one can see how the amount of vitamin B_1 necessary for optimal health is not obtained.

DR. MARTIN G. VORHAUS, New York: I want to add one point to the discussion of the frequency of B_1 deficiency. It is one of the few vitamins that the experimental workers in the field believe is not stored in the body, so that, without the normal protection of storage that exists with other vitamins, the probability of a deficiency state is that much more frequent; secondly, experimental workers have shown, and our clinical experience is along the same line, that there is some relation between the degree of carbohydrate intake and the utilization of the vitamin; i. e., the larger the carbohydrate intake, the greater the demand for vitamin B_1 in the human and animal body. Consequently a depletion of B_1 will take place more rapidly on a high carbohydrate diet than it will on a low carbohydrate diet.

DIURETIC ACTION OF POTASSIUM SALTS

NORMAN M. KEITH, M.D.
AND
MELVIN W. BINGER, M.D.
ROCHESTER, MINN.

For two centuries certain potassium salts have been employed as diuretics in clinical medicine. In 1679 Thomas Willis [1] recommended the use of potassium nitrate or "salt of niter" in the treatment of dropsy. Wilks and Taylor [2] used it successfully in 1863. In 1921 Blum [3] and Magnus-Levy [4] were able to show that potassium chloride could be administered safely by mouth in relatively large doses and that it produced frequently a satisfactory diuresis. Since then, McCann and his co-workers,[5] Osman [6] and Barker [7] have obtained similar results with potassium citrate, bicarbonate and chloride. Barker emphasized the importance of giving a diet in which the sodium content was low and that of potassium relatively high. It occurred to us in 1932 that potassium nitrate might be the salt of choice, if potassium itself should have an additional diuretic action to the well known effect of the nitrate radical. We then outlined the present study, which included observations on the relative effect of different potassium salts in both the normal individual and patients having various types of dropsy.

From the Division of Medicine, the Mayo Clinic.
Owing to lack of space, this article is abbreviated in THE JOURNAL. The complete article appears in the authors' reprints.
Read before the Section on Pharmacology and Therapeutics at the Eighty-Sixth Annual Session of the American Medical Association, Atlantic City, N. J., June 14, 1935.

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2. Wilks, Samuel, and Taylor, A. S.: A Case in Which a Large Quantity of Nitrate of Potash Was Taken Medicinally: Elimination of This Salt by the Urine: With Remarks, Guy's Hosp. Rep. **9**: 173-179, 1863.
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4. Magnus-Levy, A.: Alkalichloride und Alkalikarbonate bei Oedemen, Deutsche med. Wchnschr. **46**: 594-596 (May 27) 1920.
5. Basset, Samuel; Elden, C. A., and McCann, W. S.: The Mineral Exchanges of Man: II. Effect of Excess Potassium and of Calcium on Two Normal Men and on an Edematous Nephritic, J. Nutrition **5**: 1-27 (Jan.) 1932.
6. Osman, A. A.: Studies in Bright's Disease: The Use of Alkalis in the Treatment of Bright's Disease and Their Prophylactic Value in This and Other Conditions Associated with Impairment of Renal Function, Guy's Hosp. Rep. **77**: 386-435 (July-Oct.) 1927.
7. Barker, M. H.: Edema as Influenced by a Low Ratio of Sodium to Potassium Intake: Clinical Observations, J. A. M. A. **98**: 2193-2197 (June 18) 1932.

ACTION OF POTASSIUM SALTS ON THE NORMAL INDIVIDUAL

In previous studies [8] on the action of acid-forming salts our procedure was to give normal individuals a measured amount of a given salt under strict experimental conditions and to compare the urinary output of water and other constituents with that in control periods before and after the ingestion of the salt. The weighed diet was low in water and mineral content, particularly as to chloride and sodium. It was calculated to be sufficient in calories and protein to keep the individual in nitrogen balance. The intake of fluid, in addition to that in the food, was limited to 800 cc. daily. The experiment extended over a period of from ten to fourteen days, a specific salt being given on five of these days. The potassium salts given were potassium chloride, bicarbonate, nitrate, acetate and citrate. Sodium chloride was given in a single experiment, chiefly to bring out by contrast the relative effects of the potassium and sodium radicals. The salts were administered in 25 per cent solution in a single dose of from 7.5 to 14 Gm. (0.13 to 0.2 Gm. per kilogram of body weight). All five potassium salts produced diuresis with loss of weight (charts 1 and 2).

The sudden decrease in the excretion of water and minerals after discontinuing administration of the salt was a striking finding in each experiment. The nitrate caused a relatively greater diuresis than any of the other salts. The chloride was next in efficiency, and still less efficient were the bicarbonate, acetate and citrate. The nitrate also caused a greater excretion of chloride and sodium than the bicarbonate, acetate and citrate. Potassium was readily excreted after the ingestion of all five salts.[9] The concentration rose from 0.50 to 0.96 Gm. per hundred cubic centimeters. Thus even with diuresis the normal kidney excreted a urine in which the concentration of potassium reached a figure approximately fifty times greater than that of the blood serum. Such results indicate that potassium concentration by the kidney is similar to that of creatinine, urea and sulphate. It is obviously concentrated in a much greater degree than sodium. The excretion of calcium remained unaltered throughout these experiments. A decrease in ammonia nitrogen, and an increase in the excretion of bicarbonate along with a rise in p_H, invariably occurred after the ingestion of potassium bicarbonate, acetate and citrate. These results are similar to those reported with sodium bicarbonate, carbonate and citrate.[10] Changes in the excretion of total nitrogen and inorganic sulphates and phosphates were not uniform and were difficult to interpret. Each twenty-four hour specimen was tested qualitatively for protein, and the result was invariably negative.

The results in subject V (chart 1) after taking sodium chloride are in sharp contrast to those after taking potassium salts. There is an early retention of water, chloride and sodium with a gain in body weight. Later there is an increased excretion of these con-

8. Keith, N. M., and Whelan, Mary: A Study of the Action of Ammonium Chloride and Organic Mercury Compounds, J. Clin. Investigation **3**: 149-202 (Oct.) 1926. Keith, Whelan and Baunick.[81]
9. Potassium was estimated by the Kramer and Tisdall methods in blood serum and urine. Any serum suggesting the presence of hemolysis was discarded. (Kramer, Benjamin, and Tisdall, F. F.: A Clinical Method for the Quantitative Determination of Potassium in Small Amounts of Serum, J. Biol. Chem. **46**: 339-349 [April] 1921. Tisdall, F. F., and Kramer, Benjamin: Methods for the Direct Quantitative Determination of Sodium, Potassium, Calcium and Magnesium in Urine and Stools, ibid. **48**: 1-12 [Sept.] 1921.)
10. Stadelmann, Ernst: Ueber den Einfluss der Alkalien auf den menschlichen Stoffwechsel, Stuttgart, F. Enke, 1890, 176 pp.

stituents and a slight fall in weight. These results simply confirm many similar previous experiments with sodium salts.[11]

In all of our eight experiments with normal individuals (colleagues who kindly consented to undergo the tests), the serum potassium was estimated before the ingestion of the given salt, sometime during its ingestion, and after its administration was discontinued.

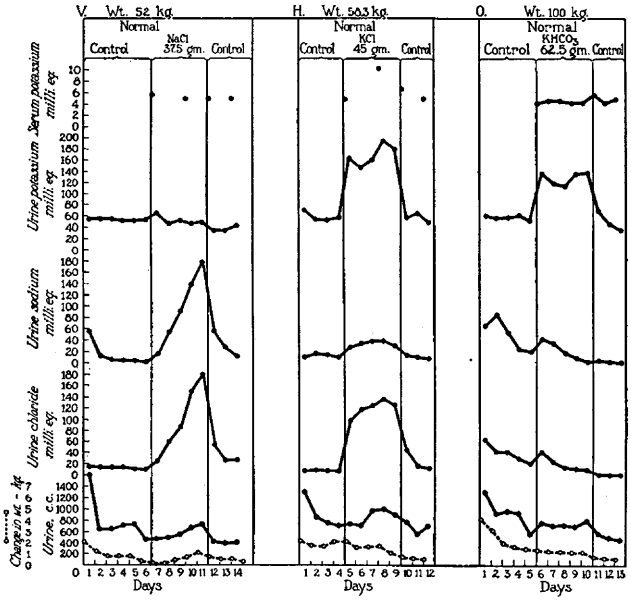

Chart 1.—Normal subjects V., H. and O., showing daily excretion of water, chloride, sodium and potassium in the urine and the concentration of potassium in the serum after they had ingested sodium chloride, potassium chloride and potassium bicarbonate.

The sample of serum was withdrawn in the morning at the end of the twenty-four hour period. No change was observed in the serum of subject V, who received sodium chloride. This constituted a control for the seven individuals who were given potassium salts. In the latter, the potassium of the serum either rose a few milligrams or, as in M. (chart 2), T. and H. (chart 1), increased distinctly to 33, 37 and 40 mg. per hundred cubic centimeters, or 8.4, 9.5, 10.2 milliequivalents, respectively.[12] No toxic symptoms were noted in any of the seven individuals. Thus, in seven normal subjects under the same experimental conditions, including diet and intake of fluid, the potassium was readily absorbed and excreted, yet the concentration of the serum varied only from 20 to 40 mg. per hundred cubic centimeters (5.1 to 10.2 milliequivalents). Further study is necessary to explain these variations in the concentration of the serum.

In order to study the initial effects produced by administration of potassium salts, two short experiments, nine hours in duration, were carried out with two normal individuals, K. and B. (chart 3). No food was taken for twelve hours preceding or during the experiment; however, 600 cc. of water was ingested during the experiment. A control specimen of urine was collected from 7 to 8 a. m. At 8 a. m., 12.5 Gm. of potassium acetate or nitrate was ingested and specimens of urine were collected at 8:15, 8:30, and 9 o'clock, and subsequently at hourly intervals for the next seven hours. Specimens of venous blood were withdrawn frequently during the experiment. After potassium acetate was taken by subject K. there was an increase in the renal excretion of water, chloride, carbonate and potassium; the p_H of the urine rose from 5.9 to 8.3. The changes in the blood were a small increase in the carbon dioxide capacity of the plasma, from 62 to 69 volumes per cent, and a slight rise in the serum concentration of potassium, from 18 to 20 mg. per hundred cubic centimeters, 4.6 to 5.1 milliequivalents. The concentration of potassium in the urine rose to 0.95 Gm. per hundred cubic centimeters, or fifty times that of the serum. After deducting the probable excretion of potassium by a starving individual, estimated from the excretion on the first day of a prolonged fast by Benedict's subject,[13] this individual excreted 49 per cent of that ingested in eight hours.

The experiment with subject B. was similar in every detail to that with K. with the single exception that the same amount of potassium nitrate was ingested instead of potassium acetate. The results were in many respects similar, although there was a relatively greater diuresis and a greater excretion of chloride and potassium than in the previous experiment. The p_H did rise, but it fluctuated quite markedly from specimen to specimen. The changes in the blood were: (1) a slight decrease in the carbon dioxide capacity of the plasma, from 66 to 55 volumes per cent, and (2) a small rise in the concentration of potassium in the serum from 18 to 23 mg. per hundred cubic centimeters (4.6 to 5.9 milliequivalents). The maximal concentration of potassium in the urine was 0.76 Gm. per hundred cubic centimeters, or forty-two times that of the serum. This is a slightly lower figure than in the previous experiment and is probably to be accounted for by the greater

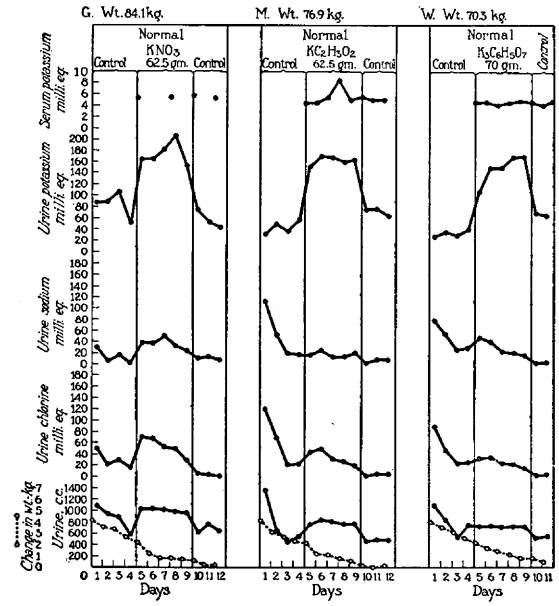

Chart 2.—Normal subjects G., M., and W., showing daily excretion of water, chloride, sodium and potassium in the urine and the concentration of potassium in the serum after they had ingested potassium nitrate, potassium acetate and potassium citrate.

increase in the volume of urine. The calculated percentage excretion of potassium ingested was 64. A routine qualitative test for protein was made in each specimen of urine in these two experiments, and no protein was demonstrated.

11. Blum, Léon: Ueber die Rolle von Salzen bei der Entstehung von Oedem Verhandl. d. Kong. f. inn. Med. 122-126, 1909. Meyer, L. F.: Verhandl. d. Versamml. d. Gesellsch. f. Kinderh. **14**: 1909.

12. Twenty milligrams per hundred cubic centimeters of potassium, a mean normal figure = 5.1 milliequivalents per liter.

13. Benedict, F. G.: A Study of Prolonged Fasting, Washington, Carnegie publication 203, 1915.

These two short experiments indicate that potassium salts are promptly absorbed and readily excreted and that the changes in blood and urine are very similar to those obtained in the previous experiments extending over a period of several days.

ACTION OF POTASSIUM SALTS ON PATIENTS WITH EDEMA

During the last three years we have administered potassium salts to sixty patients with edema. Twenty-nine patients had chronic nephritis with edema, twenty had myocardial degeneration with decompensation, seven had cirrhosis of the liver with ascites and edema, one had polyserositis with tuberculosis of the peritoneum, and in three cases there was edema of indeterminate origin. The diuretic results were very satisfactory in twenty-nine cases (48 per cent), fair in twenty (33 per cent), and a failure in eleven (18 per cent). An increased urinary output was thus observed in 80 per cent of the cases. In four cases quantitative studies similar to those just described for normal subjects were carried out.

CASE 1 (subject A., chart 4).—A youth, aged 19 years, who had had albuminuria and edema for five weeks, was given potassium chloride. Preliminary examination showed that he had a moderate degree of general edema, some anemia, with a hemoglobin concentration of 11.1 Gm. per hundred cubic centimeters, and erythrocytes numbering 3,560,000 per cubic millimeter. The urinary changes were characteristic of subacute glomerulonephritis and there were definite renal functional disturbances. The blood pressure was usually normal and the ocular fundi showed no abnormalities. The values for certain constituents of the blood are given in the accompanying table.

Following the exhibition of a weighed diet consisting of from 1,600 to 2,500 calories, 40 to 50 Gm. of protein, a low mineral and water content, 600 cc. of extra fluid, and 105 Gm. of potassium chloride in thirteen days, the edema disappeared and the patient's weight decreased 24 pounds (11 Kg.). Diuresis was indicated by a rise in the daily volume of urine from 600 to 1,480 cc. There was an increased excretion of chloride, sodium and potassium. The potassium concentration rose to 0.41 per cent, seventeen times the concentration in the serum. The total output of sodium was relatively much greater than that of potassium. The comparatively small urinary output of potassium indicated that potassium was retained in considerable quantity. The amount of potassium excreted in the stools and sweat obviously could not account for this marked discrepancy between intake and urinary output. This result suggested replacement of sodium by potassium in the tissues. Throughout diuresis the daily excretion of protein in the urine was from 1.5 to 5.2 Gm. per hundred cubic centimeters.[14] At the time the patient was free from edema, the analysis of the chemical constituents of the blood indicated a slight reduction in the plasma alkali reserve, but otherwise there was an improvement in renal function. In spite of a retention of potassium the rise in serum concentration was slight.

CASE 2 (subject G, chart 4).—A woman, aged 24, gave a history of albuminuria for one year and of general edema for six months. On examination there was no gross anemia, but there was slight puffiness of the eyelids and moderate edema of the lower part of the back and legs. The blood pressure in millimeters of mercury was 105 systolic and 75 diastolic, and the ocular fundi appeared normal. Routine urinalyses revealed a heavy precipitation of albumin, a few hyaline casts and a few leukocytes, but no erythrocytes. Values for certain constituents of the blood are given in the table. A diagnosis of chronic glomerulonephritis with features of chronic lipoid nephrosis was made.

Results of Examination of the Blood of Various Subjects

				Whole Blood		Plasma				Serum					
Subject	Chart	Potassium Salt Given	Diuresis	Hemoglobin, Gm. per 100 Cc.	Urea, Mg. per 100 Cc.	Chloride,* Mg. per 100 Cc.	Carbon Dioxide Combining Power, Volumes per Cent	Nitrate Nitrogen, Mg. per 100 Cc.	Cholesterol, Mg. per 100 Cc.	Protein, Gm. per 100 Cc.	Albumin, Gm. per 100 Cc.	Sulphate, Mg. per 100 Cc.	Sodium, Mg. per 100 Cc.	Potassium, Mg. per 100 Cc.	Calcium, Mg. per 100 Cc.
A.	4	Potassium chloride	Before	11.1	72	627	47	...	340	4.1	1.7	11.0	...	..	...
			During	....	42	668	40	...	...	...	...	8.4	330	24	...
			After	....	40	627	43	...	268	3.6	0.9	8.5	340	23	...
G.	4	Potassium nitrate	Before	14.9	20	627	..	...	595	4.6	1.9	6.0	...	..	...
			After	....	22	585	59	4.1	512	4.3	1.9	...	318	19	8.1
S.		Potassium nitrate	Before	12.6	22	627	47	...	133	2.7	1.4	3.5	387	18	6.5
			During	....	21	627	48	0.7	...	3.1	1.9	4.3	301	24	8.3
			After	14.4	18	618	54	...	181	3.4	2.4	5.6	296	18	8.5
Pe.†	5	Potassium chloride	Before	13.7	22	585	51	...	...	...	...	5.2	310	20	...
			During	....	..	...	..	...	...	...	...	...	310	37	...
			After	13.5	22	593	46	...	...	...	...	5.6	327	20	...
Pw.		Potassium nitrate	Before	13.7	40	660	46	...	476	3.4	1.2	6.8	...	10	...
			After	....	33	561	53	...	...	...	...	...	...	..	...
B.	6	Potassium nitrate	Before	....	100	...	..	...	...	...	...	...	...	..	...
			After	....	26	...	..	...	...	...	...	...	...	..	...

* Calculated as NaCl.
† Very slight or no diuresis occurred in this case (chart 5).

Treatment consisted of a weighed diet of 2,500 calories, 77 Gm. of protein, a low mineral and water content and 600 cc. of extra fluid, and potassium nitrate, 12 Gm. (0.2 Gm. per kilogram of body weight) daily. Mild diuresis followed, with a loss of weight of 15 pounds (6.8 Kg.) in five days. The patient was now free from visible edema. The diuresis was accompanied by a considerable increase in the excretion of potassium, chloride and nitrate, but by a relatively small increase in sodium. The concentration of potassium rose to 0.95 Gm. per hundred cubic centimeters, or fifty times that of the serum. These results in regard to the relative amounts of sodium and potassium excreted are somewhat the reverse of the results in case 1 (subject A.). The excretion of calcium was extremely small. The daily output of protein was considerable, varying from 5.2 to 8.2 Gm. Both in this and in the previous case the presence of a considerable amount of protein in the urine did not seem to hinder the diuretic response, nor was the function of the kidney further impaired. At the termination of diuresis the changes in the blood were a slight retention of nitrate, without retention of potassium or a notable shift in the alkali reserve.

CASE 3 (subject S. in the table).—A married woman, aged 35, complained chiefly that for six months she had had edema of the feet, legs and face. On physical examination there was no

14. The protein in the urine was determined by subtracting the nonprotein nitrogen from the total nitrogen and by multiplying the result by 6.25. The nonprotein nitrogen was estimated after precipitating the protein with Folin's tungstic acid reagent.

demonstrable anemia. The blood pressure was 100 systolic and 60 diastolic. There was definite edema of the feet, legs and lumbosacral region, reaching as high as the eighth thoracic vertebra. Further studies showed that there were no abnormal constituents in the urine, which included examination for lipoid bodies. The basal metabolic rate was +2. The serologic test for syphilis was negative. All tests of renal function gave normal readings. However, the concentration of serum protein was very greatly reduced, to 2.7 Gm., the albumin content to 1.4 Gm. and the calcium content to 6.5 Mg. per hundred cubic centimeters, as shown in the table. Edema fluid obtained through a needle inserted in the leg was water clear and contained only 0.1 per cent of protein. A diagnosis of an indeterminate type of edema associated with hypoproteinemia was made.

Treatment consisted of a weighed diet of approximately 2,000 calories, from 80 to 100 Gm. of protein, and a low mineral and water content. Extra fluid was limited to 800 cc. Nine grams of potassium nitrate was administered daily for fourteen days and, because of the low serum calcium from the fifth to the fourteenth day, 12 Gm. of calcium lactate was also given daily. On this regimen diuresis developed, the volume of urine varying from 900 to 2,080 cc. There was an increased excretion of chloride, nitrate, sodium and potassium. The concentration of potassium increased to 0.41 Gm. per hundred cubic centimeters, seventeen times that of the serum. A slight increase in calcium output occurred. No demonstrable amount of protein was excreted during this experimental period. When the patient became edema free, she had lost 14 pounds (6.4 Kg.).

The noticeable changes in the blood were the considerable rise in serum protein and albumin and calcium contents. During diuresis the serum potassium rose to 24 mg. per hundred cubic centimeters (6.2 milliequivalents), but it fell to 18 mg. (4.6 milliequivalents) at the termination of the diuresis. Similarly, the plasma nitrate rose to 0.7 mg. per hundred cubic centimeters during diuresis.

CASE 4 (subject Pe., chart 5).—A man, aged 58, a city clerk, had always been a heavy drinker of alcohol, and five months before admission the abdomen had become swollen. During the last four months abdominal paracentesis was performed on five occasions, several liters of fluid being drained at each operation. The patient's ankles had been swollen for three

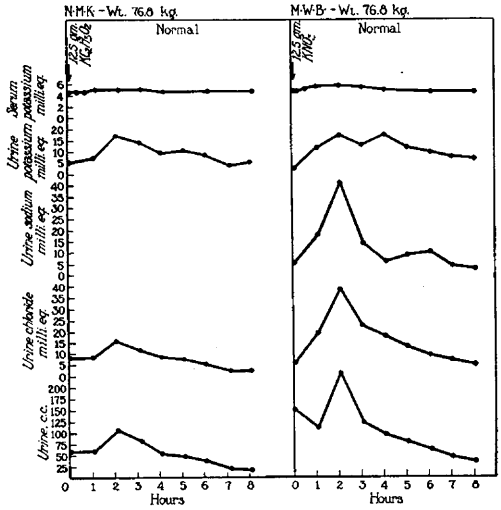

Chart 3.—Normal subjects K. and B., showing hourly excretion of water, chloride, sodium (B.) and potassium in the urine and the concentration of potassium in the serum after they had ingested potassium acetate and potassium nitrate.

months. On examination there was evidence of fluid in the left pleural cavity, marked ascites was present, and there was moderate edema of the lumbosacral region and of the legs. There were no definite evidences of myocardial insufficiency. Secondary anemia was slight. Routine urinalyses and tests of renal function were essentially normal. The serologic test for syphilis was negative. The dye test of hepatic function revealed marked retention in the blood, and the serum bilirubin was 2.5 mg. per hundred cubic centimeters (direct reaction). A provisional diagnosis of hepatic insufficiency, cirrhosis (?), ascites and left pleural effusion was made. The etiology of the patient's disease remained obscure. Treatment consisted of paracentesis of the left pleural cavity on three occasions and of the abdominal cavity twice. Fluid in the amount of 12,500 cc. was removed in this manner. After paracentesis a firm edge, presumably of the liver, was palpated 6 cm. below the right costal margin. The results of examination of the blood are given in the table.

For a period of twelve days the patient was given a weighed diet consisting of from 1,335 to 2,350 calories, 35 to 49 Gm. of protein, and a low intake of minerals and water. Extra fluid was limited to 800 cc. The patient also ingested potassium chloride, 5 Gm. daily. On this regimen there was a loss in weight of 2 Kg., probably due to withdrawal of 1,000 cc. from the left part of the chest and 2,500 cc. from the peritoneal cavity, a decrease in the dependent edema and at times a slight increase in the volume of urine, but no actual and steady diuresis. The excretion of chloride and potassium was increased, the concentration of the latter rising to 0.6 Gm. per hundred cubic centimeters. The excretion of sodium was very small and was uniform throughout. On the seventh day the serum potassium rose to 37 mg. per hundred cubic centimeters (9.1 milliequivalents), but later fell to the initial figure of 20 mg. (5.1 milliequivalents). In this case there occurred a distinct retention of potassium and a slight decrease in the alkali reserve, even though the dose of potassium chloride was small.

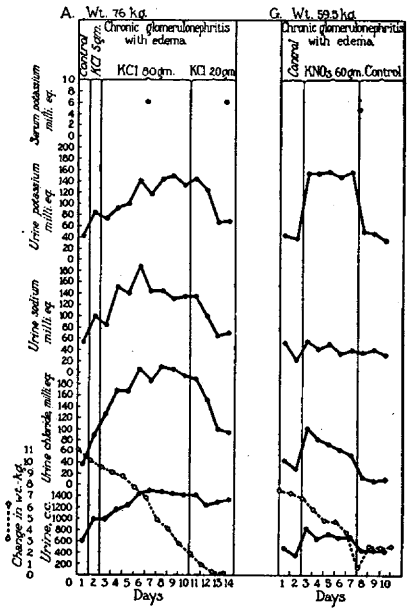

Chart 4.—Subjects A. and G., showing daily excretion of water, chloride, sodium and potassium in urine and the concentration of potassium in the serum after they had ingested potassium chloride and potassium nitrate.

Two further cases are of interest because of the excellent diuretic response obtained. Detailed chemical analyses of the urine were not made as in the previous four cases.

CASE 5 (subject Pw. in the table).—A farmer, aged 39, when admitted to the clinic stated that his illness had begun eight months previously with general edema and albuminuria. A diagnosis of chronic glomerulonephritis with edema was made.

CASE 6 (subject B., chart 6).—The patient was a rancher, aged 56. A diagnosis of myxedema, myocardial degeneration with decompensation, and renal insufficiency was made.

DOSE OF POTASSIUM SALTS

The amount of a given salt administered in order to produce diuresis is considerably greater than the dose given in the United States and British pharmacopeias. Taking 12.5 Gm. of potassium nitrate as a useful standard daily dose, we gave to normal individuals, for comparative purposes, approximately its atomic equivalent of the other potassium salts. The content of potassium was about 5 Gm. This amount has been the usual maximal dose given to patients with edema. However, subject H. was given 24.5 Gm. of potassium salts, 12 Gm. of nitrate, and 12.5 Gm. of the bicarbonate, daily, for a period of thirteen days. The

potassium content amounted to 9.5 Gm. daily. No ill effects were observed. Similar maximal daily doses of the chloride, nitrate, bicarbonate, acetate and citrate have been successfully employed previously by Blum,[3] Wilks and Taylor,[2] Nonnenbruch,[15] Fleckseder,[16] and Basset, Elden and McCann.[5] Their doses varied from 16.5 to 30 Gm. of the salt and from 6.6 to 13 Gm. of potassium.

Caution must be used in administering these large doses, and all are agreed that smaller trial doses should be given initially. Our plan has been to give from 6 to 12 Gm. of potassium nitrate, or its atomic equivalent in other potassium salts, daily to a given subject, the exact dose depending on the individual's needs and condition. A simple clinical danger signal is the absence of diuresis after administering a salt for a few days. Some patients were able to take 10 per cent solutions of a salt, or the salt itself on food, without discomfort. Others complained of epigastric discomfort or even nausea. Potassium nitrate, 0.5 Gm. in the form of an enteric coated pill, has been the most satisfactory method of administering any one of these salts. The combined use of potassium salts and other diuretics, such as the organic compounds of mercury and the caffeine-containing compound aminophylline, sometimes has produced excellent results. The combined effect is similar to that of the acid-producing salts and organic mercury and these salts and caffeine compounds.

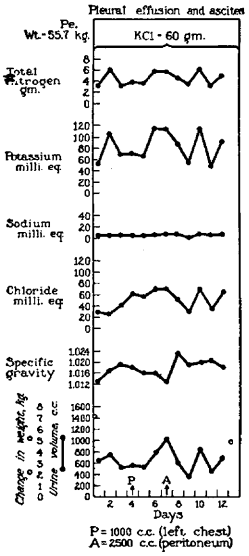

Chart 5. — Subject Pe., showing daily excretion of water, chloride, sodium, potassium and total nitrogen in the urine after ingestion of potassium chloride. Paracentesis of left pleura at *P* and of peritoneal cavity at *A*.

TOXIC ACTION

Potassium salts, when injected intravenously into animals, can cause rapid toxic effects, particularly on the heart. The experiments of Blake,[17] Grandeau [18] and Traube [19] carried out years ago are often quoted to emphasize this fact. Mathison [20] in 1911 was able to show that potassium chloride, when injected into the central portion of the carotid artery of the cat, not only was less toxic but actually caused a rise in blood pressure in contrast to a fall after intravenous injection. He attributed the toxic action after intravenous injection to the high concentration of potassium, which almost at once reaches the heart muscle. Amberg and Helmholz [21] in 1916 determined the toxicity of intravenously injected potassium chloride and sulphate in the guinea-pig. They found that the lethal dose was very small, from 10 to 17.5 mg. per hundred grams of body weight, when the solutions, 1 per cent potassium chloride and 1.75 per cent sulphate, were injected at the rate of 1 cc. per minute. A much larger dose was necessary to kill the animal if it had received a previous injection of sodium chloride. In 1925 Whelan,[22] studying some biochemical effects of intravenously injected chlorides in dogs, noted that seven animals, when given 0.1 Gm. of potassium chloride per kilogram of body weight, in ten minutes showed no obvious toxic effects. Such results seem to show that slowing the rate of injection is an important factor in protecting the heart from too concentrated a solution of the potassium salt. Two experiments reported by Nicholson and Soffer [23] early this year also support the view that slow intravenous injections can be much better tolerated than rapid ones.

What is the concentration of potassium in the blood serum that is toxic to the heart? McLean, Bay and Hastings [24] have recently carried out a series of perfusion experiments on the isolated heart of the rabbit and found that when the concentration of potassium in the perfusion fluid was increased to 48 mg. per hundred cubic centimeters (12.0 milliequivalents per liter) ventricular fibrillation and minimal ventricular contractions were observed. These results support Cushny's statement [25] that a concentration of potassium in the serum of greater than about 50 mg. per hundred cubic centimeters (12.8 milliequivalents) is highly poisonous to the heart. The highest concentration of potassium in the serum of our normal controls and of patients when taking potassium salts has been 40 mg. per hundred cubic centimeters (10.2 milliequivalents), or well under this figure. Rabinowitch,[26] however, reported serum concentration of 58 and 72 mg. per hundred cubic centimeters (14.9 and 18.5 milliequivalents) in two cases, one of eclampsia and the other of uremia, but he does not mention any outspoken and noticeably toxic effect on the heart. Magnus-Levy [4] and others have stressed

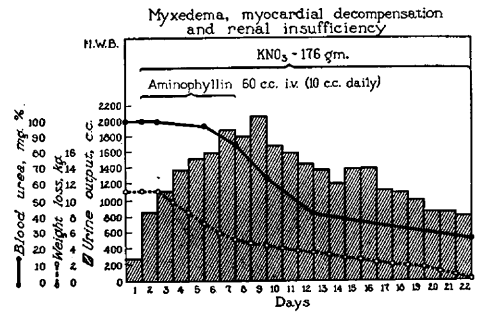

Chart 6.—Subject B., showing daily volume of urine and changes in blood urea and body weight after ingestion of potassium nitrate.

that toxic effects produced during a perfusion experiment may not necessarily occur in the intact animal.

We believe that the results of experimental studies on animals contraindicate, at present at least, the intravenous administration of any considerable amount of

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potassium salts in clinical medicine. On the other hand we have shown that normal individuals can take a large dose of a potassium salt by mouth without demonstrable toxic effects. Many observers have given really enormous doses of potassium salts for a considerable period to patients with edema and no untoward effects have occurred. In our present series subject H., previously mentioned, took by mouth 871 Gm. of potassium salts (358 Gm. of potassium) in a period of sixty-eight days. The patient during this entire period took the diet and potassium salts regularly, the salts including potassium nitrate, chloride and bicarbonate. There were no complaints and no definite toxic symptoms. These large doses of potassium salts failed to establish satisfactory diuresis but produced a condition favorable for the accumulation of potassium in the body. However, the rise of potassium in the serum was very small, 26 mg. per hundred cubic centimeters (6.6 milliequivalents), on the thirty-ninth day, and 24 mg. (6.2 milliequivalents), on the sixty-eighth day.

Even the aforementioned large doses of potassium by mouth are often exceeded by normal individuals whose diet includes large quantities of food rich in potassium. Bunge [27] stated that certain Irish laborers eating chiefly potatoes and certain African tribes living on native foods may ingest as much as 50 Gm. of potassium daily without toxic symptoms. The daily ration of our hospital diets contains from 3 to 5 Gm. of potassium. The comparative safety with which one can administer food containing potassium and potassium salts by mouth is probably due to several factors, the most important being the rate of absorption from the intestine into the portal system, the dilution or detoxification of the salts in the blood stream or during their passage through the liver, and their rapid excretion by the kidney.

Magnus-Levy,[4] Blum [3] and Smellie [28] reported toxic effects in a few patients with cardiac decompensation and edema but no fatalities. Estimations of potassium in serum or urine were not made. We have found it difficult in the written descriptions of these few cases to eliminate entirely the possibility of independent accidents, such as coronary occlusion and acute myocardial failure, so that it is not possible to ascribe the symptoms definitely to potassium intoxication. Pilcher, Calhoun, Cullen and Harrison [29] have also shown that the potassium content of skeletal muscle is decreased in congestive heart failure and have administered potassium dibasic phosphate (up to 14 Gm. daily) in such cases. In order to avoid any toxic effects, Blum [3] and Magnus-Levy [4] advise giving small, initial trial doses in this type of cardiac case, and this is undoubtedly a wise procedure. Up to the present we have never given potassium salts to a patient with extreme oliguria or anuria, or to one whose blood urea was greater than 100 mg. per hundred cubic centimeters. In case 6 (subject B.) a urea content of 100 mg. per hundred cubic centimeters did not prevent satisfactory diuretic action. Small initial doses, advocated in cardiac cases, would also seem to be indicated in cases of dropsy with severe renal insufficiency. Bolliger and Breh [30] demonstrated that in experimental chronic renal insufficiency in the dog the potassium concentration of the blood serum invariably rises. On the other hand, Rabinowitch [26] found a remarkable variation in the concentration of potassium in the serum of patients in severe uremia. In one such case the concentration rose to 72 mg. per hundred cubic centimeters (18.5 milliequivalents), but in several other cases with just as severe retention of urea and creatinine in the blood the values were normal. The distribution of potassium in the tissues of uremic patients would therefore appear to be regulated by factors other than simply a reduced permeability of the kidneys for potassium.

In the experiments of Amberg and Helmholz just mentioned, a preliminary injection of sodium chloride made it necessary to increase the lethal dose of a potassium salt. Osman,[6] in giving large amounts of alkalis to patients with edema, combined potassium and sodium salts in order to protect the patient against the possible toxic effects of potassium. These facts bring up the question as to whether the actual amount of sodium in the body is a determining factor in potassium poisoning. In adrenal insufficiency the amount of sodium is reduced both in the blood serum and in the tissues, while there is often an increase in the concentration of potassium in the serum. Potassium poisoning, therefore, has been suggested as a cause of the serious symptoms. No such toxic symptoms or relationship have been observed in the present study. The concentration of sodium in the serum varied from 285 to 374 mg. per hundred cubic centimeters without any demonstrable relation to the potassium content. Rabinowitch's observations on uremic blood did not show any definite relationship between the sodium and the potassium content. Further experimental work in actual potassium toxemia is necessary to determine the relative significance of the potassium, the sodium and possibly the calcium content of the blood serum.

In any discussion of toxicity of potassium salts the action of the specific anion must be considered. One of us [31] has described the possible toxic effects of the nitrate radical and how these can usually be prevented. The chloride ion has a stronger tendency than the nitrate ion to cause a shift in the acid-base equilibrium to the acid side. Undoubtedly the acid producing salts ammonium chloride and ammonium nitrate have produced an acidosis, with further reduction of renal function in certain types of renal disease.[32] Potassium, bicarbonate, acetate and citrate cause an increased renal excretion of carbonate with a decided shift of the urinary p_H to the alkaline side, and we have not seen any definite harmful action from these effects. This observation agrees with previous clinical experience that potassium bicarbonate, citrate and acetate can be given safely in comparatively large doses.

COMMENT

These biochemical studies indicate that potassium is readily absorbed from the intestine, disappears quickly into the tissues, and can be rapidly excreted by the kidney. The small amount in the blood serum, even after ingestion of a considerable quantity, raises the question as to its manner of storage and subsequent liberation for excretion. The two chief storehouses of potassium are the erythrocytes of the blood stream and the cells of voluntary muscle. In health, any excess

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seems to be quickly removed from the blood serum and is then gradually excreted by the kidneys. Following depletion of potassium due to starvation and that seen in cardiac edema, there is retention with a refilling of the muscle storehouse. Was the potassium retention in case 1 (subject A.) with anemia due to an analogous need for the refilling of the potassium storehouse in the erythrocytes? The efficiency with which the kidney concentrates potassium, at least fifty times, readily explains the rapid elimination of a great excess taken in the diet by eaters of potatoes, for example. The sustained high concentration in the urine in case 2 (subject G.), in which there was a definite renal lesion, suggests that the ability of the kidney to excrete potassium may be maintained late in chronic nephritis in a similar way to its ability to eliminate creatinine. The much greater concentration by the kidneys of potassium than sodium may possibly be explained by less reabsorption of the former in the renal tubules.

Bunge [27] suggested that potassium and sodium may replace each other in the animal organism. The experimental evidence he gave was that the ingestion of potassium salts resulted in a definitely increased excretion of sodium in the urine. Our data reveal an increased excretion of sodium by some of our normal individuals and in case 1 (subject A.); in the normal individual M. and in cases 2 and 4 (subjects G. and Pe. respectively), however, the increase was insignificant. These results together with those of Miller [33] again emphasize the well known fact that potassium and sodium have certain independent biologic functions, as, for instance, the high concentration of sodium in blood serum and interstitial fluid in contrast to the small content of potassium, the high concentration of potassium in the erythrocytes with little or no sodium present, and also the initial retention of water with the ingestion of sodium salts in contrast to loss of water after taking potassium salts.

In the present study five potassium salts have been shown to cause diuresis. The cation potassium is readily excreted in each instance by the kidney; it also brings about a definite shift of the acid-base equilibrium in the urine toward the alkaline side. These two facts offer a possible explanation for its diuretic action. It should be pointed out, however, that of the five salts the nitrate produced the most marked effect, which emphasizes the importance of the anion as well as the cation in considering the diuretic action of a given salt.

Our clinical results with potassium salts have been encouraging. They confirm the results of the therapeutists of the last eighty years.[35] We prefer potassium nitrate because, after its use, diuresis frequently occurs. In our experience it is less likely to cause toxic symptoms than ammonium nitrate. Its action, when combined with other diuretics, is also often satisfactory. Diuresis from potassium nitrate may be initiated more slowly and be of longer duration than that of other diuretics, but it is less likely to cause untoward effects. Organic compounds of mercury act more rapidly but in so doing may injure tissues, such as those of a diseased kidney. Potassium salts, more particularly the bicarbonate, acetate and citrate, produce a rapid shift in the acid-base balance, rendering the plasma and urine more alkaline. This action suggests that these potassium salts may be more effective and less likely to cause edema in combating acidosis than sodium salts. They might also be used when a strongly alkaline urine is desired.

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ABSTRACT OF DISCUSSION

DR. HERBERT BARKER, Chicago: Drs. Keith and Binger's paper brings out two points that are of special interest to me: that the potassium salts may be used in a variety of conditions for their diuretic effect and that they may be used in those conditions without fear of toxicity. Their report should aid in dispelling fears in connection with the administration of potassium to patients with renal disease. Five years' use of potassium chloride has not given any untoward effects except in possibly three instances. All three patients were suffering from advanced glomerular nephritis with edema, hypertension and nitrogen retention, so that there were many factors entering into the symptomatology. The symptoms in question were those of weakness and increased feeble heart action with a gallop rhythm. The blood potassiums at that time were 35, 35 and 40 mg. per hundred cubic centimeters. These are the highest blood potassium readings I have obtained with doses ranging from 3 to 10 Gm. daily. Doses as great as 60 Gm. daily have been reported in the literature and the only untoward effects recorded are nausea, vomiting and diarrhea. I have had no experience with potassium nitrate. Chemically it should be effective when the acid-base equilibrium is not greatly disturbed. My experience with potassium chloride has been largely confined to the chronic cardiac edemas of valvular and hypertensive vascular types. In these cases the reduction of chlorides in the body due to long standing salt restriction renders a diuresis very poor with diuretics, especially the mercurials. It is therefore especially important to administer chlorides, as the potassium or ammonium salts, until blood chlorides are raised to 500 mg. or more per hundred cubic centimeters. I feel, therefore, that the mineral control of fluid balance, though relatively simple to operate, is often much more effective when blood chemical determinations are used to assist in choosing the proper salt for administration, and it is equally important as a guide to probable desirable changes from one salt to another as the course of the disorder progresses.

DR. CARL H. GREENE, New York: A great deal of credit is due to the men who pointed out the relationship between water retention and salt metabolism in the body and demonstrated the clinical application of these facts in the management of cases of renal disease. When ammonium chloride and calcium chloride were first introduced it was believed that diuresis was due to the acidifying action of the chloride ion. When ammonium nitrate was introduced it was suggested that the nitrate ion perhaps had a specific diuretic action of its own. The diuretic action of potassium chloride, on the other hand, has been explained in part at least as the displacement of sodium salts in the body by potassium salts. I hope that the authors will tell us a little more with regard to their conclusions as to the relative importance of these various effects in determining the diuretic action of potassium nitrate. The administration of ammonium salts must be carried out with care to avoid unpleasant gastro-intestinal symptoms. How do the authors administer potassium nitrate and in what medium or vehicle? Do they consider that there are specific indications which would lead them to use potassium nitrate in a case instead of the other acid salts with which the profession is more familiar?

DR. MELVIN W. BINGER, Rochester, Minn.: Dr. Greene has asked a difficult question regarding the point of action of potassium salts. I feel that there is certain displacement of sodium in the blood and in the tissues by potassium, but I do not feel that this is the total action of potassium as a diuretic. The red blood cells contain a larger percentage of potassium than the plasma. The plasma contains more sodium, and it is not known whether there is a shift in this balance in the administration of potassium salts. I rather feel that there is some shift in electrolytic ionization, although there may be a direct action on the kidney itself. Regarding the administration of potassium nitrate, we are using enteric-coated pills of 0.5 Gm., and we

give from sixteen to twenty-four of these daily. Potassium nitrate can be given in a 12 per cent solution, two tablespoonfuls three or four times a day, but it does upset the stomach and, if given on an empty stomach in a 12 or 25 per cent solution, it will cause irritation. In fact, the morning that I took 12.5 Gm. (25 per cent solution) I developed severe abdominal cramps, which lasted about half an hour. Of course, it was on an empty stomach and double the concentration that is usually given. We advise patients to take potassium nitrate after their meals. They are put on a salt-free, low-fluid (from 800 to 1,000 cc.) diet and usually 50 Gm. of protein daily unless the serum protein is low, as in the nephrosis type of case. In such cases the protein intake is increased to 75 or 100 Gm. daily.

PRIMARY ESOPHAGEAL CARCINOMA, WITH ESPECIAL REFERENCE TO A NONSTENOSING VARIETY

A CLINICOPATHOLOGIC STUDY BASED ON ONE HUNDRED AND EIGHT NECROPSIES

ROBERT W. MATHEWS, M.D.
AND
TRUMAN G. SCHNABEL, M.D.
PHILADELPHIA

Recently, within a comparatively short period, autopsies revealed esophageal carcinoma in four patients who had not presented dysphagia, pain, regurgitation of food and vomiting, the characteristic symptoms. In the absence of the usual clinical picture presented by the disease, their physicians had not appreciated the presence of a new growth in the esophagus; they found some consolation for their failure in diagnosis, however, in the fact that the postmortem examination presented carcinomatous lesions which were nonstenosing and therefore did not obstruct the passage of food.

The evidence in these four cases prompted the undertaking of a clinicopathologic analysis of the Philadelphia General Hospital series of patients from 1920 to 1933. It was hoped that such a study might point the way to certain conclusions concerning the incidence of nonobstructive carcinomatous lesions in the esophagus, that distinguishing clinical evidences might be brought to light, that the relative degree of clinical and pathologic malignancy of stenosing and nonstenosing tumors might be illuminated, and that perhaps other important changes concerning both the obstructive and the nonobstructive variety might be revealed.

MATERIAL

During the thirteen year period approximately 260,000 patients were admitted to this institution. Of this number, 247 had carcinoma of the esophagus, making an admission rate of slightly less than 0.1 per cent. Two hundred and twenty-six of this group died in the hospital and the remainder died after being discharged. One hundred and eight came to autopsy; of this number twenty-two, or 20.3 per cent, exhibited a nonstenosing variety of lesion, and in eighty-six the lesion was certainly obstructive. The results of the clinicopathologic study of these autopsies are presented herewith.

SEX

The general admission records of this hospital show that 56 per cent are females. The general autopsy record shows that 40 per cent are females. In this especial group of 247 patients presenting esophageal carcinoma, including both the 108 cases that came to autopsy and the 139 cases in which an autopsy was not done, 7.3 per cent were women. Among the number with obstructive tumors 5.8 per cent were women, and among the number with the nonobstructive variety of the disease 13.6 per cent were women.

AGE AND RACE

A majority of the patients were between 50 and 70 years of age. Among those with stenosing carcinoma 67 per cent were within this age range, and among those with the nonstenosing form 68 per cent were within the same range. In the first group the youngest patient was 42 and the oldest 85, while in the latter group the youngest was 35 and the oldest was 91.

There were eighty-four white (77.7 per cent), twenty-two Negro (20.3 per cent), and two Chinese (1.9 per cent) patients in the autopsy series of 108. Both the admission and the autopsy records show that 33.3 per cent were Negroes. In the entire series of 247, the percentage of Negroes was 11.5.

HISTORICAL DATA

The historical data obtained from these patients were much alike as to both the obstructive and the nonobstructive type. In the combined group the history of five patients showed familial cancer, and in the history of two patients there was a vague suggestion of it. The father of one patient had died of carcinoma of the esophagus. The histories as to previous illnesses, occupations and habits of life were so varied that they did not warrant definite conclusions. The fact that the group history was singularly free from evidence of alcoholism may be the more in point because the patients represented, generally speaking, a low economic and cultural level. It has been suggested, indeed, that hardship may be a predisposing factor in the development of cancer of the esophagus. Five of the autopsy group had positive Wassermann reactions and a few had pulmonary tuberculosis.

TABLE 1.—*Incidence*

Sex	Stenosing	Nonstenosing
Males	81	19
Females	5	3

TABLE 2.—*Metastases*

	Stenosing	Nonstenosing
Number of cases	86	22
Regional nodes	59	21
Abdominal nodes	34	10
Lungs	16	4
Liver	21	9

PATHOLOGIC CHANGES

The three gross anatomic types of esophageal carcinoma found at postmortem examination were:

First, a large fungating carcinoma which protruded into the lumen, producing obstruction with dilatation proximal to the new growth. This type was responsible for the well known clinical syndrome of obstruction.

Second, an annular type, often partially or completely surrounding the lumen of the esophagus, extending out-

From the Departments of Medicine, Radiology and Pathology, Philadelphia General Hospital.
Read before the Section on Gastro-Enterology and Proctology at the Eighty-Sixth Annual Session of the American Medical Association, Atlantic City, N. J., June 14, 1935.