BLADDER STONES -- THE PREVENTATIVE VALUE OF DRIED FRUITS

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Among the many troubles that afflict mankind, especially the male sex, is the formation of stones in the urinary tract. Chemically speaking, these stones are usually calcium phosphate or calcium oxalate and sometimes both kinds are present. These stones may be in the kidneys, the ureters which conduct urine from the kidneys to the bladder, and finally in the bladder. The stones may vary in size from small ones, which may be harmlessly eliminated in the urine without producing symptoms, to larger sizes which cause intense pain and hemorrhage during passage into the bladder. Again, the stones may be large enough to block the ureters and result in serious kidney damage unless removed by surgical intervention. Stones which successfully enter the bladder may grow in size until they cannot be eliminated, but remain to produce irritation. If not removed from the bladder, the irritant action of the stones over long periods of time may result in tumors as demonstrated in experimental animals and observed by us and others in male rats fed high dietary levels of either ethylene glycol or diethylene glycol. Figure I shows a calcium oxalate stone removed from the bladder of a rat fed diethylene glycol.

Interest of the dried fruit industry in this subject is two-fold. First, will the formation of calcium oxalate stones resulting from high dietary levels of ethylene or diethylene glycol result in the Federal Food and Drug Administration's disapproval of the use of ethylene oxide as a sterilizing agent for high-moisture dried fruit? Second, are there any natural constituents in dried fruits potentially capable of counteracting calcium oxalate stone formation from these glycols?

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The industry has been using ethylene oxide as one of the agents for sterilizing high-moisture dried fruits. Part of the ethylene oxide reacts with water in the fruit to produce ethylene and diethylene glycols. These two glycols are of concern to the Federal Food and Drug Administration because at high dosage levels they are not completely burned to carbon dioxide in the animal body, but give rise to oxalic acid which is excreted by way of the urinary tract as calcium oxalate. Doubtless there are segments of the dried fruit industry that would like to continue or revert to the use of ethylene oxide as a sterilizing agent. To do so depends upon a favorable decision by the Federal Food and Drug Administration authorities who are conditioned adversely at the present time due to an unfortunate incident in 1937.

In 1937 many people died as the result of taking elixir of sulfanilamide for treatment of infections. Death was due largely to uremia resulting from blockage of the urinary tract due to crystals of the acetylated sulfa drug and calcium oxalate resulting from the metabolism of diethylene glycol used as a solvent in the elixir. This unfortunate incident resulted in the first major amendment to the Federal Food and Drug Act in 1938. It should be emphasized that these deaths were due to acute toxicity resulting from the ingestion of rather massive doses of the elixir. In contrast, the eating of high-moisture dried fruits treated with ethylene oxide permits the periodic ingestion of only a few parts per million of ethylene and diethylene glycols. The situation is obviously quite different than in the elixir of sulfanilamide incident. Moreover, dried fruit contains three natural constituents which offer potential protection against oxaluria, the name given to abnormal amounts of oxalate in the urine. These constituents are magnesium, vitamin B_6 (pyridoxine), and benzoic acid. The remainder of this discussion will concern the mechanisms by which these natural constituents may protect against oxaluria, and will present experimental evidence suggesting a protective action of dried fruits.

Ethylene and diethylene glycols are not the only substances giving rise to oxalic acid. Glycerine, present in all fats, and the amino acids serine, and glycine (an important constituent of gelatine) also give rise to oxalic acid. We are, therefore, concerned with the pool, or the sum total of substances in the daily diet, that contributes to the formation of oxalic acid. Prunes rank second to cranberries in their content of benzoic acid. Benzoic acid is detoxified in the animal body by combining with glycine to form a compound known as hippuric acid which is excreted in the urine. The benzoic acid of prunes is, therefore, capable of removing at least part of the glycine from the pool that can contribute to oxalate formation.

Time does not permit a discussion of all the literature concerning the relationship of magnesium and vitamin B_6 to oxalate formation. Suffice it to say that a deficiency of either one or both of these substances enhances oxalate formation. The complete metabolism of the glycols, glycerine, and the amino acids serine and glycine is dependent upon the action of a number of enzymes which require the presence of magnesium or vitamin B_6.

Values have not been found for the vitamin B_6 content of all the dried fruits. Unpublished data obtained in research sponsored by the California Raisin Advisory Board give a value of 0.23 milligram of vitamin B_6 per 100 grams of raisins on a 17.0% moisture basis. One report on prunes gives a value of 0.27 and another a value of 0.87 milligram per 100 grams of prunes with 24% moisture.

Analysis of 13 samples of natural Thompson seedless raisins (dry weight basis) gave an average magnesium content of 80 milligram per 100-gram sample, and the average value of 8 samples of golden bleached Thompson seedless raisins was 72 milligrams per 100-gram sample. Reports in the literature for the magnesium content of other dried fruits are as follows:

Prunes	(24% moisture)	55 mg./100 g.
"	(raw, dried)	83 "
Dates	(raw, dried)	63.8 "
Figs	(raw, dried)	91.5 "

Do these potentially protective constituents in dried fruits provide any protective action against calcium oxalate stone formation? During the course of the two-year feeding tests of diethylene glycol to rats and dogs, the following experiment was performed by Dr. M. Alice Brown.

Albino male rats (the more susceptible sex), 6 to 12 months old, were placed on five different diets for periods ranging from 40 to 65 days. They were fed the diets ad libitum. At the end of the experimental period they were sacrificed and their urinary tracts examined under a dissecting microscope. The diets had the following compositions:

1. An adequate basal diet plus 1% ethylene glycol by weight.
2. An adequate basal diet plus 0.5% ethylene glycol by weight.
3. Equal weights of basal diet and dried fruit which had been ground with ethylene glycol, 2% by weight.
4. Equal weights of basal diet and dried fruit which had been ground with ethylene glycol, 1% by weight.
5. Basal diet plus 1% ethylene glycol as a magnesium salt-glycol compound.

The dried fruit in diets 3 and 4 consisted of 73% prunes, 9% figs, and 18% dates, representing the relative United States consumption of these fruits. The magnesium acetate-glycol compound used in the fifth diet was prepared in the laboratory. It was chromatographically pure and upon analysis showed one molecule of ethylene glycol (36% by weight of the compound) for each magnesium acetate molecule.

At the end of 40 days the rats fed the basal diet plus 1% ethylene glycol were sacrificed because of their obviously poor condition. Examination showed that all these rats had swollen, yellow, spongy looking kidneys with deposits of calcium oxalate and in some instances stones in kidney pelvis, ureters, and bladder. The incidence of these findings was appreciably less in rats receiving 50% dried fruit and a total dietary level of 1% ethylene glycol. The incidence was still less in rats receiving the same amount of glycol as the magnesium salt-glycol compound. Rats fed 50% dried fruit and a total dietary level of 0.5% ethylene glycol were almost completely protected against the damaging effects of the glycol. This protection was consistent with the marked difference in urinary oxalate values, which were 1.37 mg. per 100-gram of rat in 24 hrs. on a diet containing 0.5% glycol as compared with 0.17 mg. per 100 grams of rat in 24 hrs. on a diet containing the same amount of glycol and 50% dried fruit. These data are summarized in Tables I and II.

While the data are interesting and suggest a protective action of dried fruit against formation of calcium oxalate stones, we should take a realistic look at the facts. The protective action of dried fruit was demonstrated with a dietary level of 50%. No one is going to eat that much dried fruit daily. We should have information on the smallest amount of dried fruit that will protect against an amount of glycol that produces a small incidence of bladder stones rather than a 100% incidence of stones. This might indicate a more reasonable level of dried fruit consumption. The exact mechanisms by which vitamin B_6 and magnesium prevent oxaluria are not settled, and should be investigated. Are there other factors in dried fruit playing a role in the protective action? Even if the industry stops using ethylene oxide it may be desirable to sponsor research on the protective value of dried fruit against other causes of oxaluria and stone formation in the urinary tract.

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TABLE 1

Feeding of 1% Ethylene Glycol (EG) to Male Rats -- (40 days on diet)

Diet	Deaths	"Spongy" kidneys	Kidney stones	Ureteral stones	Bladder stones
1% EG in basal	2/22	22/22	22/22	2/22	4/22
1% EG in dried fruit diet	0/15	10/15	5/15	3/15	2/15
1% EG as MgACEG in basal	0/15	5/15	2/15	1/15	1/15

TABLE II

Feeding of 0.5% Ethylene Glycol (EG) to Male Rats

Diet	Days on Diet	Deaths	"Spongy" kidneys	Kidney stones	Ureteral stones	Bladder stones	Urinary oxalate
0.5% EG in basal	40	0/15	15/15	4/15	4/15	5/15	
0.5% EG in dried fruit diet	40	0/15	0/15	0/15	0/15	1/15	
0.5% EG in basal	65	1/12	12/12	6/12	1/12	3/12	1.37
0.5% EG in dried fruit diet	65	0/12	0/12	1/12	0/12	2/12	0.17