THE METABOLISM OF AZELAIC ACID*

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The evidence concerning the utilization of dibasic fatty acids in the animal organism has been reviewed by Dakin (3) and more recently by Flaschenträger (4). Oxalic acid is burned to a limited extent, and in large amounts is toxic. Malonic and succinic acids are utilized, and glutaric acid is completely oxidized in the dog (3), but is nephrotoxic to the rabbit, while the higher acids affect the rabbit kidney only slightly (7). Adipic acid is recovered in the urine of rabbits (5), dogs (4), and men (4) to the extent of 50 to 60 per cent of that injected or ingested. Flaschenträger recovered 30 per cent of adipic, 60 per cent of suberic, and 61 per cent of sebacic acid from the urine of injected dogs. Baer and Blum (2) recovered from the urine of phlorhizinized dogs after injection of the acids: adipic, 12 per cent, pimelic, 47 per cent, suberic, 62 per cent, azelaic, 50 per cent, and sebacic, 45 and 13.6 per cent. The information concerning azelaic acid consists of the one experiment of Baer and Blum.

In the naturally occurring unsaturated fatty acids the double bond nearest the carboxyl group is, with rare exceptions, in the 9:10 position. Oxidation of these acids with potassium permanganate yields, among other products, azelaic acid. If oxidation in vivo in any way parallels that in vitro, azelaic acid should be formed in the body. The experiments described below demonstrate that approximately half the amount of azelaic acid fed to dogs can be recovered unchanged in the urine. The accumulat-
Metabolism of Azelaic Acid

ing evidence thus seems to indicate that the metabolic oxidation of fatty acids proceeds in a manner independent of the presence or position of a double bond (6).

**EXPERIMENTAL**

Two dogs, weighing approximately 25 kilos each, were fed daily 450 gm. of chopped lean beef, 120 gm. of sucrose, and 10 gm. of bone ash. They remained in excellent health throughout the experiments. During each of a number of 6 day experimental periods azelaic acid was fed in amounts of 20 to 45 gm. Control periods were variously interspersed. Weighed quantities of the acid were dissolved in 10 per cent sodium carbonate and thoroughly mixed with the food. Any food uneaten on a given day was preserved and added to the next day's ration. Urine collection was continued for 36 hours beyond the 6 day period. The urine was kept cold and saturated with chloroform. The feces were marked with charcoal and preserved in 95 per cent alcohol.

The azelaic acid was prepared by the oxidation of oleic acid (1). In the later experiments an Eastman product was used. It was recovered from the urine by the following procedure. The urine was acidified with sulfuric acid and thoroughly extracted with ether. In case a permanent emulsion formed, the urine was evaporated to a small volume, acidified with sulfuric acid, mixed with plaster of Paris to form a dry powder, and extracted with hot alcohol. The alcohol was distilled off in a partial vacuum and the residue extracted with ether. The ether extracts were combined, concentrated to a small volume by distillation, the last traces of ether removed by heating on the steam bath, and the residues completely extracted with 100 cc. portions of petroleum ether in which azelaic acid is practically insoluble. This treatment removed the lipid material which had followed the azelaic acid in the ether extractions. The petroleum ether-insoluble residue was then treated by methods outlined below in order to obtain purified azelaic acid.

The feces were treated with 500 cc. of 20 per cent sodium hydroxide, heated for 24 hours on a steam bath, acidified with 50 per cent sulfuric acid, and filtered hot. Both residue and filtrate were extracted with ether. The ether extracts were combined and treated like those of the urine. Since the average weights of
the petroleum ether-insoluble fractions were fairly uniform in the control and in the azelaic acid periods (Table I), it was assumed that the feces contained no azelaic acid and the material was discarded.

The petroleum ether-insoluble material from the urines containing azelaic acid was dissolved in ether, decolorized with animal charcoal, the ether distilled off, and the residues dried on the steam bath. They varied considerably in physical properties, some of the fractions being black and tarry and others consisting of a slightly colored solid, occasionally having a definite melting point. In a few cases, azelaic acid separated in almost pure form from the ether solution. Attempts were made to purify the material by crystallization from solvents but efforts in this direction met with little success. The most successful method for the preparation of

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Control experiments</th>
<th>Azelaic acid experiments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of experiments</td>
<td>Weight (gm.)</td>
</tr>
<tr>
<td>A-7</td>
<td>6</td>
<td>2.9</td>
</tr>
<tr>
<td>23-6</td>
<td>4</td>
<td>3.1</td>
</tr>
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</table>

the pure acid was through its copper salt. A weighed amount of the material was dissolved in concentrated ammonium hydroxide, the excess ammonia was driven off by boiling, and the azelaic acid precipitated from the almost neutral solution by the addition of an excess of 20 per cent copper sulfate. Analyses for copper indicated that the precipitate probably consisted of a mixture of the neutral and acid copper azelates. The copper salt was filtered off, washed thoroughly, suspended in water, and decomposed with hydrogen sulfide while being heated on the steam bath. The mixture was filtered hot. Azelaic acid separated from the concentrated solution in pure form. In four experiments in which pure azelaic acid was used an average of 94 per cent was recovered. The purification of the material extracted from the urine in the various experiments outlined in Table II was ac-

TABLE I

Average Weight of Ether-Soluble, Petroleum Ether-Insoluble Extract of Feces of Dogs with and without Addition of Azelaic Acid to Diet
Metabolism of Azelaic Acid

accomplished by several procedures, or combinations of different procedures. The calculation of the per cent recovery of ingested azelaic acid was based on the weight of purified azelaic acid recovered. Although the melting point of this acid in each case was not absolutely correct, as a rule it varied only a degree or so from the correct value (107°), and when mixed with pure azelaic acid, the depression in melting point was never greater than a degree.

**TABLE II**

*Excretion of Ingested Azelaic Acid in Urine of Dogs*

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Azelaic acid</th>
<th>Excreted</th>
<th>Recovered</th>
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<td>A*</td>
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<td></td>
<td></td>
<td>gm.</td>
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<td>23-6</td>
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<td>18.9</td>
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Average...……………………………………………………………………………….57.9

Each entry represents a 6 day period. In six control experiments on Dog A-7 and four on Dog 23-6 the average weight of the ether-soluble, petroleum ether-insoluble fractions was 2.2 gm. No azelaic acid could be isolated.

* Ether-soluble, petroleum ether insoluble fraction.
† Purified azelaic acid.
Azelaic acid, a dibasic acid formed by in vitro oxidation of the majority of naturally occurring unsaturated fatty acids, was fed to dogs in amounts smaller than would be produced normally in the body if oxidation took place at the unsaturated linkages. It was found to be but little utilized by the animals; an average of 60 per cent of the ingested acid was recovered from the urine. The acid was not excreted in the feces.

BIBLIOGRAPHY

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