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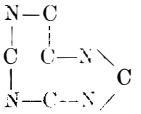
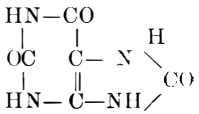
Within a few years our knowledge of the formation and destruction of uric acid in the body has been much broadened. For a long time after its isolation its origin, significance, place of formation and the agents active in its production and decomposition were unknown. In these respects the facts differ much in the cases of birds and mammals and only the cases of mammals will be here considered.

At the present time it is the belief of physiologists that uric acid is largely formed in the liver through the action of ferments upon the nucleins. A synthetic formation of uric acid in the body may take place, but convincing proof of this is wanting. The nucleins which furnish much of the material for uric acid belong to the conjugate proteins. They contain 5 per cent or more of phosphorus and, in addition to a simple protein, the purin ring,



found likewise in uric acid,



The relationship of the purin bodies to uric acid may be seen from the following:

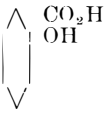
$C_5H_4N_4$	Purin
$C_5H_3N_4NH_2$	Amino-purin (Adenin)
$C_5H_3N_4NH_2O$	Amino-oxypurin (Guanin)
$C_5H_4N_4O$	Oxypurin (Hypoxanthin)
$C_5H_4N_4O_2$	Dioxypurin (Xanthin)
$C_5H_4N_4O_3$	Trioxypurin (Uric Acid)

From the liver have been extracted ferments which will destroy nucleins and will oxidize hypoxanthin and xanthin to uric acid. The uric acid thus formed is referred to as of two varieties, the endogenous—that derived from the nucleins of the tissues—and the exogenous—that coming directly from the nucleins of the foods. Of the uric acid which is produced in this manner a considerable part, varying in different animals, appears to be destroyed before elimination, so that the uric acid found in the urine represents merely the difference between the amounts produced and destroyed. This decomposition appears to be, at least in part, due to a ferment, the uricolytic.

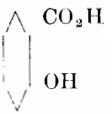
This paper may be regarded as a report on some uncompleted work which is being carried on in our laboratory. Its purpose it to throw more light upon

the nature of these ferments and the conditions which may modify their action in the human body. In order to simplify the problem the exogenous uric acid was excluded by limiting the subjects to a purin-free diet. This consisted of the wheat foods, milk, eggs, cheese, butter, with no potatoes or very little. The kinds and amounts were practically the same each day of the experiment. As has been found by a number of investigators the endogenous uric acid of the same individual, although there may be variations from day to day, has a remarkably constant average amount. Hence on such a diet as the above the effect of changing the other conditions can be readily seen. The experiments here described were made in the attempt to learn of the modification of the action of the uricolytic and uric acid forming ferments from the administration of drugs.

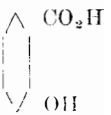
As is well known, salicylic acid (ortho-hydroxy-benzoic acid),



markedly increases the output of uric acid in the urine, where it makes up about nine-tenths of the total purins. Not only the free acid, but also its salts and some other derivatives like aspirin (the acetic acid ester of salicylic acid) do this. Among the drugs used were the isomers of salicylic acid, meta-hydroxy-benzoic acid,



and para-hydroxy-benzoic acid,



The endogenous uric acid was determined for a drug-free period, usually of several days, then the amount eliminated during the administration of the drug and also in an after period when no drug was taken. The uric acid was determined by Folin's method, as was the creatinin; nitrogen by Kjeldahl's method and phosphoric acid by titration with uranium acetate. The results are shown below:

TABLE I.

Subject A.

Date	Conditions	Volume, cc.	Creatinin, grm.	P_2O_5, grm.	Nitrogen, grms.	Uric acid, grm.
May 23	Endogenous					0.388
24	Endogenous					0.289
	Average, endogenous					0.328
25	1.7 grms. aspirin					0.328
26	3.7 grms. aspirin	980	1.04	2.42	10.12	0.601
27	2.0 grms. aspirin	950	1.07	2.33	10.12	0.481
28	2.0 grms. aspirin	980		2.48	10.41	0.446
29	2.3 grms. aspirin	1085	1.14	2.50	12.03	0.413
30	2.6 grms. aspirin	1580	1.23	2.84	12.92	0.465
31	2.6 grms. aspirin	780	1.01	2.30	8.62	0.414
June 1	3.3 grms. aspirin	730	1.17	2.28	10.89	0.341
2	4.0 grms. aspirin	1480	1.09	2.10	11.75	0.411
3	1.3 grms. aspirin	800	1.09	2.40	10.89	0.360
4	2.6 grms. aspirin	950	1.07	2.26	10.96	0.366
5	3.7 grms. aspirin	1116	1.03	2.55	11.67	0.458
	Average, aspirin period		1.07	2.41	10.22	0.424
6	Endogenous	1025	1.06	2.60	10.57	0.096
7	Endogenous	1130	1.13	2.74	9.24	0.278
8	Endogenous	1130				0.268
	Average, endogenous		1.10	2.67	9.91	0.214

From Table I can be seen the response of the organism to the administration of salicylic acid. Folin has shown that the creatinin can be taken as a measure of the bodily metabolism. If we note the amount of creatinin and total nitrogen eliminated we find that the general metabolism was very little affected; whereas in general the uric acid increases with the drug. Since there was no increase in the phosphorus output the indication is that the increased elimination was due to an inhibition of the uricolytic or destructive ferment rather than to an increased destruction of the nucleins through a stimulation of the oxidizing ferment. The great decrease in eliminated uric acid in the after period with no corresponding change in the other protein decomposition products has been observed in other experiments. Possibly the uricolytic ferment becomes under these circumstances more than ordinarily active, although some more satisfactory explanation may be found.

TABLE II.

Subject B.

Date	Conditions	Volume, cc.	P_2O_5, grm.	Creatinin grm.	Nitrogen, grms.	Uric acid, grm.
Feb. 13	Endogenous	1350	1.90	1.62	11.07	0.361
14	Endogenous	1100	2.35	2.08	12.90	0.424
15	Endogenous	1025	2.13	2.20	11.32	0.434
17	Endogenous	1030	2.00	1.78	10.09	0.436
18	Endogenous	1250	1.89	1.56	9.36	0.413
	Average, endogenous period		2.05	1.85	10.95	0.415
19	33 grms. para-hydroxy-benzoic acid	950	1.58	1.97	9.59	0.446
20	Endogenous	1070	2.80	1.68	10.70	0.503
23	Endogenous	1175	2.44	1.83	11.26	0.478
24	Endogenous	850	1.43	1.84		0.417
	Average endogenous		2.22	1.78	10.98	0.467
25	1 grm meta-hydroxy-benzoic acid	1075	1.75	1.90	9.70	0.310
26	3 grms. meta-hydroxp-benzoic acid	1150	1.80	1.58		0.380
27	9 grms. meta-hydroxy-benzoic acid	2200	2.20	1.85	11.96	0.396
	Average meta-hydroxy-benzoic acid		1.98	1.78	10.83	0.362
28	Endogenous	1180	2.18	1.67	10.30	0.376
29	Endogenous	700				0.357
	Average endogenous					0.367
Mar. 1	4 grms. sodium salicylate	1250				0.588

A comparison of the results from Subject B shows that the para and meta compounds cause no apparent increase in nuclein cleavage; the oxidizing ferment does not appear to be stimulated. At least if it is there is a corresponding decomposition of the uric acid. That this is improbable is proved by there being no marked variation of the phosphorus; that the subject was susceptible to the ortho compound is seen from the action of the salicylate. Similar results were obtained from the use of the meta-hydroxy-benzoic acid with Subject A.

TABLE III.

Subject C.

Date	Conditions	Volume, cc.	P_2O_5, grm.	Nitrogen, grms.	Uric acid, grm
Jan. 14	Endogenous	725		9.43	0.419
15	Endogenous	720	1.94	10.25	0.448
16	Endogenous	680	2.09	9.72	0.453
17	Endogenous	755	1.73	9.70	0.496
	Average endogenous		1.92	9.70	0.454
18	0.7 grm. para-hydroxy-benzoic acid	855	1.50	9.63	0.139
19	2.0 grm. para-hydroxy-benzoic acid	810	2.20	9.09	0.439
20	3.0 grm. para-hydroxy-benzoic acid	1020	1.77	9.11	0.340
	Average para-hydroxy-benzoic acid		1.82	9.28	0.306
21	Endogenous	775	1.74	10.29	0.439
22	Endogenous	900	1.37	10.34	0.398
23	Endogenous	810	1.75		0.356
24	Endogenous	905	1.99	10.61	0.432
	Average endogenous		1.71	10.41	0.406
26	2 grms. sodium salicylate	805	1.95	11.26	0.534
27	3 grms. sodium salicylate	805	1.74	10.39	0.586

Again with Subject C susceptibility to salicylic acid is evident while the para compound actually decreases the urinary uric acid. A possible explanation is the decreased nuclein cleavage, but in view of there being no such drop in the total nitrogen nor in the uric acid eliminated under similar conditions by Subject B, also of the danger of drawing too positive conclusions from a single experiment in physiological chemistry, final decision should be postponed. The experiments seem to clearly indicate that neither of the hydroxy-benzoic acids affect nitrogen metabolism except in the case of uric acid. Furthermore, when the side chains are in the ortho position the uric acid is increased in the urine; when in the meta or para positions this is not true. If Emil Fischer's hypothesis be correct that in order to produce decomposition a ferment must have a configuration corresponding to that of the compound which it changes, we can apply it here to explain the different effects of these three isomeric substances; otherwise we must await the discovery of additional facts to devise a more rational theory.