effect of acetylcholine when used in low concentrations. They increased the effect of acetylcholine when present in higher concentrations. 4. Nucleic acid, alloxan, urea, thiourea, and piperidine decreased the effect of acetylcholine when used in higher concentrations. 5. Adenosine, adenine, guanine, xanthine, adenylic acid, uric acid, methylxanthines, uracil, thiouracil, pyridine, 2-methyl-5-ethoxymethyl-6-amino pyrimidine, 4-methyl-5-β-hydroxyethyl thiazole, thiourea, urea, methylguanidine, and pyrol increased the effect of potassium in inducing muscle contraction. 6. Nucleic acid, alloxan, and piperidine decreased the effect of potassium in inducing muscle contraction.

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Effect of Alloxan on Carbohydrate and Uric Acid Metabolism of the Pigeon.*

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Alloxan in a dose of 150 to 200 mg per kg injected intravenously into a pigeon causes an elevation of the blood sugar from the normal level of about 150 mg% to values between 300 and 400 mg% within 24 to 48 hours. One day after the injection the animals appear very sick; they are weak and drowsy, sit with their eyes closed, make no attempt to move or fly and usually die in this stupor within 2 or 3 days. Smaller doses of alloxan (60-125 mg per kg) may cause a similar syndrome except that the blood sugar may remain within the normal range. A disturbed carbohydrate metabolism can therefore not be the only cause of this condition.

At autopsy such pigeons present a very unusual picture. All serous membranes, especially the pericardium, the pleura, and the surface of the liver are covered with a thin whitish layer which at first glance may look very much like fibrin as seen in polyserositis. This material, however, can easily be removed from the membranes, and identified chemically and microscopically as sodium urate. In one instance 8 mg of sodium urate were collected from the pericardium and the liver surface alone.

Histological examination of the kidneys reveals massive infiltration with sodium urate which is deposited mainly in the greatly dilated tubules, but also in the interstitial tissue. Smaller collections of crystals are found on the serosal surfaces and occasionally in the parenchyma of the liver. Evaluation of the changes in the pancreatic islets is very difficult because even the normal pigeon pancreas may contain extremely few beta cells. However, in some cases which showed hyperglycemia no beta cells could be found at all, or the occasional cells found looked profoundly degranulated. In other cases the islets were normal.

In view of these findings, it seemed of importance to study the effect of alloxan on the uric acid metabolism of pigeons. A series of more than 30 pigeons was injected with various doses of alloxan, and the blood uric acid level was determined before and at intervals after the injection. Folin's[1] method for the estimation of uric acid was used. Blood samples were taken from the wing vein. The normal blood uric acid content of our pigeons

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[1] Folin, O., *J. Biol. Chem.*, 1933, **101**, 111.

TABLE I.

Alloxan mg/kg	Before	Blood uric acid mg per 100 cc Hr after injection 6	24	48	72	96
60	5.2	11.0	40	18.3	10.5	8
75	7	34	135	died	—	—
75	6	8	28.3	14.3	8.5	10.0
75	5.4	9.3	9.3	8	6.5	6.0
75	4.3	8	35.5	11	8	5.1
125	4.2	9.2	90	weak	killed	—

ranged between 4 and 8 mg%. About one-third of the birds maintained a normal blood uric acid level after the injection of alloxan, and exhibited none of the symptoms described in the others, however, symptoms developed and the uric acid content of the blood increased markedly, reaching its peak about 24 hours after injection. The birds usually died within 48 hours if blood levels higher than 60 mg% were reached; if the peak was lower, they recovered slowly from their weakness and drowsiness and appeared normal from the third or fourth day on. At the same time the blood uric acid level returned to normal. Table I illustrates the course of the blood uric acid level in 6 pigeons over a period of 4 days.

The serous membranes of pigeons which had survived the alloxan injection and whose blood uric acid levels had returned to normal showed only very slight deposits of sodium urate or none at all. The kidney parenchyma appeared normal. An infiltration with uric acid, if it had occurred, must have been transitory and the sodium urate was excreted. The 24-hour excretions of 10 pigeons, which during the experiment had been placed in individual metabolism cages, were analyzed for their pyrimidine content. Though these estimates were rather crude, the increase in blood uric acid was apparently accompanied and followed for a few days by an increased excretion of pyrimidine compounds. Some of the birds which had apparently recovered later became weak again, and died after 2 or 3 weeks in a state of emaciation, the most striking autoptic finding being a marked muscular atrophy, especially in the breast muscles. Microscopically, there were severe degenerative changes, ranging from waxy homogenization and vacuolation to complete breakdown and disappearance of the fibers. Sarcolemma nuclei were very numerous and in addition there were small lymphocytic infiltrates scattered throughout the interstitial tissue.

After our first observations were made, we learned that a similar syndrome has been produced in fowls by feeding large amounts of protein; it is known to the zoologist as "visceral gout."[2] The protein fraction responsible for the condition seems not to have been determined.

Among the compounds related to alloxan, barbituric acid, uracil, and violuric acid did not change the blood uric acid level, but dialuric acid, the reduction product of alloxan, proved to be just as effective as alloxan on the uric acid metabolism of the pigeon. This is surprising since it does not have an alloxan-like effect on the islet cells. The components of dialuric acid, urea and tartronic acid, injected separately, were both ineffective.

Summary. Alloxan, injected into pigeons in a single dose of 60 to 125 mg/kg (less than one-half of the diabetogenic dose) sometimes causes a marked elevation of the blood uric acid level and a deposition of sodium urate in the tissues. A conspicuous atrophy of the musculature is observed as a late effect in pigeons which recover from the acute stage of alloxan poisoning. Among several compounds, related to alloxan, only dialuric acid was found to possess a similar effect.

[2] Kionka, K., *Arch. f. exp. Path.*, 1900, **44**, 186.