supplied with water are preferred by many people to homes in more humid areas. (v) It has not yet been clearly established whether the building of Echo Park Dam would be an "invasion" of the national park system, or whether the extension of Dinosaur National Monument to cover Echo Park was an "invasion" of the reclamation program. (vi) The Colorado Basin is so rich in undeveloped scenic resources that the Echo Park region must be regarded as a relatively small part of the total recreational capacity.

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12 September 1955

6-Aminonicotinamide—a Potent Nicotinamide Antagonist

During the course of investigations on the inhibition of sulfonamide acetylation, it was observed that 6-aminonicotinamide was extremely toxic to rabbits (*1*). The delayed effect of the compound, the first sign of which was loss of control of the hind legs (*2*), suggested that 6-aminonicotinamide might be an antimetabolite of nicotinamide. This was confirmed by experiments in rats. In fact, it appears to be the most potent known antagonist of nicotinamide.

The median lethal dose (LD_{50}) of 6-aminonicotinamide (*3, 4*) for mice, shown in Table 1, is 35 mg/kg of body weight, as compared with 305 mg/kg for 3-acetylpyridine (*5*). Table 1 also shows that the simultaneous administration of 50 mg/kg of nicotinamide brings about an eightfold increase in the LD_{50} of 6-aminonicotinamide. Nictotinic acid, also, gives significant protection in contrast to its ineffectiveness against 3-acetylpyridine, when administered simultaneously with the latter (*2, 5*). Tryptophan appears to give some protection. The administration of 50 mg/kg of 6-aminonicotinamide resulted in 100-percent mortality within a week. When tryptophan was given simultaneously (50 mg/kg orally) with 6-aminonicotinamide, there were no deaths the first week, and 30 percent of the animals were alive at the end of 30 days.

On the assumption that 6-aminonicotinamide may give rise to an inactive DPN analog, it was of interest to compare the rate of oxygen uptake of tissues from treated animals with that of normal controls. The results of one experiment are shown in Table 2. In the absence of added substrate the oxygen uptake of mouse liver homogenate prepared from the treated animals was only 30 percent of the normal. Apparently the treated mice were depleted of both oxidizable substrate and DPN, since the addition of these substances *in vitro* greatly increased the rate of oxidation, while the addition of both together restored it almost to normal. The treated mice had received an intraperitoneal injection of 100 mg/kg of 6-aminonicotinamide and 25 mg/kg of nicotinic acid 72 hours prior to the experiment. No appreciable effect on oxygen uptake was observed when 50 mg/kg of 6-aminonicotinamide was used, or upon the addition of 6-aminonicotinamide *in vitro* to liver homogenate prepared from normal mice.

In view of the recent findings of Kaplan *et al.* (*5*) the toxicity of 6-aminonicotinamide may be due to the formation of an inactive DPN analog, with consequent depletion in certain tissues of DPN. It is of some interest that one of the pathological changes observed after an animal had received a toxic dose was involution of the spleen, a fact that may be related to the high rate of analog formation in this organ (*5*). Frequently, animals survived until 20 to 30 days after the administration of 6-aminonicotinamide. This may indicate, as is suggested by Zatman *et al.* (*6*), irreversibility of analog formation, with consequent inability of the tissues to rid themselves of the antimetabolite. These matters are at present under investigation in this laboratory. 6-Aminonicotinamide and its congeners are also being tested for their effect on neoplastic growths.

Table 1. Effect of nicotinamide and nicotinic acid on the median lethal dose (LD_{50}) of 6-aminonicotinamide in mice. Metabolite and 6-aminonicotinamide were administered simultaneously intraperitoneally. Mice: CF-70 strain, 18 to 22 g.

Metabolite	Dose (mg/kg)	6-Aminonicotinamide (LD_{50} mg/kg)	No. of mice	95-percent fiducial limits
None		35	30	33– 37
Nicotinamide	25	121	30	113–129
Nicotinamide	50	308	40	281–331
Nicotinic acid	25	75	70	64– 89

Table 2. Oxygen consumption of liver from 6-aminonicotinamide-treated mice

Substrate	Oxygen uptake (μlit)*			
	15-min incubation		30-min incubation	
	Control	6-aminonicotinamide treated	Control	6-aminonicotinamide treated
None	55	16.5	100	30
Lactate 0.015*M*	69	35	129	66
Lactate 0.015*M* + DPN 0.002*M*	105	116	206	183

* Average values of duplicate vessels. Each vessel contained homogenate equivalent to 100 mg of tissue (wet weight). Homogenates were prepared in 0.25*M* sucrose under closely identical conditions and were incubated at 37°C in modified Krebs-Ringer phosphate.

In addition, 6-aminonicotinamide and its congeners are also being tested for their effect on neoplastic growths.

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References and Notes

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30 June 1955

The great desideratum for any science is its reduction to the smallest number of dominating principles.—J. CLERK MAXWELL, *Matter and Motion.*