was due to destruction of protein bound iodine before protein precipitation was most unlikely as thyroxine derivatives are known to be stable in the blood and the procedure was performed within 30 minutes after collection of samples. In one experiment the blood was collected directly into trichloroacetic acid without altering the results. The possibility that the increase of radioactivity in the unprecipitated fraction was due to free thyroxine, triiodothyronine, or iodotyrosine was excluded since most of the radioactivity was located in the inorganic iodine zone on the radiopaperchromatogram of this unprecipitated fraction. The observation that 50 USP milliunits of TSH released both inorganic and protein bound iodine indicated that this release was not caused by unphysiological dose of TSH.

Whether the release of inorganic iodine is due to deiodination of some products by the increase in thyroglobulin proteolysis, or due to change of permeability of cell membrane is still to be determined.

This phenomenon may explain the slowing of iodide disappearance in the plasma which occurs shortly after TSH administration in man(9) and also the increased urinary output of iodine within 24 hours after injection of TSH in man(7,8).

Summary. Measurement of inorganic I^{131} and PBI^{131} in thyroid venous blood obtained by catheterization was performed in 17 dogs to study the early effect of TSH. Following a latent period of about 15 minutes, output of both inorganic I^{131} and PBI^{131} started to increase sharply. The increased output continued for about 10 hours, and thereafter the thyroid gland started to accumulate inorganic iodine. The inorganic I^{131} fraction, represented in the trichloroacetic acid supernatant fraction, was confirmed by radiopaperchromatography. TSH apparently releases inorganic iodine, in addition to PBI, from the thyroid in the early phase of its action.

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Potentiation of Lathyrogenic Effect of Beta Aminopropionitrile in Turkey Poults.* (25392)

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Cyanoacetic acid (CAA) has been isolated from urine of rats and rabbits as a final product of metabolism of beta-aminopropionitrile (BAPN)(1,2). It is assumed that this conversion of BAPN to CAA is possible under the influence of the enzyme monoamine oxidase (MO). It has been shown that 1-isonicotinyl-2-isopropyl hydrazine (IIH) or iproniazid inhibits monoamine oxidase activity of rat liver *in vitro*(3), and the mode of action of IIH on mitochondrial MO of mammalian liver has been investigated(4). The inhibitory ef-

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TABLE I. Relative Toxicity of Beta Aminopropionitrile (BAPN) and Cyanoacetic Acid (CAA) to Turkey Poults.

Supplements to basal diet	Avg wt, 5 wk, g	Avg leg score*	Mortality, %	Hemorrhage, % of original group	CAA in blood serum, mg/100 ml
None	704.2	5.0	20	0	0–1†
.026% BAPN fumarate	669.2	4.0	10	10	6.54
.053% " "	639.1	3.0	40	40	11.9
.024% CAA	749.5	5.0	20	0	11.3
.048% "	739.5	5.0	0	0	12.1
.12% "	751.9	5.0	10	0	29.7
.24% "	755.5	5.0	10	0	27.9

* Leg scores (avg of surviving birds): 1. Both legs severely bent; joints swollen. 2. One leg slightly, one severely bent; joints swollen. 3. Both legs slightly bent; joints swollen. 4. One leg normal; other slightly affected. 5. Normal.

† *cf.* ref.(7).

fect was also observed *in vivo*, as the monoamine oxidase activity of liver homogenates, liver mitochondria and brain mitochondria was inhibited almost completely in rats and guinea pigs after subcutaneous injection of IIH(5). The inhibitory activity of isonicotinic acid hydrazide (INAH) against MO was not as strong as that of IIH(3,5). INAH even at 10^{-3} molar concentration *in vitro* had slight or no effect on rat liver(3) and no apparent inhibitory activity *in vivo*(5). It was our purpose (1) to identify CAA as a metabolite in turkeys and measure its toxicity, (2) to study the effect of INAH and IIH when fed with and without BAPN fumarate, and (3) to determine whether non-toxic levels of n-propylamine would influence the toxicity of BAPN.

Methods. In all experiments day-old Broad Breasted Bronze turkey poults were used. They were kept in electrically heated, wire-floored batteries throughout the experiment. Each group contained 10 birds. The basal ration was a practical starting mash of composition given by Barnett, *et al.*(6). Feed and water were given *ad lib.* throughout the experiment. The birds were weighed at end of each week and any abnormalities found were recorded. Dead birds were examined for internal hemorrhage. Criteria of toxicity were depression of growth, mortality, thoracic or abdominal hemorrhage and leg deformity. The method for estimation of CAA in blood serum was that described by Sievert *et al.*(7). In experiments with n-propylamine, this compound was fed at predetermined levels from hatching to termination of experiment, and BAPN was fed from 2 weeks of age to end of experiment.

Results. The effects of feeding BAPN fumarate† and CAA are shown in Table I. CAA even at 0.24% of diet did not depress growth, increase mortality, or cause leg deformity or internal hemorrhage. BAPN fumarate at levels of 0.026% and 0.053% produced the usual toxic symptoms.

At termination of experiment, blood was taken by heart puncture and the blood sera analyzed for CAA content. Results have been presented elsewhere(7), but are included in Table I for comparison. Feeding of CAA produced blood serum levels more than twice as high as those produced by feeding BAPN, but the birds having these high blood levels showed no toxic symptoms.

Table II shows that isonicotinic acid hydrazide (INAH) alone caused depression of growth rate, but no hemorrhage and no leg deformity except at highest level. BAPN fumarate caused the usual toxic symptoms. The toxicity of BAPN was increased by INAH as evidenced by incidence of hemorrhage and the leg score of 1 in groups fed lowest level of BAPN in presence of the hydrazide.

Table III shows that 1-isonicotinyl-2-isopropyl hydrazine (IIH) increased toxicity of BAPN fumarate in the same manner as did INAH.

N-propylamine alone did not produce toxic symptoms, but caused some depression of

† BAPN fumarate (2 BAPN-1 fumaric acid) was generously supplied by Abbott Labs., and 1-isonicotinyl-2-isopropyl hydrazine phosphate by Hoffmann-LaRoche.

TABLE II. Potentiating Effect of Isonicotinic Acid Hydrazide (INAH) on Toxicity of BAPN in Turkey Poults.

BAPN fumarate, % of diet	INAH, % of diet	Avg wt, 4 wk, g	Mortality, %	Hemorrhage, % of original group	Avg leg score*
.0	.0	469.4	10	0	5.0
.02	.0	525.5	0	0	4.1
.04	.0	457.7	30	30	3.4
.08	.0	153.0	100	40	1.0
.0	.04	352.2	10	0	5.0
.02	.04	233.0	80	30	1.0
.04	.04		100	10	
.08	.04		"	0	
.0	.08	300.0	10	0	5.0
.02	.08	174.7	80	20	1.0
.04	.08		100	20	
.08	.08		"	0	
.0	.16	156.5	80	0	3.0
.02	.16	235.7	80	20	1.5
.04	.16		100	0	
.08	.16		"	0	

* *cf.* Table I.

growth rate, (Table IV, Exp. 23). When fed with BAPN, it increased mortality and incidence of hemorrhage and leg deformity. With n-propylamine, some birds that died did not show massive abdominal hemorrhages, but did have massive hemorrhages in the leg musculature. Incidence of each type of hemorrhage is given in Table IV.

Conversion of BAPN into CAA presumably occurs *in vivo* under the active influence of enzyme MO. It is suggested that when inhibitors like INAH or IIH are fed along with BAPN this conversion is inhibited and higher effective concentrations of BAPN result *in vivo*. This would account for the greater toxicity observed.

Similar effects of MO inhibitors on metabolism of several physiologically active amines have recently been reported(8,9,10). Such observations emphasize the importance of careful attention to possibly dangerous side effects of MO inhibiting drugs.

N-propylamine was fed prior to BAPN to stimulate MO formation. It was anticipated that animals conditioned in this manner might show an increased resistance to BAPN toxicity. However, the experimental results were just the opposite. Although no evidence is available to explain this finding, it is possible that the high level of n-propylamine may act competitively to retard the oxidation of BAPN.

Summary. Cyanoacetic acid (CAA) produced no toxicity symptoms when fed to turkey poults in quantities which induced relatively high blood levels. Two known inhibitors of monoamine oxidase, isonicotinic acid hydrazide and 1-isonicotinyl-2-isopropyl hydrazine at 0.04-0.08% of the diets were also not toxic, but when fed at same levels in

TABLE III. Potentiating Effect of 1-Isonicotinyl-2-Isopropyl Hydrazine (IIH) on the Toxicity of BAPN in Turkey Poults.

BAPN fumarate, % of diet	IIH phosphate, % of diet	Avg wt, 5 wk, g	Mortality, %	Hemorrhage, % of original group	Avg leg score*
.0	.0	742.5	0	0	5.0
.02	.0	630.8	20	20	4.6
.04	.0	555.0	60	30	3.0
.0	.04	610.0	0	0	4.8
.02	.04	400.1	90	60	1.0
.04	.04		100	40	
.0	.08	627.6	0	0	5.0
.02	.08		100	60	
.04	.08		100	20	

* *cf.* Table I.

TABLE IV. Potentiating Effect of n-Propylamine (n-PA) on the Toxicity of BAPN in Turkey Poults.

Exp.	n-PA, % of diet	BAPN fumarate,* % of diet	Avg wt, g†	Mortality, %	Hemorrhage, % of original group A.R.‡	Hemorrhage, % of original group L.M.H.‡	Avg leg score§
21	.0	.0	495.2	0	0	0	5.0
	.0	.079	424.0	10	0	0	3.4
	.0	.12	413.0	40	10	0	2.3
	.5	.079	396.6	50	10	0	2.6
	.5	.12	360.8	40	20	20	2.3
23	.0	.0	742.5	0	0	0	5.0
	.0	.08	601.6	20	20	0	3.5
	.5	.08		100	40	10	
	.5	.0	623.4	10	0	0	5.0
	1.0	.08		100	10	10	
	1.0	.0	448.8	20	0	0	5.0

* BAPN fumarate additions to diet were not started until beginning of third week of experiment.

† Durations of experiments 21 and 23 were 4 and 5 wk, respectively.

‡ A.R. = aortic rupture; L.M.H. = massive hemorrhage in leg muscles.

§ *cf.* Table I.

combination with BAPN, the characteristic toxicity symptoms of the latter substance were greatly enhanced. This is interpreted as the result of a decreased *in vivo* conversion of BAPN to CAA. N-propylamine at 0.5-1.0% of the diet did not itself produce toxic symptoms, but it enhanced the toxicity of BAPN.

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