Although these lymphocyte changes are not found in healthy normal subjects, their short- or long-term influence on the health of the Michigan dairy farmers who were exposed to PBB's has not been established. Nor is it known what influence these alterations and associated metabolic changes will have on other individuals who have consumed PBB-contaminated food and who now bear PBB burdens.

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6. Michigan dairy farm residents who lived within 50 miles of Reed City were selected for immunological study on 17 to 18 January 1977.
7. On 26 to 28 March 1977, Wisconsin dairy farmers underwent identical clinical and laboratory examinations.
8. Control blood samples obtained from New York scientific research personnel were sent with the study samples from both Wisconsin (26 to 28 March 1977) and Michigan (4 to 11 November 1976 and 17 to 18 January 1977) to ascertain whether the plane journey might in some way cause abnormalities. None were seen.
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15 August 1977; revised 21 November 1977

Pyrazole-Induced Thyroid Necrosis: A Distinct Organ Lesion

Abstract. *One oral dose of pyrazole caused necrosis of rat thyroid follicular epithelial cells but spared the parafollicular (C) cells and the parathyroid glands. Serum thyroxine (T_4) and triiodothyronine (T_3) were significantly decreased on day 3 after pyrazole administration and were immeasurable on day 5. At day 5 the thyroid was enlarged and the concentration of thyroid-stimulating hormone in the serum was increased, indicating an appropriate pituitary response to a primary lesion in the thyroid. Doses of pyrazole which produced no morphologic change in the thyroids also significantly depressed the concentrations of T_4 and T_3 in the serum.*

Endocrine glands, unlike the liver, kidney, or lung, are rarely the target of chemically induced lesions. The experimental diabetes (damage to the islet cells of the pancreas) produced by alloxan or streptozotocin (*1*), the parathyroid necrosis induced by asparaginase (*2*), the hexadimethrine bromide–caused necrosis of the pituitary gland and adrenal cortex (*3*), as well as the hemorrhage or necrosis in the adrenal gland following the administration of 7,12-dimethylbenz(*a*)anthracene (*4*), acrylonitrile (*5*), or thioguanine (*6*) are examples of the few rare endocrine lesions related to chemicals. Although extensive studies have been undertaken on the relations between structure and activity of antithyroid drugs (that is, inhibitors in various steps of thyroid hormone synthesis) (*7*) and on the goitrogenic action of chemicals (*8*) only radioactive iodine has been available to induce necrosis in the thyroid gland.

During structure-activity studies with chemicals inducing adrenal necrosis or duodenal ulcer, or both, in the rat (*9*) we found that pyrazole consistently produces structural and functional alterations in the thyroid gland. Pyrazole is an inhibitor of hepatic alcohol dehydrogenase, and hence it has been extensively used in biochemical research (*10*).

Sprague-Dawley derived Charles River CD female rats (200 g) were given unlimited access to Purina Lab Chow and tap water. They each received one dose of 30, 70, 100, or 140 mg of pyrazole

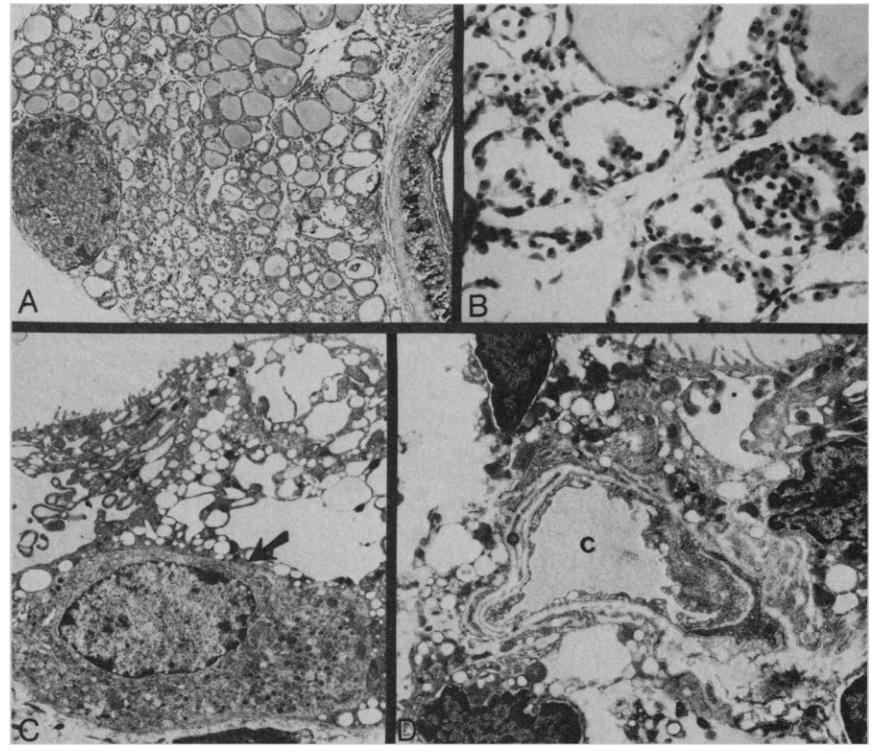

Fig. 1. (A) Extensive damage in the thyroid: only a few follicles are intact (gray). Most of the follicular cells are desquamated, the colloid is in various stages of dissolution, and the follicles appear empty (white) (×50). (B) Higher magnification of the damaged thyroid. The colloid is not visible and the desquamated follicular epithelial cells (with dark pycnotic nuclei) are aggregated. On top, two follicles are only partially involved (×280). (C) Electron micrograph of the thyroid of a rat given one dose of pyrazole (140 mg/100 g). The follicular epithelium shows marked injury (for example, dilation and vesiculation of endoplasmic reticulum) while a parafollicular C cell (arrow) appears to be intact (×6500). (D) Advanced destruction and desquamation of the follicular epithelium are evident (×8900). Notice the normal capillary (*C*).

0036-8075/78/0317-1209$00.50/0

Table 1. Time-dependent action of a single dose (140 mg/100 g, by mouth) of pyrazole in rats. The data (means ± standard error) were analyzed by Student's *t*-test.

Group	Day of autopsy	Final body weight (g)	Thyroid (mg/100 g body weight)	Serum		
				T_4 (μg/dl)	T_3 (ng/dl)	TSH (ng/ml)
Control	3 and 5	215 ± 9.4	6.8 ± 0.56	5.4 ± 0.6	97 ± 8	274 ± 24
Pyrazole	3	198 ± 4.9	7.05 ± 0.34	1.3 ± 0.2*	33 ± 13†	370 ± 88
Pyrazole	5	188 ± 3.5	9.05 ± 0.89*	<1.0	11 ± 5†	558 ± 45†

*$P < .05$. †$P < .005$ for difference from control.

Table 2. Dose-dependent effect of pyrazole in rats 5 days after the administration of a single dose. The data (means ± standard error) were analyzed by Student's *t*-test.

Group	Dose (mg/100 g)	Thyroid		Serum	
		Weight (mg/100 g)	Histology	T_4 (μg/dl)	T_3 (ng/dl)
Control		7.39 ± 0.65	No change	4.2 ± 0.5	94 ± 10
Pyrazole	100	9.75 ± 1.11	Minor change	1.0 ± 0.2*	46 ± 8†
Pyrazole	70	13.00 ± 0.95*	No change	0.9 ± 0.2*	40 ± 5*
Pyrazole	30	8.20 ± 1.02	No change	2.6 ± 0.5	100 ± 12

*$P < .005$ for difference from control. †$P < .05$.

(Aldrich) per 100 g of body weight as an aqueous solution by mouth (administered by a rubber stomach tube). Groups of five rats each were killed on days 3 and 5 after the 140 mg/100 g dose or only on day 5 after other doses, and tissues were prepared for examination by light and electron microscopy. Thyroids were fixed by immersion either in Karnovsky's fixative or in 10 percent buffered formaldehyde. Additional groups of eight rats each were killed by decapitation, and blood was collected for measurement of serum concentrations of L-thyroxine (T_4), 3,5,3′-triiodothyronine (T_3), and thyroid-stimulating hormone (TSH) by radioimmunoassay.

A single dose of pyrazole (140 mg/100 g) resulted in a 90 to 100 percent incidence of thyroid lesion and about 50 percent mortality by day 5. The speed with which changes developed in the thyroid varied from rat to rat, but those revealed by light microscopic examination can be divided into three stages. First a few thyroid follicular cells showed desquamation and necrosis involving only some follicles. Subsequently, cellular injury and necrosis were extensive, sparing only a few follicles (Fig. 1, A and B). Finally, alterations were uniform throughout the gland. Interstitial edema was extensive, whereas inflammatory infiltrate was sparse. The adjacent parathyroid glands showed no histologic evidence of injury (Fig. 1A).

Electron microscopy revealed an early dilation of the endoplasmic reticulum in follicular epithelial cells on days 2 or 3 (Fig. 1C). The parafollicular cells appeared ultrastructurally intact (Fig. 1C). The lesion progressed to vesiculation of the endoplasmic reticulum, mitochondrial damage, clumping of the chromatin along the nuclear membrane (days 3 to 4), and then the terminal event, necrosis and desquamation of the cells, was usually detected on days 4 or 5 (Fig. 1D).

Table 1 shows that the most potent dose of pyrazole (140 mg/100 g) significantly decreased serum T_4 and T_3 concentrations by day 3, when no marked change was detected in the body weights or thyroid weights of the rats. On day 5 after pyrazole administration, serum T_4 and T_3 concentrations were almost immeasurably low, whereas concentrations of TSH and thyroid weights were significantly increased, despite the decrease in body weight. A dose-response study showed (Table 2) that the 100 or 70 mg/100 g doses of pyrazole also significantly depressed serum T_4 and T_3 concentrations, whereas thyroid weight increased (probably because of edema) and body weight diminished. No marked changes were revealed by light microscopy. The 30 mg/100 g dose of pyrazole did not significantly modify thyroid structure and function.

Correlation of the structural and functional changes in the thyroid of rats given pyrazole shows that marked hypofunction of the gland (for example, on day 3, Table 1) is associated with relatively mild morphologic damage. At the late stage of thyroid necrosis, when the plasma T_4 and T_3 concentrations are almost immeasurable, the amount of TSH in the circulation is significantly increased. This further confirms that the site of the primary lesion is the thyroid with a resultant appropriate pituitary response.

In higher doses, pyrazole causes focal adrenocortical necrosis and central nervous system depression (for example, obtundation). Its distinct and prominent action on the thyroid is unexpected. Doses which lead to complete necrosis of the thyroid spare the parafollicular cells and the parathyroids. This selective damage is comparable to the specific action of alloxan on the beta cells of pancreas.

The mechanism of this action of pyrazole is not understood. The role, if any, of the pyrazole-induced inhibition of hepatic alcohol dehydrogenase in the pathogenesis of thyroid necrosis is unknown. Nevertheless, in small doses pyrazole might be suitable for inducing "chemical thyroidectomy" to control hyperthryoidism or to suppress thyroid neoplasms (*11*).

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21 November 1977