were eliminated, suggesting a correlation between the inhibition of aggregation and that of formation of PAF-acether. Failure to suppress aggregation by thrombin, when formation of PAF-acether was abrogated, may imply that PAF-acether is not responsible for the non-ADP and non-thromboxane-dependent effects of thrombin. Alternatively, residual aggregation by thrombin may still be accounted for by formation of PAF-acether within the cell, which cannot be detected by our present bioassay.

In an attempt to eliminate this possible undetectable PAF-acether, we recently incubated C_3ado plus HCy with the platelets at 37 °C in place of 22 °C, under the assumption that at the physiological temperature inhibition would be better observed. We noted indeed that aggregation by thrombin was more markedly reduced (experiments in progress).

This is the first description of biochemical interference with the generation of PAF-acether by mechanisms other than inhibition of phospholipase A_2[16], correlating with suppression of aggregation by collagen and by convulxin, and with a significant increase in the threshold for thrombin. Further studies, particularly better-adapted protocols for the use of the inhibitors, as well as their use in other cell systems, should provide a better understanding of the role of phospholipid methylation in its formation and/or release and, overall, of its role in the activation of inflammatory cells in general.

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Species difference in sensitivity to the diabetogenic action of triphenyltin hydroxide

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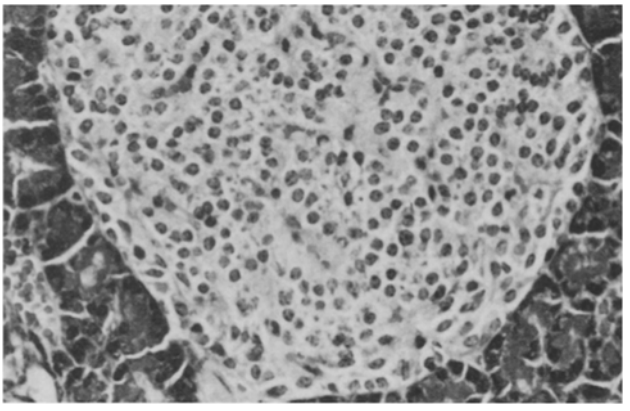
Summary. The sensitivity to the diabetogenic action of triphenyltin hydroxide (TPTOH) was investigated in 5 species of experimental animals. A single oral administration of TPTOH produced marked hyperglycemia and triglyceridemia in rabbits and hamsters, but no evidence of diabetes was found in mice, rats and guinea-pigs. No morphological abnormality was observed in islet tissue from TPTOH-treated hamsters.

Triphenyltin compounds are widely used in agricultural fungicides and antifoulants[1]. However, the potential hazard from occupational exposure to the compounds is not fully understood. Hyperglycemia has been observed in humans[2] and rabbits[3] after exposure to triphenyltin compounds. The hyperglycemia induced in rabbits was explained by an interference of the compounds with the process(es) leading to the release of insulin into the blood[3].

We found that the administration of TPTOH to rats did not produce hyperglycemia. This prompted us to determine whether there is a species variability in the induction of the diabetic state by triphenyltin.

Materials and methods. Animal studies were carried out on male Japan white rabbits (2.5–3.0 kg), male Wistar rats (140–160 g), male ddY mice (28–32 g), male Hartley guinea-pigs (230–260 g) and male golden hamsters (110–125 g). Animals were allowed commercial food (Oriental Kobo Co., Tokyo, Japan) and water ad libitum throughout the study unless otherwise stated. A single oral dose of TPTOH was administered in



Islet tissue from the pancreas of a hamster 3 days after treatment with a single oral dose of triphenyltin hydroxide (100 mg/kg). None of the islet cells showed significant changes. Hematoxylin and eosin, × 300.

sesame oil suspension. The doses used are described in the table. Control animals received appropriate volumes of vehicle. Blood samples were obtained from the marginal ear vein with a heparinized syringe in rabbits. In the other 4 species, blood samples were obtained from the posterior vena cava with a heparinized syringe while the animals were under ether anesthesia. In all 5 species, blood samples were collected at 3 days after administration. Plasma glucose was determined by the glucose oxidase method[4] with kits supplied by Wako Pure Chemical (Osaka, Japan). Plasma triglyceride was determined by the enzyme method of Spayd et al.[5], using a kit (Wako). Pancreatic tissue for light microscopic examination was fixed in buffered, pH 7.4, 10% formalin. Tissue was embedded in paraffin and sections were stained with either hematoxylin and eosin or Gomori's aldehyde fuchsin. The statistical significance of the differences between sample means was assessed by Student's t-test.

Results and discussion. Our findings are given in the table. TPTOH produced marked hyperglycemia and hypertriglyceridemia in rabbits and hamsters after a single oral administration of the compound. In contrast, the administration of TPTOH to mice, rats and guinea-pigs showed no evidence of diabetes although the depression in weight gain indicated that the compound had an effect in these species. Although the TPTOH-treated hamsters showed marked hyperglycemia and hypertriglyceridemia (table), morphological examinations showed no abnormality in the islet tissue of the animals (fig.). These results are the same as those in triphenyltin fluoride-treated rabbits[3]. No hypertriglyceridemia was seen in species in which no elevation of blood glucose occured after TPTOH administration. These data suggest that TPTOH-induced hypertriglyceridemia is due to insulin deficiency as suggested previously[3].

The reasons for the difference between species are unclear. The species specificity could reflect a difference in the disposition of TPTOH or a difference in the fundamental mechanisms of insulin secretion. Another possible explanation would be differences in absorption or metabolism of the compound in the gastrointestinal tract. Furthermore, it may be necessary to consider the influence of the stage of animal development or/and dose of the chemical on the different sensitivity of the various species. Studies designed to elucidate the mechanisms involved in this variability are in progress.

Effect of triphenyltin hydroxide (TPTOH) administration on plasma glucose, triglyceride and body weight in 5 species[a]

Species	TPTOH (mg/kg)	N[b]	Glucose (mg/100 ml)	Triglyceride (mg/100 ml)	Percentage change from initial weight
Rabbit	0	5	104 ± 6	36 ± 3	1.4 ± 3.1
	100	5	337 ± 55*	1538 ± 603*	− 3.3 ± 1.0
Hamster	0	5	142 ± 13	224 ± 28	0.9 ± 1.1
	100	5	417 ± 75*	671 ± 181*	− 9.5 ± 2.1*
Rat	0	6	151 ± 6	44 ± 6	12.4 ± 6.2
	200	6	147 ± 7	53 ± 7	− 14.4 ± 8.9*
Mouse	0	8	237 ± 8	77 ± 9	1.6 ± 0.4
	100	8	210 ± 11	56 ± 7	− 11.0 ± 1.2*
Guinea-pig	0	5	147 ± 4	32 ± 3	2.6 ± 0.3
	100	5	150 ± 8	35 ± 5	− 4.4 ± 0.8*

[a] Values are the mean ± SE at day 3 after the administration of TPTOH. [b] N is the number of animals studied.
* Indicates a significant difference ($p < 0.05$) from control.

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Isonicotinic acid hydrazide: Early effects on peripheral nerve conduction velocity

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Summary. This report describes the effects of short treatments with isonicotinic acid hydrazide (isoniazid), 300 mg/kg/day, on conduction velocity in the rat tail dorsal nerve trunk. After 6 days of continuous treatment, conduction velocity falls significantly for measurements made at 35 °C. After 10 days it falls significantly at both 25 °C and 35 °C. This appears to be the first electrophysiological corroboration of the early neuropathological changes recently observed in isoniazid treated rats and seems to provide evidence that the temperature at which the experiments are made is important in determining conduction velocity changes.

The neurotoxic effects of isonicotinic acid hydrazide (INH), initially reported in humans by Pegum[2], were further studied experimentally by Zbinden and Studer[3] who found that rats show degeneration of peripheral nerves after 15 days of continuous treatment but functional disturbances do not appear for several months. Subsequently a great number of studies have been published, mainly from the histological and biochemical points of view, and only a few papers deal with the effect of INH on electrophysiological parameters such as conduction velocity[4-6]. In the first of these, only a few animals were tested and the method used did not allow proper temperature control, nerve length mesurement or serial in vivo determinations. In the others, both performed in humans, the first is only a case report and the second presents effects involving long treatments. Since it seems to have been clearly established in recent works[7,8] that short periods of administration are sufficient to produce axonal degeneration, we thought it interesting to