convulsive doses of strychnine were also employed. With this drug generalized motor excitability increased, but unlike with picrotoxin the righting coordination remained poor. Another group of animals was kept on the alcohol regime for 2 weeks to develop tolerance. Animals were not allowed access to alcohol for 4 h prior to testing, but were given ethanol by intubation immediately prior to testing. Some of these animals were given the GABA transaminase (E.C. 4.1.1.15) inhibitor AOAA (amino-oxyacetic acid) 3 h before testing. Prior to being given ethanol, treated animals were selected so that a group was obtained that was able to right themselves as well as the non-treated control animals. As illustrated in figure 2B the AOAA-treated animals were more adversely affected by the administered alcohol as judged by this motor test.

Discussion. By 2 weeks the mean cerebellum GABA level in the alcohol group was significantly different from that of the control group, and by 4 weeks this statistically significant difference was also observed between the alcohol group and glucose group values. The lack of a statistically significant difference between the 2-week alcohol and glucose values was probably because the glucose group GABA level values were consistently, but non-significantly, lower than the control group values at the same time period. This may suggest a nutritional effect on brain GABA levels. Such a nutritional effect could have been related to the shift of the diet towards a greater proportion of carbohydrate, and an associated change in precursor metabolic pools fed by glucose and amino acids[11]. By 2 weeks the alcohol group animals had also developed tolerance, as demonstrated with the righting reflex. There was a significant difference in the height required for righting between the 2-week alcohol and glucose animals, even though the difference between their mean cerebellum GABA levels was not significant at this time period. With this exception it can be said that a depression in cerebellum GABA levels accompanied the development of alcohol tolerance by this reflex. However, no cause and effect relationship can be concluded from these data. A reduction in neuronal GABA levels would contribute to the development of tolerance by reducing central inhibition, thereby compensating for the depressant effect of the alcohol. Attempts to correlate brain GABA levels with excitability generally have variable success[12], perhaps because GABA levels per se do not distinguish between transmitter synthesis, release and restorage, or degradation, or whether the origin is neuronal or glial. We found that a drug that interferes with GABA neurone activity, picrotoxin[13], mimiced tolerance, while a drug known to increase brain GABA levels, AOAA[14], reduced tolerance that had already developed. These data could be interpreted as being manifestations of the generalized depressant qualities of endogenous GABA, or they could be interpreted as indirectly supporting the view that alcohol tolerance development involves a reduction in brain GABA levels, with an attendant reduction in inhibition or disfacilitation. The apparent specificity of the picrotoxin effect compared to the action of strychnine favours the latter explanation.

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Hypertrophy of pulmonary arteries and arterioles with cor pulmonale in rats induced by seneciphylline, a pyrrolizidine alkaloid

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Summary. Seneciphylline, one of the hepatotoxic pyrolizidine alkaloids, induced, as do also monoclotaline, etc., a marked arterial and arteriolar hypertrophy of the lung of young Wistar rats a month after a single s. c. injection of 50–80 mg/kg. Cor pulmonale with leftward shift of the ventricular septum was also noted.

Recently seneciphylline, m.p. 216 °C $[\alpha]_D^{21°}$ −134 °C ($CHCl_3$), has been isolated from the roots of Japanese Senecio cannabifolius Less (Japanese name: Hangonso) in large content using silica gel column chromatography[1]. Seneciphylline has been known as one of the hepatotoxic pyrrolizidine alkaloids[2] and found in a wide variety of plants of Senecio and Crotalaria species[3]. Some pyrrolizidine derivatives, such as monocrotaline and retrorsine, have been known to cause, besides the liver injury, cor pulmonale, occasionally accompanied by pulmonary arteritis and arteriolitis when fed per os[4,5] as well as single[6] or successive[5] injections. The present preliminary experiment showed that seneciphylline can also induce pulmonary changes with cor pulmonale in rats, similar to those caused by monocrotaline. Although the number of animals used was small, pulmonary and cardiac lesions were convincing.

Materials and methods. 16 male Wistar rats (Nihon Rat Co., Tokyo) of 4 weeks old (40–50 g) were used. They were caged in pairs in a screen-bottom cage and fed commercial pellet food (CE-II, Clea Japan Co.) and water ad libitum. Seneciphylline solution was prepared by dissolving it in 1 N HCl, diluting and then neutralizing with 0.5 N NaOH just before use; it was injected s.c. into the interscapular region (table). The animals were autopsied as soon as they were sacrificed or found dead. After gross examination, the heart, lungs and liver were fixed in 10% neutral buffered formalin, embedded in paraffin, cut and stained with hematoxylin and eosin. Special stainings were used when required.

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Results and discussion. Each rat which was given 80 mg/kg of seneciphylline was sacrificed after 1, 2 and 3 weeks. The rest died at 28, 34 and 37 days after injection. 1 of 3 animals of 50 mg/kg-group died at 34 days. Except for the reduced rate of body weight gain, these rats showed symptoms such as weakness, dyspnea and anorexia only a few days before death. On autopsy of the deceased animals, the lungs were atelectatic, with petechial hemorrages and slight edema, due to profuse serous pleural exudate (table). The heart showed remarkable right ventricular hypertrophy and dilatation with leftward shift of the septum. The liver was congested presenting the nutmeg appearance. Other organs were unremarkable. Survivors were killed at 34, 89 and 157 days of experiment, with moderate dilatation of the right heart ventricle in 2 animals (table). 2 control rats and 4 rats given 30 mg/kg of seneciphylline showed no pathological changes.

Survival and macroscopic findings of rats given single s.c. injection of seneciphylline

No. of rats	Dose (mg/kg)	Survival (days)	Lung	Heart	Liver
1	80	K (7)	N	N	N
2	80	K (15)	N	N	N
3	80	K (21)	N	RVD	N
4	80	D (28)	A, PF	RVH	C
5	80	D (34)	A, PF	RVH	C
6	80	D (37)	A, PF	RVH	C
7	50	D (34)	A, PF	RVH	C
8	50	K (34)	N	N	N
9	50	K (89)	N	N	N
10	50	K (157)	N	RVD	N

D, died; K, killed; RVH(D), right ventricle hypertrophy (dilatation); PF, pleural fluid; A, atelectasis; C, chronic congestion; N, normal appearance.

The lungs of the rats which died spontaneously showed histological changes very similar to those treated with monocrotaline[6,8] or fulvine[7]. The most conspicuous change was medial thickening of the arterioles composed of plump smooth muscle cells. Both internal and external elastic laminae were sharply stained. Hyalinization of the media was rarely seen but there was no necrosis. In the surviving rats given 50 mg/kg of seneciphylline, mild to moderate perivascular edema of the lung was found after 34 and 89 days.

Myocardial changes were noticeable after 3 weeks. The myocardium showed hypertrophy of the muscle cells in the right ventricular wall and septum with enlarged, irregular, often bizzare-shaped hyperchromatic nuclei. Patchy loose scars were also found. In contrast, myocardial cells of the left ventricle was unremarkable.

The similarity of the lesions with those induced by other pyrrolizidine alkaloids, such as monocrotaline[4–6], retrorsine and fulvine[7], relevant compounds to seneciphylline, indicates similar a pathogenic process with this alkaloid. At present, however, pathogenesis of hypertrophy (and arteritis ?[5,8]) of pulmonary arteries has not been clearly elucidated, even though extensively studied with monocrotaline[4,9] and its activated metabolite, dehydromonocrotaline[10–12], using electron microscopy.

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Production of underweight embryos in rats treated with barbiturates during pregnancy

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Summary. The effect of administering barbital sodium, phenobarbitone or butobartitone during pregnancy was investigated in rats. The study shows that these bartiturates affect the litter-size and retard the foetal growth markedly. The embryos produced are significantly undersized.

Nutritional[2] and hormonal imbalances[3], or the metabolic changes caused by the administration of drugs[4], have adverse effects on pregnancy and the foetal growth in man and other animals. The drugs administered into the maternal body during pregnancy may find their way to the developing foeti[5–7]. Barbiturates are commonly used as sedative, anticonvulsant and anaesthetic drugs. They are known to induce abortions and foetal resorptions in experimental animals[8,9]. This investigation is an attempt to study the effect of these sedatives on the foetal development when the mothers are given treatment during pregnancy.

Adult female albino rats of Wistar strain weighing 150–200 g were mated with fertile males and the days of pregnancy were recorded[10]. Three barbiturates, namely

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