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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Effect of 3 barbiturates on the foetal growth in rats

Treatment	Number of rats used	Dose (mg) per ml/100 g b. wt	Foetal weight (M ± SE) g
Controls (Distilled water)	9	–	3.20 ± 0.06
Treated (Barbital sodium)	5	10	2.97 ± 0.03
Treated (Barbital sodium)	6	15	2.24 ± 0.08
Treated (Barbital sodium)	6	20	1.83 ± 0.02
Treated (Barbital sodium)	7	25	2.20 ± 0.03
Phenobarbitone	6	10	2.80 ± 0.80
Phenobarbitone	6	15	2.20 ± 0.05
Butobarbitone	5	10	1.50 ± 0.20

barbital sodium (5:5 diethyl sodium barbitone M and B), phenobarbitone (5:5 diphenyl barbiturate, 'Gardinal', Boots, Pure Drug Co.,) and butobarbitone (Soneryl, M and B) were either dissolved or suspended in distilled water so that 1 ml contained the dose employed (table). They were administered s.c. in the forenoons, before feeding the animals, from day 7 to 19 of pregnancy. Rats receiving an equal volume of distilled water for the same duration served as the controls. All rats were maintained individually on standard diet, water ad libitum, exposed to natural light conditions and at a room temperature of 25 ± 1 °C. They were autopsied 24 h after the last injection and the gravid uteri were dissected out. The embryos were carefully separated from the extra-embryonic tissues and examined closely for the detection of any malformations. They were weighed accurately on a torsion balance and the results were statistically analyzed.

The study shows that treatment of rats chronically with any of these barbiturates during pregnancy affects the foetal growth to a remarkable extent. Barbiturates are classified as long, short and ultra-short acting sedatives based on the production of graded sleep. Butobarbitone is a short-acting drug while the other 2 are considered as fairly long-acting ones. 10 mg of Butobarbitone per 100 g of body-weight administered s.c. from day 7 to 19 of pregnancy (table) decreased the weight of the foetuses significantly (1.50 ± 0.2 g) when compared with the controls (3.20 ± 0.06 g). Both barbital sodium and phenobarbitone also depressed the foetal weight. No malformations have been noticed in any of the groups.

The adverse effects of barbiturates on pregnancy are shown to be due their depressant action on the central nervous system and chiefly through the mediation of the hypothalamo-hypophyseal axis which results in the production of altered ACTH release[11]. The retardation of the foetal growth recorded during this study may have resulted from an action of these sedatives directly and/or indirectly on the metabolism of the maternal body which forms the immediate environment of the developing foetus. These effects do not appear to be related to the degree of sedation since the drug considered as short-acting causes greater damage than long-acting ones.

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Arthrite à adjuvant chez le rat: Influence de l'oxonate et de l'allopurinol[1]

Adjuvant arthritis in rat: influence of oxonate and allopurinol

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Summary. Adjuvant arthritis in rats is inhibited by oxonate and not by allopurinol. Pyrimidine metabolism seems not to be involved in the mechanism of inhibition.

Il existe chez l'homme une forte corrélation négative entre la goutte et la polyarthrite rhumatoïde[2]. Un modèle expérimental de cette exclusion est obtenu en combinant chez le rat l'arthrite à adjuvant et l'hyperuricémie provoquée par l'oxonate de potassium, un inhibiteur de l'urate-oxydase[3,4]. Comme l'oxonate agit aussi sur le métabolisme des pyrimidines en inhibant l'orotate phosphoribosyltransférase (OPRT) et l'orotidine décarboxylase (ODC)[5,6], nous avons voulu évaluer l'importance de ce métabolisme dans l'inhibition de l'arthrite à adjuvant par l'oxonate. Pour cela, nous avons comparé les effets de 2 inhibiteurs de l'OPRT et de l'ODC, l'allopurinol et l'oxonate, qui agissent en sens opposé dans le métabolisme des purines, en inhibant soit la synthèse de l'acide urique (allopurinol), soit la dégradation de l'acide urique (oxonate)[7,8].

Matériel et méthodes. 60 rats Wistar mâles, pesant environ 210 g, ont été répartis en 4 groupes de 15 animaux: un groupe témoin à nourriture normale (Purina), un groupe à l'oxonate (Purina additionné de 5% d'oxonate de potassium et de 1% d'acide urique) et 2 groupes à l'allopurinol (Purina additionné d'allopurinol en quantités correspondant à 25 et à 75 mg par kg et par jour). 3 semaines après le début des différents régimes, 10 rats dans chaque groupe ont reçu une injection d'adjuvant de Freund dans le coussinet plantaire de la patte arrière gauche (0,5 mg de Mycobacterium butyricum dans 0,1 ml d'huile minérale). L'évolution de la réaction primaire

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