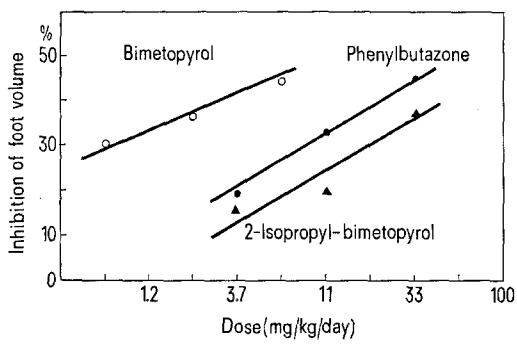
therapeutic potency of bimetopyrol and its 2-isopropyl analogue were calculated as 8.46 (4.27–17.4) and 0.49 (0.21–0.91) times as potent as phenylbutazone, respectively.

Toxicological investigations in mice have shown that the values of acute LD_{50} of bimetopyrol were 3.6 g/kg (male) and 3.4 g/kg (female) by mouth, and 2.7 g/kg (male) and 1.9 g/kg (female) by i.p. injection. In rats, those were 2.3 g/kg (male) and 1.8 g/kg (female) by mouth. In chronic toxicity tests, rats were dosed daily for 6 months by mouth with 100, 50, 25, and 5 mg/kg. During the course of investigation, 2 of 10 female animals receiving the highest dose died. The death was assumed to result from gastro-intestinal ulceration and systemic peritonitis. At the termination of the experiment, none of the abnormalities were observed in the animals which had received bimetopyrol at doses not more than 25 mg/kg/day, while 5 of 38 animals receiving higher doses had ulcers in stomach or intestine and also there was a slight increase in liver weight. Dogs tolerated daily dose of 150 mg/kg for 3 months without any significant signs of abnormality in pathological examinations.



Curative effect of selected pyrrole compounds on established arthritis in rats. Sprague Dawley female rats were injected intracutaneously in the right hind paw with 0.5 mg of heat-killed *M. butyricum* in 0.05 ml of mineral oil. 18 days after adjuvant injection, the well-established arthritic animals were selected and subjected to the 7 days therapy with drugs. The mean value of the increased foot volume at 18th day after injection was 4.31±0.11 ml. 3 doses for each drug and 7 animals for each group were used. Drugs suspended in aqueous tragacanth were given orally, and the foot volume of right hind paw of each animal was measured before and after the therapy.

Zusammenfassung. Die antiinflammatorischen Eigenschaften von verschiedenen Diaryl-pyrrol-Derivaten wurden untersucht. Es wurde festgestellt, dass eine repräsentative Verbindung, 2-Methyl-4, 5-*bis*(*p*-metoxyphenyl)-pyrrol, eine ausgeprägte Hemmung gegen das akute Ödem und die chronische Arthritis der Ratte zeigt.

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17 January 1972.

[7] We thank Messrs. K. WACHI, Y. UMEMURO and T. KOJIMA for their technical assistance.

Abnormalities of Lung Lipids Following Inhalation of Quartz

After inhalation of quartz for extended periods and prolonged survival thereafter, specific pathogen-free (SPF) rats failed to acquire typical silicotic lesions but instead responded by the development of pulmonary alveolar lipo-proteinosis[1]. Analysis of this condition by histochemical, chemical and immunological means established that, apart from the presence of quartz, the experimental disorder was essentially similar to the human disease[2]. The same samples of quartz were shown to be fibrogenic by intraperitoneal and intratracheal injection into other rats, both conventional and SPF. The outstanding feature of experimental lipo-proteinosis was the large lipid component of the alveolar material and histochemically both neutral lipids and phospholipids were identified. Ultrastructural observations on the same material[3] demonstrated extensive alveolar accumulation of phospholipid structures which assumed several morphological forms characteristic of the liquid-crystalline phase. However, the earlier chemical procedures did not distinguish particular groups of lipids and we now report a refined analysis, indicating implications of the quantitative and qualitative changes.

Methods. Male SPF rats were exposed for 8 or 26 weeks to the inhalation of Minusil quartz at an atmospheric concentration of 37 or 12 mg/m³ and survived subsequently for 20 or 30 weeks. The lungs were quickly removed and frozen in liquid nitrogen. They were sealed in plastic tubes and remained frozen under nitrogen until required for chemical fractionation. The biochemical procedures employed have been described elsewhere[4]. In other rats exposed to quartz simultaneously it was confirmed that the histological changes were typically those of alveolar lipo-proteinosis and not of silicosis.

Results. To demonstrate the overall directions of change, the experimental animals are compared with control rats

Table I. Quantitative changes in lipid categories

	Control Mean (mg)	Experimental Mean (mg)	Increase factor
Total lipids	73	1605	22
Neutral lipids (including cholesterol)	27.1	232	8
Cholesterol	6.1	106	17
Phospholipids			
Total	35.6	1210	34
Lecithins	19.1	1056	55
Dipalmityl lecithin	10.9	699	64
Phosphatidylethanolamines	7.7	70	9
Sphingomyelins	4.7	35	7

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Table II. Percentage composition of the fatty acids from control and silica-exposed animals

		Total lipid fatty acids		Neutral lipid fatty acids	
		Control	Experimental	Control	Experimental
Myristate	14:0	17	5.7	1.6	2.9
Palmitate	16:0	27.8	60.9	18.9	47.4
Stearate	18:0	5.8	3.4	2.5	5.0
Oleate	18:1	40.0	13.1	54.2	27.6
Linoleate	18:2	13.4	5.2	17.7	9.7
Belenate	22:0	6.1	5.7	0.8	5.9
Lignocerate	24:0	1.5	0.8	—	—
Unidentified		3.7	5.0	4.3	1.5

of the same sex and of comparable age and carcase weight. The wet weight of the lungs of test rats increased fivefold but the total lipids rose by a factor of 22, whilst the residue consisting mainly of protein was approximately doubled. The details of lipid composition are given in Table I.

Fatty acid analyses were performed on both the total lipid and the neutral lipid fractions, the difference very largely representing the fatty acid composition of the phospholipid fraction (Table II). There was a pronounced rise in the proportion of palmitate in the experimental lungs, reflected in both the neutral and the phospholipid elements, combined with a corresponding depression of the proportion of oleate. Approximately 66% of the lecithins in the experimental rats consisted of dipalmityl lecithin (DPL), that is each animal had accumulated about 700 mg of this compound in its lungs.

Discussion. The present biochemical findings not only confirm the deductions made from previous histochemical and ultrastructural observations[2,3] but establish the extent to which the the various categories of lipids are increased in experimental lipo-proteinosis and emphasise that the disease is essentially a lipidosis. Phospholipids were elevated to a much greater degree than neutral lipids, though their quantity was 8 times as great as in controls. Of the phospholipids, much the most prominent were the phosphatidylcholines, the amount of which was over 50 times that of controls. The phosphatidylethanolamines and sphingomyelins were also elevated but to a much lesser degree. Phosphatidylserines could not be distinguished with certainty from inositol, but only small amounts were present and there appeared to be less of this group of compounds in the experimental animals.

Dipalmityl lecithin, believed to be a principal component of lung surfactant[5], constituted the main element of the alveolar material. The surface properties of pulmonary extracts from other rats of the same experimental and control groups have accordingly been examined. Although lung extracts from affected rats possessed surface activity, there were pronounced qualitative differences from control rats in film behaviour on the Wilhelmy balance. Human alveolar lipo-proteinosis is also characterized by abnormal surface activity of lung extracts[6]. Under normal conditions, however, neutral lipid and cholesterol are able to counteract the surface properties of phospholipid[7]; variations in the proportions of the lung lipids may thus serve as a means of adjusting alveolar tension.

Recent evidence[5] supports the view that the granular pneumocytes (type B or type II alveolar epithelial cells) but not the bronchiolar Clara cells are a major source of pulmonary lecithin. Histochemically the type B cells were both numerous and active in experimental alveolar lipoproteinosis[2] and evidence is now being sought on the nature of the stimulus leading to this hyperplasia, which is not accompanied by the fibrosis expected from the long-continued retention of quartz. Excess lipid is a feature of both silicotic lungs and silicotic nodules, and pulmonary phospholipids, especially the phosphatidylcholines, were increased after intratracheal injection of quartz into rats[8]. Production of phospholipids, in particular the phosphatidylcholine dipalmityl lecithin, may represent a basic biochemical reaction of the lung to quartz that assumes greatly exaggerated proportions in alveolar lipo-proteinosis. There is evidence that the metabolism of phosphatidylserine and inositol phosphatide is increased by the phagocytic process[9], but our results raise the possibility that, unlike other phospholipid groups, production of the phosphatidylserines or inositol may have been depressed. This may be taken as a reflection of diminished ingestion of quartz by phagocytes in alveolar lipo-proteinosis, with consequent impairment of silicotic fibrosis.

The earlier observations[2,3] suggested that in lipoproteinosis overproduction of neutral lipids and phospholipids in the alveoli rather than defective removal from them might be primarily responsible for the accumulation of these materials. Now that DPL has been revealed as the principal phospholipid concerned, metabolic studies of palmitate turnover will be needed to elucidate the mechanism of this unusual response to inhaled silica.

Zusammenfassung. Lungen alveolare Lipo-proteinose, durch Inhalation Quarzstaubes herbeigeführt, zeigt eine starke Vermehrung neutraler Lipide und Phospholipide, wobei Phosphatidylcholin und besonders Dipalmityl-Lecithin hervortreten. Eine silikotische Fibrose lässt sich nicht nachweisen. Diese ungewöhnliche Reaktion auf Quartz wird diskutiert.

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