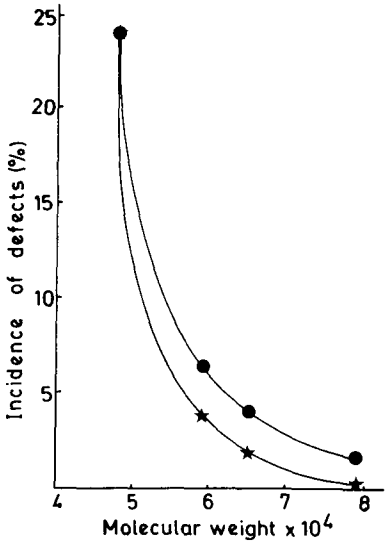

FIG. 3. The effect of molecular weight of hydroxypropyl methylcellulose on the incidence of edge splitting on tablets coated with ● commercially available grades and ★ blends prepared from a low and high molecular weight grade.

is an inverse relationship between the incidence of edge splitting and polymer tensile strength, and that the molecular weight at which the incidence of the defect becomes negligible is the same as that at which there is no further increase in tensile strength. This implies that this defect is related to the tensile strength of the polymer used to prepare the film and confirms the mechanism postulated.

From the results (Fig. 3) it would appear that polymer blends had a greater influence on the reduction of the incidence of edge splitting than commercially available grades of the same molecular weight. Although small, this effect is significant and is attributable to the presence in the blends of an increased proportion of a very high molecular weight ($>5 \times 10^5$) component obtained from the Methocel E50 portion (Rowe 1980) compared with the commercially available grade. These high molecular weight components are thought to increase the effective tensile strength of the polymer and hence lower the incidence of edge splitting.

The trends reported here for hydroxypropyl methylcellulose are likely to be the same for all polymers and hence this study illustrates the usefulness to the formulator of such data as tensile strength, molecular weight and molecular weight distribution in optimizing film formulations.

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April 10, 1980

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Action of sodium aurothiopropanol, chloroquine, D-penicillamine and levamisole on picryl chloride-delayed hypersensitivity in mice

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Little is known of the mechanisms of action of gold salts, chloroquine, D-penicillamine and levamisole in rheumatoid arthritis. Delayed hypersensitivity processes play a major part in the pathology of the disease (Dumonde 1971; Sheldon et al 1974; Stastny et al 1975; Loewi et al 1975; Van Boxel & Paget 1975). In animal pharmacology, the most used delayed hypersensitivity test in investigations for antirheumatic or anti-inflammatory activities is Freund's adjuvant polyarthritis in rats. Gold salts reduce this condition (review by Walz et al 1974), but the effects of chloroquine (Newbould 1963; Graeme et al 1966; Ward & Cloud 1966; Winter & Nuss 1966; Perrine & Takesue 1968), D-penicillamine (Liyanage & Currey 1972; Arrigoni-Martelli & Bramm 1975; Watnick 1975) and levamisole (Dieppe et al 1976; Trabert et al 1976) are null or controversial. We have studied the action of sodium aurothiopropanol sulphonate (Sarbach), chloroquine diphosphate (Rhône-Poulenc), D-penicillamine (Fluka) and levamisole (Specia) on contact delayed hypersensitivity to picryl chloride in mice (Asherson & Ptak 1968) which gives reproducible results and is easy to perform.

Swiss male mice, 25 g at the beginning of the experiment, were used. The laboratory and the animal house were lit by daylight supplemented by electric lighting from 8 a.m. to 6 p.m. Tests were performed in Summer and Autumn. 0·1 ml of a 3% picryl chloride (BDH) solution in acetone was applied to the shaved abdomen of the animals. 7 days later, early in afternoon, 0·025 ml of an antigen solution prepared in the same conditions was applied on both sides of the right ear. 24 h later, the animals were killed and both ears weighed. The delayed hypersensitivity reaction was measured by the increase in weight of the right compared with the left ear. In non-sensitized animals the increase in weight at

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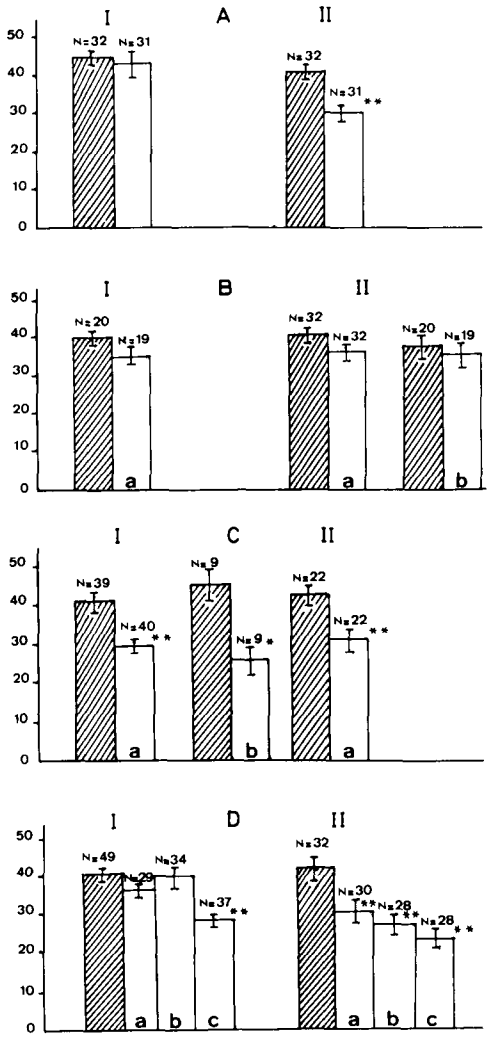

FIG. 1. Action of the compounds on picryl chloride-reaction I. Treatment around the challenge period. II. Chronic treatment from the time of sensitization. A. Sodium aurothiopropanol sulphonate 10 mg kg^{-1} dose. B. Chloroquine diphosphate: a, 10 mg kg^{-1}; b, 30 mg kg^{-1}. C. D-Penicillamine: a, 25 mg kg^{-1}; b, 50 mg kg^{-1}. D. Levamisole: a, 5 mg kg^{-1}; b, 25 mg kg^{-1}; c, 50 mg kg^{-1}. Hatched columns controls; open columns treated animals; bars represent standard errors. The number of mice is given above each column. ** $P < 0.01$ compared with controls. Ordinate: increase (mg) of ear weight.

24 h due to an irritant response was 12·9 ± 2·8 mg (11 mice). The drugs were given 24 and 2 h before and 2 h after the challenge. They were also tested after chronic treatment: the first administration of the drug was 2 h before sensitization was induced; then the drug was given once a day, late in the morning, except on the challenge day when it was given 2 h before and 2 h after the challenge. The mice thus received 9 doses of a drug. The gold salt was injected by the i.m. route, the other drugs were given orally. Controls received vehicle in the same manner as treated animals. The results are in Fig. 1.

Chloroquine did not induce any change in the reaction with the two treatment schedules used. The gold salt, while inactive when injected around the challenge period, reduced inflammation after chronic treatment. D-Penicillamine at 25 mg kg^{-1} had an action of the same level in both regimens; at 50 mg kg^{-1} activity increased. Only the highest dose of levamisole led to a significant decrease in the first regimen while activity was present after the lowest dose in the chronic experiment.

The test thus appears to be a means of assessing anti-rheumatic drugs. The mode of action in rheumatoid arthritis is probably different for the four agents and multifactorial for each of them. However, in consideration of the results, it could be assumed that gold salts, D-penicillamine and levamisole are effective in rheumatoid arthritis through some action or actions on cellular immune responses.

Although chloroquine did not induce any change in this model, other results suggest it to have an action in some delayed hypersensitivity reactions (Rybczyńska et al 1978; Tarayre & Lauressergues 1978).

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Use of whole saliva for bioavailability studies with reference to phenytoin

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The most popular method of determining the relative bioavailability of a drug formulation is to undertake single dose crossover studies in healthy volunteers and compare the area under the serum drug concentration-time curve (AUC) extrapolated to infinity (Koch-Weser 1974). The method entails the collection of enough blood samples to define the absorption and elimination portion of the concentration-time curve. We wondered whether bioavailability testing could be undertaken using whole saliva samples instead of blood in single dose crossover studies. As differences in the bioavailability of phenytoin formulations (Neuvonen 1979) have been reported to produce relapses in seizure control (Lund 1974) or signs of intoxication (Tyrer et al 1970) when one formulation is substituted for another, we have examined two oral phenytoin formulations available in New Zealand. These were 100 mg phenytoin sodium capsules (Parke-Davis) and 100 mg phenytoin sodium tablets (Kempthorne Prosser).

Methods. Five healthy adult volunteers (3 males and 2 females) gave their informed consent for the study which was conducted under clinical supervision. All declared that they were in good health with no known intolerance to any drug. On general physical examination they were normal with normal hepatic and renal function. No other medication was taken for at least one week before and during the study.

Subjects were fasted overnight until 1200 h on day 1. A single oral dose of 300 mg phenytoin (3 capsules or tablets) was given at 0800 h with 200 ml cold water. This dose is small enough to avoid the complication of non-exponential decline in serum concentrations in most subjects (Paxton et al 1977c). The first drug was assigned at random and alternated by crossover after at least 2 weeks. Venous blood samples were withdrawn immediately before drug administration and twice daily until 80 h after in four subjects. For subject 1, blood sampling was at 2 hourly intervals over days 1 and 2 and thereafter twice daily to 80 h. Blood samples were allowed to clot and the serum separated by centrifugation and stored frozen at − 20 °C for not more than 2 weeks. Whole saliva samples were obtained at 2 hourly intervals during the 4 days after drug administration. The saliva specimens were collected (after stimulation with one crystal of citric acid if necessary) by expectoration into universal containers and stored frozen. Before assaying, the whole saliva samples were

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Table 1. Serum and salivary bioavailability parameters for two formulations of phenytoin administered orally.

Subject	AUC^{∞} (μmol litre^{-1} h)		Peak concn (μmol litre^{-1})		Time to peak concn. (h)		$t_{\frac{1}{2}\beta}$ (h)	
	C	T	C	T	C	T	C	T
1. Serum	738	706	13·0	18·1	3·0	7·3	15·6	13·1
Saliva	62	44	1·49	1·22	3·0	3·0	14·3	15·2
2. Serum	483	502	14·7	12·8	8·3	7·0	13·9	14·0
Saliva	46	40	1·82	1·07	6·0	5·0	14·7	15·4
3. Serum	780	827	18·9	24·7	8·4	7·0	16·6	16·7
Saliva	57	78	1·48	2·23	10·0	5·0	16·4	14·8
4. Serum	774	745	16·7	15·1	7·0	8·7	15·7	16·0
Saliva	72	70	1·73	1·78	7·0	13·0	14·9	16·4
5. Serum	840	823	20·7	19·6	9·0	9·0	17·6	19·6
Saliva	61	62	1·62	1·52	7·0	8·7	17·5	19·4
* Serum	723 (140)	721 (133)	16·8 (3·1)	18·1 (4·5)	7·1 (2·4)	7·7 (0·9)	15·9 (1·4)	15·9 (2·5)
Saliva	60 (9)	59 (16)	1·63 (0·15)	1·56 (0·46)	6·6 (2·5)	7·0 (4·0)	15·6 (1·3)	16·2 (1·9)

C, phenytoin capsules; T, phenytoin tablets.
* Mean (with s.d.). None of the differences between tablets and capsules were statistically significant.