Heberden Society

Clinical Meeting, March, 1975

At a clinical meeting held at The Norfolk and Norwich Hospital, Norwich, on March 14, 1975, the Heberden Round was conducted by Dr. N. Cardoe and the following papers were presented.

Assessment of anti-inflammatory drugs in the rat using subcutaneous implants of polyurethane foam impregnated with dead tubercle bacilli. A. K. CLARKE, B. VERNON-ROBERTS, and H. L. F. CURREY (*Bone and Joint Research Unit, The London Hospital Medical College*) Published in the *Annals*, 34, 326.

Effects of prostaglandins PGE₁, PGE₂, PGF_{1α}, and PGF_{2γ} on the synovial microcirculation. D. M. GRENNAN, I. J. ZEITLIN, W. S. MITCHELL, and W. C. DICK (*The Centre for Rheumatic Diseases and University Department of Medicine, Royal Infirmary, Glasgow, and Department of Pharmacology, University of Strathclyde*)

Prostaglandins are now thought to be important mediators of the inflammatory response (Willis, 1969) and have been shown in increased amounts in the joints of experimentally induced arthritis in rabbits (Blackham and others, 1973) and in the synovial fluid of patients with rheumatoid arthritis (Levine, 1973). We considered the documentation of the effects of the various prostaglandins on synovial perfusion to be fundamental to further understanding of their role in joint disease and in this study we have investigated the effects of prostaglandins E₁, E₂, F₁, and F₂ on synovial perfusion in the diarthrodial joints of 20 normal dogs. We have compared the effects of the prostaglandins in our model with those of similar dose ranges of bradykinin and serotonin.

The animals were anaesthetized with a standard technique and blood pressure and blood gases were monitored throughout all experiments. Synovial perfusion was followed indirectly by calculating the T_½ value (min) of the clearance rate of the inert gas radioactive xenon (¹³³Xe) from the knee and elbow joints after intra-

articular injection of the isotope in 0.1 ml. This method has been shown to reflect synovial perfusion (Dick, 1972) and has been used in the past to show the effects of histamine and various adrenergic and cholinergic agents on the synovial microcirculation (Dick, 1972; Grennan and others, 1974). A decrease in the T_½ value denotes a vasodilator response and an increase denotes a vasoconstrictor response. In our experiments base-line recordings of the clearance of xenon alone were followed for 15 to 20 minutes by further 15- to 20-minute recordings of the clearance after intra-articular injection of 0.1 ml of the drugs in various concentrations.

PGE₁ produced a dose-related vasodilatation (Table) with doses of 10⁻⁹ g and above and PGE₂ produced significant vasodilatation with doses of 10⁻⁸ g and above. PGF_{1α} however, produced no significant vasodilatation up to a dose of 10⁻⁶ g and PGF_{2α} produced a significant vasodilator response in high dosage only (10⁻⁶ g). Bradykinin caused a dose-related vasodilator response in doses of 10⁻⁸ g and above, whereas serotonin produced a vasodilator response only at doses of 10⁻⁷ g and above.

The relative potencies of the various compounds on a molar basis in their effects on synovial perfusion were PGE₁, bradykinin, PGE₂, serotonin, and PGF_{2α}. In these experiments we have also shown the sensitivity of the synovium to small amounts of PGE₁, while showing a relative lack of potency of PGF_{1α} and PGF_{2α}. The effects of PGF₂ in other vascular beds differ from those of PGE₁ and PGE₂ (Nakano, 1972) and our results are consistent with this. This potency of PGE and relative lack of potency of PGE_{2γ} in affecting synovial perfusion is also interesting in the context of joint inflammation in view of the fact that PGE₁ elsewhere has been said to be associated with increase in experimentally induced inflammation while PGF_{2α} was associated with its diminution (Giroud, 1973).

References
BLACKHAM, M. A., FARMER, J. B., RADZIWIŃ, H., AND WESTWICK, T. (1973) *Brit. J. Pharmacol.*, 48, 343 (Rabbit monoarticular arthritis and synovial prostaglandins)

Table Effect of PGE, on T_½ value of ¹¹³Xe clearance

Dose in g in 0.1 ml.	10 ⁻¹¹	10 ⁻¹⁰	10 ⁻⁹	10 ⁻⁸	10 ⁻⁷
Molar concentration	2.8 × 10 ⁻¹⁰	2.8 × 10 ⁻⁹	2.8 × 10 ⁻⁸	2.8 × 10 ⁻⁷	2.8 × 10 ⁻⁶
	16.7 20.0	77.8 63.1	78.6 46.5	67.8 8.8	72.6 40.0
	25.1 25.0	23.3 18.5	206.7 44.2	43.6 15.7	49.8 7.7
	14.8 16.9	27.8 21.2	68.7 45.5	57.6 38.6	257.5 7.6
	194.8 178.5	43.2 26.7	50.3 30.9	63.1 23.8	67.5 17.2
	117.1 68.8	40.7 41.2	89.2 42.5	21.2 15.9	80.4 20.8
	33.4 43.6	51.8 32.6		26.5 14.2	82.4 27.3
				34.4	
Mean % change	+2.1%	+22.8%	+39.7%	+52.5%	+74.1%
SEM	±10.6	±5.9	±11.2	±7.9	±7.2

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Wrist Cysts and Fistulae. An Arthrographic Study of the Rheumatoid Wrist. J. M. I. IVESON, A. G. S. HILL, and V. WRIGHT. (Rheumatism Research Unit, The General Infirmary, Leeds, and the Oxford Regional Rheumatic Diseases Research Centre, Stoke Mandeville Hospital, Aylesbury) Published in the *Annals*, 34, 388.

Impairment of Proteoglycan-Collagen Interaction in Early Experimental Osteoarthritis. C. A. McDEVITT, H. MUIR, AND E. M. M. GILBERTSON (Kennedy Institute of Rheumatology, Bute Gardens, London, and the Department of Veterinary Surgery, University of Glasgow)

The early biochemical events in osteoarthritis have been investigated in a disease model (McDevitt and Muir, 1975; McDevitt, Muir, and Pond, 1974). The experimental osteoarthritis was induced by severing the anterior cruciate ligament in the right knee of skeletally mature dogs with the cartilage of the other knee serving as a control. The fibrillation induced in the tibial cartilage of the operated joint represented progressive osteoarthritis by the criteria of Byers, Conteponi, and Farkas (1970) in that it occurred in the area (area A) of the medial tibial condyle not covered by the meniscus, and became more severe with time after surgery as assessed by indian ink staining (Meachim, 1972). The cartilage of the operated joint had a

Table I Total uronic acid extracted sequentially by (1) 0.15 mol/l sodium acetate, (2) 2 mol/l CaCl₂, and (3) 4 mol/l guanidinium chloride. The areas are (A) medial tibial condyle next to the intercondylar notch (B) remainder of medial condyle, and (C) lateral tibial condyle. Grade 1 (Meachim, 1972) represents intact cartilage surface; grade 2, minimal fibrillation; grade 3, over fibrillation

Duration of instability (weeks after surgery)		Tibia						
		OA	Con	OA	Con	OA	Con	
3	Area Grade	A+B 2	A+B —	C 1	C —			
		% of total tissue uronic acid						
		6.7	3.8	3.8	3.4			
	Extract 1	44.5	26.6	36.0	34.5			
		Extract 2	11.7	18.2	17.2	20.4		
			Extract 3					
Total extracted	62.9	48.6		57.0	58.3			
	In residue	37.1	51.4	43.0	41.7			
48		Area Grade	A 3	A —	B 1	B —	C 2	C —
	% of total tissue uronic acid							
	17.2		7.0	19.8	7.5	19.6	8.8	
	Extract 1	51.5	58.0	56.4	48.2	54.7	50.2	
		Extract 2	10.6	12.8	8.1	21.1	11.1	15.6
			Extract 3					
Total extracted	79.3	77.8		84.3	76.8	85.4	74.6	
	In residue	20.7	22.2	15.7	23.2	14.6	25.4	

Table II Galactosamine-glucosamine molar ratios of proteoglycans from osteoarthrotic (OA) and control cartilage. The proteoglycans were sequentially extracted with (A) 0.15 mol/l sodium acetate pH 6.8, and (B) 4 mol/l guanidinium chloride pH 4.5 and purified by both 'associative' and 'dissociative' equilibrium density gradient centrifugation. The 0.15 mol/l sodium acetate extracts of areas A, B, and C of the tibia were pooled. The dog was killed 10 weeks after section of the anterior cruciate ligament—

Tissue	Tibia		Tibia		Tibia	
	OA	Control	OA	Control	OA	Control
Area A	A	A	B	B	C	C
Grade of OA	3	—	2	—	2	—
Galactosamine-glucosamine molar ratios						
0.15 mol/l sodium acetate	—	—	3.5	3.6	—	—
4 mol/l guanidinium chloride	4.3	4.1	6.3	4.6	6.5	4.4
Cartilage residue	2.6	2.0	2.6	2.5	2.5	2.1