UNIVERSITAT AUTONOMA DE BARCELONA

Facultad de Medicina

MODULACION FARMACOLOGICA Y DIETETICA DEL METABOLISMO DEL ACIDO ARAQUIDONICO. IMPLICACIONES EN LA PSORIASIS.

Memoria del trabajo realizado por Lluís Puig i Sanz para optar al grado de Doctor en Medicina bajo la dirección del Profesor José M. de Moragas, Director del Servei de Dermatologia del Hospital de la Santa Creu i Sant Pau.

7. CONCLUSIONES.

1. El piriprost y el lonapalene son inhibidores de la 5-lipoxigenasa en los leucocitos polimorfonucleares humanos, siendo sus IC_{50} 50 μM y 20 μM respectivamente. El piriprost es asimismo un inhibidor débil de la tromboxano sintetasa y un inhibidor muy débil de la ciclooxigenasa plaquetar. El lonapalene inhibe la ciclooxigenasa plaquetar, con una IC_{50} de 40 μM, determinando un aumento en la síntesis de 12-HETE por derivación del substrato.

2. El bifonazol, el clotrimazol y el ketoconazol inhiben la 5-lipoxigenasa en los leucocitos polimorfonucleares humanos (las respectivas IC_{50} son 20 μM, 15 μM y 100 μM), con un rango de potencias similar al de otros inhibidores de la 5-lipoxigenasa ensayados en el tratamiento tópico de la psoriasis. También inhiben la ω-oxidación del LTB_4 en los leucocitos polimorfonucleares humanos (con IC_{50} comprendidas entre 50 μM y 100 μM), lo que se podría contraponer al anterior efecto in vivo. Actúan asimismo sobre las plaquetas humanas como inhibidores de la tromboxano sintetasa (las respectivas IC_{50} son 7 μM, 75 μM y 100 μM) y como inhibidores débiles de la ciclooxigenasa (las respectivas IC_{50} son aproximadamente 100 μM, 150 μM y 750 μM), determinando un ligero aumento en la síntesis de prostaglandinas y 12-HETE por derivación del substrato.

3. La ciclosporina A, en el intervalo de concentraciones que ejercen un efecto citostático sobre los queratinocitos humanos, no produce cambios en el metabolismo del ácido araquidónico exógeno en suspensiones de queratinocitos humanos sometidas a incubaciones breves (minutos).

4. La ciclosporina A, en el intervalo de concentraciones comprendido entre 0 y 5 μg/mL, no determina efecto citotóxico alguno sobre cultivos de fibroblastos dérmicos humanos en fase

de confluencia temprana, lo que permite evaluar su posible efecto sobre el metabolismo del ácido araquidónico exógeno en fibroblastos dérmicos humanos en cultivo.

5. La ciclosporina A ejerce a largo plazo (24 horas) un efecto inhibidor dependiente de la dosis sobre la síntesis de PGE_2 y de PGI_2, los principales productos de la ciclooxigenasa, en cultivos de fibroblastos dérmicos humanos procedentes de piel sana.

6. La manipulación dietética, junto con la administración durante 8 semanas de aceite de pescado conteniendo 2.59 g/día de ácido eicosapentaenoico y 0.55 g/día de ácido docosahexaenoico, produjo una mejoría clínica significativa y progresiva en el índice PASI, así como en el grado de eritema, infiltración y descamación en pacientes con psoriasis en placas estable y de intensidad moderada. El grado de mejoría observado en el curso del período de tratamiento alcanza significación estadística incluso en comparación con la mejoría que tiende a producirse en el grupo control al que se administró aceite de oliva.

7. Por lo que respecta a la evaluación histológica, se apreció una mejoría significativa en el grado de acantosis epidérmica, que se correlacionó con la respuesta clínica a la 8ª semana de tratamiento en el grupo tratado con aceite de pescado.

8. No se detectaron efectos adversos, alteraciones en los parámetros hematológicos o bioquímicos de la analítica estándar ni diferencias o alteraciones en el perfil lipídico con el transcurso del tratamiento en ningún paciente.

9. No se detectaron diferencias significativas, ni entre grupos de tratamiento ni entre el principio y final del mismo, en cuanto al metabolismo del ácido araquidónico endógeno en

suspensiones de leucocitos polimorfonucleares. En base a la menor dispersión estadística de los resultados correspondientes a producción máxima (5 minutos de incubación), este parámetro parece ser el más apropiado para evaluar el metabolismo del ácido araquidónico endógeno por los leucocitos polimorfonucleares en ulteriores estudios.

10. A las 8 semanas de tratamiento se detectaron sistemáticamente nuevos picos cromatográficos en las incubaciones de leucocitos polimorfonucleares procedentes de pacientes tratados con aceite de pescado. Estos picos, que corresponden con toda probabilidad a LTB_5 y otros metabolitos de los ácidos grasos ω-3 administrados, permiten la monitorización del cumplimiento de la prescripción y de la absorción del aceite de pescado. Mediante la cuantificación de dichos picos puede determinarse el cociente LTB_5/LTB_4, que al parecer se correlaciona con la mejoría clínica y constituye un parámetro útil a evaluar en ulteriores estudios.

11. En los pacientes tratados con aceite de pescado se apreció una disminución en la producción plaquetar máxima de eicosanoides por las vías de la ciclooxigenasa y la 12-lipoxigenasa, especialmente significativa en el caso del 12-HETE, y que tendía a correlacionarse con la mejoría clínica, mientras que en el grupo de pacientes tratados con aceite de oliva se apreció un aumento significativo en la producción de HHT y 12-HETE en la semana 8 con respecto a la semana 0 del protocolo.

12. El estudio del metabolismo del ácido araquidónico endógeno en suspensiones de plaquetas parece ser un buen parámetro indicador de la eficacia metabólica del tratamiento dietético de la psoriasis con aceite de pescado.

En relación con las anteriores conclusiones pueden efectuarse los siguientes comentarios:

El potencial terapéutico teórico del piriprost en el tratamiento tópico de la psoriasis se ve limitado por su escasa potencia como inhibidor de la 5-lipoxigenasa y el resultado negativo en modelos experimentales de inflamación por leucocitos polimorfonucleares. La eficacia clínica del lonapalene como tratamiento tópico de la psoriasis debe correlacionarse con su efecto sobre el metabolismo del ácido araquidónico en las placas de psoriasis, puesto que existen posibles vías alternativas en la biosíntesis epidérmica del 12-HETE y otros eicosanoides con actividad biológica relevante en la psoriasis.

La demostración del efecto inhibidor de la 5-lipoxigenasa por parte de diversos imidazoles y la posibilidad de que actúen como inhibidores de la monooxigenasa epidérmica, posiblemente responsable de la síntesis de 12-HETE, justifica el estudio de la relación estructura-actividad y los mecanismos de acción bioquímica de los imidazólicos, así como el desarrollo de nuevos derivados y su posible ensayo clínico en el tratamiento tópico de la psoriasis.

La ciclosporina ejerce un efecto no inmediato, sino a largo plazo, sobre el metabolismo del ácido araquidónico exógeno en cultivos de fibroblastos dérmicos humanos, inhibiendo la síntesis de productos de la ciclooxigenasa. Este efecto podría explicarse a través de una inhibición directa de la síntesis de ciclooxigenasa o un efecto sobre la modulación de la misma por diversos mediadores y citocinas, siendo necesarios estudios adicionales para aclarar el posible mecanismo responsable. Los eicosanoides producidos por la epidermis y la dermis, y en particular los derivados de la ciclooxigenasa, pueden intervenir en la regulación de las respuesta inflamatorias y de proliferación epidérmica que caracterizan a la psoriasis. Se requieren ulteriores estudios para aclarar si dicho efecto de la ciclosporina A sobre la síntesis de eicosanoides puede tener relación con los mecanismos de acción terapéutica de dicho fármaco en la psoriasis y otras enfermedades cutáneas.

El efecto del tratamiento dietético sobre el metabolismo del ácido araquidónico en suspensiones de plaquetas podría explicarse por la substitución del ácido araquidónico por ácido eicosapentaenoico en la membrana plaquetar, cuya demostración requeriría la determinación del cociente ácido eicosapentaenoico/ácido araquidónico. También podrían reflejar una tendencia a la normalización de las alteraciones previamente descritas en el metabolismo plaquetar del ácido araquidónico en pacientes psoriásicos, que se correlacionarían con hiperagregabilidad plaquetar y tendencia a los fenómenos trombóticos. Las posibles implicaciones terapéuticas del tratamiento dietético con ácido eicosapentaenoico o ácido docosahexaenoico sobre la función plaquetar en pacientes psoriásicos deben evaluarse con mayor detalle en el futuro.

El importante papel de los eicosanoides en el desarrollo, mantenimiento y eventual resolución espontánea o terapéutica de las lesiones de psoriasis requiere el desarrollo de estudios adicionales que atiendan al origen celular de los eicosanoides in situ, su destino biológico (retención, exportación, metabolismo transcelular), los mecanismos de regulación de su síntesis y actividad biológica, y la investigación de la posible modulación farmacológica y papel fisiopatológico de las diferentes vías metabólicas (ciclooxigenasa, 5-, 12- y 15-lipoxigenasas, monooxigenasas) del ácido araquidónico y otros ácidos grasos, en especial los ω-3, en diferentes tipos morfológicos y momentos evolutivos de la psoriasis.

8. BIBLIOGRAFIA.

1. Glickman FS. Lepra, psora, psoriasis. J Am Acad Dermatol 1986;14:863-866.

2. Fry L. Psoriasis. Br J Dermatol 1988;119: 445-461.

3. Ackerman AB. Histologic diagnosis of inflammatory skin diseases. Philadelphia: Lea & Febiger, 1978.

4. Pinkus H, Mehregan AH, eds. A guide to dermatohistopathology, 3ª ed. New York: Appleton-Century-Crofts, 1981;101-105.

5. Lever WF, Schaumburg-Lever G, eds. Histopathology of the skin, 6ª ed. London: Lippincott, 1983;139-147.

6. Chowaniec O, Jablonska S, Beutner EH, Proniewska M, Jarzabek-Chorzelska M, Rzesa G. Earliest clinical and histological changes in psoriasis. Dermatologica 1981;163:42-51.

7. Jablonska S, Chowaniec O, Maciejowska E. Histology of psoriasis: the role of polymorphonuclear neutrophils. En: Beutner EH, ed. Autoimmunity in psoriasis. Boca Raton: CRC Press, 1982;21-36.

8. Braun-Falco O. The initial psoriatic lesion. En: Farber E, Cox A, eds. Psoriasis. Proceedings of 2nd symposium. New York: Yorke Medical Books, 1977;1-11.

9. Ragaz A, Ackerman A. Evolution, maturation, and regression of lesions of psoriasis. Am J Dermatopathol 1979;1:199-214.

10. Braun-Falco O, Scherer R. Immunoinflammatory phenomena in psoriasis. En: Beutner EH, ed. Autoimmunity in psoriasis. Boca Raton: CRC Press, 1982;165-183.

11. Ackerman AB, Ragaz A. The lives of lesions. New York: Masson, 1984.

12. Brody I. Mast cell degranulation in the evolution of acute eruptive guttate psoriasis. J Invest Dermatol 1984;82:460-464.

13. Brody I. Dermal and epidermal involvement in the evolution of acute eruptive guttate psoriasis vulgaris. J Invest Dermatol 1984;82:465-470.

14. Schubert C, Christophers E. Mast cells and macrophages in early relapsing psoriasis. Arch Dermatol Res 1985;277:352-358.

15. Schaumburg-Lever G, Orfanos C, Lever WF. Histopathology and electron microscopy. En: Roenigk HH Jr, Maibach HI, eds. Psoriasis. New York: Marcel Dekker, 1985;299-307.

16. Cox AJ. Polymorphonuclear leukocytes in psoriasis. En: Farber

E, Cox A, eds. Psoriasis. Proceedings of the Third International Symposium. New York: Grune & Stratton,1981; 233-234.

17. Van de Kerkhof PCM, Lammers AM. Intraepidermal accumulation of polymorphonuclear leukocytes in chronic stable plaque psoriasis. Dermatologica 1987;174:224-227.

18. Burks JW, Montgomery H. Histopathologic study of psoriasis. Arch Dermatol 1943;48:479-493.

19. Van Scott EJ, Ekel TM. Kinetics of hyperplasia in psoriasis. Arch Dermatol 1963;88:373-381.

20. Fry L, McMinn RMH. The action of chemotherapeutic agents on psoriatic epidermis. Br J Dermatol 1968;80:373-383.

21. Weinstein GD, Frost P. Abnormal cell proliferation in psoriasis. J Invest Dermatol 1968;50:254-259.

22. Weinstein GD, van Scott EJ. Autoradiographic analysis of turnover times of normal and psoriatic epidermis. J Invest Dermatol 1965;45:257-262.

23. Marks R. Epidermal activity in the involved and uninvolved skin of patients with psoriasis. Br J Dermatol 1978;98:399-404.

24. Krueger GG. Psoriasis: current concepts of its etiology and pathogenesis. En: Dobson RL, Thiers BH, eds. Year book of dermatology. Chicago, Year Book Medical Publishers, 1981;13-69.

25. Weinstein GD, McCullough JL. Cell proliferation kinetics. En: Roenigk HH Jr, Maibach HI, eds. Psoriasis. New York: Marcel Dekker, 1985;233-247.

26. Bauer FW. Cell kinetics. En: Mier PD, van de Kerkhof PCM, eds. Textbook of psoriasis. Edinburgh: Churchill Livingstone, 1986:100-112.

27. Heenen EM, Galand P. On cell kinetics in psoriasis. Br J Dermatol 1984;110:241-245.

28. Christophers E, Krueger GG. Psoriasis. En: Fitzpatrick TB, Eisen AZ, Wolff K, Freedberg IM, Austen KF, eds. Dermatology in general medicine. 3rd. ed. New York: McGraw Hill,1987:461-491.

29. Christophers E, Schubert C. Psoriasis. En: Thody AJ, Friedman PS, eds. Scientific basis of dermatology. A physiological approach. Edinburgh: Churchill Livingstone,1986:151-171.

30. Van Erp PEJ, Mier PD. Molecular biology. En: Mier PD, van de Kerkhof PCM, eds. Textbook of psoriasis. Edinburgh:Churchill Livingstone,1986:125-149.

31. Baden HP, McGilvray N, Chen CK, Lee LD, Kubilus J. The keratin polypeptides in psoriatic epidermis. J Invest Dermatol 1978;70:294-297.

32. Skerrow D, Hunter L. Protein modifications during the keratinization of normal and psoriatic human epidermis. Biochim Biophys Acta 1978;537:474-484.

33. Bowden PE, Wood EJ, Cunliffe WJ. Comparison of prekeratin and keratin polypeptides in normal and psoriatic human epidermis. Biochim Biophys Acta 1983;743:172-179.

34. Bernard BA, Asselineau D, Schaffar-Deshayes L, Darmon MY. Abnormal sequence of expression of differentiation markers in psoriatic epidermis: inversion of two steps in the differentiation program?. J Invest Dermatol 1988;90:801-805.

35. Dubertret L, Bertaux B, Fosse M, Touraine R. Localization of proteolytic activity in psoriatic skin. Br J Dermatol 1982;107:499-504.

36. Dubertret L, Bertaux B, Touraine R. Psoriasis: a defect in the regulation of epidermal proteases, as shown by serial biopsies after cantharidin application. Br J Dermatol 1984; 110:405-410.

37. Fräki JE, Briggaman RA, Lazarus GS. Uninvolved skin from psoriatic patients develops signs of involved psoriatic skin after being grafted onto nude mice. Science 1982;215:685-686.

38. Fräki JE, Briggaman RA, Lazarus GS. Transplantation of psoriatic skin onto nude mice. J Invest Dermatol 1983;80 (Suppl):31s-35s.

39. Grøndahl-Hansen J, Ralfkiær E, Nielsen LS, Kristensen P, Frentz G, Danø K. Immunohistochemical localization of urokinase- and tissue-type plasminogen activators in psoriatic skin. J Invest Dermatol 1987;88:28-32.

40. Lotti T, Bonan P, Panconesi E. Epidermal plasminogen activator activity, tPA-dependent, is a marker of disease activity in psoriasis. J Invest Dermatol 1988;90:86-87.

41. Roelfzema H, Bergers M, van Erp P, Gommans JM, Mier PD. Studies on the plasma membrane of normal and psoriatic keratinocytes. 1. Characterization of glycoconjugates. Br J Dermatol 1981;105:509-516.

42. Roelfzema H, van Erp P. Studies on the plasma membrane of normal and psoriatic keratinocytes. 6. Cell surface and shed glycoproteins. J Invest Dermatol 1983;80:24-26.

43. Commans JM, van den Hurk JJMA, Bergers M, van Erp P, Mier PD, Roelfzema H. Studies on the plasma membrane of normal and psoriatic keratinocytes. 5. Lectin binding. Br J Dermatol 1982;106:317-322.

44. Weinstein GD, McCullough JL, Ross PA. Cell kinetic basis for pathophysiology of psoriasis. J Invest Dermatol 1985;85:579-583.

45. Patterson JAK, Eisinger M, Haynes BF, Berger CL, Edelson RLE. Monoclonal antibody 4F2 reactive with basal layer keratinocytes: studies in the normal and a hyperproliferative state. J Invest Dermatol 1984;83:210-213.

46. Leigh IM, Pulford KA, Ramaekers FCS, Lane EB. Psoriasis: maintenance of an intact monolayer basal cell differentiation compartment in spite of hyperproliferation. Br J Dermatol 1985;113:53-64.

47. Mansbridge JN, Knapp AM, Strefling AM. Evidence for an alternative pathway of keratinocyte maturation in psoriasis from an antigen found in psoriatic but not normal epidermis. J Invest Dermatol 1984;83:296-301.

48. Bernard BA, Robinson SM, Vandaele S, Mansbridge JN. Abnormal maturation pathway of keratinocytes in psoriatic skin. Br J Dermatol 1985;112:647-653.

49. Bernard BA, Réano A, Darmon YM, Thivolet J. Precocious appearance of involucrin and epidermal transglutaminase during differentiation of psoriatic skin. Br J Dermatol 1986;114:279-283.

50. Bell CM, Skerrow CJ. Lectin binding to psoriatic epidermis. Br J Dermatol 1985;113:205-212.

51. Voorhees JJ, Duell EA. Psoriasis as a possible defect of the adenyl-cyclase-cyclic AMP cascade. A defective chalone mechanism? Arch Dermatol 1971;104:352-358.

52. Voorhees JJ. Commentary: cyclic adenosine monophosphate regulation of normal and psoriatic epidermis. Arch Dermatol 1982;118:869-874.

53. Anderson TF, Voorhees JJ. Cyclic nucleotides. En: Roenigk HH Jr, Maibach HI, eds. Psoriasis. New York: Marcel Dekker, 1985:271-284.

54. Lowe NJ, Breeding J, Ruissel DH. Cutaneous polyamine in psoriasis. Br J Dermatol 1982;107:21-26.

55. Lowe NJ. Cutaneous polyamines and their biosynthetic enzymes. En: Roenigk HH Jr, Maibach HI, eds. Psoriasis. New York: Marcel Dekker, 1985:249-254.

56. Van de Kerkhof PCM, van Erp PEJ. Calmodulin levels are grossly elevated in the psoriatic lesion. Br J Dermatol 1983;108:217-218.

57. Van de Kerkhof PCM, van Erp PEJ. Epidermal calmodulin and skin disease. Int J Dermatol 1985;24:507-508.

58. Tucker WFG, MacNeil S, Blechen SS, Tomlinson S. Biologically active calmodulin levels are elevated in both involved and uninvolved epidermis in psoriasis. J Invest Dermatol 1984;82: 298-299.

59. Fairley JA, Marcelo CL, Hogan VA, Voorhees JJ. Increased calmodulin levels in psoriasis and low Ca^{++} regulated mouse epidermal keratinocyte cultures. J Invest Dermatol 1985;84; 195-198.

60. MacNeil S, Tucker WFG, Dawson RA, Blechen SS, Tomlinson S. The calmodulin content of the epidermis in psoriasis. Clin Sci 1985;69:681-686.

61. Mizumoto T, Hashimoto Y, Hirokawa M, Ohkuma N, Iizuka H, Ohkawara A. Calmodulin activities are significantly increased in both uninvolved and involved epidermis in psoriasis. J Invest Dermatol 1985;85:450-452.

62. Nanney LB, Stoscheck CM, Magid M, King LEJr. Altered [^{125}I]epidermal growth factor binding and receptor distribution in psoriasis. J Invest Dermatol 1986;86:260-265.

63. Bartel RL, Marcelo CL, Voorhees JJ. Partial characterization of phospholipase C activity in normal, psoriatic uninvolved, and lesional epidermis. J Invest Dermatol 1987;88:447-451.

64. Gentleman S, Martensen TM, Digiovanna JJ, Chader GJ. Protein tyrosine kinase and protein phosphotyrosine phosphatase in normal and psoriatic skin. Biochim Biophys Acta 1984;53:798-801.

65. Pike MC, Lee CS, Elder JT, Voorhees JJ, Fisher GJ. Phosphatidylinositol (PI) kinase activity is increased in psoriatic epidermis. Clin Res 1988;36:685A.

66. Pike MC, Lee CS, Elder JT, Voorhees JJ, Fisher GJ. Increased phosphatidylinositol kinase activity in psoriatic epidermis. J Invest Dermatol 1989;92:791-797.

67. Horn F, Marks F, Fisher GJ, Marcelo CL, Voorhees JJ. Decreased protein kinase C activity in psoriatic versus normal epidermis. J Invest Dermatol 1987;88:220-222.

68. Liu CC, Parsons CS. Serial cultivation of epidermal keratinocytes from psoriatic plaques. J Invest Dermatol 1983;81:54-61.

69. Fräki JE, Lazarus GS, Gilgor RS, Marchase P, Singer KH. Correlation of epidermal plasminogen activator activity with disease activity in psoriasis. Br J Dermatol 1983;108:39-44.

70. Nickoloff BJ. Role of gamma interferon in cutaneous trafficking of lymphocytes with emphasis on molecular and cellular adhesion events. Arch Dermatol 1988;124:1835-1843.

71. Nickoloff BJ, Griffiths CEM, Barker JNWN. The role of adhesion molecules, chemotactic factors, and cytokines in inflammatory and neoplastic skin disease - 1990 update. J Invest Dermatol 1990;94:151S-157S.

72. Krueger JG, Krane JF, Carter M, Gottlieb AB. Role of growth factors, cytokines, and their receptors in the pathogenesis of psoriasis. J Invest Dermatol 1990;94:135S-140S.

73. Cunningham DJ, Wilkinson DI, Orenberg EK. Is the dermal fibroblast significant in psoriasis?. Cutis 1986;38:93-94.

74. Priestley GC. Hyperactivity of fibroblasts cultured from psoriatic skin. II.Synthesis of macromolecules. Br J Dermatol 1983;109:157-164.

75. Priestley GC, Adams LW. Hyperactivity of fibroblasts cultured from psoriatic skin. I. Faster proliferation and effect of serum withdrawal. Br J Dermatol 1983;109:149-156.

76. Priestley GC, Adams LW. Mitogenic effects of sera from normal and psoriatic subjects on human skin fibroblasts. Arch Dermatol Res 1985;277:13-15.

77. Nagao S, Seishima M, Mori S, Nozawa Y. Increased protein kinase C activity in fibroblast membranes from psoriatic patients. J Invest Dermatol 1988;90:406-408.

78. Coulomb B, Lebreton C, Dubertret L. Influence of dermal fibroblasts on epidermalization. J Invest Dermatol 1989;92:122-125.

79. Saiag P, Coulomb B, Lebreton C, Bell E, Dubertret L. Psoriatic fibroblasts induce hyperproliferation of normal keratinocytes in a skin equivalent model in vitro. Science

1985;230:669-672.

80. Horiuchi A, Marshall J, Cedarholme-Williams S, Ryan TJ. Stimulation of extra- and intracellular urokinase in epidermal cells in the presence of psoriasis fibroblast conditioned medium. Jap J Derm 1987;97:600.

81. Kragballe K, Voorhees JJ. Eicosanoids in psoriasis - 15-HETE on the stage. Dermatologica 1987;174:209-213.

82. Nyfros A, Rothenborg HW. Cutaneous blood flow in psoriasis measured by [133]xenon clearance. J Invest Dermatol 1970;54:381-385.

83. Klemp P, Staberg B. Cutaneous blood flow in psoriasis. J Invest Dermatol 1983;81:503-506.

84. Pinkus H, Mehregan AH. The primary histologic lesion of seborrheic dermatitis and psoriasis. J Invest Dermatol 1966;46:109-116.

85. Aschheim E, Farber E. Blood-tissue exchange in psoriatic skin. Acta Derm Venereol 1966;46:310-313.

86. Telner P, Fekete Z. The capillary responses in psoriatic skin. J Invest Dermatol 1961;36:225-230.

87. Braverman IM, Yen A. Ultrastructure of the capillary loops in the dermal papillae of psoriasis. J Invest Dermatol 1977;68: 53-60.

88. Ryan TJ. Microcirculation in psoriasis: blood vessels, lymphatics, and tissue fluid. Pharmacol Ther 1980;10:27-64.

89. Braverman IM, Sibley J. Role of the microcirculation in the treatment and pathogenesis of psoriasis. J Invest Dermatol 1982;78:12-17.

90. Mordotsev VN, Albanova VI. Morphology of skin microvasculature in psoriasis. Am J Dermatopathol 1989;11:33-42.

91. Van de Kerkhof PCM, van Rennes H, de Grood RM, et al. Response of the clinically uninvolved skin of psoriatic patients to standard injury. Br J Dermatol 1983;109:287-294.

92. Brassinne M, Lachapelle JM. Epidermal and dermal cell renewal in pustular psoriatic erythroderma. En: Farber EM, Cox AJ, eds. Psoriasis: Proceedings of the Second International Symposium. New York: Yorke Medical Books, 1977;368-370.

93. Majewski S, Tigalonowa M, Jablonska S, Polakowski I, Janczura E. Serum samples from patients with active psoriasis enhance

lymphocyte-induced angiogenesis and modulate endothelial cell proliferation. Arch Dermatol 1987;123:221-225.

94. Majewski S, Kaminski M, Jablonska S, et al. Angiogenic capability of peripheral blood mononuclear cells in psoriasis. Arch Dermatol 1985;121:1018-1021.

95. Barnhill RL, Parkinson EK, Ryan TJ. Supernatants from cultured human epidermal keratinocytes stimulate angiogenesis. Br J Dermatol 1984;110:273-281.

96. Soltani K, van Scott EJ. Patterns and sequence of tissue changes in incipient and evolving lesions of psoriasis. Arch Dermatol 1972;106:484-490.

97. Tagami H, Iwatsuki K, Takematsu H. Psoriasis and leukocyte chemotaxis. J Invest Dermatol 1987;88(Suppl):18s-23s.

98. Bjerke JR, Krogh HK, Matre R. Characterisation of mononuclear cell infiltrates in psoriatic lesions. J Invest Dermatol 1978;71:340-343.

99. Bos JD, Hulsebosch HJ, Krieg SR, Bakker PM, Cormane RH. Immunocompetent cells in psoriasis; in situ immunophenotyping by monoclonal antibodies. Arch Dermatol Res 1983;275:181-189.

100. Baker BS, Swain AF, Fry L, Valdimarsson H. Epidermal T lymphocytes and HLA-DR expression in psoriasis. Br J Dermatol 1984;110:555-564.

101. Bos JD, Krieg SR. Psoriasis infiltrating cell immunophenotype: changes induced by PUVA or corticosteroid treatment in T-cell subsets, Langerhans cells and interdigitating cells. Acta Derm Venereol (Stockh) 1985;65:390-397.

102. Kaudewitz P, Braun-Falco O, Kind P, Galosi A, Rieber P, Riethmuller G. Distribution of T-cell subsets as defined by monoclonal antibodies in skin lesions of psoriasis vulgaris. Arch Dermatol Res 1984;276:33-35.

103. Ramirez-Bosca A, Martinez-Ojeda L, Valcuende-Cavero F, Castells-Rodellas A. A study of local immunity in psoriasis. Br J Dermatol 1988;119:587-595.

104. Baker BS, Swain AF, Valdimarsson H, Fry L. T-cell subpopulations in the blood and skin of patients with psoriasis. Br J Dermatol 1984;110:37-44.

105. Valdimarsson H, Baker BS, Jonsdittir I, Fry L. Psoriasis: a disease of abnormal keratinocyte proliferation induced by T-lymphocytes. Immunology Today 1986;7:256-259.

106. Bos JD. The pathomechanisms of psoriasis; the skin immune system and cyclosporin. Br J Dermatol 1988;118:141-155.

107. Reimer G, Leonhardi G, Schwalera U. DNA-binding proteins of psoriatic scales. III. Biochemical characterisation as non-histone proteins. Arch Dermatol Res 1978;262:185-189.

108. Ashgar SS, Ali-Briggs EF, Reimer G, Cormane RH. Interaction of psoriasis scale non-histone proteins with the antiboidies eluted from lymphocytes of psoriasis patients reactive with basal cell nuclei. Acta Derm Venereol (Stockh) [Suppl] 1984;113:50-54.

109. Beutner EH, Binder WL, Jablonska S, Kumar V. Immunofluorescence findings on stratum corneum antibodies, antigens and their reaction in vitro and in vivo as related to repair and psoriasis. En: Beutner EH, ed. Autoimmunity in psoriasis. Boca Raton: CRC Press, 1982;51-79.

110. Swerlick RA, Cunningham MW, Hall NK. Monoclonal antibodies cross-reactive with Group-A Streptococci and normal and psoriatic human skin. J Invest Dermatol 1986;87:367-371.

111. Iversen O-J, Rodahl E, Dalen AB. Rabbit antibodies against the major internal protein of a retrovirus-like particle bind to epidermal cells in psoriatic skin. Arch Virol 1985;86:341-346.

112. Cohen S, Elliott GA. The stimulation of epidermal keratinization by a protein isolated from the submaxillary gland of the mouse. J Invest Dermatol 1963;40:1-5.

113. Barrandon Y, Green H. Cell migration is essential for sustained growth of keratinocyte colonies: The roles of transforming growth factor-(alpha) and epidermal growth factor. Cell 1987;50:1131-1137.

114. Carpenter G, Cohen S. Epidermal growth factor. Ann Rev Biochem 1979;48:193-216.

115. King LE. What does epidermal growth factor do and how does it do it? J Invest Dermatol 1985;84:165-167.

116. Ellis DL, Kafka SP, Chow JC, et al. Melanoma, growth factors, acantosis nigricans, the sign of Leser-Trélat, and multiple acrochordons. A possible role for alpha-transforming growth factor in cutaneous paraneoplastic syndromes. N Engl J Med 1987;317:1582-1587.

117. Coffey RJ, Derynck R, Wilcox JN, Bringman TS, Goustin AS, Moses HL, Pittelkow MR. Production and autoinduction of transforming growth factor-(alpha) in human keratinocytes. Nature (London) 1987;328:817-823.

118. Gottlieb AB, Chang CK, Posnett DN, Fanelli B, Tam JP. Detection of transforming growth factor (alpha) in normal, malignant, and hyperproliferative human keratinocytes. J Exp Med 1988;167:670-675.

119. Bjorge JD, Paterson AJ, Kudlow JE. Phorbol ester or epidermal growth factor (EGF) stimulates the concurrent accumulation of mRNA for the EGF receptor and its ligand transforming growth factor-(alpha) in a breast cancer cell line. J Biol Chem 1989;264:4021-4027.

120. Sauder DN, Arsenault TV, Stetsko D, Harley CB. Isolation and partial purification of a putative DNA clone (kIL-1): ETAF is distinct from IL-1 alpha or IL-1 betha. J Invest Dermatol 1987;88:515.

121. Camp R, Fincham N, Cunningham F, Morris J, Chu A, Greaves MW. Characterization and quantification of chemokinetic peptides in psoriatic scale. J Invest Dermatol 1986;86:467.

122. Konnikov N, Ree BJ, Dinarello CA, Pincus SH. Interleukin-1 (IL-1) is present in psoriatic plaques. J Invest Dermatol 1987;88:499.

123. Dowd PM, Camp RDR, Greaves MW. In vivo effects of human recombinant interleukin-1 alfa (IL-1-alfa) in normal human skin. J Invest Dermatol 1987;88:485.

124. Camp R, Fincham N, Ross J, Bird C, Gearing A. Potent inflammatory properties in human skin of interleukin-1 alpha-like material isolated from normal skin. J Invest Dermatol 1990;94:735-741.

125. Pentland AP, Mahoney MG. Keratinocyte prostaglandin synthesis is enhanced by IL-1. J Invest Dermatol 1990;94:43-46.

126. Le J, Vilcek J. Tumor necrosis factor and interleukin-1: cytokines with multiple overlapping biological activities. Lab Invest 1987;56:234-248.

127. Hancock GE, Kaplan G, Cohn ZA. Keratinocyte growth regulation by the products of immune cells. J Exp Med 1988;168:1395-1402.

128. Grossman RM, Krueger J, Yourish D, et al. Interleukin 6 is expressed in high levels in psoriatic skin and stimulates proliferation of cultured human keratinocytes. Proc Natl Acad Sci USA 1989;86:6367-6371.

129. McColl SR, Krump E, Naccache PH, Borgent P. Enhancement of human neutrophil leukotriene synthesis by human granulocyte-macrophage colony-stimulating factor. Agents Actions 1989;27:

465-468.

130. Bjerke JR, Haukenes G, Livden JK, et al. Activated T-lymphocytes, interferon and retrovirus-like particles in psoriatic lesions. Arch Dermatol 1983;119:955-956.

131. Bjerke JR, Livden JK, Degre M, Matre R. Interferon in suction blister fluid from psoriatic lesions. Br J Dermatol 1983;108:295-299.

132. Nickoloff BJ. Lymphocyte-keratinocyte interactions mediated through interferon. New observations relevant to psoriasis. Cutis 1984;34:445-446.

133. Nickoloff BJ. Interferons and psoriasis. 1987 perspective. Dermatologica 1987;175:1-4.

134. Nickoloff BJ, Mitra RS, Elder JT, Fisher GJ, Voorhees JJ. Decreased growth inhibition by recombinant gamma interferon is associated with increased production of transforming growth factor alpha in keratinocytes cultured from psoriatic lesions. Br J Dermatol 1989;121:161-174.

135. Quesada JR, Gutterman JV. Psoriasis and alpha-interferon. Lancet 1986;1:1466-1468.

136. Harrison PV, Peat MJ. Effect of interferon on psoriasis. Lancet 1986;2:457-458.

137. Neumann R, Pohl-Markl H, Aberer E. Parenteral interferon-Alpha treatment of psoriasis. Dermatologica 1987;175:23-28.

138. Fierlbeck G, Rassner G, Muller C. Psoriasis induced at the injection site of recombinant interferon gamma. Arch Dermatol 1990;126:351-355.

139. Schröder J-M, Christophers E. Identification of C5a des arg and an anionic neutrophil-activating peptide (ANAP) in psoriatic scales. J Invest Dermatol 1986;87:53-58.

140. Johannesson A, Hammar H, Sunqvist K-G. The deposition of immunoglobulins and complement in stratum corneum in microscopic lesions in patients with active psoriasis: the relationship to hyperproliferation. Acta Derm Venereol (Stockh) 1982;62:21-25.

141. Hammarström S, Hamberg M, Samuelsson B, Duell EA, Stawiski M, Voorhees JJ. Increased concentrations of nonesterified arachidonic acid, 12L-hydroxy-5,8,10,14-eicosatetraenoic acid, prostaglandin E_2, and prostaglandin $F_{2\alpha}$ in epidermis of psoriasis. Proc Natl Acad Sci USA 1975;72:5130-5134.

142. Barr RM, Brain S, Camp RDR, et al. Levels of arachidonic acid and its metabolites in the skin in human allergic and irritant contact dermatitis. Br J Dermatol 1984;111:23-28.

143. Barr R, Wong E, Mallet A, Olins L, Greaves M. The analysis of arachidonic acid metabolites in normal, uninvolved and lesional psoriatic skin. Prostaglandins 1984;28:57-65.

144. Camp RDR, Mallet AI, Woollard PM, Brain SD, Kobza Black A, Greaves MW. The identification of hydroxy fatty acids in psoriatic skin. Prostaglandins 1983;26:431-447.

145. Grabbe J, Czarnetzki BM, Rosenbach T, Mardin M. Identification of chemotactic lipoxygenase products of arachidonate metabolism in psoriatic skin. J Invest Dermatol 1984;82:477-479.

146. Brain SD, Camp RD, Charleson S, et al. The release of LTC_4-like material from the involved lesional skin in psoriasis. Br J Clin Pharmacol 1984;17:650P.

147. Brain S, Camp R, Dowd P, Kobza Black A, Greaves M. The release of leukotriene B_4-like material in biologically active amounts from the lesional skin of the patients of psoriasis. J Invest Dermatol 1984;83:70-73.

148. Brain S, Camp R, Black A, et al. Leukotrienes C_4 and D_4 in psoriatic skin lesions. Prostaglandins 1985;29:611-619.

149. Ruzicka T, Simmet T, Peskar B, Ring J. Skin levels of arachidonic acid-derived inflammatory mediators and histamine in atopic dermatitis and psoriasis. J Invest Dermatol 1986;86:105-108.

150. Duell EA, Fortune J, Petersen C, Ellis C, Voorhees JJ. Eicosanoids (LTB_4, 12-HETE, PGE2, PGF2-alfa) quantitated simultaneously from keratomed epidermal strips of psoriatic skin. J Invest Dermatol 1986;87:137.

151. Duell EA, Ellis CN, Voorhees JJ. Determination of 5,12, and 15-lipoxygenase products in keratomed biopsies of normal and psoriatic skin. J Invest Dermatol 1988;91:446-450.

152. Greaves MW, Camp RDR. Prostaglandins, leukotrienes, phospholipase, platelet activating factor, and cytokines: an integrated approach to inflammation of human skin. Arch Dermatol Res 1988;280[Suppl]:S33-S41.

153. Forster S, Ilderton E, Summerly R, Yardley HJ. The level of phospholipase A_2 activity is raised in the uninvolved epidermis of psoriasis. Br J Dermatol 1983;108:103-105.

154. Verhagen A, Bergers AM, Jongerius M, Mier PD. A unique

phospholipase A_2 in human epidermis: its physiological function and its levels in certain dermatoses. J Invest Dermatol 1986;87:173.

155. Bartel RL, Marcelo CL, Gorsulowsky D, Voorhees JJ. Phospholipase A_2 and C activity in normal, and psoriatic uninvolved and lesional epidermis. J Invest Dermatol 1986;86:462.

156. Talwar H, Fisher GJ, Voorhees JJ. sn-1,2-diacylglycerol is increased in psoriatic involved versus uninvolved and normal epidermis. Clin Res 1988;36:698A.

157. Braquet P, Touqui L, Shen TY, Vargaftig BB. Perspectives in platelet-activating factor research. Pharmacol Rev 1987;39:97-145.

158. Farber EM, Nickoloff BF, Recht B, Fraki JE. Stress, symmetry, and psoriasis: possible role of neuropeptides. J Am Acad Dermatol 1986;14:305-311.

159. Krebs EG. Protein kinases. Curr Top Cell Regul 1972;5:99-133.

160. Marcelo CL, Tomich J. Cyclic AMP, glucocorticoid, and retinoid modulation of in vitro keratinocyte growth. J Invest Dermatol 1983;81:64s-68s.

161. Nemoto O, Adachi K, Takeda J, et al. Cyclic AMP-dependent protein kinase isoenzymes of pig skin and human skin from normal and psoriatic subjects. J Invest Dermatol 1983;80:111-115.

162. Sefton BM, Hunter T. Tyrosine protein kinases. Adv Cyclic Nucleotide Protein Phosphorylation Res 1984;18:195-227.

163. Chen WS, Lazar CS, Poenie M, Tsien RY, Gill GN, Rosenfeld MG. Requirement for intrinsic protein tyrosine kinase in the immediate and late actions of the EGF receptor. Nature 1987;328:820-823.

164. Aoyagi T, Suya H, Miura Y. Effect of epidermal growth factor on phosphatidylinositol turnover of pig epidermis. J Invest Dermatol 1985;84:301.

165. Pepinsky RB, Sinclair LK. Epidermal growth factor-dependent phosphorylation of lipocortin. Nature 1986;321:81-84.

166. Touqui L, Rothhut B, Shaw AM, Fradin A, Vargaftig BB, Russo-Marie F. Platelet activation - a role for a 40K anti-phospholipase A_2 protein indistinguishable from lipocortin. Nature 1986;321:177-180.

167. Brugge JS. The p35/p36 substrates of protein-tyrosine kinases

as inhibitors of phospholipase A_2. Cell 1986;46:149-150.

168. Iizuka H, Kajita S, Mizumoto T, Kawaguchi H. Glucocorticoid-induced modulation of the beta-adrenergic adenylate cyclase response of epidermis: its relation to epidermal phospholipase A_2 activity. J Invest Dermatol 1986;87:577-581.

169. Takai Y, Kishimoto A, Iwasa Y, et al. Calcium-dependent activation of a multifunctional protein kinase by membrane phospholipids. J Biol Chem 1979;254:3692-3695.

170. Bell RM. Protein kinase C activation by diacyl glycerol second messengers. Cell 1986;45:631- 632.

171. McPhail LC, Clayton C, Snyderman R. A potential second messenger role for arachidonic acid: activation of Ca^{2+}-dependent protein kinase. Trans Assoc Am Phys 1984;97:222-231.

172. Nishizuka Y. The molecular heterogeneity of protein kinase C and its implications for cellular regulation. Nature 1988;334: 661-665.

173. Nishizuka Y. The role of protein kinase C in cell surface signal transduction and tumour promotion. Nature 1984;308:693-698.

174. Gilman AG. G proteins: transducers of receptor-generated signals. Ann Rev Biochem 1987;56:615-649.

175. Rasmussen H. The calcium messenger system. N Engl J Med 1986;314:1094-1101, 1164-1170.

176. Kaplan DR, Whitman M, Schaffhausen B, et al. Common elements in growth factor stimulation and oncogenic transformation: 85 Kd phosphoprotein and phosphatidylinositol kinase activity. Cell 1987;50:1021-1029.

177. Walker DH, Pike LJ. Phosphatidylinositol kinase is activated in membranes derived from cells treated with epidermal growth factor. Proc Natl Acad Sci USA 1987;84:7513-7517.

178. Manalan AS, Klee CB. Calmodulin. Adv Cyclic Nucleotide Protein Phosphorylation Res 1984;18:227-278.

179. Tucker WFG, MacNeil S, Dawson RA, Tomlinson S, Bleehen S. Calmodulin levels in psoriasis: the effect of treatment. Acta Derm Venereol (Stockh) 1986;66:241-244.

180. Cantieri JS, Graff G, Goldberg ND. Cyclic GMP metabolism in psoriasis: activation of soluble epidermal guanylate cyclase by arachidonic acid and 12-h9droxy-5,8,10,14-eicosatetraenoic acid. J Invest Dermatol 1980;74:234-237.

181. Aktories K, Schultz G, Jakobs KH. Inhibitory regulation of adenylate cyclase by prostaglandins. Adv Prostaglandin Thromboxane Leukotriene Res 1983;12:283-290.

182. Gerzer R, Brash AR, Hardman JG. Activation of soluble guanylate cyclase by arachidonic acid and 15-lipoxygenase products. Biochim Biophys Acta 1986;886:383-389.

183. O'Flaherty JT. Phospholipid metabolism and stimulus-response coupling. Biochem Pharmacol 1987;36:407-412.

184. Baldassare JJ, Fisher GJ, Voorhees JJ. GTP-dependent hydrolysis of phosphatidylinositol-4,5-bisphosphate by phospholipase C from adult epidermis. J Invest Dermatol 1987;88:476.

185. Boron WF. The 'basic' connection. Nature 1984;312:312.

186. Michell B. Oncogenes and inositol lipids. Nature 1984;308:770.

187. Berridge MJ, Irvine RF. Inositol trisphosphate, a novel second messenger in cellular signal transduction. Nature 1984;312:315-321.

188. Ruzicka T. Inflammatory mediators as modulators of cell growth and differentiation. Skin Pharmacol 1988;1:139-140.

189. Gross E, Ruzicka T, Restorff B, Stolz W, Klotz K-N. High affinity binding and lack of growth-promoting activity of 12(S)-hydroxyeicosatetraenoic acid (12(S)-HETE) in a human epidermal cell line. J Invest Dermatol 1990;94:446-451.

190. Reusch MK, Wastek GJ. Leukotriene B_4 receptor on human keratinocytes in vitro. Clin Res 1988;36:687A.

191. Muller A, Michel L, Basset-Seguin N, Modat G, Dubertret L, Bonne C. Characterization of specific leukotriene C_4 binding sites on cultured human keratinocytes. Br J Dermatol 1988;119:275-280.

192. Boyce ST, Ham RG. Calcium-regulated differentiation of normal human epidermal keratinocytes in chemically defined clonal culture and serum-free serial culture. J Invest Dermatol 1983;81:33s-40s.

193. Stewart AF, Battaglini-Sabetta J, Millstone L. Hypocalcemia-induced pustular psoriasis of von Zumbusch. Ann Intern Med 1984;100:677-679.

194. Smith EL, Pincus SH, Donovan L, Holick MF. A novel approach for the evaluation and treatment of psoriasis. Oral or topical use of 1,25-dihydroxyvitamin D_3 can be a safe and effective

therapy for psoriasis. J Am Acad Dermatol 1988;19:516-528.

195. Fisher GF, Harris VA, Talwar H, Voorhees JJ. Protein kinase C regulates terminal differentiation in cultured adult human keratinocytes. Clin Res 1988;36:645A.

196. Fitzpatrick FA, Murphy RC. Cytochrome p450 metabolism of arachidonic acid: formation and biological actions of "epoxygenase" derived eicosanoids. Pharmacol Rev 1988;40:229-241.

197. Smith WL. The eicosanoids and their biochemical mechanisms of action. Biochem J 1989;259:315-324.

198. Lands WEM, Samuelsson B. Phospholipid precursors of prostaglandins. Biochim Biophys Acta 1968;164:426-429.

199. Irvine RF. How is the level of free arachidonic acid controlled in mammalian cells? Biochem J 1982;204:3-16.

200. Ziboh VA, Lord JT. Phospholipase A_2 activity in the skin. Biochem J 1979;184:283-290.

201. Hsueh W, Desai U, Gonzales-Crussi F, Lamb R, Chu A. Two phospholipase pools for prostaglandin synthesis in macrophages. Nature 1981;290:710-713.

202. Van den Bosch H. Intracellular phospholipases A. Biochim Biophys Acta 1980;604:191-246.

203. Moskowitz N, Shapiro L, Schook W, Puszkin S. Phospholipase A_2 modulation by calmodulin, prostaglandins and cyclic nucleotides. Biochem Biophys Res Commun 1983;115:94-99.

204. Hirata F, Axelrod J. Phospholipid methylation and biological signal transmission. Science 1980;209:1082-1090.

205. Hirata F, Schiffmann E, Venkatasubramanian K, Salomon D, Axelrod J. A phospholipase A_2 inhibitory protein in rabbit neutrophils induced by glucocorticoids. Proc Natl Acad Sci USA 1980;77:2533-2536.

206. Blackwell GJ, Carnuccio R, Di Rosca M, Flower RJ, Parente L, Persico P. Macrocortin: a polypeptide causing the antiphospholipase effect of glucorticoids. Nature 1980;287:147-149.

207. Hirata F, Yoshitada N, Yamada R, et al. Isolation and characterisation of lipocortin (lipomodulin). Agents Actions 1985;17:263-266.

208. Verhagen A, Bergers M, Van Erp PEJ, Commans JM, van de Kerkhof

PCM, Mier PD. Confirmation of raised phospholipase A_2 activity in the uninvolved skin of psoriasis. Br J Dermatol 1984;110: 731-732.

209. Korner CF, Hausmann G, Gemsa D, Resch K. Rate of prostaglandin synthesis is controlled not by phospholipase A activity but by reincorporation of released fatty acids into phospholipids. Agents Actions 1984;15:28-30.

210. Kurzok R, Lieb C. Biochemical studies of human semen: II. The action of semen on the human uterus. Proc Soc Exp Biol Med 1930;28:268-274.

211. Goldblatt MW. Properties of human seminal plasma. J Physiol 1935;84:208-218.

212. von Euler VS. On the specific vasodilating and plain muscle stimulating substances from accessory genital glands in man and certain animals (prostaglandin and vesiglandin). J Physiol 1936;88:213-234.

213. Hamberg M, Svensson J, Wakabayashi T, Samuelsson B. Isolation and structure of two prostaglandin endoperoxides that cause platelet aggregation. Proc Natl Acad Sci USA 1974;71:345-349.

214. Ohki S, Ogino N, Yamamoto S, Hayaishi O. Prostaglandin hydroperoxidase, an integral part of prostaglandin endoperoxide synthetase from bovine vesicular gland microsomes. J Biol Chem 1979;254:829-836.

215. Ogino M, Miyamoto T, Yamamoto S, Hayaishi O. Prostaglandin endoperoxide E isomerase from bovine vesicular microsomes, a glutathione-requiring enzyme. J Biol Chem 1977;253:890-898.

216. Nugteren DH, Hazelhof E. Isolation and properties of intermediates in prostaglandin biosynthesis. Biochim Biophys Acta 1973;326:448-461.

217. Ziboh VA, Lord JT, Penneys NS. Alterations of prostaglandin E_2-9-ketoreductase activity in proliferating skin. J Lipid Res 1977;18:37-43.

218. Christ-Hazelhof E, Nugteren DH, van Dorp DA. Conversions of prostaglandin endoperoxides by glutathione S-transferases and serum albumins. Biochim Biophys Acta 1976;450:450-461.

219. Hamberg M, Svensson J, Samuelsson B. Thromboxanes: a new group of biologically active compounds derived from prostaglandin endoperoxides. Proc Natl Acad Sci USA 1975;72:2994-2998.

220. Moncada S, Gryglewski R, Bunting S, Vane JR. An enzyme isolated from arteries transforms prostaglandin endoperoxides

to an unstable substance that inhibits platelet aggregation. Nature 1976;263:663-665.

221. Yoshimoto T, Yamamoto S, Okuma M, Hayasishi O. Solubilization and resolution of thromboxane synthesizing system from microsomes of bovine blood platelets. J Biol Chem 1977;252:5871-5877.

222. Anderson MW, Crutchley DJ, Tainer BE, Eling TE. Kinetic studies on the conversion of prostaglandin endoperoxide PGH_2 by thromboxane synthase. Prostaglandins 1978;16:563-570.

223. Samuelsson B, Dahlén S-E, Lindgren JA, Rouzer CA, Serhan CN. Leukotrienes and lipoxins: structures, biosynthesis, and biological effects. Science 1987;237:1171-1176.

224. Hamberg M, Samuelsson B. Prostaglandin endoperoxides: novel transformations of arachidonic acid in human platelets. Proc Natl Acad Sci USA 1974;71:3400-3404.

225. Bryant RW, Simon TC, Bailey JM. Role of glutathione peroxidase and hexose monophosphate shunt in the platelet lipoxygenase pathway. J Biol Chem 1982;257:14927-14943.

226. Samuelsson B, Borgeat P, Hammarstrom S, et al. Introduction of a nomenclature: leukotrienes. Prostaglandins 1979;17:785-787.

227. Hammarström S. Conversion of ^{14}C-labeled eicosapentaenoic acid (n-3) to leukotriene C_5. Biochim Biophys Acta 1981;663:575-577.

228. Hammarström S. Conversion of 5,8,11-eicosatrienoic acid to leukotrienes C_3 and D_3. J Biol Chem 1981;256:2275-2279.

229. McColl SR, Krump E, Naccache PH, Caon AC, Borgeat P. Activation of the human neutrophil 5-lipoxygenase by exogenous arachidonic acid; involvement of pertussis toxin-sensitive guanine nucleotide-binding proteins. Br J Pharmacol 1989;97:1265-1273.

230. Rouzer CA, Kargman S. Translocation of 5-lipoxygenase to the membrane in human leukocytes challenged with ionophore A23187. J Biol Chem 1988;263:10980-10988.

231. Dixon RAF, Diehl RE, Opas E, et al. Requirement of a 5-lipoxygenase-activating protein for leukotriene synthesis. Nature 1990;343:282-284.

232. Rouzer CA, Ford-Hutchinson AW, Morton HE, Gillard JW. MK886, a potent and specific leukotriene biosynthesis inhibitor blocks and reverses the membrane association of 5-lipoxygenase

in ionophore-challenged leukocytes. J Biol Chem 1990;265:1436-1442.

233. Borgeat P, Hamberg M, Samuelsson B. Transformation of arachidonic acid and homo-γ-linolenic acid by rabbit polymorphonuclear leukocytes. Monohydroxy acids from novel lipoxygenases. J Biol Chem 1976;251:7816-7820.

234. Radmark O, Malmsten C, Samuelsson B, et al. Leukotriene A. Isolation from human polymorphonuclear leukocytes. J Biol Chem 1980;255:11828-11831.

235. Conroy MC, Orange RP, Liechtenstein LM. Release of slow reacting substance of anaphylaxis (SRS-A) from human leukocytes by the calcium ionophore A 23187. J Immunol 1976;116: 1677.

236. Samuelsson B. Leukotrienes: mediators of immediate hypersensitivity reactions and inflammation. Science 1983;220:568-575.

237. Rosenbach T, Grabbe J, Möller A, Schwanitz HJ, Czarnetzki BM. Generation of leukotrienes from normal epidermis and their demonstration in cutaneous disease. Br J Dermatol 1985;113 (Suppl 28):157-167.

238. Wong E, Greaves MW, O'Brien T. Increased concentrations of immunoreactive leukotrienes in cutaneous lesions of eosinophilic cellulitis. Br J Dermatol 1984;110:653-656.

239. Talbot SF, Atkins PC, Goetzl EJ, Zweiman B. Accumulation of leukotriene C4 and histamine in human allergic skin reactions. J Clin Invest 1985;76:650-656.

240. Ruzicka T, Simmet T, Peskar BA, Braun-Falco O. Leukotrienes in skin of atopic dermatitis. Lancet 1984;1:222-223.

241. Takematsu H, Terui T, Torinuki W, Tagami H. Incontinentia pigmenti: eosinophil chemotactic activity of the crusted scales in the vesiculobullous stage. Br J Dermatol 1986;115: 61-66.

242. Ruzicka T, Przybilla B. Eicosanoid release in polymorphous light eruption: selective UV-A-induced LTB_4 generation by peripheral blood leukocytes. Skin Pharmacol 1988;1:186-191.

243. Kawana S, Ueno A, Nishiyama S. Increased levels of immunoreactive leukotriene B_4 in blister fluids of bullous pemphigoid patients and effects of a selective 5-lipoxygenase inhibitor on experimental skin lesions. Acta Derm Venereol (Stockh) 1990;70:281-285.

244. Dale HH. Progress in autopharmacology. A survey of present

knowledge of the chemical regulation of certain functions by natural constituents of the tissues. Bull Johns Hopkins Hosp 1934;53:297-347.

245. Hammarström S, Lindgren JA, Marcelo C, Duell EA, Anderson TF, Voorhees JJ. Arachidonic acid transformations in normal and psoriatic skin. J Invest Dermatol 1979;73:180-183.

246. Takematsu H, Terui T, Tagami H. Demonstration of leukotriene B_4 in the scale extracts of psoriasis and inflammatory pustular dermatoses. Acta Derm Venereol (Stockh) 1986;66: 610.

247. Barr RM, Wong E, Brain SD, Greaves MV, Olins LA, Mallet AI. The assay of arachidonic acid metabolites in normal and psoriatic skin using a skin chamber technique. J Invest Dermatol 1984;82:403-403.

248. Kondoh H, Sato Y, Kanoh H. Arachidonic acid metabolism in cultured mouse keratinocytes. J Invest Dermatol 1985;85:64-69.

249. Ziboh VA, Marcelo C, Voorhees JJ. Induced lipoxygenation of arachidonic acid in mouse epidermal keratinocytes by calcium ionophore, A23187. J Invest Dermatol 1981;76:307.

250. Ziboh VA, Casebolt TL, Marcelo CL, Voorhees JJ. Lipoxygenation of arachidonic acid by subcellular preparations from murine keratinocytes. J Invest Dermatol 1984;84:248-251.

251. Galey CI, Ziboh VA, Marcelo CL, Voorhees JJ. Modulation of phospholipid metabolism in murine keratinocytes by tumor promoter, 12-O-tetradecanoylphorbol-13-acetate. J Invest Dermatol 1985;85:319-323.

252. Rice RH, Levine L. Melittin-stimulated arachidonic acid metabolism by cultured malignant human epidermal keratinocytes. Biochem Biophys Res Commun 1984;124:303-307.

253. Pentland AP, Needleman P. Modulation of keratinocyte proliferation in vitro by endogenous prostaglandin synthesis. J Clin Invest 1986;77:246-251.

254. Pentland AP, Marcelo CL, Jordan MA, Voorhees JJ. Effects of gas tension on epidermal keratinocyte DNA synthesis and prostaglandin production. J Invest Dermatol 1986;86:177-180.

255. Pentland A, Moran C, George J, Needleman P. Culture confluence determines increased prostaglandin E_2 synthesis by human keratinocyte cultures after injury. J Invest Dermatol 1986;86:490.

256. Burrall BA, Wintroub BU, Goetzl EJ. Selective expression of

15-lipoxygenase activity by cultured human keratinocytes. Biochem Biophys Res Commun 1985;133:208-213.

257. Burrall BA, Wintroub BU, Goetzl EJ. Cytosolic localization of the 15-lipoxygenase of human neonatal foreskin keratinocytes. J Invest Dermatol 1986;86:466.

258. De Leo VA, Horlick H, Hanson D, Eisinger M, Harber LC. Ultraviolet radiation induces changes in membrane metabolism of human keratinocytes in culture. J Invest Dermatol 1984;83:323-326.

259. DeLeo V, Hanson D, Scheide S. Human epidermal arachidonate metabolism: an in vitro model. Clin Res 1985;33:297A.

260. Brain SD, Camp RDR, Leigh IM, Ford-Hutchinson AW. The synthesis of leukotriene B_4-like material by cultured human keratinocytes. J Invest Dermatol 1982;78:328.

261. Blacker KL, Williams ML, Goldyne ME. Prostaglandin synthesis is preserved in mitomycin C-treated 3T3 fibroblast feeder layers used in keratinocyte cultures. J Invest Dermatol 1986;86:464.

262. Blacker KL, Williams ML, Goldyne MR. 6-keto-prostaglandin $F_{1\alpha}$ is a marker for keratinocyte-fibroblast interactions. J Invest Dermatol 1986;86:464.

263. Blacker KL, Williams ML, Goldyne M. Mitomycin C-treated 3T3 fibroblasts used as feeder layers for human keratinocyte culture retain the capacity to generate eicosanoids. J Invest Dermatol 1987;89:536-539.

264. Fairley JA, Weiss J, Marcelo CL. Increased prostaglandin synthesis by low calcium-regulated keratinocytes. J Invest Dermatol 1986;86:173-176.

265. Möller A, Schwanitz H-J, Czarnetzki BM. In vitro generation of chemotactic leukotrienes from unfractionated murine epidermal cells. J Invest Dermatol 1986;87:489-493.

266. Grabbe J, Rosenbach T, Czarnetzki BM. Production of LTB_4-like chemotactic arachidonate metabolites from human keratinocytes. J Invest Dermatol 1985;85:527-530.

267. Kvedar J, Levine L. Modulation of arachidonic acid metabolism in a cultured newborn rat keratinocyte cell line. J Invest Dermatol 1987;88:124-129.

268. Grabbe J, Czarnetzki BM, Mardin M. Release of lipoxygenase products of arachidonic acid from freshly isolated human keratinocytes. Arch Dermatol Res 1984;276:128-130.

269. Fincham N, Camp R, Leigh I. Synthesis of arachidonic lipoxygenase products by epidermal cells. J Invest Dermatol 1985;84:447.

270. Tramposch KM, Stevens VJ, Quigley JW. The synthesis of arachidonic acid metabolites by human keratinocytes. J Invest Dermatol 1985;84:361.

271. Woollard PM, Leigh I. Stereochemical analysis of 12-hydroxy-5,8,10,14-eicosatetraenoic acid (12-HETE) from adult human epidermal cells in vitro. Br J Dermatol 1987;116:437.

272. Ruzicka T, Vitto A, Printz MP. Epidermal arachidonate lipoxygenase. Biochim Biophys Acta 1983;751:369-374.

273. Miller CC, Ziboh VA, Jones AD. Guinea pig epidermis synthesizes 15-hydroxy-8,11,13-eicosatrienoic acid (15-OH-20:3n6) from dihomogammalinolenic acid (DGLA): a potent lipoxygenase inhibitor derived from dietary primrose oil. J Invest Dermatol 1987;88:507.

274. DeLeo V, Hanson D, Scheide S. Metabolism of 5-hydroxy-eicosatetraenoic acid by human epidermal keratinocytes in culture. J Invest Dermatol 1987;88:481.

275. Morelli JG, Norris DA, Lyons MB, Murphy RC. Metabolism of exogenous leukotrienes by cultured human keratinocytes and melanocytes. Clin Res 1988;36:676A.

276. Holtzman MJ, Turk J, Pentland A. A regiospecific monooxygenase with novel stereopreference is the major pathway for arachidonic acid oxygenation in isolated epidermal cells. J Clin Invest 1989;84:1446-1453.

277. Burrall BA, Cheung M, Chiu A, Goetzl EJ. Enzymatic properties of the 15-lipoxygenase of human cultured keratinocytes. J Invest Dermatol 1988;91:294-297.

278. Green FA. Generation and metabolism of lipoxygenase products in normal and membrane-damaged cultured human keratinocytes. J Invest Dermatol 1989;93:486-491.

279. Bryant RW, Feinmark SJ, Makheja AN, Bailey JM. Lipid metabolism in cultured cells. Synthesis of vasoactive thromboxane A_2 from [^{14}C]arachidonic acid by cultured lung fibroblasts. J Biol Chem 1978;253:8134-8142.

280. Feinmark SJ, Bailey JM. Lipid metabolism in cultured cells. Activators of endogenous thromboxane A_2 synthesis in cultured lung fibroblasts. J Biol Chem 1982;257:2816-2821.

281. Mayer B, Rauter L, Zenzmaier E, Gleispach H, Esterbauer H. Characterisation of lipoxygenase metabolites of arachidonic acid in cultured human skin fibroblasts. Biochem Biophys Acta 1984;795:151-161.

282. Shak S, Goldstein IM. Leukotriene B_4 ω-hidroxylase in human polymorphonuclear leukocytes. J Clin Invest 1985;76:1218-1228.

283. Ruzicka T, Radspieler H, Strasser T, Przybilla B, Ring J. Polymorphonuclear leukocyte 5-lipoxygenase activity in psoriasis. Prostaglandins Leukotrienes Med 1985;18:313-319.

284. Maurice PDL, Bazer PC, Allen BR. Arachidonic acid metabolism by polymorphonuclear leukocytes in psoriasis. Br J Dermatol 1986;114:57-64.

285. Maurice PDL, Allen BR, Heptinstall S, Bather PC. Arachidonic acid metabolism by peripheral blood cells in psoriasis. Br J Dermatol 1986;114:553-566.

286. Maurice PDL, Camp RDR, Allen BR. The metabolism of leukotriene B_4 by peripheral blood polymorphonuclear leukocytes in psoriasis. Prostaglandins 1987;33:807-818.

287. Stüning M, Schultz-Ehrenburg U, Altmeyer P, Raulf M, König W. Metabolism of [^{14}C]arachidonic acid by polymorphonuclear leukocytes in patients with psoriasis. Br J Dermatol 1987;116:153-159.

288. McDonald CJ, Calabresi P. Psoriasis and occlusive vascular disease. Br J Dermatol 1978;99:469-475.

289. Wolf R, Machtey I, Feuerman EJ, Creter D. Blood hyperviscosity in psoriasis. Acta Derm Venereol (Stockh) 1981;61:153-154.

290. Kragballe K, Fallon JD. Increased aggregation and arachidonic acid transformation by psoriatic platelets: evidence that platelet-derived 12-hydroxy-eicosatetraenoic acid increases keratinocyte DNA synthesis in vitro. Arch Dermatol Res 1986;278:449-453.

291. Berrettini M, Parise P, Constantini V, Grasselli S, Nenci GG. Platelet activation in psoriasis. Thromb Haemost 1985;53:195-197.

292. Hayashi S, Shimizu I, Miyauchi H, Watanabe S. Increased platelet aggregation in psoriasis. Acta Derm Venereol (Stockh) 1985;65:258-262.

293. Fallon JD, Kragballe K. Increased platelet metabolism of arachidonic acid in psoriasis associated with stimulation of

platelet aggregation and epidermal keratinocyte proliferation. J Invest Dermatol 1984;82;400.

294. Borgeat P, Samuelsson B. Arachidonic acid metabolism in polymorphonuclear leukocytes: effects of ionophore A23187. Proc Natl Acad Sci USA 1979;76:2148-2151.

295. Kragballe K, Desjarlais L, Altman DE, Voorhees JJ. Uninvolved psoriatic epidermis has increased capacity to synthesize 12-hydroxyeicosatetraenoic acid. J Invest Dermatol 1985;84:348.

296. Kragballe K, Desjarlais L, Altman DA, Voorhees JJ. Uninvolved psoriatic epidermis has increased capacity to synthesize 12-hydroxy-eicosatetraenoic acid. J Invest Dermatol 1986;87:47-52.

297. Hamberg M, Svensson J, Samuelsson B. Prostaglandin endoperoxides. A new concept concerning the mode of action and release of prostaglandins. Proc Natl Acad Sci USA 1976;73:3824-3828.

298. Woollard PM. Stereochemical difference between 12-hydroxy-5,8,10,14-eicosatetraenoic acid (12-HETE) in platelets and psoriatic lesions. J Invest Dermatol 1985;84;455.

299. Heng MCY, Kloss SG, Kuehn CS, Chase DG. The sequence of events in psoriatic plaque formation after tape-stripping. Br J Dermatol 1985;112:517-532.

300. Hammar H, Yu SQ, Johannesson A, Sundkvist KG, Biberfeld P. Subpopulations of mononuclear cells in microscopic lesions of psoriatic patients. Selective accumulation of suppressor/cytotoxic T cells in epidermis during the evolution of the lesion. J Invest Dermatol 1984;83:416-420.

301. Crunkhorn P, Willis AL. Cutaneous reactions to intradermal prostaglandins. Br J Pharmacol 1971;41:49-56.

302. Sondergaard J, Greaves MW. Prostaglandin E_1: effect on cutaneous vasculature and skin histamine. Br J Dermatol 1971;84:424-428.

303. Williams TJ. Prostaglandin E_2, prostaglandin I_2 and the vascular changes of inflammation. Br J Pharmacol 1979;65:517-524.

304. McGivern DV, Basran G. Synergism between platelet activating factor (PAF acether) and prostaglandin E_2 in man. Eur J Pharmacol 1984;102:183-185.

305. Soter NA, Lewis RA, Corey EJ, Austen KF. Local effects of synthetic leukotrienes (LTC_4, LTD_4, LTE_4, and LTB_4) in human

skin. J Invest Dermatol 1983;80:115-119.

306. Flower RJ, Harvey EA, Kingston WP. Inflammatory effects of prostaglandin D_2 in rat and human skin. Br J Pharmacol 1976;56:229-233.

307. Barnes VF, Heavey DJ. Effect of prostaglandin D_2 on histamine-induced weals in human skin. Br J Pharmacol 1986;87:357-360.

308. Maurice PDL, Barr RM, Koro O, Greaves MW. The effect of prostaglandin D_2 on cutaneous response to histamine in human subjects. J Invest Dermatol 1986;87:154.

309. Robinson C, Benyon C, Holgate ST, Church MK. The IgE- and calcium-dependent release of eicosanoids and histamine from human purified cutaneous mast cells. J Invest Dermatol 1989;93:397-404.

310. Ford-Hutchinson AW, Chan CC. Pharmacological actions of leukotrienes in the skin. Br J Dermatol 1985;113 [Suppl 28]: 95-97.

311. Camp RDR, Coutts AA, Greaves MW, Kay AB, Walport MJ. Responses of human skin to intradermal injection of leukotrienes C_4, D_4 and B_4. Br J Pharmacol 1983;80:497-502.

312. Peck MJ, Piper PJ, Williams TJ. The effects of leukotrienes C_4 and D_4 on the microvasculature of guinea pig skin. Prostaglandins 1981;21:315-321.

313. Ueno A, Tanaka K, Katori M, Hayashi M, Arai Y. Species differences in increased vascular permeability by synthetic leukotrienes C_4 and D_4. Prostaglandins 1981;21:637-648.

314. Ruzicka T, Burg G. Effects of chronic intracutaneous administration of arachidonic acid and its metabolites. Induction of leukocytoclastic vasculitis by leukotriene B_4 and 12-hydroxyeicosatetraenoic acid and its prevention by prostaglandin E_2. J Invest Dermatol 1987;88:120-123.

315. Dowd PM, Woollard PM, Kobza Black A, Camp R, Greaves MW. The effect of intradermal infusions of 12-hydroxy-eicosatetraenoic acid (12-HETE) in normal human skin. Br J Dermatol 1983;109: 693-694.

316. Dowd PM, Kobza Black A, Woollard PM, Camp RDR, Greaves MW. Cutaneous responses to 12-hydroxy-5,8,10,14-eicosatetraenoic acid (12-HETE). J Invest Dermatol 1985;84:537-541.

317. Dowd PM, Greaves MW. Cutaneous responses to lipoxygenase products of arachidonic acid. Acta Derm Venereol [Suppl] (Stockh) 1985;120:18-22.

318. Wong E, Camp R, Greaves MW. Topical application of leukotriene B_4 in psoriatic and normal subjects. J Invest Dermatol 1984;82:414.

319. Wong E, Camp RD, Greaves MW. The responses of normal and psoriatic skin to single and multiple topical applications of leukotriene B_4. J Invest Dermatol 1985;84:421-423.

320. Camp R, Russel Jones R, Brain S, Woollard PM, Greaves MW. Production of intraepidermal microabscesses by topical application of leukotriene B_4. J Invest Dermatol 1984;82:202-204.

321. Winkelmann RK, Camp R, English JSC, Greaves MW. The perivascular cell populations in human skin after topical application of leukotriene B_4. Acta Derm Venereol 1986;66:340-343.

322. Dowd PM, Kobza Black A, Woollard PM, Camp RDR, Greaves MW. The in vivo properties of 12-hydroxyeicosatetraenoic acid (12-HETE) in normal skin. J Invest Dermatol 1984;82:413-414.

323. Dowd PM, Kobza Black A, Woollard PM, Camp RDR, Greaves MW. Cutaneous responses to 12-hydroxy-5,8,10,14-eicosatetraenoic acid (12-HETE) and 5,12-dihydroxyeicosatetraenoic acid (leukotriene B_4) in psoriasis and normal human skin. Arch Dermatol Res 1987;279:427-434.

324. Woollard PM. Stereochemical difference between 12-hydroxy-5,8,10,14-eicosatetraenoic acid in platelets and psoriatic lesions. Biochem Biophys Res Commun 1986;136:169-176.

325. Woollard PM, Murphy GM, Cunningham FM, Camp RDR, Greaves MW. Proinflammatory effects of 12(R)-hydroxy-5,8,10,14-eicosatetraenoic acid in human skin. Br J Dermatol 1988;118:277.

326. Dowd PM, Kobza Black A, Woollard PM, Greaves MW. Leukotriene B_4 and 12-HETE: induction of pharmacological tolerance and clinical significance. J Invest Dermatol 1985;84:349.

327. Lammers AM, van de Kerkhof PCM. Leukotriene B_4 fails to induce penetration of polymorphonuclear leukocytes into psoriatic lesions. Br J Dermatol 1987;117:541-544.

328. Goldman DW, Goetzl EJ. Specific binding of leukotriene B_4 to receptors on human polymorphonuclear leukocytes. J Immunol 1982;129:1600-1604.

329. Meier F, Gross E, Klotz K-N, Ruzicka T. Leukotriene B_4 receptors on neutrophils in patients with psoriasis and atopic eczema. Skin Pharmacol 1989;2:61-67.

330. Goetzl EJ, Woods JM, Gorman RR. Stimulation of human eosinophil and neutrophil polymorphonuclear leukocyte chemotaxis and random migration by 12-L-hydroxy-5,8,10,14-eicosatetraenoic acid. J Clin Invest 1977;59:179-183.

331. Ternowitz T, Fogh K, Kragballe K. 15-hydroxyeicosatetraenoic acid (15-HETE) specifically inhibits LTB_4-induced chemotaxis of human neutrophils. Skin Pharmacol 1988;1:93-99.

332. Kragballe K, Voorhees J. Leukotrienes are potent stimulators of DNA synthesis of human keratinocyte cultures. J Invest Dermatol 1984;82:398.

333. Kragballe K, Desjarlais L, Voorhees JJ. Leukotrienes B_4, C_4 and D_4 stimulate DNA synthesis in cultured human epidermal keratinocytes. Br J Dermatol 1985;113:43-52.

334. Chan CC, Duhamel L, Ford-Hutchison A. Leukotriene B_4 and 12-hydroxyeicosatetraenoic acid stimulate epidermal proliferation in vivo in the guinea pig. J Invest Dermatol 1985;85:333-334.

335. Bauer FW, van de Kerkhof PCM, Maassen-de Grood RM. Epidermal hyperproliferation following the induction of microabscesses by leukotriene B_4. Br J Dermatol 1986;114:409-412.

336. Otto WR, Barr RM, Dowd PM, Wright NA, Greaves MW. 12-hydroxy-5,8,10,14-eicosatetraenoic acid (12-HETE) does not stimulate proliferation of human neonatal keratinocytes. J Invest Dermatol 1989;92:683-688.

337. Reusch MK, Wastek GJ. Human keratinocytes in vitro have receptors for leukotriene B_4. Acta Derm Venereol (Stockh) 1989;69:429-431.

338. Wheeler LA, Horowitz N. Leukotriene B_4 induces calcium mobilization in neonatal foreskin keratinocytes. J Invest Dermatol 1987;88:524.

339. Baden HP, Kubilus J, Macdonald MJ. Normal and psoriatic keratinocytes and fibroblasts compared in culture. J Invest Dermatol 1981;76:53-55.

340. Payan DG, Goetzl EJ. Recognition of leukotriene B_4 by a unique subset of T-lymphocytes. J Allergy Clin Immunol 1984;74:403-406.

341. Gualde N, Atluru D, Goodwin JS. Effect of lipoxygenase metabolites of arachidonic acid on proliferation of human T cells and T cell subsets. J Immunol 1985;134:1125-1129.

342. Goodwin JS, Atluru D, Sierakowski S, Lianos EA. Mechanism of action of glucocorticosteroids. Inhibition of T cell prolifer-

ation and interleukin 2 production by hydrocortisone is reversed by leukotriene B_4. J Clin Invest 1986;77:1244-1250.

343. Johnson HM, Torres BA. Leukotrienes: positive signals for regulation of γ-interferon production. J Immunol 1984;132:413-416.

344. Rola-Pleszczinsky M, Lemaire I. Leukotrienes augment interleukin-1 production by human monocytes. J Immunol 1985;135:3958-3961.

345. Kunkel SL, Chensue SW, Phan SH. Prostaglandins as endogenous mediators of interleukin-1 production. J Immunol 1986;136:186-192.

346. Otterness IG, Bliven ML, Eskra JD, Reinke M, Hanson DC. The pharmacologic regulation of interleukin-1 production: The role of prostaglandins. Cell Immunol 1988;111:385-397.

347. Hammarström S, Hamberg M, Duell EA, Stawiski MA, Anderson JF, Voorhees JJ. Glucocorticoid in inflammatory proliferative skin disease reduces arachidonic acid and hydroxyeicosatetraenoic acids. Science 1977;197:994-996.

348. Penneys NS, Eaglstein W, Ziboh V. Petrolatum: interference with the oxidation of arachidonic acid. Br J Dermatol 1980;103:257-262.

349. Czarnetzki BM. Effect of sulfonated shell oil extracts (ichthyol) on the generation and the biological activity of chemotactic leukotrienes. J Invest Dermatol 1985;84:364.

350. Czarnetzki BM. Inhibitory effects of shale oils (Ichthyols) on the secretion of chemotactic leukotrienes from human leukocytes and on leukocyte migration. J Invest Dermatol 1986;87:694-697.

351. Bedord CJ, Young JM, Wagner BM. Anthralin inhibition of mouse epidermal arachidonic acid lipoxygenase in vitro. J Invest Dermatol 1983;81:566-571.

352. Schröder J-M. Anthralin (1,8-dihydroxyanthrone) is a potent inhibitor of leukotriene production and LTB_4 ω-oxidation by human neutrophils. J Invest Dermatol 1986;87:624-629.

353. Lawrence CM, Shuster S. Non-enzymic degradation of arachidonic acid to inflammatory products by anthralin free radicals. Br J Dermatol 1985;113:780.

354. Wong E, Cunningham F, Barr R, Mallet A, Greaves MW. Dithranol treatment of psoriasis does not affect lesional levels of arachidonate lipoxygenase products. Br J Dermatol 1987;116:

451-452.

355. Kobza Black A, Barr RM, Wong E, et al. Lipoxygenase products of arachidonic acid in human inflammed skin. Br J Clin Pharmacol 1985;20:185-190.

356. Remy W, Sigl I, Leipold B. Prostaglandin E_2 gel improvement of psoriatic lesions. Int J Dermatol 1986;25:266-268.

357. Schröder J-M, Kosfeld U, Christophers E. Multifunctional inhibition by anthralin in nonstimulated and chemotactic factor stimulated human neutrophils. J Invest Dermatol 1985; 85:30-34.

358. Anderson R, Lukey PT, Dipennar U, et al. Dithranol mediates pro-oxidative inhibition of polymorphonuclear leukocyte migration and lymphocyte proliferation. Br J Dermatol 1987;117:405-418.

359. Chang A, Alkemade JAC, van de Kerkhof PCM. Dithranol modulates the leukotriene B_4-induced intraepidermal accumulation of polymorphonuclear leukocytes. J Invest Dermatol 1989;92:806-808.

360. Chang A, van de Kerkhof PCM. Topical application of clobetasol-17- propionate inhibits the intraepidermal accumulation of polymorphonuclear leukocytes. Acta Derm Venereol (Stockh) 1988;68:57-60.

361. Van de Kerkhof PCM, Bauer FW, Maasen-de Grood RM. Methotrexate inhibits the leukotriene B_4 induced intraepidermal accumulation of polymorphonuclear leukocytes. Br J Dermatol 1985;113:251-255.

362. Lammers AM, van de Kerkhof PCM, Mier PD. Reduction of leukotriene B_4-induced intra-epidermal accumulation of polymorphonuclear leukocytes by methotrexate in psoriasis. Br J Dermatol 1987;116:667-671.

363. Lammers AM, van de Kerkhof PCM. Etretinate modulates the leukotriene B_4 induced intra-epidermal accumulation of polymorphonuclear leukocytes. Br J Dermatol 1987;117:297-300.

364. Wong E, Barr R, Cunningham F, Kobza Black A, Greaves M, Mallet A. Topical clobetasol propionate suppresses leukotriene B_4 in psoriasis. J Invest Dermatol 1985;84:364.

365. Wong E, Barr RM, Cunningham FM, Mistry K, Woollard PM, Mallet AI, Greaves MW. Topical steroid treatment reduces arachidonic acid and leukotriene B_4 in lesional skin of psoriasis. Br J Clin Pharmacol 1986;22:627-632.

366. Ternowitz T, Herlin T. Neutrophil and monocyte chemotaxis in methotrexate-treated psoriasis patients. Acta Derm Venereol [Suppl] (Stockh) 1985;120:23-26.

367. Wong E, Barr RM, Brain SD, Olins LA, Greaves MW. The effect of etretinate on cyclo-oxygenase and lipoxygenase products of arachidonic acid in psoriatic skin. Br J Dermatol 1984;111:703.

368. Barr RM, Brain SD, Greaves MW, Olins LA, Wong E. The effect of etretinate therapy on arachidonic acid metabolism in psoriatic skin. Br J Clin Pharmacol 1984;17:648P-649P.

369. Bray MA. Retinoids are potent inhibitors of the generation of rat leukocyte leukotriene B_4 like activity in vitro. Eur J Pharmacol 1984;98:61-67.

370. Nigam S. Inhibition of lipoxygenase products by retinoids in human blood cells. Dermatologica 1987;175 (Suppl 1):73-80.

371. Fiedler-Nagy C, Wittreich BH, Georgiadis A, Hope WC, Welton AF, Coffey JW. Comparative study of natural and synthetic retinoids as inhibitors of arachidonic acid release and metabolism in rat peritoneal macrophages. Dermatologica 1987;175 (Suppl 1):81-92.

372. Ellis CN, Kang S, Grekin RC, et al. Etretinate therapy reduces polymorphonuclear leukocyte chemotaxis-enhancing properties of psoriatic serum. J Am Acad Dermatol 1985;13:437-443.

373. Ellis CN, Gorsulowsky DC, Hamilton TA, et al. Cyclosporine improves psoriasis in a double-blind study. JAMA 1986;256:3110-3116.

374. Fan T-PD, Lewis GP. Mechanism of cyclosporin-A-induced inhibition of prostacyclin synthesis by macrophages. Prostaglandins 1985;30:735-747.

375. Niwa Y, Kano T, Taniguchi S, et al. Effect of cyclosporin A on the membrane-associated events in human leukocytes with special reference to the similarity with dexamethasone. Biochem Pharmacol 1986;35:947-951.

376. Kobza Black A, Greaves MW, Hensby CN, Plummer NA. Increased prostaglandins E_2 and $F_{2\alpha}$ in human skin at 6 and 24 hours after ultraviolet B irradiation (290-320 nm). Br J Clin Pharmacol 1978;5:431-436.

377. Camp RD, Greaves MW, Hensby CN, Plummer NA, Warin AP. Irradiation of human skin by short wavelength ultraviolet radiation (100-290 nm) (u.v.C): increased concentrations of arachidonic acid and prostaglandins E_2 and $F_{2\alpha}$. Br J Clin

Pharmacol 1978 6:145-148.

378. Kobza Black A, Greaves MW, Hensby CN, Plummer NA, Warin AP. The effects of indomethacin on arachidonic acid and prostaglandins E_2 and $F_{2\alpha}$ levels in human skin 24 h after u.v.B and u.v.C irradiation. Br J Clin Pharmacol 1978;6:261-266.

379. Plummer NA, Hensby CN, Warin AP, Camp RD, Greaves MW. Prostaglandins E_2, $F_{2\alpha}$ and arachidonic acid levels in irradiated and unirradiated skin of psoriatic patients receiving PUVA treatment. Clin Exp Dermatol 1978;3:367-369.

380. Chang A, Alkemade JAC, van de Kerkhof PCM. PUVA and UVB inhibit the intra-epidermal accumulation of polymorphonuclear leukocytes. Br J Dermatol 1988;119:281-287.

381. Millar B, Ferguson J, Green C, MacLeod T, Raffle E. Leukotriene (LTB_4) photodegradation by ultraviolet irradiation (UVB): a possible mechanism for the action of UVB phototherapy in psoriasis. Br J Dermatol 1988;118:277-278.

382. Millar B, Green C, Ferguson J, Raffle EJ, MacLeod TM. A study of the photodegradation of leukotriene B_4 by ultraviolet irradiation (UVB, UVA). Br J Dermatol 1989;120:145-152.

383. Katayama H, Kawada A. Exacerbation of psoriasis induced by indomethacin. J Dermatol (Tokio) 1981;8:323-327.

384. Ellis CN, Fallon JD, Heezen JL, Voorhees JJ. Topical indomethacin exacerbates the lesions of psoriasis. J Invest Dermatol 1983;80:362.

385. Ellis CN, Fallon JD, Kang S, Vanderveen EE, Voorhees JJ. Topical application of non-steroidal anti-inflammatory drugs prevents vehicle-induced improvement of psoriasis. J Am Acad Dermatol 1986;14:39-43.

386. Green CA, Shuster S. Lack of effect of topical indomethacin on psoriasis. Br J Clin Pharmacol 1987;24:381-384.

387. Abramson S, Korchak H, Ludewig R, et al. Modes of action of aspirin-like drugs. Proc Natl Acad Sci USA 1985;82:7227-7231.

388. Vanderhoek JY, Ekborg SL, Bailey JM. Nonsteroidal anti-inflammatory drugs stimulate 15-lipoxygenase/leukotriene pathway in human polymorphonuclear leukocytes. J Allergy Clin Immunol 1984;74:412-417.

389. Walker JR, Dawson W. Inhibition of rabbit PMN lipoxygenase activity by benoxaprofen. J Pharm Pharmacol 1979;31:778-780.

390. Kragballe K, Herlin T. Benoxaprofen improves psoriasis: a

double blind study. Arch Dermatol 1983;119:548-552.

391. Allen BR, Littlewood SM. The aetiology of psoriasis: clues provided by benoxaprofen. Br J Dermatol 1983;109(Suppl 25):126-129.

392. Salmon JA, Higgs GA, Tilling L, et al. Mode of action of benoxaprofen. Lancet 1984;1:848.

393. Salmon JA, Tilling LC, Moncada S. Benoxaprofen does not inhibit formation of leukotriene in a model of acute inflammation. Biochem Pharmacol 1984;33:2928-2930.

394. Salmon JA, Tilling LC, Moncada S. Evaluation of inhibitors of eicosanoid synthesis in leukocytes: possible pitfall of using the calcium ionophore A23187 to stimulate 5-lipoxygenase. Prostaglandins 1985;29:377-385.

395. Yamamoto S, Yoshimoto T, Furukawa M, Horie T, Watanabe-Kohno S. Arachidonate 5-lipoxygenase and its new inhibitors. J Allergy Clin Immunol 1984;74:349-352.

396. Young JM, Bedord CJ, Murthy DVK, et al. The biological activities of the novel topical antipsoriatic agent, 6-chloro-1,4-diacetoxy-2,3-dimethoxynaphthalene (RS-43179). J Invest Dermatol 1985;84:358.

397. Jones GJ, Venuti MC, Young JM, et al. Topical nonsteroidal antipsoriatic agents. 1. 1,2,3,4-tetraoxygenated naphthalene derivatives. J Med Chem 1986;29:1504-1511.

398. Argenbright LW, Opas EE, Meurer RD, Fenney WP, Bonney RJ, Humes JL. Inhibition of arachidonic acid metabolism in pig skin by L-651,896, a novel inhibitor of cyclooxygenase/ lipoxygenase. Clin Res 1986;34:735A.

399. Bonney RJ, Hand K, Opas EE, et al. L-651,896, a novel dual inhibitor of prostaglandin and leukotriene synthesis that possesses potent topical anti-inflammatory and analgesic activity. Clin Res 1986;34:739A.

400. Chan C-C, Young V. <u>In vivo</u> antiproliferative effect of a novel inhibitor of leukotriene and prostaglandin synthesis in an animal model of epidermal hyperplasia. Clin Res 1986;34: 742A.

401. Capetola RJ, Argentieri DC, Tolman EL, et al. Topical pharmacology of tepoxalin (ORF 20485) - A new cyclooxygenase (CO)/lipoxygenase (LO) inhibitor. Clin Res 1988;36:636A.

402. Degreef H, Dockx P, De Donker P, De Beule K, Cauwenbergh G. A double-blind vehicle-controlled study of R 68 151 in

psoriasis: A topical 5-lipoxygenase inhibitor. J Am Acad Dermatol 1990;22:751-755.

403. Batt DG, Maynard GD, Petraitis JJ, Shaw JE, Galbraith W, Harris RR. 2-substituted-1-naphthols as potent 5-lipoxygenase inhibitors with topical antiinflammatory activity. J Med Chem 1990;33:360-370.

404. Newton JA, Boodle KM, Barr R, Dowd PM, Greaves MW. Topical nordihydroguaiaretic acid (NDGA) in psoriasis. Br J Dermatol 1988;119:404-406.

405. Newton JA, Boodle KM, Barr R, Dowd PM, Greaves MW. Topical nordihydroguaiaretic acid (NDGA) in psoriasis. Br J Dermatol 1989;120:286-287.

406. Lassus A, Forsstrom S. A dimethoxynaphthalene derivative (RS-43179 gel) compared with 0.025% fluocinolone acetonide gel in the treatment of psoriasis. Br J Dermatol 1985;113:103-106.

407. Jansen CT, Lamminlausta K, Bullingham RES, Forsstrom S. A clinical trial of lonapalene, fluocinolone acetonide and vehicle in psoriasis. Clin Res 1986;34:757A.

408. Kobza Black A, Camp R, Cunningham F, Mallet A, Hofbauer M, Greaves MW. The clinical and pharmacological effect of lonapalene (RS-43179), a 5-lipoxygenase inhibitor, applied topically in psoriasis. Br J Dermatol 1988;119(Suppl 33):33.

409. Kobza Black A, Camp RDR, Mallet AI, Cunningham FM, Hofbauer M, Greaves MW. Pharmacologic and clinical effects of lonapalene (RS 43179), a 5-lipoxygenase inhibitor, in psoriasis. J Invest Dermatol 1990;95:50-54.

410. Sircar JC, Schwender CF, Carethers ME. Inhibition of soya bean lipoxygenase by sulphasalazine and 5-aminosalicylic acid: a possible mode of action in ulcerative colitis. Biochem Pharmacol 1983;32:170-173.

411. Allgayer H, Eisenburg J, Paumgartner G. Soya bean lipoxygenase inhibition: studies with the sulphasalazine metabolite N-acetylaminosalicylic acid, 5-aminosalicylic acid and sulphapyridine. Eur J Pharmacol 1984;26:449-451.

412. Menné T, Larsen U, Veien N, Klemp P, Brandbjerg PE. 5-aminosalicylic acid in a cream base improves psoriasis. A double blind study. J Dermatol Treatment 1989;1:5-7.

413. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. N Engl J Med 1986;317:1625-1629.

414. Staerk Laursen L, Naesdal J, Bukhave K, Lauritsen K, Rask-Madsen. Selective 5-lipoxygenase inhibition in ulcerative colitis. Lancet 1990;335:683-684.

415. Gupta AK, Ellis CN, Siegel MT, Voorhees JJ. Sulfasalazine: a potential psoriasis therapy?. J Am Acad Dermatol 1989;20:797-800.

416. Gupta AK, Ellis CN, Siegel MT, et al. Sulfasalazine improves psoriasis. A double-blind analysis. Arch Dermatol 1990;126:487-493.

417. Beetens JR, Loots W, Somers Y, Coene MC, de Clark F. Ketoconazole inhibits the biosynthesis of leukotrienes in vitro. Biochem Farmacol 1986;35:883-891.

418. Petri H, Tronnier H, Hass P. Investigations into the antiinflammatory effect of bifonazole. En: Hay RJ, ed. Advances in topical antifungal therapy. Berlin: Springer-Verlag, 1986: 26-31.

419. Janssen PAJ, Vanden Bossche HFA, Van Wauwe, Cauwenbergh GMFJ, DeGreef HJ. The role of cytochrome P-450 in dermatology. Int J Dermatol 1989;28:493-496.

420. Ellis CN, Gorsulowsky DC, Voorhees JJ. Experimental therapies for psoriasis. Semin Dermatol 1985;4:313-319.

421. Kromann N, Green A. Epidemiological studies in the Upernavik district, Greenland: incidence of some chronic diseases 1950-1974. Acta Med Scand 1980;208:401-406.

422. Bang HO, Dyerberg J, Sinclair HM. The composition of the Eskimo food in north western Greenland. Am J Clin Nutr 1980;33: 2657-2661.

423. Corey EJ, Shih C, Cashman JR. Docosahexaenoic acid is a strong inhibitor of prostaglandin but not leukotriene biosynthesis. Proc Natl Acad Sci USA 1983;80:3581-3584.

424. Fischer S, Schacky CV, Siess W, et al. Uptake, release and metabolism of docosahexaenoic acid (DCHA, C22:6,w3) in human platelets and neutrophils. Biochem Biophys Res Commun 1984;120:907-918.

425. von Schacky C, Weber PC. Metabolism and effects on platelet function of the purified eicosapentaenoic and docosahexaenoic acids in humans. J Clin Invest 1985;76:2446-2450.

426. Fischer S, Vischer A, Preac-Mursic V, Weber PC. Dietary docosahexaenoic acid is retroconverted in man to eicosapentaenoic acid, which can quickly be transformed to prostaglandin

I_3. Prostaglandins 1987;34:34:367-375.

427. Marcel YL, Christiansen K, Holman RT. The preferred metabolic pathway from linoleic acid to arachidonic acid in vitro. Biochim Biophys Acta 1968;164:25-34

428. Chapkin RS, Ziboh VA, Marcelo CL, et al. Metabolism of essential fatty acids by human epidermal enzyme preparations. Evidence of chain elongation. J Lipid Res 1986;27:945-954.

429. von Schacky C. Prophylaxis of atherosclerosis with marine omega-3 fatty acids. A comprehensive strategy. Ann Intern Med 1987;107:890-899.

430. Galloway JH, Cartwright IJ, Woodcock BE, Greaves M, Russell RG, Preston FE. Effects of dietary fish oil supplementation on the fatty acid composition of the human platelet membrane: demonstration of selectivity in the incorporation of eicosapentaenoic acid into membrane phospholipid pools. Clin Sci 1985;68:449-454.

431. Lee TH, Hoover RL, Williams JD, et al. Effect of dietary enrichment with eicosapentaenoic acid and docosahexaenoic acids on in vitro neutrophil and monocyte leukotriene generation and neutrophil function. N Engl J Med 1985;312:1217-1224.

432. Dyerberg J, Bang HO, Stoffersen E, Moncada S, Vane JR. Eicosapentaenoic acid and prevention of thrombosis and atherosclerosis. Lancet 1978;2:117-19.

433. Lee TH, Mencia-Huerta JM, Shih C, Corey EJ, Lewis RA, Austen KF. Effects of exogenous arachidonic, eicosapentaenoic, and docosahexaenoic acids on the generation of 5-lipoxygenase pathway products by ionophore-activated human neutrophils. J Clin Invest 1984;74:1922-1933.

434. Needle P, Raz A, Minkes MS, Ferrendelli JA, Sprecher H. Triene prostaglandins: prostacyclin and thromboxane biosynthesis and unique biological properties. Proc Natl Acad Sci USA 1979;76:944-948.

435. Prescott SM. The effect of eicosapentaenoic acid on leukotriene B production by human neutrophils. J Biol Chem 1984;259:7615-7621.

436. Strasser TH, Fischer S, Weber PC. Leukotriene B_5 is formed in human neutrophils after dietary supplementation with icosapentaenoic acid. Proc Natl Acad Sci USA 1985;82:1540-1543.

437. Prescott SM, Zimmerman GA, Morrison AR. The effects of a diet rich in fish oil on human neutrophils: identification of LTB_5

as a metabolite. Prostaglandins 1985;30:209-227.

438. Payan DG, Wong MY, Chernov-Rogan T, et al. Alterations in human leukocyte function by ingestion of eicosapentaenoic acid. J Clin Immunol 1986;6:402-410.

439. Endres S, Ghorbani R, Kelley VE, et al. The effect of dietary supplementation with n-3 polyunsaturated fatty acids on the synthesis of interleukin-1 and tumor necrosis factor by mononuclear cells. N Engl J Med 1989;320:265-271.

440. Ziboh VA, Miller C, Kragballe K, Cohen K, Ellis CN, Voorhees JJ. Effects of an 8-week dietary supplementation of eicosapentaenoic acid in serum, PMNs, and epidermal fatty acids of psoriatic subjects. J Invest Dermatol 1985;84:300.

441. Allen BR, Maurice PDL, Goodfield MW, Cockbill S, Stammers J. The effects on psoriasis of dietary supplementation with eicosapentaenoic acid. Br J Dermatol 1985;113:777.

442. Ziboh VA, Cohen KA, Ellis CN, et al. Effects of dietary supplementation of fish oil on neutrophil and epidermal fatty acids. Arch Dermatol 1986;122:1277-1282.

443. Bittiner SB, Tucker WFG, Blechen SS. Fish oil in psoriasis - a double-blind randomised placebo-controlled trial. Br J Dermatol 1987;117:25-26.

444. Bittiner SB, Tucker WFG, Cartwright I, Blechen SS. A double-blind, randomised, placebo-controlled trial of fish oil in psoriasis. Lancet 1988;1:378-380.

445. Maurice PDL, Allen BR, Barkley ASJ, Cockbill SR, Stammers J, Bather PC. The effects of dietary supplementation with fish oil in patients with psoriasis. Br J Dermatol 1987;117:599-606.

446. Kettler AH, Baughn RE, Orengo IF, Black H, Wolf JE. The effect of dietary fish oil supplementation on psoriasis. Improvement in a patient with pustular psoriasis. J Am Acad Dermatol 1988;18:1267-1273.

447. Bjørneboe A, Smith AK, Bjørneboe GA, Thune PO, Drevon CA. Effect of dietary supplementation with n-3 fatty acids on clinical manifestations of psoriasis. Br J Dermatol 1988;118:77-83.

448. Kragballe K, Fogh K. A low-fat diet supplemented with dietary fish oil (Max-EPA) results in improvement of psoriasis and in formation of leukotriene B_5. Acta Derm Venereol (Stockh) 1989;69:23-28.

449. Kragballe K. Dietary supplementation with a combination of n-3 and n-6 fatty acids (Super Gamma-Oil Marine) improves psoriasis. Acta Derm Venereol (Stockh) 1989;69:265-268.

450. Kojima T, Terano T, Tanabe E, Okamoto S, Tamura Y, Yoshida S. Effect of highly purified eicosapentaenoic acid in psoriasis. J Am Acad Dermatol 1989;21:150-151.

451. DiMinno G, Coraggio F, Cerbone AM, et al. A myeloma paraprotein with specificity for platelet glycoprotein IIIa in a patient with a fatal bleeding disorder. J Clin Invest 1986;77:157-164.

452. Liu SC, Karasek M. Isolation and growth of adult human epidermal keratinocytes in cell culture. J Invest Dermatol 1978;71:157-162.

453. Fredriksson BT, Petterson U. Severe psoriasis-oral therapy with a new retinoid. Dermatologica 1978;157:238-244.

454. Gómez JA, González MJ, de Moragas JM, Serrat J, González-Sastre F, Pérez M. Apolipoprotein E phenotypes, lipoprotein composition, and xanthelasmas. Arch Dermatol 1988;124:1230-1234.

455. Sun FF, McGuire JC. Inhibition of human neutrophil arachidonate 5-lipoxygenase by 6-9-(phenylimino)-Δ^6,8-prostaglandin I_1 (U-60257). Prostaglandins 1983;26:211-221.

456. Dahl ML, Puustinen T, Uotila P. U-60,257 has no effect on the metabolism of arachidonic acid in nonstimulated human polymorphonuclear leukocytes. Res Commun Chem Pathol Pharmacol 1984;44:355-365.

457. Bach MK, Brashler JR, Fitzpatrick FA, et al. In vivo and in vitro actions of a new selective inhibitor of leukotriene C and D synthesis. Advances in prostaglandin, thromboxane, and leukotriene research, Vol. 11. Editado por Samuelson B, Paloetti R, Ramwell P. Raven Press, New York, 1983.

458. Mehta JL, Mehta P, Ward MB, Lawson D. Inhibition of human platelet and neutrophil function by piriprost (U-60,257). Prostaglandins Leukotrienes Med 1987;29:259-267.

459. Barr RM, Kobza Black A, Dowd PM, et al. The in vitro 5-lipoxygenase and cyclooxygenase inhibitor L-652,343 does not inhibit 5-lipoxygenase in vivo in human skin. Br J Clin Pharmacol 1988;25:23-26.

460. Smith RJ, Sun FF, Bowman BJ, Iden SS, Smith HW, McGuire JC. Effect of 6,9-deepoxy-6,9-(phenylimino)-Δ^6,8-prostaglandin I_1 (U-60257), an inhibitor of leukotriene synthesis, on human

neutrophil function. Biochem Biophys Res Commun 1982;109:943-949.

461. Flament J, Schandene L, Boeynaems J-M. Effect of the 5-lipoxygenase inhibitor piriprost on superoxide production by human neutrophils. Prostaglandins Leukotrienes Essent Fatty Acids 1988;34:175-180.

462. Smith RJ, Epps DE, Justen JM, et al. Human neutrophil activation with interleukin-1. A role for intracellular calcium and arachidonic acid lipoxygenation. Biochem Pharmacol 1987;36:3851-3858.

463. Richards IM, Griffin RL, Oostveen JA, Elfring G, Conder GA. Role of cyclooxygenase products of arachidonic acid metabolism in Ascaris antigen-induced bronchoconstriction in sensitized dogs. J Pharmacol Exp Ther 1988;245:735-741.

464. Johnson HG, Stout BK, Ruppel PL. Inhibition of the 5-lipoxygenase pathway with piriprost (U-60,257) protects normal primates from ozone-induced methacholine hyperresponsive small airways. Prostaglandins 1988;35:459-466.

465. Kreutner W, Sherwood J, Rizzo C. The effect of leukotriene antagonists, lipoxygenase inhibitors and selected standards on leukotriene-mediated allergic bronchospasm in guinea pigs. Agents Actions 1989;28:173-184.

466. Lebidois J, Soifer SJ, Clyman RI, Heymann MA. Piriprost: a putative leukotriene synthesis inhibitor increases pulmonary blood flow in fetal lambs. Pediatr Res 1987;22:350-354.

467. Snyder DS, Castro R, Desforges JF. Antiproliferative effects of lipoxygenase inhibitors on malignant human hematopoietic cell lines. Exp Hematol 1989;17:6-9.

468. Nakagawa H, Takahashi H. Remarkable elevation of leukotriene B_4 in rat skin after induction of UV photodermatitis. Inflammation 1990;14:195-203.

469. Camp R, Kobza Black A, Cunningham F, Mallet A, Greaves M. Pharmacological effects of topical lonapalene in psoriasis. Clin Res 1988;36:637A.

470. Cunningham FM, Woollard PM. 12(R)-Hydroxy-5,8,10,14-eicosatetraenoic acid is a chemoattractant for human polymorphonuclear leukocytes in vitro. Prostaglandins 1987;34:71-78.

471. Evans JF, Leblanc Y, Fitzsimmons BJ, Charleson S, Nathaniel D, Leveille C. Activation of leukocyte movement and displacement of [^{3}H]leukotriene B_4 from leukocyte membrane preparations by (12R)- and (12S)-hydroxyeicosatetraenoic acid. Biochim

Biophys Acta 1987;917:406-410.

472. Opas EE, Argenbright LW, Humes JL. An enzymatic method for distinguishing the stereoisomers of 12-hydroxyeicosatetraenoic acid in human epidermis and psoriatic scale. Br J Dermatol 1989;120:49-58.

473. Opas EE, Argenbright LW, Pacholok SG, et al. Differential effects of inhibitors on 12-lipoxygenase derived from porcine, murine and human skin and human platelet cytosol. Clin Res 1987;35:795.

474. Bonney RJ, Davies P, Dougherty H, et al. Biochemical and biological activities of 2,3-dihydro-6-[3-(2-hydroxymethyl)-phenyl-2-propenyl]-5-benzofuranol (L-651,896), a novel topical anti-inflammatory agent. Biochem Pharmacol 1987;36:3885-3891.

475. Capdevila J, Yadagiri P, Manna S, Falck RJ. Absolute configuration of the hydroxyeicosatetraenoic acids (HETEs) formed during catalytic oxygenation of arachidonic acid by microsomal cytochrome P-450. Biochem Biophys Res Commun 1986;141:1007-1011.

476. Humes JL, Opas EE. On the origin of 12-hydroxyeicosatetraenoic acid in psoriatic scale. Adv Prostaglandin Thromboxane Leukotriene Res 1989;19:152-155.

477. Nakadate T, Aizu E, Yamamoto S, Kato R. Some properties of lipoxygenase activities in cytosol and microsomal fractions of mouse epidermal homogenate. Prostaglandins Leukotrienes Med 1986;21:305-319.

478. Mukhtar H, Bik DP, Ruzicka T, Merk HF, Bickers DR. Cytochrome P-450-dependent omega-oxidation of leukotriene B_4 in rodent and human epidermis. J Invest Dermatol 1989;93:231-235.

479. Oliw EH, Guengerich FP, Oates JA. Oxygenation of arachidonic acid by hepatic mono-oxygenases. J Biol Chem 1982;257:3771-3781.

480. Vanden Bossche H, Marichal P, Gorrens J, et al. Biochemical approaches to selective antifungal activity. Focus on azole antifungals. Mycoses 1989;32 (Suppl 1):35-52.

481. Shak S, Goldstein IM. W-oxidation is the major pathway for the catabolism of leukotriene B_4 in human polymorphonuclear leukocytes. J Biol Chem 1984;259:10181-10187.

482. Shak S, Goldstein IM. Carbon monoxide inhibits ω-oxidation of leukotriene B_4 by human polymorphonuclear leukocytes: evidence that catabolism of leukotriene B_4 is mediated by a cytochrome P-450 enzyme. Biochem Biophys Res Commun 1984; 123:475-481.

483. Rosenberg EW, Noah PW, Skinner RB Jr: Treatment of psoriasis with antimicrobial agents. En: Roenigk HH Jr, Maibach HI, eds. Psoriasis. New York: Marcel Dekker, 1985:505-511.

484. Farr PM, Krause LB, Marks JM, Shuster S. Response of scalp psoriasis to oral ketoconazole. Lancet 1985;2:921-922.

485. Döring HF. Zur Therapie und Ätiologie der Sebopsoriasis. Z Hautkr 1985;60:1940-1942, 1947-1950.

486. Döring HF. Treatment of sebopsoriasis. A clinical trial - an etiological approach. Dermatologica 1984;169(Suppl 1):125-133.

487. Faergemann J. Treatment of sebopsoriasis with itraconazole. Mykosen 1985;28:612-618.

488. Alford RH, Vire CG, Cartwright BB, King LE Jr. Ketoconazole's inhibition of fungal antigen-induced thymidine uptake by lymphocytes from patients with psoriasis. Am J Med Sci 1986;291:75-80.

489. Döring HF. Experience gained with topical therapy with bifonazole in unusual indications. En Hay RJ, ed. Advances in topical antifungal therapy. Berlin: Springer-Verlag, 1986:120-124.

490. Beetens JR, Somers Y, Goossens J, et al. R 68 151 inhibits the metabolism of arachidonic acid via the 5-lipoxygenase. Poster No. 404. Seventeenth World Congress of Dermatology. Berlin, Alemania, 24-29 Mayo, 1987.

491. Koponen M, Grieder A, Loor F. The effects of cyclosporins on the cell cycle of T-lymphoid cell lines. Exp Cell Res 1982; 140:237-250.

492. Berger R, Majdic O, Meingassner JG, Knapp W. In vitro effects of cyclosporin A (CSA) on human hematopoietic cell lines. Immunopharmacology 1982;5:123-127.

493. Lau DCW, Wong KL. Effect of cyclosporine on microvascular endothelial cell growth in culture. Transplant Proc 1987;19 :3496-3498.

494. Bartold PM. Cyclosporine and gingival overgrowth. Oral Pathol 1987;16:463-468.

495. Lucia MG, Moan MC, Schweizer RT, Kosciol CM, Johnson RM, Sharpe RJ. Cyclosporine inhibits the proliferation of squamous cells. Fed Proc 1986;45:272.

496. Kato N, Halprin KM, Taylor JR. Cyclosporin A does not inhibit

epidermal cell growth at therapeutic levels. J Invest Dermatol 1987;88:52-54.

497. Duell EA, Fisher GJ, Annesley TM, et al. Levels of cyclosporine in epidermis of treated patients do not inhibit growth of cultured keratinocytes. J Invest Dermatol 1987;88:486.

498. MacNeil S, Dawson RA, Crocker G, et al. Investigation of the mode of action of cyclosporin A in psoriasis. Br J Dermatol 1988;118:295-296.

499. Ramirez Bosca A, Kanitakis J, Haftek M, Faure M, Castells Rodellas A, Thivolet J. Effects of cyclosporin A on cultured human epidermal keratinocytes. Acta Derm Venereol (Stockh) 1990;70:6-10.

500. Ramírez-Bosca A, Kanitakis J, Haftek M, Faure M, Castells-Rodellas A, Thivolet J. Nonimmunosupressive ciclosporin H inhibits the growth and DNA synthesis of cultured normal human epidermal keratinocytes. Skin Pharmacol 1989;2:175-179.

501. Nickoloff BJ, Fisher GJ, Mitra RS, Voorhees JJ. Additive and synergistic antiproliferative effects of cyclosporin A and gamma interferon on cultured human keratinocytes. Am J Pathol 1988;131:12-18.

502. Fisher GJ, Duell EA, Nickoloff BJ, et al. Levels of cyclosporin in epidermis of treated psoriasis patients differentially inhibit growth of keratinocytes cultured in serum-free versus serum-containing media. J Invest Dermatol 1988;91:142-146.

503. Furue M, Gaspari AA, Katz SI. The effect of cyclosporin A on epidermal cells. II. Cyclosporin A inhibits proliferation of normal and transformed keratinocytes. J Invest Dermatol 1988;90:796-800.

504. Ried M, Gibbons S, Kwok D, van Buren CT, Flechner S, Kahan BD. Cyclosporine levels in human tissues of patients treated for one week to one year. Transplant Proc 1983;4(Suppl 1):2419-2437.

505. Urabe A, Kanitakis J, Viac J, Thivolet J. Cyclosporin A inhibits directly in vivo keratinocyte proliferation of living human skin. J Invest Dermatol 1989;92:755-757.

506. Dykes PJ, Brunt J, Marks R. The effect of cyclosporin on human epidermal keratinocytes in vitro. Br J Dermatol 1990;122:173-180.

507. Sharpe GR, Fischer C. Time-dependent inhibition of growth of human keratinocytes and fibroblasts by cyclosporin A: effect

on keratinocytes at therapeutic blood levels. Br J Dermatol 1990;123:207-213.

508. Fidelus R, Laughter A, Twomey J, Taffet S, Haddox M. The effect of cyclosporine on ornithine decarboxylase induction with mitogens, antigens and lymphokines. transplantation 1984;37:383-387.

509. Kahan BD. Cyclosporine. N Engl J Med 1989;321:1725-1738.

510. Mitra RS, Voorhees JJ, Nickoloff BJ. Modulation of ^{125}I-EGF ligand binding to cultured keratinocytes (KC8). J Invest Dermatol 1989;92:482.

511. Sraer J, Bens M, Ardaillou R. Dual effects of cyclosporine A on arachidonate metabolism by peritoneal macrophages. Phospholipase activation and partial thromboxane-synthase blockage. Biochem Pharmacol 1989;38:1947-1954.

512. Stahl RA, Adler S, Baker PJ, et al. Cyclosporin A inhibits prostaglandin E_2 formation by rat mesangial cells in culture. Kidney Int 1989;35:1161-1167.

513. Brown Z, Neild GH, Lewis GP. Mechanism of inhibition of prostacyclin synthesis by cyclosporine in cultured human umbilical vein endothelial cells. Transplant Proc 1988;20 (Suppl 3):654-657.

514. Voss BL, Hamilton RK, Samara EN, McKee PA. Cyclosporine suppression of endothelial prostacyclin generation. A possible mechanism for nephrotoxicity. Transplantation 1988;45:793-796.

515. Hattori Y, Kasai K, Emoto T, Hiraiwa M, Shimoda S. The inhibitory effect of cyclosporine on prostacyclin production by cultured endothelial cells from porcine aorta. Transplant Proc 1989;21:3461-3463.

516. Rosenthal RA, Chukwuogo NA, Ocasio VH, Kahng KU. Cyclosporine inhibits endothelial cell prostacyclin production. J Surg Res 1989;46;593-596.

517. Brown Z, Neild GH, Lewis GP. Inhibition of prostacyclin formation by cyclosporin is not due to reduced availability of arachidonic acid in membrane phospholipids of cultured human endothelial cells. Biochem Pharmacol 1990;39:1136-1138.

518. Bennet WM, Elzinga L, Kelley V. Pathophysiology of cyclosporin nephrotoxicity: role of eicosanoids. Transplant Proc 1988;20 (Suppl 3):628-633.

519. Muller MK, Degenhardt H, Kloppel G, Goebell H, Bergmann K, Lohr M. Prevention of toxic effects of cyclosporin on pancreatic

B-cells of rats by Rioprostil, a new prostaglandin analogue. Gut 1988;29:1524-1530.

520. Muller MK, Degenhardt H, Bergmann K, et al. Rioprostil, a new prostaglandin E_1, prevents cyclosporin A-induced damage to endocrine and exocrine pancreas. Scand J Gastroenterol Suppl 1989;164:35-41.

521. Moran M, Mozes MF, Maddux MS, et al. Prevention of acute graft rejection by the prostaglandin E_1 analogue misoprostol in renal-transplant recipients treated with cyclosporine and prednisone. N Engl J Med 1990;322:1183-1188.

522. ElAttar TMA, Lin HS, Shultz R. Effect of minocycline on prostaglandin formation in gingival fibroblasts. J Periodont Res 1988;23:285-286.

523. Harper RA. Effect of prostaglandins on [^{3}H]-thymidine uptake into human epidermal cells in vitro. Prostaglandins 1976;12: 1019-1025.

524. Sharpe RJ, Arndt KA, Bauer SI, Maione TE. Cyclosporine inhibits basic fibroblast growth factor-driven proliferation of human endothelial cells and keratinocytes. Arch Dermatol 1989;125:1359-1362.

525. Terano T, Hirai A, Tamura Y, et al. Effect of dietary supplementation of highly purified eicosapentaenoic acid and docosahexaenoic acid on arachidonic acid metabolism in leucocyte and leucocyte function in healthy volunteers. Adv Prostaglandin Thromboxane Leukotriene Res 1987;17:880-885.

526. Marks R, Barton SP, Shuttleworth D, Finlay AY. Assessment of disease progress in psoriasis. Arch Dermatol 1989;125:235-240.

527. Griffin TD, Lattanand A, VanScott EJ. Clinical and histological heterogeneity of psoriatic plaques. Arch Dermatol 1988;124:216-220.

528. Chapman DM, Ross JB. Objective measurements of three epidermal parameters in psoriasis vulgaris and in dermatopathology in general. Br J Dermatol 1988;119:333-343.

529. Gupta AK, Ellis CN, Tellner DC, Anderson TF, Voorhees JJ. Double-blind, placebo-controlled study to evaluate the efficacy of fish oil and low-dose UVB in the treatment of psoriasis. Br J Dermatol 1989;120:801-807.

530. Saynor R, Verel D, Gillot T. The long-term effect of dietary supplementation with fish lipid concentrate on serum lipids, bleeding time, platelets and angina. Atherosclerosis 1984;50: 3-10.

531. Knapp HR, Reilly AG, Alessandrini P, FitzGerald GA. In vivo indexes of platelet and vascular function during fish-oil administration in patients with atherosclerosis. N Engl J Med 1986;314:937-942.

532. Vila L, SolA J, Puig L, de Castellarnau C, de Moragas JM. Exogenous arachidonic acid metabolism in platelets from psoriatic patients. Acta Derm Venereol (Stockh) 1990;70:110-114.

533. Goodnight SH Jr, Harris WS, Connor WE, et al. Polyunsaturated fatty acids, hyperlipidemia, and thrombosis. Arteriosclerosis 1982;2:117-119.

534. Harris WS, Connor WE, McMurry MP. The comparative reduction of the plasma lipids and lipoproteins by dietary polyunsaturated fats: salmon oil versus vegetable oil. Metabolism 1983;32:179-184.

535. Illingworth DR, Harris WS, Connor WE. Inhibition of low density lipoprotein synthesis by dietary omega-3 fatty acids in man. Arteriosclerosis 1984;4:270-275

536. Phillipson BE, Rothrock DW, Connor WE, Harris WS, Illingworth DR. Reduction of plasma lipids, lipoproteins, and apoproteins by dietary fish oils in patients with hypertriglyceridemia. N Engl J Med 1985;312:1210-1216.

537. Harris WS, Dujovne CA, Zucker M, Johnson B. Effects of a low saturated fat, low cholesterol fish oil supplement in hypertriglyceridemic patients. A placebo-controlled trial. Ann Intern Med 1988;109:465-470.

538. Wilt TJ, Lofgren RP, Nichol KL, et al. Fish oil supplementation does not lower plasma cholesterol in men with hypercholesterolemia. Results of a randomized, placebo-controlled crossover study. Ann Intern Med 1989;111:900-905.

539. Vahlquist C, Michaelsson G, Vessby B. Serum lipoproteins in middle-aged men with psoriasis. Acta Derm Venereol (Stockh) 1987;67:12-15.

540. Marsden JR. Reduction of retinoid hyperlipidemia with Max-EPA. Br J Dermatol 1987;116:450.

541. Lowe NJ, Borok ME, Ashley JM, et al. Fish oil consumption reduces hypertriglyceridemia in psoriatic patients receiving etretinate therapy. Arch Dermatol 1988;124:177

542. Ashley JM, Lowe NJ, Borok ME, Alfin-Slater RB. Fish oil supplementation results in decreased hypertriglyceridemia in

patients with psoriasis undergoing etretinate or acitretin therapy. J Am Acad Dermatol 1988;19:76-82.

543. Gorlin R. The biological actions and potential clinical significance of dietary ω-3 fatty acids. Arch Intern Med 1988;148:2043-2048.

544. Terano T, Salmon JA, Higgs GA, Moncada S. Eicosapentaenoic acid as a modulator of inflammation. Biochem Pharmacol 1986;35:779-785.

545. Lee TH, Mencia-Huerta JM, Shih C, Corey EJ, Lewis RA, Austen KF. Characterization and biologic properties of 5,12-dihydroxy derivatives of eicosapentaenoic acid, including leukotriene B_5 and the double lipoxygenase product. J Biol Chem 1984;259:2383-2389.

546. Kragballe K, Voorhees JJ, Goetzl EJ. Leukotriene B_5 derived from eicosapentaenoic acid does not stimulate DNA synthesis of cultured human keratinocytes but inhibits the stimulation induced by leukotriene B_4. J Invest Dermatol 1985;84:349.

547. Kragballe K, Voorhees JJ, Goetzl EJ. Inhibition by leukotriene B_5 of leukotriene B_4-induced activation of human keratinocytes and neutrophils. J Invest Dermatol 1987;88:555-558.

548. Wozel G, Chang A, Barth J, Happle R, van de Kerkhof PCM. Effect of leukotriene B_5 on the accumulation of polymorphonuclear leukocytes in unstimulated and leukotriene B_4-stimulated human skin. Skin Pharmacol 1990;3:45-48.

549. Miller CC, Ziboh VA. Human epidermis transforms eicosapentaenoic acid to 15-hydroxy-5,8,11,13,17-eicosapentaenoic acid: a potent inhibitor of 5-lipoxygenase. J Am Oil Chemists Soc 1988;65:474.

550. Miller C, Yamaguchi RY, Ziboh VA. Guinea pig epidermis generates putative anti-inflammatory metabolites from fish oil polyunsaturated fatty acids. Lipids 1989;24:998-1003.

551. Fogh K, Helmer S, Troels H, et al. Improvement of psoriasis vulgaris after intralesional injections of 15-hydroxyeicosatetraenoic acid (15-HETE). J Am Acad Dermatol 1988;18:279-285.

552. Doherty NS, Beaver TH, Rheins LA, Nordlund JJ. Multiple topical applications of arachidonic acid to mouse ears induce inflammatory and proliferative changes. J Invest Dermatol 1988;91:298-302.

553. Miller CC, Ziboh VA. Induction of epidermal hyperproliferation by topical n-3 polyunsaturated fatty acids on guinea pig skin linked to decreased levels of 13-hydroxyoctadecadienoic acid

(13-Hode). J Invest Dermatol 1990;94:353-358.

554. Dewsbury CE, Graham P, Darley CR. Topical eicosapentaenoic acid (EPA) in the treatment of psoriasis. Br J Dermatol 1989;120:581-584.

555. Hebborn P, Jablonska S, Beutner EH, Langner A, Wolska H. Action of topically applied arachidonic acid on the skin of patients with psoriasis. Arch Dermatol 1988;124:387-391.

556. von Schacky C, Fischer S, Weber PC. Long term effects of dietary marine ω-3 fatty acids upon plasma and cellular lipids, platelet function and eicosanoid formation in humans. J Clin Invest 1985;76:1626-1631.

557. Akos K. Eicosapentaenoic acid. Lancet 1987;1:1083.

558. Solá J, Vila L, Puig L, de Moragas JM. In vitro cyclooxygenase activity is increased in platelets from psoriatic patients. J Invest Dermatol 1990;95:490.

559. Terano T, Hirai A, Hamazaki T, et al. Effect of oral administration of highly purified eicosapentaenoic acid on platelet function, blood viscosity, and red cell deformability in healthy human subjects. Atherosclerosis 1983;46:321-331.