生長激素與老化

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摘　要

於正常的生理情形，老化會伴有生長激素分泌的逐年減少，類胰島素生長因子-1平行減少、肌肉組織減少、脂肪組織增加。老化也伴隨著身體機能的衰退，尤其是體力及活動力的下降，導致生活獨立度及品質下降。由於老化的身體組成變化與生長激素缺乏症很相似，因此人們常質疑到底生長激素分泌隨年齡增長而減少是一生理的保護機轉，還是它像停經症候群一樣表示生長激素缺乏而可用生長激素置換治療取得改善。基因合成生長激素使得生長激素的取得不只無限量，而且也比先前由腦垂體捽取者要安全。1989 年 Salomon 等人首先報告以基因合成生長激素治療生長激素缺乏的成人 6 個月可增加 10 - 12 % 無脂組織。嗣後的研究亦證明以生長激素治療生長激素缺乏症可減少脂肪組織、增加肌肉組織；長期治療（至 2 年）則可使骨密度增加；生長激素治療更能改善病人的精神狀態。雖然生長激素之療效已漸被確認，但長期療效、副作用、使用不便及藥價太貴皆使得生長激素置換治療在生長激素缺乏症之使用受到很大的限制。

截至目前為止，老化的生長激素分泌減少與老化的身體、精神變化的因果關係仍然未定論，尤其大部分的研究發現類胰島素生長因子-1 的血清濃度與身體組成於老年人之相關性不是沒有便是薄弱。雖然也有研究指出生長激素之分泌與身體脂肪量及血脂有相關，但顯然的老化還有其他重要的干擾因素存在，如性激素的減少、營養狀況、活動力等。因此老化引起的變化不能預期生長激素治療可以返老還童。

儘管如此已有許多研究顯示生長激素的補充確可改善一些老化的身體變化，但是副作用頻率仍高，尤其有些副作用又是本來就好發於老人的如糖尿病、高血壓、腫瘤等，因此在尚無足夠實證之前，生長激素是不應使用於無腦垂腺疾病的老人。倒是有些研究顯示體能訓練可大幅改善老年人的體力，其改善程度甚至大於使用生長激素，因此非藥物性的生活型態改變應是較符合生理及經濟效益的，有部分老人確為生長激素缺乏是使用生長激素治療的對象，唯此群”老人”需要進一步的臨床研究來界定。

一、老化對生長激素分泌的影響

以分析 24 小時生長激素分泌動態來看，中年以上的男女（40 歲）生長激素的分泌比年青人減少 15～70%[1-5]，每增加 10 年生長激素的產量減少 14%，而其血清半衰期也減少 6%[6]。雖然早晚分泌的節律於中老年人（> 50 歲）並未變化[2,3]，但分泌的次數及數量皆減少[7]。生長激素對胰島素低血糖刺激之反應無變化

[9] 或減少 [9]，對精胺酸灌注之反應沒有變化 [10-12]。而對運動刺激之反應減少 [13,14]，對生長釋素之反應也減少 [12,15,16]。

二、老化引起生長激素分泌減少之機轉

生長激素的分泌受生長釋素的刺激而增加，受體抑素的抑制而減少。老化使得生長激素對生長釋素之反應減少 [12,15,16]，但經多次生長釋素注射後，生長激素對生長釋素之反應又恢復正常 [17,18]。另外於老人注射精胺酸可提高生長激素對生長釋素之反應，而年青人無此現象 [12]，精胺酸可抑制體抑素，這也間接證明老化會有體抑素活性增加的現象。由免疫細胞化學研究也證明生長激素細胞的數目及大小皆隨老化減少 [19]，這與老年人腦垂腺生長激素含量減少的結果一致 [20]。用 theophylline 灌注可改善老人生長激素對生長釋素之反應 [21]，但年青人無此現象，間接證明生長釋素在老化生長激素細胞的訊息傳遞發生了內在的變化。由此看來，老化引起生長激素分泌減少源自多層次的缺陷。

三、老化引起的身體組成變化及其機轉

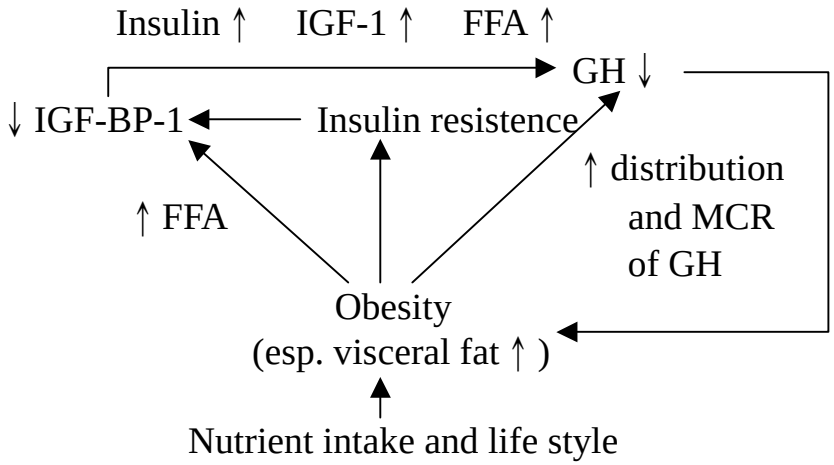
（A）肌肉組織減少

老化會造成肌肉組織減少及脂肪組織增加 [22-24]。20 歲後每增加 10 年，無脂組織減少 4.4%[25]，而肌肉的橫切面面積也跟著減少 [26,27]。雖然肌肉組織的大小與尖峰肌力成正比 [27-27]，但是其相關性在老年人較年青人為薄弱 [27-29]，40 歲以後每增加 10 年尖峰肌力減 10%[28,29]。若在一般情形減少的程度可能更大，因這些研究不包括不健康之老年人。老化對肌肉耐力的影響較不清楚，但研究指出肌肉內氧化酵素活性降低 [30,31]，而 VO_2 max 之減少一方面是周邊肌肉組織及氧化能力之減少 [35]，一方面也與氧之輸量減少有關 [36]。即使將肌肉大小考慮進去，肌肉之功能於老年人仍然較差。高齡也伴有興奮一收縮訊息傳路之損傷及尖峰縮短速率和肌力之減少 [37-39]。收縮蛋白的減少，結締組織及肌肉內脂肪的增加，第二型肌纖維變小都是原因。肌纖維型態與 fast myosin heavy chain 含量可受活動力的影響，抗力訓練 1 年可使第二型肌纖維增生 [40,41]，這些研究暗示 deconditioning 是失去快速收縮蛋白的主因之一。此外，神經因素如運動單位減少、運動神經終極板的衰退、運動神經元的減少及去神經化神經再分佈也是造成肌力減少的原因 [42-44]。儘管如此，阻力訓練不論年齡可在肌肉大小無甚改變下大幅改善肌力 [45-48]，如 12 星期訓練可使腿伸張力增加 110%，而四頭肌橫切面只增加 9%[4-8]，可見大部分肌力的增加是經由運動單位功能的改變，亦即增加協同肌肉的合作而減少拮抗肌的阻抗 [45,47]，亦即運動的介入可改善高齡肌力的衰退。由最近的研究發現老年人全身蛋白合成率下降 19%，而全身肌肉蛋白合成率降低 55%，而非肌肉蛋白合成則不變 [49,50]。更精確一點是肌纖維蛋白合成下降 [51,52]，在細胞層次即粒腺體及 myosin heavy chain 蛋白合成率下降 [53,54]，前者是 ATP 之製造中心，後者是肌肉收縮馬達；前者與氧化酵素及 VO_2 max 有關，後者與肌力及肌肉大小有關。這些研究更發現老化由中年（45－55 歲）開始。對於特定肌肉蛋白之測定或許更能早期發現肌肉的老化，至於何種機轉造成肌肉蛋白合成的減少，目前不明。最近的研究發現 myosin heavy chain 及 actin 的 mRNA 及 DNA 含量在年青人與老年人並無不同 [55]，暗示轉錄後的變化是造成這些蛋白合成率下降的原因；而粒腺體蛋白則屬於轉錄前的變化引起，有愈來愈多證據顯示隨著老化，

肌肉粒腺體 DNA 的氧化傷害逐年累積，而且一些粒腺體基因 mRNA 也減少，但這些變化之間或與蛋白合成之關係仍未釐清[56,57]。

（B）脂肪組織增加

生長激素可以溶解脂肪，老化造成生長激素分泌減少，顯然是脂肪組織增加的一重要原因，而且使用生長激素確也使脂肪組織減少，這間接證明生長激素所扮演角色。但是老化也造成生活行為的改變，亦即活動力減少、甜食增加，這也會造成脂肪組織增加，而運動訓練確也減少脂肪組織，但並未影響生長激素之分泌。因此老化引起的脂肪組織增加應是多種原因的，而生長激素分泌的減少只是造成惡性循環的原因之一。下列圖表顯示老化造成脂肪組織增加之惡性循環。



四、生長激素的作用

以人工合成生長激素注射健康老人可增加無脂組織，肌肉組織及力量[58-60]，於一群女性老人注射 1 個月可增加 50%肌肉蛋白合成[60]，但較大劑量在另一群老人注射 3 個月卻無法增加肌纖維蛋白合成[58]，原因不明。當與抗力訓練一齊進行時，生長激素並無法加強抗力訓練的效果[61]，生長激素雖增加無脂組織及全身蛋白合成，但對肌肉蛋白合成率無加強作用[50,62]。因此最近的研究發現生長激素雖可增加肌肉體積，但對肌力、耐力並沒有改善[63]，這與 cross-sectional 資料顯示 IGF-1 與老人的日常生活能力無關是一致[64]。由這些研究看來，生長激素或可無特異性的增加肌蛋白的合成，增加肌肉組織，而老化除了普遍肌蛋白合成的減少，更有特異性肌纖維的萎縮，因此老化的變化無法單用生長激素缺乏來解釋。抗力訓練可恢復老化特異性肌肉萎縮，也可恢復肌力，如此看來 disuse atrohphy 應是老化肌肉變化的主因；生長激素的治療顯然無法恢復正常。當然不排除一些老人確有生長激素缺乏症，這些老人經過治療可以得到明顯的改善。

老人對生長激素是非常敏感的，因此先前的臨床試驗可看到一些明顯的副作用，諸如，糖尿病、高血壓、水腫、隧道症候群、關節痛[65,66]，至於長期可能的副作用如心臟血管疾病、腦血管疾病、腫瘤等[67-68]，則須待長時間追蹤才知道，所以對每一個老人注射生長激素是不合邏輯的，生長激素不能返老還童，若要改善老人生活品質，應以更合乎生理的方法來促進。

參考文獻

01. Ho KY, Evans WS, Blizzard RM Veldhuis JD, Merriam GR, Somojlik E, Furlanetto R, Rogol AD, Kaiser DL, Thorner MO 1987 Effects of sex and age on 24-hour profile of growth hormone secretion in men: importance of endogenous estradiol concentrations. J Clin Endocrinol Metab 64:51-58.
02. Corpas E, Harman SM, Piñeyro MA, Roberson R, Blackman MR 1992 GHRH 1-29 twice daily reverses the decreased GH and IGF-I levels in old men. J Clin Endocrinol Metab, 75:530-535.
03. Vermeulen A 1987 Nyctohemoral growth hormone profiles in young and aged men: correlations with somatomedin-C levels. J Clin Endocrinol Metab 64:884-888.
04. Finkelstein J, Roffwarg H, Boyar P, Kream J, Hellman L 1972 Age-related changes in the twenty-four hour spontaneous secretion of growth hormone in normal individuals. J Clin Endocrinol Metab 35:665-670.
05. Zadik Z, Chalew SA, McCarter RJ, Meistas M, Kowarski AA 1985 The influence of age on the 24-hour integrated concentration of growth hormone in normal individuals. J Clin Endocrinol Metab 60:513-516.
06. Iranmanesh A, Lizarralde G, Veldhuis JD 1991 Age and relative adiposity are specific negative determinants of the frequency and amplitude of growth hormone (GH) secretory bursts and the half-life of endogenous GH in healthy men. J Clin Endocrinol Metab 73:1081-1088.
07. Carlson HE, Gillin JC, Gorden P, Snyder F 1972 Absence of sleep-related growth hormone peaks in aged normal subjects and in acromegaly. J Clin Endocrinol Metab 34:1102-1105.
08. Kalk WJ, Vinik AI, Pimstone BL, Jackson WP 1973 Growth hormone responses to insulin hypoglycemia in the elderly. J Gerontol 28:431-433.
09. Muggeo M, Feddele D, Tiengo A, Molinari M, Crepaldi G 1975 Human growth hormone and cortisol responses to insulin stimulation in aging. J Gerontol.
10. Dudl J, Ensinck J, Palmer E, Williams R 1973 Effect of age on growth hormone secretion in man. J Clin Endocrinol Metab 37:11-16.
11. Blichert-Toft M 1975 Stimulation of the release of corticotrophin and somatotrophin by metyrapone and arginine. Acta Endocrinol (Copenh) [Suppl] 195:65-85.
12. Ghigo E, Goffi E, Nicolosi M, Arvat E, Valente F, Mazza E, Ghigo C, Camanni F 1990 Growth hormone (GH) responsiveness to combined administration of arginine and GH-releasing hormone does not vary with age in man. J Clin Endocrinol Metab 71:1481-1485.
13. Hagberg JM, Seals DR, Yerg JE, Gavin J, Gingerich R, Bhartur P, Holloszy J 1988 Metabolic responses to exercise in young and old athletes and sedentary men. J Appl Physiol 65:900-908.
14. Craig BW, Brown R, Everhart J 1989 Effects of progressive resistance training on growth hormone and testosterone levels in young and elderly subjects. Mech ageing Dev 49:159-169.
15. Lang I, Schernthaner G, Pietschmann P, Kurz R, Stephenson JM, Templ M 1987 Effects of sex and age on growth hormone response to growth hormone releasing

hormone in healthy individuals. J Clin Endocrinol Metab 65:535-540.
16. Shibasaki T, Shizume K, Nakahara M, Masuda A, Kazuko J, Denura H, Wakabayashi I, Ling N 1984 Age-related changes in plasma growth hormone response to growth hormone-releasing factor in man. J Clin Endocrinol Metab 58:212-214.
17. Iovino M, Monteleone P, Steardo L 1989 Repetitive growth hormone-releasing hormone administration restores the attenuated growth hormone (GH) response to GH releasing hormone testing in normal aging. J Clin Endocrinol Metab 69:910-913.
18. Franchimont P, Urbain-Choffray D, Lambelin P, Fontaine MA, Frangin G, Reginster JY 1989 Effects of repetitive administration of growth hormone-releasing hormone on growth hormone secretion, insulin-like growth factor I, and bone metabolism in postmenopausal women. Acta Endocrinol (Copenh) 120:121-128.
19. Sun Y-K, Xi Y-P, Fenoglio CM, Pushparaj N, O'Toole KM, Kledizik GS, Nette EG, King DW 1984 The effect of age on the number of pituitary cells immunoreactive ot growth hormone and prolactin. Hum Pathol 15:169-180.
20. Pasteels JL, Gausset P, Danguy A, Gausset P, Danguy A, Ectors P, Nicoll CS, Veravudhi P 1972 Morphology of the lactotropes and somatotropes of man and rhesus monkeys. J Clin Endocrinol Metab 34:959-967.
21. Coiro V, Volpi R, Cavazzini U, Bertoni P, Corradi A, Bianconi L, Davoli C, Rossi G, Chiodera P 1991 Restoration of normal growth hormone responsiveness to GHRH in normal aged men by infusion of low amounts of theophylline. J Gerontol 46:M155-158.
22. Novack LP 1972 Aging, total body potassium, fat-free mass, and cell mass in males and females between ages 18 and 85 years. J Gerontol 27:438-443.
23. Shimokata H, Tobin JD, Muller DC, Elahi D, Coon PJ, Andres R 1989 Studies in the distribution of body fat. I. Effects of age, sex, and obesity. J Gerontol 44:M67-M73.
24. Enzi G, Gasparo M, Biondetti P, Fiore D, Semissa M, Zurlo F 1986 Subcutaneous and visceral fat distribution according to sex, age, and overweight, evaluated by computed tomography. Am J Clin Nutr 44:739-746.
25. Kehayias JJ, Fiatrone MA, Zhuang H, Roubenoff R 1997 Total body potassium and body fat: relevance to aging. Am J Clin Nutr 66:904.
26. lexell J, Taylor C, Sjöström M 1988 What is the cause of the aging atrophy? Total number, size and proportion of different fibre types studied in whole vastus lateralis muscle from 15- to 83-year old men. J Neurol Sci 84:275.
27. Overend TJ, Cunningham DA, Kramer JF, Lefcoe MS, Paterson DH 1992 Knee extensor and knee flexor strength: cross-sectional area ratios in young and elderly men. J Gerontol 47:M204.
28. Lindle RS, Metter EJ, Lynch NA, Fleg JL, Fozard JL, Tobin J, Roy TA, Hurley BF 1997 Age and gender comparisons of muscle strength in 654 women and men aged 20-93 yr. J Appl Physiol 83:1581.
29. Jubrias SA, Odderson IR, Esselman PC, Conley KE 1997 Decline in isokinetic force with age: muscle cross-sectional area and specific force. Pflüg Arch Eur J

Physiol 434:246.
30. Coggan AR, Spina RJ, King DS, Rogers MA, Brown M, Nemeth PM, Holloszy JO 1992 Histochemical and enzymatic comparison of the gastrocnemius muscle of young and elderly men and women. J Gerontol Biol Sci 46B:71.
31. Trappe SW, Costill DL, Fink WJ, Pearson DR 1995 Skeletal muscle characteristics among distance runners: a 20-yr follow-up study. J Appl Physiol 78:823.
32. Trappe SW, Costill DL, Vukovich MD, Jones J, Melham T 1996 Aging among elite distance runners: a 22-yr longitudinal study. J Appl Physiol 80:285.
33. Fleg JL, Lakatta EG 1998 Role of muscle loss in the age-associated reduction in VO_{2max}. J Appl Physiol 65:1147.
34. Rosen MJ, Sorkin JD, Goldberg AP, Hagberg JM, Katzel LI 1998 Predictors of age-associated decline in maximal aerobic capacity: a comparison of four statistical models. J Appl Physiol 84:2163.
35. Proctor DN, Joyner MJ 1997 Skeletal muscle mass and the reduction of VO_{2max} in trained older subjects. J Appl Physiol 82:1411.
36. Essen-gustavsson B, Borges O 1986 Histochemical and metabolic characteristics of human skeletal muscle in relation to age. Acta Physiol Scand 126:107.
37. Brooks SV, Faulkner JA 1988 Contractile properties of skeletal muscles from young, adult and aged mice. J Physiol 404:71.
38. Larsson L, Li X, Frontera WR 1997 Effects of aging on shortening velocity and myosin iso-form composition in single human skeletal muscle. Am A Physiol 272:C638.
39. Delbono O, O'Rourke KS, Ettinger WH 1995 Excitation-calcium release uncoupling in aged single human skeletal muscle fibers. J Membrane Biol 148:211.
40. Charette SL, McEvoy L, Pyka G, Snow-Harter C, Guido D, Wiswell RA, Marcus R 1991 Muscle hypertrophy response to resistance training in older women. J Appl Physiol 70:1912.
41. Pyka G, Lindenberger E, Charette S, Marcus R 1994 Muscle strength and fiber adaptions to a year-long resistance training program in elderly men and women. J Gerontol 49:M22.
42. Balice-Gordon RJ 1997Age-related changes in neuromuscular innervation. Muscle Nerv Suppl 5:S83.
43. Ansved T, Larsson L 1990 Quantitative and qualitative morphological properties of the soleus motor nerve and the L5 ventral root in young and old rats. Relation to the number of soleus muscle fibres. J Neurol Sci 96:269.
44. Doherty TJ, Vandervoort AA, Taylor AW, Brown WF 1993 Effects of motor unit losses on strength in older men and women. J Appl Physiol 74:868.
45. Sale DG 1988 Neural adaptation to resistance training. Med Sci Sports Exerc 20:S135.
46. Sipila S, Suominen H 1995 Effects of strength and endurance training on thigh and leg muscle mass and composition in elderly women. J Appl Physiol 78:334.
47. Hakkinen K, Kallinene M, Izquierdo M, Jokelainen K, Lassila H, Malkia E, Kraemer WJ, Newton RU, Alen M 1998 Changes in agonist-antagonist EMG,

muscle CSA, and force during strength training in middle-aged and older people. J Appl Physiol 84:1341.
48. Frontera WR, Meredith CN, O;Reilly KP, Evans WJ 1988 Strength conditioning in older men: skeletal muscle hypertrophy and improved function. J Appl Physiol 64:1038.
49. Balagopal P, Rooyackers OE, Adey DB, Ades PA, Nair KS 1997 Effects of aging on in vivo synthesis of skeletal muscle myosin heavy-chain and sarcoplasmic protein in humans. Am J Physiol 273:E790.
50. Yarasheski KE, Zachwieja JJ, Campbell JA, Bier DM 1995 Effect of growth hormone and resistance exercise on muscle growth and strength in older men. Am J Physiol 268:E268.
51. Welle S, Thornton C, Jozefowicz R, Statt M 1993 Myofibrillar protein synthesis in young and old men. Am J Physiol 264:E693.
52. Welle S, Thornton C, Statt M 1995 Myofibrillar protein synthesis in young and old human subjects after three months of resistance training. Am J Physiol 268:E422.
53. Balagopal P, Ljungquist O, Nair KS 1997 Skeletal muscle myosin heavy-chain synthesis rate in healthy humans. Am J Physiol 272:E45.
54. Rooyackers OE, Adey DB, Ades PA, Nair KS 1996 Effect of age on in vivo rates of mitochondrial protein synthesis in human skeletal muscle. Proc Natl Acad Sci U.S.A. 93:15364.
55. Welle S, Bhatt K, Thomton C 1996 Polyadenylated RNA, actin mRNA, and myosin heavy chain mRNA in young and old human skeletal muscle. Am J Physiol 270:E224.
56. Zhang C, Liu VWS, Addessi CL, Sheffield DA, Linnane AW, Nagley P 1998 Differential occurrence of mutatuions in mitochondrial DNA of human skeletal muscle during aging. Hum Mutat 11:360.
57. Wei YH 1998 Wxidative stress and mitochondrial DNA mutations in human aging. Proc Soc Exp Biol Med 217:53.
58. Welle S, Thornton C, Statt M, McHenry B 1996 Growth hormone increases muscle mass and strength but does not rejuvenate myofibrillar protein synthesis in healthy subjects over 60 years old. J Clin Endocrinol Metab 81:3239.
59. Rudman D, Feller AG, Nagraj HS, Gergans GA, Lalitha PY, Goldberg AF, Schlenker RA, Cohn L 1990 Effects of human growth hormone in men over 60 years old. N Engl J Med 323:1.
60. Butterfield GE, Thompson J, Rennie MJ, Marcus R, Hintz RL, Hoffman AR 1997 Effect of rhGH and rhlGF-1 treatment on protein utilization in elderly men. Am J Physiol 272:E94.
61. Taffe DR, Jin IH, Vu TH, Hoffman AR, Marcus R 1996 Lack of effect of recombinant human growth hormone (GH) on muscle morphology and GH-insulin-like growth factor expression in resistance trained elderly men. J Clin Endocrinol Metab 81:421.
62. Yarasheski KE, Zachwieja JJ, Angelopoulos TJ, Bier DM 1993 Short-term growth hormone treatment does not increase muscle protein synthesis in experienced weight lifters. J Appl Physiol 74:3073.

63. Papadakis MA, Grady D, Black D, Tierney MJ, Gooding GAW, Schambelan M, Grunfels C 1996 Growth hormone replacement in healthy older men improves body composition but not functional ability. Ann Intern Med 124:708-716.
64. Papadakis MA, Grady D, Tierney MJ, Black D, Wells L, Grunfeld C 1995 Insulin-like growth factor 1 and functional status in healthy older men. JAGS 43:1350-1355.
65. Jørgensen JOL, Thuesen L, Ingemann-Hansen T Pedersen SA, Jørgensen J, Skakkebaek NE, Christiansen JS 1989 Beneficial effects of growth hormone treatment in GH-deficient adults. Lancet 1:1221-1225.
66. Salomon F, Cuneo RC, Hesp R, Sönksen PH 1989 The effects of treatment with recombinant human growth hormone on body composition and metabolism in adults with growth hormone deficiency. N Engl J Med 321:1797-1803.
67. Alexander L, Appleton D, Hall R, Ross WM, Wilkinson R 1980 pidemiology of acromegaly in the Newcastle region. Clin Endocrinol (Oxf) 12:71-79.
68. Bengtsson BA, Eden S, Ernest I, Odën A, Sjögren B 1988 Epidemiology and long-term survival in acromegaly. Acta Med Scand 223:327-335.