REVIEW

Selective Insulin Action on Skin, Ovary, and Heart in Insulin-Resistant States

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States of hyperinsulinemia with resistance to insulin action on glucose disposal are frequently associated with proliferative tissue abnormalities of the skin (acanthosis nigricans), ovary, and heart. That insulin may be involved in the pathogenesis of these growth-related abnormalities despite resistance to its metabolic effects mediated through the insulin receptor is suggested by the known ability of high concentrations of insulin to stimulate DNA synthesis and cell proliferation in vitro through the insulin-like growth factor I (IGF-I) receptor. IGF-I receptors are present in skin keratinocytes, some ovarian tissue compartments, and in the heart. Furthermore, ovarian tissue from hyperinsulinemic insulin-resistant women responds to supraphysiologic insulin concentrations in vitro by enhanced steroidogenesis. Cultured, transformed T-lymphocytes from an infant with leprechaunism fail to augment basal-colony formation in response to physiologic insulin concentrations in vitro (compared to a doubling seen in normal subjects), but respond normally to supraphysiologic insulin concentrations, the effect of which is competitively inhibited by a monoclonal antibody to the IGF-I receptor. Thus, insulin action mediated through the IGF-I receptor may initiate growth-promoting tissue effects in the face of limited insulin effect on glucose metabolism. Such spillover actions may add to the morbidity associated with states of clinical insulin resistance. *Diabetes Care* 11:500–505, 1988

Resistance to the action of insulin on glucose disposal occurs in a diverse array of medical conditions, partially summarized in Table 1. Insulin resistance can be associated with normal, impaired, or diabetic glucose tolerance. Disorders characterized by severe insulin resistance may have a genetic basis involving alterations in the primary structure of DNA; such resistance is expressed in cultured cells far removed from environmental influences. Examples of primary genetic causes of insulin resistance include: leprechaunism (1), lipodystrophy (2), and the type A and C syndromes (3,4) (Table 2). In contrast, other conditions associated with insulin resistance have an epigenetic basis in which there is an alteration in genetic expression without change in the DNA sequence; in this case, the resistance appears to result from environmental factors and, therefore, is not evident in cultured cells. Examples of epigenetic forms of insulin resistance include: the type B syndrome (3) (Table 2), ataxia telangiectasia (5), counterregulatory hormone excess states such as acromegaly and Cushing's syndrome (6), and hypothyroidism (7). Still other conditions associated with insulin resistance, including the common entities of obesity and type II (non-insulin-dependent) diabetes (6), have no proven intrinsic cellular or environmental basis, although available evidence would primarily favor an environmental cause (8).

The clinical significance of insulin as a growth factor in insulin-sensitive human disease states has been briefly addressed in two recent reviews (9,10). Conditions associated with insulin resistance are frequently associated with specific growth-related tissue changes, including acanthosis nigricans, ovarian enlargement with cyst formation and hyperandrogenism (in females), and hypertrophic cardiomyopathy (Figs. 1 and 2). This review presents a potential unifying hypothesis explaining the pathogenesis of these unusual physical findings on the

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TABLE 1
Hyperinsulinemic states

	Acanthosis nigricans	Hypertrophic cardio-myopathy	Ovarian cysts/ enlargement
Insulin resistant			
Genetic			
Leprechaunism	X	X	X
Lipodystrophy	X	X	
Type A syndrome	X		X
Type C syndrome	X		X
Epigenetic			
Type B syndrome	X		X
Ataxia telangiectasia	X		
Acromegaly	X	X	
Cushing's syndrome	X		X
Hypothyroidism	X	X	X
Insulin sensitive			
Infant of diabetic mother		X	X
Nesidioblastosis		X	

TABLE 2
Syndromes of insulin resistance and acanthosis nigricans

Type	Proposed defect
A	Decreased number of insulin receptors
B	Serum autoantibodies against the insulin receptor
C	Post-binding defect in insulin action (?defect in autophosphorylation of β-subunit)

basis of persistent insulin action on specific tissues in the face of partial or even complete resistance to the traditional action of insulin on glucose disposal.

In constructing such a hypothesis, it is necessary to review the relationship between insulin and the insulin receptor, insulin-like growth factor I (IGF-I) and the IGF-I receptor, and, importantly, the crossover actions of insulin mediated via the IGF-I receptor. First, note that the insulin-like growth factors share significant structural homology with the A and B domains of human proinsulin, suggesting evolutionary divergence of the insulin-like growth factors and insulin from a common ancestral molecule (11). Second, the insulin and IGF-I receptors are homologous and appear to be heterotetramers composed of two α-subunits (125–135 K) and two β-subunits (~90 K), the latter containing intrinsic in vitro tyrosine kinase activity (12). In response to insulin, the insulin receptor clearly and rapidly mediates metabolic actions involving hexose transport and enzymes such as glycogen synthase, pyruvate dehydrogenase, and lipoprotein lipase. On the other hand, stimulation of DNA synthesis and cell growth via the insulin receptor is less well understood and at one time was thought to be limited to only certain cell types, e.g., the H-35 cultured hepatoma cell line (13), F9 embryonal carcinoma cells (14), cultured human breast cancer cells (15), and cultured adult rat hepatocytes (16). More recently, it has been shown that insulin stimulates [^{3}H]thymidine incorporation into human skin fibroblasts via either the insulin or the IGF-I receptor depending on the insulin concentrations employed (17,18).

To explore the specificity of hormone action, our laboratory has used clonogenic assays to study the growth-promoting action of insulin on two hematopoietic cells derived from human peripheral blood, erythroid progenitor cells (EPC), and cultured T-lymphocytes, immortalized with either the HTLV-1 or HTLV-2 retrovirus (19–22). EPC and T-lymphocyte lines established from normal individuals demonstrate augmentation of colony formation in response to physiologic concentrations of insulin (1–8 ng/ml or 179–1435 pM). There is, however, blunting of this response to varying degrees in patients with moderate obesity, polycystic ovarian disease (PCOD), and leprechaunism (20–22). We have also demonstrated consistent growth responsiveness of the transformed T-lymphocytes from normal individuals in response to supraphysiologic concentrations of insulin (>8–500 ng/ml or >179–89,688 pM; 22).

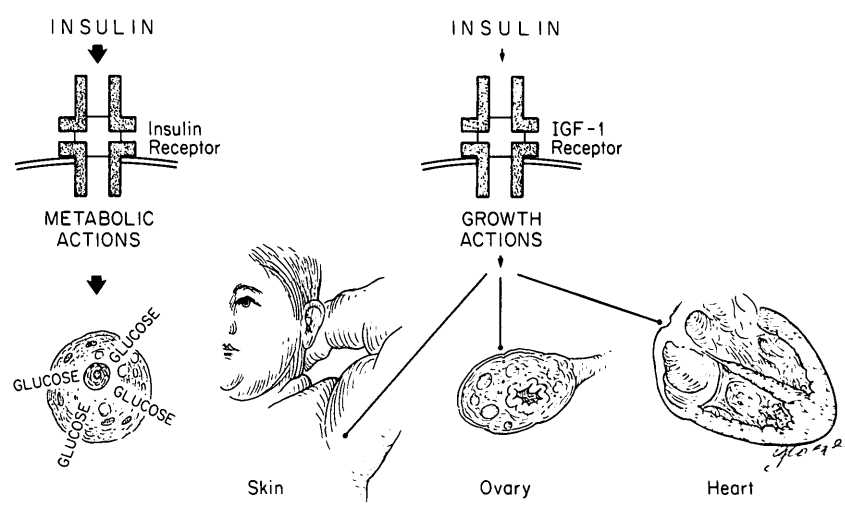

FIG. 1. Physiologic serum concentrations of insulin exert predominantly metabolic actions through insulin receptor (*thick arrows*), e.g., glucose uptake by cells (*bottom left*), with normally little, if any, growth actions, mediated by the IGF-I receptor (*thin arrows*), on skin, ovary, or heart tissues (*bottom right*).

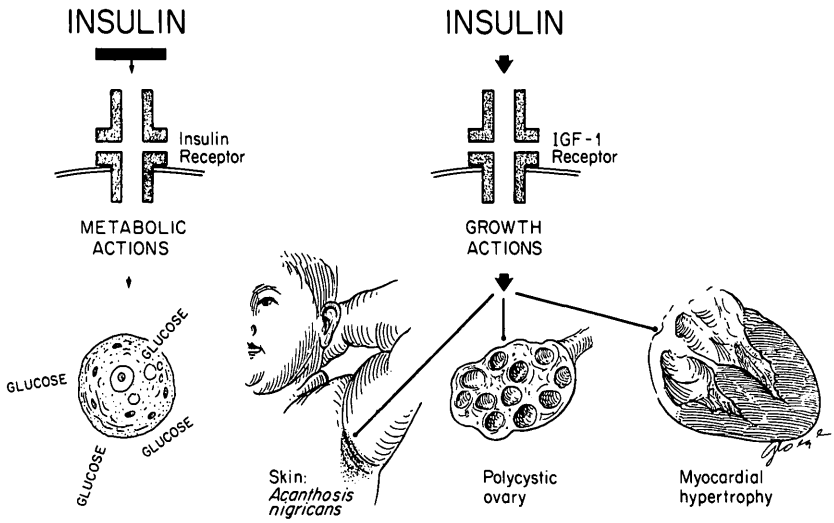

FIG. 2. In presence of hyperinsulinemia (note height of insulin lettering compared with Fig. 1) secondary to resistance to insulin action (*solid bar* through *thin arrow* above insulin receptor) on glucose uptake by cells (*bottom left*), insulin may exert potent growth actions mediated through IGF-I receptor (*thick arrows*) which can result in acanthosis nigricans, polycystic ovaries, and ventricular hypertrophy (*bottom right*).

Recently we studied EPCs from an infant with leprechaunism and found them to be completely resistant to insulin at physiologic concentrations (1–8 ng/ml or 179–1435 pM). A T-lymphocyte line established from this leprechaun patient was also completely resistant to physiologic insulin concentrations (22) consistent with a genetically transmitted defect in insulin responsiveness, as has been shown by others in previously reported patients (1). Supraphysiologic insulin concentrations, however, resulted in significant proliferation of the leprechaun T-lymphocytes. Using a monoclonal antibody directed specifically against the IGF-I receptor, we have shown in both control and leprechaun T-lymphocytes that the proliferative effects of supraphysiologic concentrations of insulin were blunted. The anti–IGF-I receptor antibody had no significant effect on normal T-lymphocyte responsiveness to physiologic insulin concentrations (22). Similarly, in studies with cultured adult human fibroblasts, [^{3}H]thymidine incorporation as an index of DNA synthesis and α-aminoisobutyric acid incorporation as an index of amino acid transport occur in response to both physiologic and supraphysiologic insulin concentrations, the latter competitively inhibited by pretreatment with the antibody to the IGF-I receptor (17,18).

These findings are consistent with insulin-stimulated growth promotion at supraphysiologic insulin concentrations mediated through the IGF-I receptor (even in insulin-resistant states) and insulin-stimulated growth promotion at physiologic insulin concentrations mediated through the insulin receptor.

ACANTHOSIS NIGRICANS

The gross clinical features of acanthosis nigricans include velvety, mossy, verrucous, and hyperpigmented skin located in the intertriginous regions including the nape of the neck, the axillae, under the breasts, and, occasionally, in the groin. Histologically, the lesion is characterized by proliferation of the keratinocyte layer of the epidermis (hyperkeratosis) with papillomatosis and hyperpigmentation (23). Acanthosis nigricans has traditionally been considered as an external marker for various adenocarcinomas, usually of the gastrointestinal tract, which may, in and of themselves, be associated with insulin resistance (24). Acanthosis nigricans has also been described in a wide variety of endocrinologic and metabolic disorders, all linked by the common finding of insulin resistance (Table 1). Most frequently, it is seen in association with morbid obesity and PCOD, but it has also been reported to occur in patients with various forms of genetic and epigenetic insulin resistance.

Acanthosis nigricans is believed to have an autoimmune basis or to be the result of the frequently concomitant overproduction of androgens seen in insulin-resistant individuals. It is tempting to relate the presence of acanthosis nigricans directly to hyperinsulinemia. In fact, studies of women with hyperandrogenism, obesity, acanthosis nigricans, and severe insulin resistance (25,26) and with acanthosis and PCOD (unrelated to obesity) (27) have shown that the acanthosis was directly related to the degree of observed hyperinsulinemia. Two patients with insulin-requiring diabetes have been described who developed hyperkeratotic, verrucous plaques at sites of repeated insulin injections (28,29). This could represent a direct effect of insulin on epidermal tissue. Recently, both insulin (30) and IGF-I (31) receptors have been identified in cultured human keratinocyte monolayers. With circulating serum insulin concentrations in the insulin-resistant states ranging between 4 and 400 ng/ml (718–71,750 pM), it is possible that insulin-induced growth promotion (hyperkeratosis) could result from the spillover action of insulin mediated via the IGF-I receptors of the keratinocyte layer.

HYPERANDROGENISM

Ovarian enlargement with abnormal steroidogenesis occurs commonly in insulin-resistant females (32). Histo-

logically, the ovaries may simply be enlarged or may develop follicular cysts of varying size with capsular thickening and stromal hyperplasia. That ovarian tissue can respond to insulin was suggested by the in vitro stimulation of pregnenolone and progesterone production in cultured swine granulosa cells (33). Subsequently, receptors for both insulin (34) and IGF-I (35) were described in the swine granulosa cell model and, more recently, in the human granulosa cell compartment (36,37). Normal human ovarian stromal tissue produced androgens in response to insulin, as did ovarian stromal tissue removed by wedge resection from obese, markedly hyperinsulinemic women with PCOD, retaining sensitivity to insulin at 50–500 ng/ml (8975–89,750 pM) concentrations as determined by accumulation of androstenedione and testosterone in vitro (38,39).

The presence of ovarian cysts in a number of insulin-resistant states is consistent with this model (Table 1). Ovarian cysts, along with sexual precocity, occur frequently in infants with leprechaunism, raising the possibility of an insulin-mediated gonadotropin-independent pathogenesis (1,40–42), which was also suggested by our observations in one such infant (22). Ovarian cysts have also been described in patients with the type A and C syndromes (3,4) and in patients with Cushing's syndrome (43). Evidence is now accumulating that hyperinsulinemia may have an etiologic role in PCOD based on the persistence of blunted insulin-dependent EPC colony formation in thin women with PCOD and no acanthosis nigricans after blockade of ovarian androgen production by 6 mo treatment with a long-acting analog of gonadotropin-releasing factor (21). Ovarian cysts have also been noted in the non-insulin-resistant hyperinsulinemic infant of the diabetic mother (IDM; 44). Thus, there is ample evidence that high circulating serum concentrations of insulin, perhaps acting in the trophic manner typical of a classical gonadotropic hormone (45), are frequently associated with disorders of ovarian morphology and function.

HYPERTROPHIC CARDIOMYOPATHY

A higher-than-expected frequency of both asymmetric septal and panventricular hypertrophy (and even aortic outflow hypertrophy) occurs in some genetic insulin-resistant states (Table 1). Clinically, this may be asymptomatic and detected only by electrocardiogram or echocardiogram, or it may be so severe as to result in heart failure. A clear association of myocardial hypertrophy with leprechaunism (1,40–41) and total lipodystrophy (2,46) has been reported. Our leprechaun patient had hypertrophy that was persistent, diffuse, and severe and may have caused aortic outflow obstruction leading to premature death (22).

A reversible cardiomyopathy, characterized by a thickened interventricular septum, has been described in adult patients with primary hypothyroidism (47). Hypertrophic cardiomyopathy, usually of the asymmetric septal variety, has also been reported to occur in patients with acromegaly (48). Hypertrophic cardiomyopathy is believed to reflect the growth hormone and/or IGF-I excess characteristic of patients with acromegaly; however, it may result from the hyperinsulinemia that occurs in these patients in response to their elevated growth hormone levels.

Myocardial tissue has been found to be rich in both insulin (49) and IGF-I (50) receptors. Thus, the hyperinsulinemia of insulin-resistant states could lead to insulin action on the myocardium through the IGF-I receptor accounting for the observed cardiomyopathy. Hypertrophy of the interventricular septum has also been described in some adolescents with type I diabetes (51), which could reflect the peripheral hyperinsulinemia that frequently occurs in insulin-treated subjects (52). That insulin can act on cardiac tissue in non-insulin-resistant states is strongly suggested by the occurrence of hypertrophic cardiomyopathy (frequently asymptomatic) in the IDM (53), in the infant with nesidioblastosis (53), and in patients with Beckwith-Wiedemann syndrome, who characteristically have omphalocele, macroglossia, gigantism, and, in one-third to one-half of cases, hypoglycemia (54). In the IDM the abnormalities resolve over the first few months of life with the loss of the in utero maternal hyperglycemic stimulus to insulin production. In the latter two situations, and in insulin-resistant states associated with persistent hyperinsulinemia, the cardiomyopathy may be progressive and debilitating.

CONCLUSIONS

It seems clear that insulin can act in a growth-promoting fashion in multiple tissues of the body in both insulin-sensitive and insulin-resistant states (Figs. 1 and 2). The prevalence of skin, ovarian, and cardiac abnormalities appears highest in the genetic forms of insulin resistance, perhaps because of higher circulating insulin levels attained in these syndromes compared to the epigenetic forms of insulin resistance. In addition, in those epigenetic forms associated with circulating antibodies to the insulin receptor (type B syndrome and ataxia telangiectasia), the known polyclonality of some of the generated antibodies (55) may allow cross-reactivity with the homologous IGF-I receptor, precluding its stimulation in some tissues by insulin. Sensitivity of the nontraditional target tissues may also depend on the density and/or affinity of their IGF-I receptors. In support of this contention, D'Ercole et al. (56) found the highest specific binding of ^{125}I-labeled somatomedin C (IGF-I) to membranes derived from adult pig ovarian tissue compared with all other pig tissues examined.

The concept of excessive concentrations of one hormone, similar in structure to another, exerting action through the second hormone's receptor, has been termed "specificity spillover" by Roth and Grunfeld (57). Representative examples of this phenomenon in-

clude insulin-induced generalized macrosomia in the IDM mediated through the IGF-I receptor (10), IGF-II–triggered hypoglycemia mediated through the insulin receptor in certain non–islet cell tumors (58), and growth-hormone–induced galactorrhea mediated through the prolactin receptor in non-hyperprolactinemic acromegalic subjects (59). Growth-promoting insulin actions, preferentially involving certain tissues, and mediated through the IGF-I receptor in states of (even complete) resistance to insulin's action on glucose disposal, appear to be another example of spillover specificity.

The possible effects of insulin on skin, ovary, and heart suggest that insulin may act on still other tissues, e.g., nephromegaly has been reported in leprechaunism (41) and in the insulin-sensitive Beckwith-Wiedemann syndrome (60). These tissue-specific spillover effects of insulin may be associated with significant morbidity, ranging from the cosmetic problem of acanthosis nigricans to the menstrual dysfunction and increased risk of endometrial carcinoma associated with PCOD and congestive heart failure and even death from the hypertrophic cardiomyopathy.

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REFERENCES

1. D'Ercole AJ, Underwood LE, Groelke J, Plet A: Leprechaunism: studies of the relationship among hyperinsulinism, insulin resistance, and growth retardation. *J Clin Endocrinol Metab* 48:495–502, 1979
2. Burn J, Baraitser M: Partial lipoatrophy with insulin resistant diabetes and hyperlipidaemia (Dunnigan syndrome). *J Med Genet* 23:128–30, 1986
3. Kahn CR, Flier JS, Bar RS, Archer JA, Gorden P, Martin MM, Roth J: The syndromes of insulin resistance and acanthosis nigricans: insulin-receptor disorders in man. *N Engl J Med* 294:739–45, 1976
4. Freychet P: Resistances a l'insuline: aspects physio-pathologiques et biochemiques. *Ann d'Endocrinol* 45:107–14, 1984
5. Bar RS, Levis WR, Rechler MM, Harrison LC, Siebert C, Podskalny J, Roth J, Muggeo M: Extreme insulin resistance in ataxia telangiectasia: defect in affinity of insulin receptors. *N Engl J Med* 298:1164–71, 1978
6. Kahn CR: Insulin receptors and syndromes of insulin resistance. *Diabetes Care* 5 (Suppl. 1):98–101, 1982
7. Matsuoka LY, Wortsman J, Gavin JR III, Kupchell CE, Dietrich JG: Acanthosis nigricans, hypothyroidism, and insulin resistance. *Am J Med* 81:58–62, 1986
8. Prince MJ, Tsai P, Olefsky JM: Insulin binding, internalization, and insulin receptor regulation in fibroblasts from type II, non-insulin-dependent diabetic subjects. *Diabetes* 30:596–600, 1981
9. Straus DS: Growth-stimulatory actions of insulin in vitro and in vivo. *Endocr Rev* 5:356–69, 1984
10. Hill DJ, Milner RDG: Insulin as a growth factor. *Pediatr Res* 19:879–86, 1985
11. Zapf J, Froesch ER: Insulin-like growth factors/somatomedins: structure, secretion, biological actions and physiological role. *Horm Res* 24:121–30, 1986
12. Czech MP, Mottola CM, Yu K-T, Oka Y: The insulinlike growth factor receptors. In *Human Growth Hormone*. Raiti S, Tolman RA, Eds. New York, Plenum, 1986, p. 539–52
13. Massague J, Blinderman LA, Czech MP: The high affinity insulin receptor mediates growth stimulation in rat hepatoma cells. *J Biol Chem* 257:13958–63, 1982
14. Nagarajan L, Anderson WB: Insulin promotes the growth of F9 embryonal carcinoma cells apparently by acting through its own receptor. *Biochem Biophys Res Comm* 106:974–80, 1982
15. Osborne CK, Monaco ME, Lippmann ME, Kahn CR: Correlation among insulin binding, degradation, and biological activity in human breast cancer cells in long-term tissue culture. *Cancer Res* 38:94–102, 1978
16. Koch KS, Shapiro P, Skelly H, Leffert HL: Rat hepatocyte proliferation is stimulated by insulin-like peptides in defined medium. *Biochem Biophys Res Comm* 109:1054–60, 1982
17. Flier JS, Usher P, Moses AC: Monoclonal antibody to the type I insulin-like growth factor (IGF-I) receptor blocks IGF-I receptor-mediated DNA synthesis: clarification of the mitogenic mechanisms of IGF-I and insulin in human skin fibroblasts. *Proc Natl Acad Sci USA* 83:664–68, 1986
18. Chaiken RL, Moses AC, Usher P, Flier JS: Insulin stimulation of aminoisobutyric acid transport in human skin fibroblasts is mediated through both insulin and type I insulin-like growth factor receptors. *J Clin Endocrinol Metab* 1181–85, 1986
19. Bersch N, Groopman JE, Golde DW: Natural and biosynthetic insulin stimulates the growth of human erythroid progenitors in vitro. *J Clin Endocrinol Metab* 55:1209–11, 1982
20. Geffner ME, Kaplan SA, Bersch N, Lippe BM, Scott ML, Bergman RN, Golde DW: Diminished in vitro responsiveness of circulating erythroid progenitor cells to insulin as an indicator of insulin resistance. *J Clin Endocrinol Metab* 60:103–108, 1985
21. Geffner ME, Kaplan SA, Bersch N, Golde DW, Landaw EM, Chang RJ: Persistence of insulin resistance in polycystic ovarian disease after inhibition of ovarian steroid secretion. *Fertil Steril* 45:327–33, 1986
22. Geffner ME, Kaplan SA, Bersch N, Lippe BM, Smith WG, Nagel RA, Santulli TV, Jr, Li CH, Golde DW: Leprechaunism: in vitro insulin action despite genetic insulin resistance. *Pediatr Res* 22:286–91, 1987
23. Brown J, Winkelmann RK: Acanthosis nigricans: a study of 90 cases. *Medicine* 47:33–51, 1968
24. Chlebowski RT, Heber D: Metabolic abnormalities in cancer patients: carbohydrate metabolism. *Surg Clin N Am* 66:957–68, 1986
25. Flier JS, Eastman RC, Minaker KL, Matteson D, Rowe JW: Acanthosis nigricans in obese women with hyperandrogenism: characterization of an insulin-resistant state dis-

tinct from the type A and B syndromes. *Diabetes* 34:101–107, 1985
26. Stuart CA, Peters EJ, Prince MJ, Richards G, Cavallo A, Meyer WJ III: Insulin resistance with acanthosis nigricans: the roles of obesity and androgen excess. *Metabolism* 35:197–205, 1986
27. Dunaif A, Graf M, Mandeli J, Laumas V, Dobrjansky A: Characterization of groups of hyperandrogenic women with acanthosis nigricans, impaired glucose tolerance, and/or hyperinsulinemia. *J Clin Endocrinol Metab* 65:499–507, 1987
28. Erickson L, Lipschutz DE, Wrigley W, Kearse WO: A peculiar cutaneous reaction to repeated injections of insulin. *JAMA* 209:934–35, 1969
29. Fleming MG, Simon SI: Cutaneous insulin reaction resembling acanthosis nigricans. *Arch Dermatol* 122:1054–56, 1986
30. Verrando P, Ortonne JP: Insulin binding properties of normal and transformed human epidermal cultured keratinocytes. *J Invest Dermatol* 85:328–32, 1985
31. Misra P, Nickoloff BJ, Morhenn VB, Hintz RL, Rosenfeld RG: Characterization of insulin-like growth factor-I/somatomedin C receptors on human keratinocyte monolayers. *J Invest Dermatol* 87:264–67, 1986
32. Barbieri RL, Ryan KJ: Hyperandrogenism, insulin resistance, and acanthosis nigricans syndrome: a common endocrinopathy with distinct pathophysiologic features. *Am J Obstet Gynecol* 147:90–101, 1983
33. Veldhuis JD, Kolp LA, Toaff ME, Strauss JF III, Demers LM: Mechanisms subserving the trophic actions of insulin on ovarian cells: in vitro studies using swine granulosa cells. *J Clin Invest* 72:1046–57, 1983
34. Veldhuis JD, Tamura S, Kolp L, Furlanetto RW, Larner J: Mechanisms subserving insulin action in the gonad: evidence that insulin induces specific phosphorylation of its immunoprecipitable receptor on ovarian cells. *Biochem Biophys Res Com* 120:144–49, 1984
35. Veldhuis JD, Furlanetto RW: Trophic actions of human somatomedin C/insulin-like growth factor I on ovarian cells: in vitro studies with swine granulosa cells. *Endocrinology* 116:1235–42, 1985
36. Poretsky L, Grigorescu F, Seibel M, Moses AC, Flier JS: Distribution and characterization of insulin and insulin-like growth factor I receptors in normal human ovary. *J Clin Endocrinol Metab* 61:728–34, 1985
37. Bayer S, Seibel M, Gates G, Moses A, Flier J: Identification of insulin-like growth factor receptors in human granulosa cells. *Sci Program and Abstr for 33rd Annu Meet of Soc Gynecol Invest*, p. 76
38. Barbieri RL, Makris A, Ryan KJ: Insulin stimulates androgen accumulation in incubations of human ovarian stroma and theca. *Obstet Gynecol* 64:73S–80S, 1984
39. Barbieri RL, Makris A, Randall RW, Daniels G, Kistner RW, Ryan KJ: Insulin stimulates androgen accumulation in incubations of ovarian stroma obtained from women with hyperandrogenism. *J Clin Endocrinol Metab* 62:904–10, 1986
40. Rosenberg AM, Haworth JC, Degroot W, Trevenen CL, Rechler MM: A case of leprechaunism with severe hyperinsulinemia. *Am J Dis Child* 134:170–75, 1980
41. Taylor SI, Samuels B, Roth J, Kasuga M, Hedo JA, Gorden P, Brasel DE, Pokora T, Engel RR: Decreased insulin binding in cultured lymphocytes from two patients with extreme insulin resistance. *J Clin Endocrinol Metab* 54:919–30, 1982
42. Kashiwa H, Kawaguchi S, Takeda M, Kobayashi M, Omori Y, Eto R: Insulin resistance in an infant with leprechaunism. *Acta Paediatr Scand* 73:701–704, 1984
43. Yen SSC: The polycystic ovary syndrome. *Clin Endocrinol* 12:177–208, 1980
44. Ahlvin RC, Bauer WC: Luteinized cysts in ovaries of infants of diabetic mothers. *Am J Dis Child* 93:107–109, 1957
45. Poretsky L, Kalin MF: The gonadotropic function of insulin. *Endocr Rev* 8:132–41, 1987
46. Rheuban K, Blizzard RM, Parker MA, Cater T, Wilson T, Gutgesell H: Hypertrophic cardiomyopathy in total lipodystrophy. *J Pediatr* 109:301–302, 1986
47. Shenoy MM, Goldman JM: Hypothyroid cardiomyopathy: echocardiographic documentation of reversibility. *Am J Med Sci* 294:1–9, 1987
48. Smallridge RC, Rajfer S, Davia J, Schaaf M: Acromegaly and the heart: an echocardiographic study. *Am J Med* 66:22–27, 1979
49. Steven J, Whitsett JA: Insulin binding to neonatal human, guinea pig, and rat myocardial membranes (Abstract). *Pediatr Res* 13:482, 1979
50. Rechler MM, Nissley SP: Receptors for insulinlike growth factors. In *Polypeptide Hormone Receptors*. Posner BI, Ed. New York, Marcel Dekker, 1985, p. 227–98
51. Lababidi ZA, Goldstein DE: High prevalence of echocardiographic abnormalities in diabetic youths. *Diabetes Care* 6:18–22, 1983
52. Rizza RA: Use of artificial devices in intensive insulin therapy of diabetes mellitus. *Clin Chem* 32:B97–102, 1986
53. Breitweser JA, Meyer RA, Sperling MA, Tsang RC, Kaplan S: Cardiac septal hypertrophy in hyperinsulinemic infants. *J Pediatr* 96:535–39, 1980
54. Greenwood RD, Sommer A, Rosenthal A, Craenen J, Nadas AS: Cardiovascular abnormalities in the Beckwith-Wiedemann syndrome. *Am J Dis Child* 131:293–94, 1977
55. Rosenfeld RG, Baldwin D Jr, Dollar LA, Hintz RL, Olefsky JM, Rubinstein A: Simultaneous inhibition of insulin and somatomedin-C binding to cultured IM-9 lymphocytes by naturally occurring antireceptor antibodies. *Diabetes* 30:979–82, 1981
56. D'Ercole AJ, Underwood LE, Van Wyk JJ, Decedue C, Foushee DB: Specificity, topography, and ontogeny of the somatomedin-C receptor in mammalian tissues. In *Growth Hormone and Related Peptides*. Pecile A, Muller EE, Eds. Amsterdam, Excerpta Med., 1976, p. 190–201
57. Roth J, Grunfeld C: Mechanism of action of peptide hormones and catecholamines. In *Williams Textbook of Endocrinology*. Wilson JD, Foster DW, Eds. Philadelphia, PA, Saunders, 1985, p. 96–98
58. Gorden P, Hendricks CM, Kahn CR, Megyesi K, Roth J: Hypoglycemia associated with non–islet-cell tumor and insulin-like growth factors. *N Engl J Med* 305:1452–55, 1981
59. Baumann G: Acromegaly. *Endocrinol Metab Clin N Am* 16:685–703, 1987
60. Cohen MM Jr, Gorlin RJ, Feingold M, ten Bensel RW: The Beckwith-Wiedemann syndrome. *Am J Dis Child* 122: 515–19, 1971