# Hyperinsulinemia: The Common Denominator of Subjective Idiopathic Tinnitus and Other Idiopathic Central and Peripheral Neurootologic Disorders

*Joseph R. Kraft, M.D.*

## ABSTRACT

### Background

Hyperinsulinemia as determined by glucose/insulin tolerance identified an etiologic relationship to idiopathic Ménière's disease. This was subsequently concurred with internationally by others. Proctor identified hyperinsulinemia in Subjective Idiopathic Tinnitus (SIT).Hyperinsulinemia and migraine with tinnitus and/or vertigo were also correlated.

### Methods

Based upon 15,000+ 100g glucose/ insulin tolerances, the presence of hyperinsulinemia as determined by radioimmunoassay became defined and statistically confirmed.

Fasting insulin levels greater than 30 µU/mL (180 pmol/L) or the sum of the 2nd and 3rd hour insulin levels greater than 60 µU/mL (360 pmol/L) following 100 g glucose load identified and thereby defined hyperinsulinemia.

The statistical database affirmed hyperinsulinemia with or without hyperglycemia as the sine qua non of the noninsulin-dependent diabetic state. Hyperinsulinemia was further statistically affirmed as the early metabolic marker in carbohydrate metabolism, preceding hyperglycemia.

### Results

Updegraff, Mangabeira-Albernaz, Fukuda, Proctor, and Malavasi-Ganança independently identified and concurred that hyperinsulinemia was the major etiologic factor in up to 84% to 92% of their idiopathic neurootologic disorders. Their cases included tinnitus, vertigo, hypoacusia, and classical Ménière's disease. Updegraff identified hyperinsulinemia in his migraine studies. Independently the investigations reported dramatic relief and sustained therapeutic response to medical nutritional therapy compliance unequaled by other modalities.

### Conclusions

Hyperinsulinemia is a dynamic process definable by glucose/insulin tolerance. It is a very cost-effective office and/or outpatient procedure.

Hyperinsulinemia with or without hyperglycemia is the major metabolic marker with diagnostic and therapeutic relationship to SIT and other idiopathic neuro-otologic disorders.

The unequaled therapeutic responses of SIT and other hyperinsulinemia idiopathic neuro-otologic disorders to medical nutritional therapy compliance mandates the earliest possible identification of hyperinsulinemia.

### Key Words

Hyperinsulinemia, Tinnitus, Vertigo, Glucose/ insulin tolerance

## GENERAL PRINCIPLES

The first major impact of hyperinsulinemia in the clinical arena was in the clinical discipline of neuro-otology. This was the identification by Updegraff[1] in 1977 of hyperinsulinemia with idiopathic Ménière's disease.

Using a bioassay for insulin, Bornstein[2] in 1951 demonstrated increased insulin in the noninsulin-dependent diabetic. Hyperinsulinemia as identified by Yallow[3] in 1960 was of greater significance. It was based on the

radioimmunoassay of insulin in known diabetic patients following a 100 g glucose load. This became the cornerstone of radioimmunoassay as an analytic chemistry tool. For this procedural development, Yallow was awarded a Nobel Prize.

From its beginning in 1960 to 1971, insulin assays were limited to research laboratories. All were made without the availability of international standard controls. The first international reference preparation of human insulin for immunoassay (WHO)[4] was established in 1974. The international standard became, and continues to be, the primary standard for insulin assay credibility comparison.

In 1971, the Phadebus insulin radioimmuno-assay test (Pharmacia Diagnostic AB, Uppsala, Sweden) became the first RIA insulin test available in the United States.

In our laboratories, this assay was applied to the standard 100 g oral glucose tolerance for procedural evaluation. By January 1972, it became our standard routine procedure and identified as *glucose/insulin tolerance*. A 4-hour procedure was standard in our laboratory. Physician-reported 3- and 5-hour procedures were included in our database.

Our initial studies of insulin assay correlated with diabetic glucose tolerances concurred Yallow's findings of hyperinsulinemia.[5] Our extended studies further identified *hyperinsulinemia as a dynamic process* manifest as insulin flow patterns coursing through the 100 g glucose/insulin tolerance.[6]

The hyperinsulin patterns with diabetic glucose tolerances became repetitive and distinctive for noninsulin-dependent diabetes mellitus, NIDDM, Type II. The unique and specific hyperinsulin patterns were *diagnostic per se* of the noninsulin-dependent diabetic state.

The insulin patterns as initially described and defined in diabetic, impaired glucose tolerance (IGT) and euglycemic glucose tolerances were unchanged in our ongoing database. The classification of tolerances according to glucose values are the guidelines of the American Diabetes Association. Our reports of 2,500+,[5] 3,500+,[6] 10,000+,[8] 14,000+,[9] and our current 15,000+ examinations provide the cumulative database. The definitions of euinsulinemia, hypoinsulinemia, and hyper-

insulinemia are statistically affirmed.

The fasting range was determined upon the mean of the first 1000 glucose/insulin tolerances. In the 0 to 100 µU range, the 1 SD for our procedure was $5 \pm \mu U/mL$. The mean of $14.65 \mu U/mL \pm 3 SD$ of our RIA procedure ($15 \pm \mu U/mL$) determined the 0 to 30 µU/mL (0 to 180 pmol/L) fasting range.

Hyperinsulinemia became defined as fasting levels above fasting range (0 to 30 µU/mL) or the sum of the second and third hour insulin levels greater than 60 µU/mL (360 pmol/L) following a 100 g glucose load. Euinsulinemia is normal fasting with 0.5 or 1 hour peak above fasting range and the second and third hour sum less than 60 µU/mL. Hypoinsulinemia has all insulin values within fasting range.

The definition of euinsulinemia holds even in the IGT with high 0.5- to 1-hour insulin peaking which mirrors the hyperglycemia peaking of gastric dumping associated with gastric resection and/or upper gastrointestinal dysfunction.

Hyperinsulinemia with hyperglycemia glucose tolerances definitively diagnosed diabetes mellitus, noninsulin-dependent diabetes mellitus (NIDDM), Type II. Hyperglycemia glucose tolerance with *hypoinsulinemia* identified insulin-dependent diabetes mellitus, (IDDM) designated Type I potential.

Hyperinsulinemia with IGT and euglycemia tolerances identified the non-insulin-dependent diabetic state of NIDDM. Hypoinsulinemia and euinsulinemia with IGT and euglycemic glucose tolerance are designated normal.

## HYPERINSULINEMIA PRECEDES HYPERGLYCEMIA

Hyperinsulinemia diabetic insulin patterns with normal glucose tolerance values established the earliest identification of the NIDDM state. As early as 1974, we defined this as diabetes mellitus in situ (occult diabetes).[5,6] This was the first laboratory-defined identification of the noninsulin-dependent diabetic state based upon glucose/insulin tolerance.

Progression and/or regression of normal glucose tolerance with hyperinsulinemia to IGT with hyperinsulinemia to hyperglycemia with

hyperinsulinemia demonstrates that *hyperinsulinemia definitely precedes hyperglycemia*. This is best illustrated in the shortened time span of pregnancy whenever hyperinsulinemia (in situ diabetic state) progresses to hyperglycemia gestational diabetes status.[8]

The pathophysiologic model of gestational hyperinsulinemia diabetic state progression is a microcosm of the identical hyperinsulin noninsulin-dependent diabetic state of NIDDM. Gestational diabetes and diabetes mellitus Type II, irrespective of patient age and gender, have an identifiable beginning in the hyperinsulinemia euglycemia status, that is, the *in situ* noninsulin-dependent diabetic state.[10]

Hyperinsulinemia has been statistically confirmed in our database as the early metabolic marker in carbohydrate metabolism preceding hyperglycemia. Hyperglycemia, especially fasting hyperglycemia, thereby becomes a late marker in the complex metabolic process of hyperinsulinemia/insulin resistance/noninsulin-dependent diabetic state. It was further affirmed that hyperinsulinemia with or without hyperglycemia (diabetic glucose values) is the *sine qua non* of NIDDM.[5-6,8-11]

## RESULTS

The XVth Scientific Meeting of the Neuro-otological and Equilibriometric Society (NES) at Bad Kissingen, in March 1988, addressed vertigo, nausea, tinnitus, and hypoacusia in metabolic disorders.[12]

Updegraff,[13-14] Mangabeira-Albernaz,[15-16] Fukuda,[17] and Proctor[18] independently identified and concurred hyperinsulinemia as the major diagnostic factor in up to 84 to 92% of their cases of idiopathic dizziness and tinnitus. Their patients included those with classic Ménière's disease. Updegraff further reported a correlation of hyperinsulinemia and migraine. The relationship of hyperinsulinemia and SIT was specifically addressed by Proctor.[18]

Updegraff had noted that certain of his patients with Ménière's, as well as his migraine patients, had Diabetes Mellitus (DM) upon glucose tolerance. Others were either IGT or normal glucose tolerant. No clinical distinction was made with the glycemia status. Challenged by our early reports that hyperinsulinemia preceded hyperglycemia, Updegraff applied glucose/insulin tolerance to his studies.

In Updegraff's series of 121 patients with Ménière's disease with glucose/insulin tolerance, there were 61 (50%) with normal glucose, 15 (12%) with IGT and 45 (37%) with hyperglycemia of DM. Each IGT and each DM glucose/insulin tolerance revealed hyperinsulinemia of NIDDM. Of the 61 with normal glucose values, 10 or 16% were euinsulinemic. 51 of 61, or 84% were hyperinsulinemic. The hyperinsulinemia of the IGT and the DM patients with Ménière's was indistinguishable from hyperinsulinemia in 111 of 121 (92%) cases of Ménière's disease, irrespective of the glycemia status.

Updegraff's 93 cases of migraine with glucose/insulin tolerance revealed 80 (86%) with hyperinsulinemia in each patient. Fifty-six of the 93 migraine patients (60%) had normal glucose tolerance values. Hyperinsulinemia indistinguishable in itself from the hyperinsulinemia of the IGT and DM glucose/insulin tolerance was identified in 43 or 77% of the migraine patients with normal glucose tolerance values. Hyperinsulinemia was identified as the common denominator in 80 of 93 (86%) cases, irrespective of the glycemia status following a 100 g glucose load.

Updegraff's identification of hyperinsulinemia as an etiologic agent and/or factor in the idiopathic disorders of Ménière's disease, migraine, and tinnitus was concurred by others.[13-18]

In Proctor's[18] study of 50 SIT cases, there were 25 with 5-hour 100 g glucose/insulin tolerances of which 21 (84%) revealed hyperinsulinemia. A simple 2-hour post-prandial test for glucose and insulin levels on the other 25 SIT cases revealed abnormal insulin levels over 50 μU (300 pmol/L) in 12 or 48%. Proctor noted that the 2-hour insulin levels average 107 μU (642 pmol/L) during the 100 g glucose/insulin tolerance and 56 μU (336 pmol/L) during a simple 2-hour post-prandial test.

Independently all the investigators achieved and reported dramatic relief and sustained therapeutic response to their medical nutritional therapy. Compliance yielded sustained response unequaled by other modalities. Proctor[19] cites results of nutritional management in 54 patients with Ménière's disease elevated insulin levels as remarkable.

Of the 54 patients, 49 (91%) achieved control of their vertigo after the initial 6 months of dietary treatment. This control had been maintained at the same 91% rate during the 10 years since this study was initiated in 1980. The patients with Ménière's disease reported hearing improved to normal levels and complete relief of tinnitus. Caovilla, Malavasi Gananca, Freitas Gananca, and Serafini[20] identified abnormal insulin levels in their 1128 outpatients who were suffering from tinnitus and other statoacoustic systems. In 6 months of diet therapy, 426 (38%) were subjectively improved or cured of tinnitus. With dietary control, the associated vertigo and other kinds of dizziness improved or were eradicated in 72% of the cases. Hearing loss was improved in 20% of the patients.

*Hyperinsulinemia Identification (see Table I).*

In 2,500+ normal glucose/euinsulin 100 g glucose/insulin tolerances the second hour insulin mean values of 27.9 µU/mL SE 4.2 (351 pmol/L) is identified. The other normal values are:

fasting 7.6 µU/mL SE 0.6 (46 pmol/L)
1/2 hour 58.5 µU/mL SE 4.2 (351 pmol/L)
1st hour 41.3 µU/mL SE 4.8 (368 pmol/L)
3rd hour 12.7 µU/mL SE 0.6 (76 pmol/L)
4th hour 7.2 µU/mL SE 0.6 (43 pmol/L)

Fasting insulin levels greater than 30 µU/mL identify hyperinsulinemia with a sensitivity/specificity of 10%. Post 100 g glucose load, second hour insulin levels greater than 40 µU/mL (240 pmol/L) yield a hyperinsulinemia sensitivity/specificity of 89%. The sum of the second plus third hour insulin greater than 60 µU/mL (360 pmol/L) yields a sensitivity/specificity of 99%. The standard 100 g 3 to 5 hour glucose/insulin tolerance, including fasting, yields a sensitivity/specificity of 100%.

## HYPERINSULINEMIA SCREEN

We have proposed a practical glucose/insulin screen procedure to identify the population at risk.[21] The post 100 g glucose load second hour insulin greater than 40 µU/mL (240 pmol/L) identified hyperinsulinemia with a sensitivity/specificity of 89%. An accompanying second hour glucose examination provides glycemia correlation.

The glucose/insulin tolerance second hour screen procedure and/or the 3 to 5 hour 100 g glucose/insulin tolerance test are functional office and/or outpatient procedures. These procedures are readily adaptable in the primary care environment.

In previous publications,[8-11] we have called attention that blood serum for insulin radio-immunoassay (RIA) can be kept frozen (up to 2 year) until sufficient specimens from multiple patient examinations are obtained. The frozen specimens are then shipped to local and/or regional laboratories. RIA insulin assay examinations thereby become practical and cost-efficient with international availability and worldwide application.

## HYPERINSULINEMIA/INSULIN RESISTANCE

Insulin resistance is a term historically identified with the insulin-dependent diabetic. Whenever antibodies to exogenous insulin of significant amounts occurred and required a markedly increased dosage, the term *insulin resistance* was originally applied. It has now been extended to include patients in whom there is evidence of a reduced biologic response to insulin as demonstrated by different investigative techniques.

The glucose clamp technique (wherein a fixed-rate insulin infusion is combined with a variable-rate glucose infusion adjusted to maintain precise euglycemia) is used to derive an index of whole-body insulin sensitivity. In absolute terms, this index is reduced by 35 to 40% in NIDDM and is thereby judged "insulin resistant". This research technique has also identified an index of insulin resistance in the euglycemic state. This affirms our identification of hyperinsulinemia with euglycemia glucose tolerance as the earliest identification of the NIDDM state. In 1974, we were the first to define and identify diabetes mellitus *in situ* (occult diabetes) by glucose insulin tolerance.[5,6] *Insulin resistance* has become an omnibus term[21] and is defined in this paper as a concept of insulin sensitivity at the cellular level. Hyperinsulinemia is the measurable parameter thereof. Hyperinsulinemia/insulin resistance are hereby employed as synonyms. Insulin resistance is therefore a concept of hyperinsulin production. Hyperinsulinemia is a defined quantitative determination by RIA, a diagnostic

tool available to the primary care physician as an office and/or outpatient procedure.

## MEDICAL NUTRITION THERAPY

The term identifies the essential therapeutic role of supervised nutrition in hyperinsulinemia. Medical nutritional therapy requires counseling expertise. An appreciation of idiopathic neuro-otologic disorders and an understanding of hyperinsulinemia are as important as the counseling skills required in diabetes mellitus. To relegate nutritional therapy exclusively to hand-out sheets is deficient therapy.

Koniz[22] and Festa[23] have identified the patient as the most important person in the management team of physician, patient, and nutritionist. Modification of a lifetime of nutritional habits is frequently required. Scheduled follow-ups provide the support and encouragement necessary for the development of self-responsibility necessary for the patient to gain and maintain management control of the metabolic disorder. Physical training also improves insulin sensitivity in subjects with hyperinsulinemia upon compliance with nutritional therapy. The normalization of hyperinsulinemia by medical nutritional therapy compliance is demonstrable by glucose/insulin tolerance.[23]

## DISCUSSION

Insulin is the key to cellular metabolism. Hyperinsulinemia is a key to selective cellular metabolic dysfunction of multiple organs and/or symptoms with varying clinical manifestations or sequelae.

In addition to the idiopathic neuro-otologic disorders of tinnitus, dizziness, classic Ménière's disease, and migraine, hyperinsulinemia with euglycemia glucose tolerance has been etiologically identified with primary ovarian follicle dysfunction,[24,25] essential hypertension,[26] atherosclerosis,[27] and coronary artery disease.[28] All of the above compose the clinical pathology of hyperinsulinemia (Table II). The clinical relevance of hyperinsulinemia has worldwide application. We are predicting that *hyperinsulinemia* will supplant *cholesterol* as the lay/medical buzzword by the year 2,000.

Shulman[29] notes that cardiac arrhythmias and hypertension have a significant incidence among patients with SIT. Early identification of tinnitus has been accompanied by an elevation of blood pressure. This demonstrates the common denominator of hyperinsulinemia with essential hypertension and SIT. Medical nutritional therapy compliance is also a shared denominator becoming the cornerstone of conjoint therapy for essential hypertension and SIT.

Identification of hyperinsulinemia with euglycemia glucose tolerance does not guarantee that hyperglycemia status is inevitable. Genetic factors as yet undetermined may indeed play a role. The potential, nevertheless, exists. Adult-onset diabetes by hyperglycemia is diagnosed most frequently in the later decades of life.

The individual's nutritional state may be sufficient to arrest and/or delay euglycemia/hyperglycemia progression. If the nutritional state is sufficient to maintain a euglycemia status and yet insufficient to reverse hyperinsulinemia, risk factors for the *clinical pathology of hyperinsulinemia* remain.

The Medical Audiologic Tinnitus Patient Protocol (MATPP) of Shulman[30] offers diagnostic and attempted treatment/control of SIT. Shulman emphasizes that flexibility in thinking is required to allow for the development of new modalities in the diagnosis and treatment of tinnitus.

Priority early exclusion of hyperinsulinemia as part of the initial examination of the patient with SIT is indicated. Hyperinsulinemia identification with SIT, secondary endolymphatic hydrops (SEH), and other idiopathic disorders will significantly narrow the *idiopathic* categorization. The unequaled therapeutic responses of SIT and other idiopathic disorders to medical nutritional therapy compliance mandates the earliest possible identification of hyperinsulinemia.

The National Diabetes Data Group (NDDDG) Classification and Diagnosis of Diabetes Mellitus and Other Categories of Glucose Intolerance[7] remains in place as of this date. From time to time, a fresh look at this classification with periodic reevaluation has been suggested. Epidemiologic data and classifications of diabetes, gestational diabetes, and other categories of glucose intolerance based

primarily and dependent on defined glucose concentrations without insulinemia status are limited, incomplete and/or obsolete.[5,7-8]

We have proposed a diabetic state classification based primarily upon the insulinemia status with a secondary glycemia designation as identified by glucose/insulin tolerance.[10] This fulfills the five classification requirements of the NDDG.[30] Our proposed classification of primary insulinemia and secondary glycemia designation is readily adaptable to incorporate new research findings on the etiopathology of the diabetic state.

The complex cellular,[31] genetic,[32] histochemical,[33] immunologic,[34] and/or other yet undetermined marker mechanism or pathways of hyperinsulinemia in the metabolic disorder of the diabetic state are not yet fully unveiled. Yet, one can now use with confidence the insulinemia glucose/insulin screen and/or tolerance as a practical laboratory tool. Future application of molecular biologic techniques will clarify the role of the insulin-receptor complex and its relationship to hyperinsulinemia production.

Identifying hyperinsulinemia provides a basis for immediate and prospective management of the associated disorders of hyperinsulinemia. Hyperinsulinemia is the common denominator of SIT and other idiopathic central and peripheral neuro-otologic disorders. In lieu of the reported unequaled therapeutic response of idiopathic neuro-otologic disorders with hyperinsulinemia to medical nutritional therapy compliance, the earliest possible identification of hyperinsulinemia becomes mandatory.

## CONCLUSIONS

(1) Hyperinsulinemia with or without hyperglycemia is the major metabolic marker and common denominator with diagnostic and therapeutic relationship to Subjective Idiopathic Tinnitus (SIT) and other idiopathic central and peripheral neuro-otologic disorders.

(2) Hyperinsulinemia is a dynamic process definable by glucose/insulin tolerance. It is cost-effective and readily available as an office and/or outpatient procedure in the primary care environment.

(3) Hyperinsulinemia is the *sine qua non* of the noninsulin-dependent diabetic state and the early metabolic marker in carbohydrate metabolism,

preceding hyperglycemia.

(4) Hyperinsulinemia and the noninsulin-dependent diabetic state are one and the same clinical pathology, irrespective of the glycemia status.

(5) The clinical pathology of hyperinsulinemia is essential hypertension, atherosclerosis, mainly coronary artery disease, primary ovarian follicle dysfunction, and the idiopathic neuro-otologic disorders of SIT, Ménière's disease, SEH, migraine, vertigo, nausea, tinnitus, and hypoacusia.

(6) The unequaled therapeutic responses of SIT and other hyperinsulinemia-related idiopathic neuro-otologic disorders to medical nutritional therapy compliance mandates the earliest possible identification of hyperinsulinemia.

*Table I.*

Hyperinsulinemia Identification: Summary
(1) Fasting Insulin > 30 μU—
    Sensitivity/specificity = 10%
(2) Post 100 g Glucose Load:
    (A) 2nd Hour > 40 μU—
    Sensitivity/specificity = 89%
    (B) 3rd Hour + 2nd Hour sum> 60 μU—
    Sensitivity/specificity = 99%
(3) Glucose Insulin Tolerance—
    Sensitivity/specificity = 100%
    (3 to 5 hours) = Hyperinsulinemia/glycemia
    classification

*Fasting insulin levels greater than 30 μU/mL or the sum of the 2nd and 3rd hour insulin levels greater than 60 μU/mL following a 100 g glucose load, defined hyperinsulinemia based upon 15,000+ glucose/insulin tolerance examinations. Hyperinsulinemia is the *sine qua non* of the noninsulin dependent diabetic state.

*Table I.I*

Clinical Pathology of Hyperinsulinemia*
Essential hypertension
Atherosclerosis
  Coronary artery disease
  Generalized
Primary ovarian follicle dysfunction
Idiopathic neuro-otology
  Ménière's disease
  migraine
  SIT
  SEH
  vertigo
  nausea
  tinnitus
  hypoacusia

*Hyperinsulinemia and the noninsulin dependent diabetic state are one and the same clinical pathology irrespective of the glycemia status.

## REFERENCES

1. Updegraff WR: Impaired carbohydrate metabolism an idiopathic Ménière's disease. Ear Nose Throat J 56:160-3, 1977.

2. Bornstein J, Lawrence RD: Plasma insulin in human diabetes mellitus. Br Med J 2:1541-44, 1951.

3. Yallow RS, Berson SA: Immunoassay of endogenous plasma insulin in man. J Clin Invest 39:1157-75, 1960.

4. WHO Handbook of resolutions and decisions, 1973-1984. Geneva: World Health Organization, 1981, pp. 135.

5. Kraft JR: Glucose/insulin tolerance a routine clinical laboratory tool enhancing diabetes detection. In Radioassay: clinical concepts. Hunter OB, Ed. Skokie, IL: Searle, 1974, pp. 91-106.

6. Kraft JR: Detection of diabetes mellitus in situ (occult diabetes). Lab Med 6:10-22, 1975.

7. National Diabetes Data Group: Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes 28:1030-57, 1979.

8. Kraft JR: Insulin and glucagon. In Nuclear Medicine in Vitro. 2nd Ed. Rothfeld B, (Ed.) Philadelphia: J.B. Lippincott, 1983, pp. 211-23.

9. Kraft JR: Insulin assay diabetic state identification, a specific diagnostic tool of the noninsulin dependent diabetic state, a metabolic disorder. In Vertigo, Nausea, Tinnitus and Hypoacusia in Metabolic Disorders. Claussen C-F, Kirtane MV, Schlitter K, Eds. Amsterdam: Elsevier, 1988, pp. 503-6.

10. Kraft JR: Hyperinsulinemia, a defined marker of in situ NIDDM and associated metabolic disorders: a review of 15,000+ glucose/insulin tolerance examinations. In Vertigo, Nausea, Tinnitus and Hypoacusia due to Central Disequilibrium. Claussen C-F, Kirtane MV, Schneider D, Eds. Proceedings of the NES, Vol 20, 1992. Hamburg: Werner Rudat, 1994, pp. 569-76.

11. Kraft JR, Sie KT: Hyperinsulinemia: a diagnostic mandate for idiopathic dizziness and its related disorders. Presented at the 21st Congress NES, March 17-20, 1994, Bad Kissingen, Germany, publication pending.

12. Claussen C-F, Kirtane MV, Schlitter K: Nausea, Tinnitus and Hypoacusia in Metabolic Disorders. Amsterdam: Elsevier, 1988.

13. Updegraff WR. Ménière's, migraine and general medicine. In Vertigo, Nausea, Tinnitus and Hypoacusia in Metabolic Disorders Claussen C-F, Kirtane MV, Schlitter K, Eds. Amsterdam: Elsevier, 1988, pp. 177-81.

14. Updegraff WR: A new metabolic approach to headache and dizziness. In: New Dimensions in Otorhinolaryngology Head and Neck Surgery, Vol. 2 Myer E, Ed. Amsterdam: Elsevier, 1985, pp. 509-10.

15. Mangabeira-Albernaz PL, Fukuda Y: Glucose, insulin and the inner ear pathology. Acta Otolaryngol 97:496-501, 1984.

16. Mangabeira-Albernaz PL: Metabolic aspects of labyrinthine disease—a progress report. In Vertigo, Nausea, Tinnitus and Hypoacusia in Metabolic Disorders. Claussen C-F, Kirtane MV, Schlitter K, Eds. Amsterdam: Elsevier, 1988, pp. 135-38.

17. Fukuda Y, Juliana L, Mangabeira-Albernaz PL: The physiopathological influence of hyperinsulinemia on the origin of Ménière's disease. In Vertigo, Nausea, Tinnitus and Hypoacusia in Metabolic Disorders Claussen C-F, Kirtane MV, Schlitter K, Eds. Amsterdam: Elsevier, 1988, pp. 257.

18. Proctor CA, Proctor TD. Hyperinsulinemia and tinnitus. In Vertigo, Nausea, Tinnitus and Hypoacusia in Metabolic Disorders. Claussen C-F, Kirtane MV, Schlitter K, Eds. Amsterdam: Elsevier, 1988, pp. 379-83.

19. Proctor CA, Proctor TB, Proctor B: Etiology and treatment of fluid retention (hydrops) in Ménière's syndrome. Ear Nose Throat J 71:631-35,1992.

20. Caovilla HH, Malavasi-Ganança M, Freitas-Gananca F, Serafini F: Nutritional diet in the

treatment of tinnitus. Presented at the 21st NES Congress, March 17-20, 1994, Bad Kissingen, Germany. Publication pending.

21. Kraft JR, Sie KT: Hyperinsulinemia/Insulin resistance/NIDDM state identification. A practical screening procedure proposal. Diabetes 39(Suppl 1):695, 1990.

22. Koniz M: On the importance of nutrition in inner ear disorders. In Vertigo, Nausea, Tinnitus and Hypoacusia in Metabolic Disorders. Claussen C-F, Kirtane MV, Schlitter K, Eds. Amsterdam: Elsevier, 1988, pp. 21-26.

23. Festa MD: Biochemistry and nutrition: the importance of nutrition in inner ear disorders. In Vertigo, Nausea, Tinnitus and Hypoacusia in Metabolic disorders. Claussen C-F, Kirtane MV, Schlitter K, Eds. Amsterdam: Elsevier, 1988, pp. 213-14.

24. Perez-Pelaez M, Jeyendran RS, Kraft JR, Sie KT: Abnormal insulin patterns and its relationship to defective folliculogenesis in infertile patients. (abstract) In: Proceedings of the 12th World Congress on Fertility and Sterility. Soon TE, Ratman SS, Min LS, Eds. Singapore: Gynecological Society of Singapore,1985, p. 1094.

25. Perez-Pelaez M, Kraft JR: Hyperinsulinemia in reproduction. Presented at: Controversias en Fertilidad, May 19-20, 1994, Madrid. Publication pending.

26. Reaven GM: Role of insulin resistance in human disease. Diabetes 37:1595-1607, 1988.

27. Stolar MW: Atherosclerosis in diabetes: the role of hyperinsulinemia. Metabolism 37 (Suppl 1):1-9, 1988.

28. Zavoroni I, Bonora E, Pagliara M, et al.: Risk factors for coronary artery disease in healthy persons with hyperinsulinemia and normal glucose tolerance. N Engl J Med 320:702-6, 1989.

29. Shulman A: Tinnitus: Diagnosis/Treatment. Philadelphia: Lea & Febiger, 1991.

30. Shulman A: Subjective idiopathic tinnitus: a unified plan of management. Am J Otolaryngol 13:63-73, 1992.

31. Olefsky JM, Garvey WT, Henry RR, et al.: Cellular mechanisms of insulin resistance in noninsulin dependent (type II) diabetes. Am J Med 85 (Suppl 5A):87-105, 1988.

32. Bogardus C, Lillika S, Nyomba BL, et al.: Evidence for a single gene, codominant mode of inheritance of insulin resistance in Pima Indians. Diabetes 37:Suppl 1:91A, abstract, 1988.

33. Porte D, Kahn SE: Hyperproinsulinemia and amyloid in NIDDM: clues to etiology of islet B-cell dysfunction? Diabetes 38:1333-36, 1989.

34. Eisenbarth GS: Type I diabetes mellitus: a chronic autoimmune disease. N Engl J Med 314:1360-67, 1986.