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Syndrome X: Is It for Real?

James V. Neel,[1]* Stevo Julius,[2] Alan Weder,[2] Michiko Yamada,[3] Sharon L.R. Kardia,[1] and Martha B. Haviland[1]

[1]Department of Human Genetics, University of Michigan Medical School, Ann Arbor
[2]Department of Medicine, University of Michigan Medical School, Ann Arbor
[3]Department of Clinical Studies, Radiation Effects Research Foundation, Hiroshima, Japan

The term syndrome X has been applied to the association of hypertension, non-insulin-dependent diabetes mellitus (NIDDM), android obesity, insulin resistance, and dyslipidemia. In this paper, based on population samples from Tecumseh, Michigan, and Hiroshima, Japan, characterized by persons ≥40 years of age, we examine the validity of regarding this constellation of traits as a true syndrome, i.e., an array of traits with a single, unifying pathophysiology underlying its components. Data were not available on insulin resistance and dyslipidemia, and obesity was expressed as body mass index (BMI) without the division into android and non-android types. The four ethnic-gender data sets were analyzed on the basis of two age classes, age ≥40 years and age ≥50 years, and two obesity classes, BMI ≥27 and ≥30. A simple χ^2 test of goodness-of-fit under a model of independence revealed non-random associations between hypertension, NIDDM, and BMI which were in part attributable to an excess of persons with all three traits. However, when the four data sets were subjected to separate log-linear analyses of the three-way association tables, none of the three-factor interaction terms (i.e., syndrome X) was significant. High significance was, however, observed in the two-factor interaction term for BMI*hypertension. It is concluded that the significant association between these three traits is driven by the BMI*hypertension interaction, and there is no evidence in these data sets of a significant role for a syndrome X. Genet. Epidemiol. 15:19–32, 1998.

Key words: syndrome X; hypertension, diabetes, obesity association; Tecumseh, disease associations; Hiroshima, disease associations

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*Correspondence to: James V. Neel, M.D., Ph.D., Department of Human Genetics, Box 0618, M4780 Medical Science I, University of Michigan, Ann Arbor, MI 48109-0618.

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INTRODUCTION

Recent years have witnessed increasing interest in an entity most commonly referred to as syndrome X, the association of non-insulin-dependent diabetes mellitus (NIDDM), essential hypertension, truncal-abdominal (android) obesity, insulin resistance, and dyslipidemia [cf. Björntorp, 1992; Gillum, 1987; Kaplan, 1989; Landsberg, 1986; McKeigue et al., 1991; Modan et al., 1985; Reaven, 1988; Sims and Berchtold, 1982]. Essentially the same complex has also been termed the insulin resistance syndrome (IRS) [Defronzo and Ferrannini, 1991; Edwards et al., 1994]. Carmelli et al. [1994], employing the twin panel approach, have suggested that this is a genetic syndrome, individuals with the constellation sharing a common latent factor of which 59% was attributed to genetic and 41% to environmental effects. There is no doubt that individuals are encountered exhibiting this association and that in some data sets they occur in numbers exceeding random expectation [Criqui et al., 1986; Ferrannini et al., 1991]. The term "syndrome," however, is in its strict (and most useful) sense applied to a non-random association of traits stemming from a single basic aberration. Given the relatively high prevalence of obesity, essential hypertension, and NIDDM in most affluent nations, instances of this association can be expected on the basis of chance alone. While one can elect to term such a chance association a syndrome, when so used the term does not carry the usual implication of a unifying pathophysiology underlying its components.

What is needed to determine whether the associations of these three entities exceed random expectation are survey data on a *total* population (or randomly selected subset thereof) whose members were not selected for study with reference to any of the traits in question. We have found no analysis of such a data set in the literature. Fortunately, we have access to two sets of observations that seem to meet most of these criteria, one involving a defined population of Japanese living in Hiroshima, Japan, and the other involving a defined population of Caucasians living in Tecumseh, Michigan.

Japanese Population

One of the major programs among the studies of the Radiation Effects Research Foundation (RERF) on the potential delayed effects of exposure to the atomic bombs is the so-called Adult Health Study (AHS). The AHS cohort at its inception comprised 19,961 subjects, about half of whom were within 2,000 m of the hypocenter, a quarter beyond 3,000 m, and the remainder not in the city (NIC) at the time of bombing. Since 1958, all subjects have been invited to participate in biennial health examinations. (For a full description of the study see Hollingsworth and Beebe [1960].) The follow-up for the 5,000 NIC subjects was discontinued after 1974. Because of high attrition and the fear that the sample would eventually become too small for the detection of radiation effects, 2,436 subjects were added to the study group in 1977. These health examinations consist of history taking, general physical examination, and laboratory tests that include blood pressure, blood sugar, and various anthropometric measurements such as height and weight. The results presented here are drawn from the data collected between January 1991 and December 1992, in Hiroshima only. This represents the 16th–17th biennial examination cycle.

Tecumseh Population

The Tecumseh Community Health Study began in 1959 as a prospective epidemiological investigation of health and disease in a geographically defined area consisting of the town of Tecumseh, MI, and the surrounding rural area [Napier, 1962; Napier et al., 1970]. During the periods 1959–1960 and 1962–1965, some 80% of the total population, including both sexes and all ages, were studied in comprehensive health examinations. Participants gave detailed medical histories to lay examiners, and positive responses were further investigated during physician interviews. Included in the survey measurements were standardized assessments of height, weight, and blood pressure [Johnson et al., 1965]. In addition, blood was obtained from all willing participants for determination of blood glucose. Most blood specimens were obtained 1 hr after administration of 100 g of glucose solution orally, without regard for the proximity to a previous meal or to time of day [Johnson et al., 1965]. There were no African-Americans in the sample.

Shortcomings of the Data Set

There are several important shortcomings to these data sets. First, in the studies involved, no clear distinction was drawn between android and non-android obesity. We are forced to treat all obesity as a single entity, quantitated as body mass index (BMI), defined as (weight in kilograms)/(height in meters^2).

Second, BMI, blood pressure level, and the impairment of glucose metabolism termed NIDDM are basically continuous variables, and a truly sophisticated analysis would treat them as such. Unfortunately for our present purposes, in countries with a high level of medical practice, such as the United States and Japan, although some fraction of undiagnosed hypertension and NIDDM is encountered in population surveys, physician intervention into the disease process following diagnosis has materially altered the expression of the disease. We are, therefore, forced to define essential hypertension either as an observed seated diastolic blood pressure ≥90 mm Hg or a history of a previous diagnosis and current antihypertensive treatment. With respect to the diagnosis of NIDDM in Tecumseh, participants were classified as diabetic even if no blood glucose determination was performed, if they reported having been diagnosed as diabetic by a physician, and had ever taken insulin or an oral hypoglycemic agent. Participants who did not meet these criteria for diabetes but had a 1 hr post-challenge blood glucose concentration greater than 224 mg/dl or a casual level greater than 124 mg/dl were classified as hyperglycemic. The criteria for the diagnostic post-challenge glucose value were based on results obtained in earlier glucose tolerance testing performed in the Tecumseh population [Hayner et al., 1965; Ostrander et al., 1980], and the criteria for the casual value on U.S. Public Health Service criteria [O'Sullivan and Mahan, 1965]. For the purpose of the present analysis, diabetes and hyperglycemia were combined, and persons not classified as diabetic or hyperglycemic were considered non-diabetic. The classifications forming the basis for earlier reports [Butler et al., 1982] are maintained in the present analysis. In the RERF data, the situation is slightly different. NIDDM has been a subject of long-standing interest to the staff, beginning with the first round of examinations in the AHS [Freedman et al., 1965]. At each round of the examinations, which now amount to 16–17 for the subjects of the present study, at a minimum a blood sugar has usu-

ally been obtained (fasting or post-prandial, as the case may be). For participants who were classified as hyperglycemic, more complete studies have been performed based on the criteria defined by the Japan Diabetes Association [Kuzuya, 1970].

On the other hand, physician intervention into the therapy for obesity is so unsuccessful that the BMI as determined at the time of examination is that employed in the analysis, with no reference to previous attempts at therapy. However, as with the arbitrary definitions of hypertension and NIDDM, the use of a specific BMI to define obesity also presents a problem. There is room for a difference of opinion as to when an individual is "plump" or "stout" and when obese. We will analyze the data with regard to two different definitions of obesity, namely, BMI ≥27, and BMI ≥30. The resulting two data sets are not independent of one another. There is a further issue with respect to BMI in that the data are cross sectional rather than longitudinal. For one reason or the other, people sometimes lose weight after the diagnosis of NIDDM. Thus, for our purposes, the best measurement would be maximum BMI, but this is simply not available.

Third, we mention that insulin resistance and dyslipidemia are often regarded as a component of syndrome X. We do not have data on all our subjects on these characteristics, and so these attributes do not enter into our statistical treatment. However, it will be shown that such data are not essential to the argument we are developing.

A further complication of the data is that all three of the entities under consideration are age-related. For purposes of analysis, and to permit comparison with similar data sets, it is necessary to introduce arbitrary age standards into the data if the prevalence of trait or syndrome frequency is to be defined. We will present the data in terms of all members of the two populations ≥40 years of age and all members ≥50 years of age. Because of the special circumstance in the construction of the Japanese cohort (i.e., alive at the time of the atomic bombings), the youngest member was actually ≥45 years of age. The four resulting data sets are again not independent of one another.

STATISTICAL METHODS

To investigate the null hypothesis that the observed frequency distribution was explained by the independent contribution of each of the three disease traits (obesity status, hypertension status, and diabetes status), a χ^2 goodness-of-fit test was applied to the data in the following manner. First, marginal relative frequencies of each disease category were calculated. Then, the expected cell frequencies were estimated by multiplying the appropriate marginal relative frequencies together for each cell of the $2 \times 2 \times 2$ table and multiplying this probability by the total sample size of that particular gender by ethnic-specific subgroup. The χ^2 goodness-of-fit between observed and expected frequencies under the model of independence had 4 degrees of freedom (8 cells – 1–3 parameters needed for estimation of expectation = 4 degrees of freedom).

To test whether the marginal frequency of each of these disease traits was independent of gender within each ethnicity or was independent of ethnicity within each gender, we used the 2×2 χ^2 test of association. We did not pool genders when testing for ethnic differences nor did we pool ethnic subgroups when testing for gender differences. We also performed a Mantel-Haenszel test on these data, with essentially the same results and inferences, but prefer to present the analysis in its

present form as providing a more descriptive picture of the combined differences in the frequencies of these diseases among the gender and ethnic groups.

To investigate the null hypothesis that the observed distribution of the data was not associated with an interaction between BMI, hypertension, and diabetes (i.e., syndrome X) log-linear models were employed. For the three-way tables (i.e., 2 × 2 × 2) represented in Table I, the complete or saturated log-linear model is:

$$\ln f_{ijk} = \mu + \alpha_i + \beta_j + \gamma_k + \alpha\beta_{ij} + \alpha\gamma_{ik} + \beta\gamma_{jk} + \alpha\beta\gamma_{ijk}$$

where α_i, β_j, and γ_k represent the deviations of the marginal frequencies from 0.5 for BMI, hypertension, and diabetes, respectively, $\alpha\beta_{ij}$, $\alpha\gamma_{ik}$, and $\beta\gamma_{jk}$ represent two-factor interactions, and $\alpha\beta\gamma_{ijk}$ is the three-factor interaction term; μ represents the overall grand mean of the log f_{ij}. The null hypothesis that $\alpha\beta\gamma_{ijk} = 0$ was tested by comparing the maximum likelihood of the saturated model with the maximum likelihood of the reduced model with only two-factor interactions using the standard likelihood ratio test. Likewise, the null hypothesis that $\alpha\beta_{ij} = 0$ was tested by comparing the maximum likelihood of a model with all three two-factor interaction terms with the maximum likelihood of a reduced model with only the $\alpha\gamma_{ik}$ and the $\beta\gamma_{jk}$ interaction terms. The other two-factor terms were tested in an analogous fashion.

DATA

The basic data are presented in Tables I and IV, following the conventions outlined earlier. We emphasize again that the four sets of ethnic-gender tabulations are independent of one another, but the four sets of age-BMI tabulations nested within the preceding sets are not independent. Table I presents the data on age ≥40 years, BMI ≥27, and the results of the χ^2 goodness-of-fit test, for males and females separately for both cities. Table II presents the results of applying the log-linear model to these data, while Table III provides numerical examples of the predictions resulting from omitting the three-factor interaction term ($\alpha\beta\gamma_{ijk}$) or all the interaction terms except BMI*hypertension ($\alpha\beta_{ij}$). Table IV presents the other three data sets, but no analysis. However, these data have been analyzed in a fashion similar to the first set, and reference will be made to the results of the analysis in what follows.

RESULTS

Eight diagnostic categories were possible based on whether or not an individual had obesity, hypertension, NIDDM, or some combination thereof. For the first set of analyses, the definition of obesity is a BMI ≥27. In Table I, the observed frequency of individuals ≥40 years of age that fall into one of the eight possible diagnostic categories is presented for each gender- and ethnic-specific subgroup. The marginal frequencies of each of the separate diagnostic categories are also presented. We note that these marginal frequencies were significantly gender dependent in the Japanese sample, and ethnic group dependent in both males and females. For example, the marginal frequency of high BMI was significantly greater in Tecumseh males than in Japanese males (marginal frequency of 0.379 compared to 0.067) and significantly

TABLE I. Observed and Expected (Under a Mode of Independence) Frequencies of the Eight BMI, Hypertension (HYT), and NIDDM Diagnostic Categories, as Well as the Marginal Frequencies, for Males and Females at Least 40 Years of Age in the Tecumseh and Japanese Samples

			Tecumseh						Japan					
Diagnoses			Males			Females			Males			Females		
BMI ≥27	HYT	NIDDM	Observed	Expected[a]	χ^2	Observed	Expected[a]	χ^2	Observed	Expected[a]	χ^2	Observed	Expected[a]	χ^2
N	N	N	391	344	6.48	385	316	14.98	656	647	0.12	1,508	1,422	5.20
Y	N	N	168	210	8.34	159	224	18.73	38	47	1.66	144	204	17.78
N	Y	N	184	228	8.53	176	233	14.00	326	333	0.14	481	553	9.23
N	N	Y	48	51	0.19	55	54	0.02	101	102	0.00	117	142	4.51
Y	Y	N	178	139	10.79	218	165	17.05	31	24	1.99	125	79	26.26
Y	N	Y	29	31	0.16	33	38	0.70	8	7	0.06	20	21	0.01
N	Y	Y	34	34	0.00	27	40	4.10	51	52	0.03	66	55	2.07
Y	Y	Y	26	21	1.35	45	28	10.10	5	4	0.39	23	8	28.55
Total			1,058			1,098			1,216			2,484		
χ^2 test of independence (df = 4)					35.849			79.680			4.398			93.612
P					<0.0001			<0.0001			0.355			<0.0001
Marginal frequencies														
High BMI			0.379**			0.414**			0.067*,**			0.126*,**		
Hypertension			0.399**			0.424**			0.340*,**			0.280*,**		
NIDDM			0.129**			0.146**			0.136*,**			0.091*,**		

[a]Expected under a model of independence.
*Marginal frequency is gender dependent within ethnic group ($P < 0.05$).
**Marginal frequency is ethnic-group dependent within gender ($P < 0.05$).

TABLE II. Results of Likelihood Ratio Tests Comparing the Likelihood of Log-Linear Models With and Without the Three- and Two-Factor Interaction Terms Between BMI, Hypertension (HYT), and NIDDM (DIAB)[†]

	Model 1 vs. model 2 (H_o: DIAB*HYT*BMI = 0)		Model 2 vs. model 3 (H_o: DIAB*HYT = 0)		Model 2 vs. model 4 (H_o: BMI*HYT = 0)		Model 2 vs. model 5 (H_o: BMI*DIAB = 0)	
	χ^2	*P*	χ^2	*P*	χ^2	*P*	χ^2	*P*
Tecumseh								
Males	2.32	0.1281	0.82	0.3652	32.17	<0.0001	0.16	0.6892
Females	0.05	0.8297	0.03	0.8625	74.91	<0.0001	3.61	0.0574
Japan								
Males	0.19	0.6604	0.00	0.9999	3.74	0.0531	0.38	0.5376
Females	0.62	0.4327	11.81	0.0006	58.28	<0.0001	5.18	0.0228

[†]Model 1: Ln(f) = DIAB + HYT + BMI + DIAB*HYT + DIAB*BMI + HYT*BMI + DIAB*HYT*BMI; model 2: Ln(f) = DIAB + HYT + BMI + DIAB*HYT + DIAB*BMI + HYT*BMI; model 3: Ln(f) = DIAB + HYT + BMI + DIAB*BMI + HYT*BMI; model 4: Ln(f) = DIAB + HYT + BMDIAB*HYT + DIAB*BMI; model 5: Ln(f) = DIAB + HYT + BMI + DIAB*HYT + HYT*BMI.

TABLE III. Expected Frequencies of the Eight BMI, Hypertension (HYT), and NIDDM Diagnostic Categories Under a Model Containing All Two-Factor Interaction Terms and Under a Model With Only the BMI*HYT Interaction Term, for Males and Females at Least 40 Years of Age in the Tecumseh and Japanese Samples

			Tecumseh						Japan					
Diagnoses			Males			Females			Males			Females		
BMI ≥27	HYT	NIDDM	Observed	Expected[a]	Expected[b]	Observed	Expected[a]	Expected[b]	Observed	Expected[a]	Expected[b]	Observed	Expected[a]	Expected[b]
N	N	N	391	387	382	385	384	376	656	655	654	1,508	1,506	1,477
Y	N	N	168	172	171	159	160	164	38	39	40	144	146	149
N	Y	N	184	188	190	176	177	173	326	327	326	481	483	497
N	N	Y	48	52	57	55	56	64	101	102	103	117	119	148
Y	Y	N	178	174	178	218	217	225	31	30	31	125	123	135
Y	N	Y	29	25	26	33	32	28	8	7	6	20	18	15
N	Y	Y	34	30	28	27	26	30	51	50	51	66	64	50
Y	Y	Y	26	30	26	45	46	38	5	6	5	23	25	13
Total			1,058			1,098			1,216			2,484		

[a]Expectation under the model with all two-factor interaction terms.
[b]Expectation under the model with only BMI*HYT interaction terms.

TABLE IV. Observed Frequencies of the Eight BMI, Hypertension (HYT), and NIDDM Diagnostic Categories Under Three Different Partitionings of the Data, Namely, BMI ≥27 kg/m^2 and Age ≥50 years; BMI ≥30 kg/m^2 and Age ≥40 years; and BMI ≥30 kg/m^2 and Age ≥50 years

			Tecumseh						Japan					
			Males			Females			Males			Females		
Diagnoses			BMI ≥27 and age ≥50	BMI ≥ 30 and age ≥40	BMI ≥ 30 and age ≥50	BMI ≥27 and age ≥50	BMI ≥30 and age ≥40	BMI ≥30 and age ≥50	BMI ≥27 and age ≥50	BMI ≥30 and age ≥40	BMI ≥30 and age ≥50	BMI ≥27 and age ≥50	BMI ≥30 and age ≥40	BMI ≥30 and age ≥50
High BMI	HYT	NIDDM	years	years	years	years	years	years	years	years	years	years	years	years
N	N	N	213	501	273	190	470	238	495	688	513	1,317	1,610	1,408
Y	N	N	95	58	35	89	74	41	22	6	4	128	42	37
N	Y	N	102	291	154	115	256	165	287	351	308	459	564	535
N	N	Y	37	66	51	35	65	44	87	108	94	108	132	121
Y	Y	N	80	71	28	145	138	95	26	6	5	110	42	34
Y	N	Y	24	11	10	26	23	17	8	1	1	17	5	4
N	Y	Y	21	46	31	21	34	27	43	56	47	65	73	72
Y	Y	Y	17	14	7	35	38	29	4	0	0	20	16	13
Total			589	1,058	589	656	1,098	656	972	1,216	972	2,224	2,484	2,224

greater in Tecumseh females than in Japanese females (marginal frequency of 0.414 compared to 0.126). In contrast, Tecumseh males and females had approximately the same marginal frequencies for each of the three diseases while Japanese males had significantly higher marginal frequencies of hypertension and NIDDM, and a significantly lower frequency of high BMI, than Japanese females.

Comparing the observed frequency distribution with the expected frequencies under a model of independence among each of the characteristics (Table I), it is evident that there are significant departures from random association ($P < 0.001$) in Tecumseh males, Tecumseh females, and Japanese females, but not Japanese males. As indicated by the χ^2 values associated with each particular combination, where the departure from random association is significant in the total sample, it is in part attributable to a substantial excess of individuals with the triad of diseases but other entries make significant contributions, and especially the association of obesity and hypertension. We thus confirm previous reports of an excess of individuals with the triad in some "populations" [Criqui et al., 1986; Ferrannini et al., 1991].

To investigate more thoroughly the nature of the association between high BMI, hypertension, and NIDDM, we used log-linear models [Bishop et al., 1975; Sokal and Rohlf, 1995]. The results from the likelihood ratio test of the complete model (model 1) including a three-factor interaction term vs. the reduced model (model 2) containing no three-factor interaction term are presented in Table II for each gender- and ethnic-specific subgroup. In every subgroup, the inference was the same, namely, that there was no statistically significant evidence for a separate three-factor association. This result is unlikely to be due to a type II error, because of the large sample sizes associated with each subgroup and because the magnitude of the *P* values associated with this test is not even close to marginal significance in three of the four subgroups.

Subsequent analyses of each two-factor interaction term are also presented in Table II and indicate that there is a significant association between the BMI and hypertension in all four subgroups: Tecumseh males, Tecumseh females, Japanese males, and Japanese females. These analyses also indicated a significant association between BMI and NIDDM in females, but not males. Finally, a significant association between hypertension and NIDDM was observed in Japanese females only. Table III illustrates the actual numerical expectations with two of the "reduced" models for which the results of significance tests were given. Note, on the one hand, the very minor effect of omitting the three-factor interaction term, and, on the other hand, how well the data are fit by a model in which the only interaction term is BMI*hypertension. For example, we point out that the model with all two-factor interaction terms predicts a larger number of individuals expected to have the purported syndrome X than we actually observed in any of our samples. Thus, there are simply no individuals where a "syndrome X" must be invoked to explain the data. This conclusion is further supported by examining the expected number of individuals with the purported "syndrome X" using the model with only the BMI*hypertension interaction term. This model explains 100% of the observed number of individuals with all three diseases in both Tecumseh males and Japanese males. We do not believe that these inferences would be influenced by additional information on insulin resistance or dyslipidemia in these subjects.

As mentioned previously, we also investigated the associations between high BMI, hypertension, and NIDDM using an alternative definition of obesity of BMI

≥30 and a second age cutoff of ≥50 years of age. In Table IV, we present the observed frequency distributions of the eight diagnostic categories when these different criteria for inclusion in the samples and for inclusion in the obesity category are followed. The same log-linear analyses as presented above were conducted on each of these different data sets, and, in each, there was still no statistically significant evidence for a three-factor interaction which would indicate a non-random association between all three diseases. In general, the original inferences from the first analysis hold with only a few, sporadic exceptions. For example, in Japanese males, the interaction between high BMI and hypertension becomes non-significant when the cutoff for inclusion in the high BMI category shifts from ≥27 to ≥30, regardless of the age cutoff. In Tecumseh males, the interaction between high BMI and hypertension becomes non-significant only in the ≥30 BMI and ≥50 years of age cutoff of the data. We also note that in females, when the inclusion criterion for the high BMI category becomes more stringent (i.e., is BMI ≥30), the strength of the association between high BMI and NIDDM becomes more significant ($P < 0.02$) (analyses not shown).

DISCUSSION

We comment first on the relatively high frequency in these two populations of the three components of syndrome X. Granted the arbitrary definition of these three traits, by these or any other reasonable definitions, the frequencies of these traits and the size of the two study populations would seem to be adequate for the detection of a syndrome X if such occurs in significant numbers. At the same time, we note an interesting difference between the two populations. Although there are significant gender-ethnic differences with respect to all three traits, this is much more marked with reference to BMI than for NIDDM or hypertension (see Table I). Otherwise stated, the Japanese exhibit roughly comparable levels of NIDDM and hypertension even though the fraction with an elevated BMI as defined is only about one quarter that observed in the Tecumseh population. In any rigorous effort to define ethnic differences in susceptibility to NIDDM and hypertension, it would be desirable to compare populations in which the BMIs were more similar. The validity of this comparison is also marred by the previously mentioned fact that because of the age composition of the cohort, the age cutoff for the Japanese data is ≥45 years, whereas for the Tecumseh cohort it is ≥40 years.

The analysis does not exclude the possibility that buried in the association of NIDDM/hypertension/BMI ≥27, there are a few cases of a "true" syndrome X, i.e., an association not explicable by the overlapping occurrence of three common diagnostic entities, but due to a specific gene or genes. Thus, the situation could be analogous to the recognition that among the many cases of NIDDM (the predisposition to which is usually treated as a oligogenic disorder), there is an uncommon dominantly inherited entity now termed maturity-onset type diabetes of youth (MODY), in which the impairment of sugar metabolism has an early onset, progresses slowly, and appears to be inherited as a simple dominant trait [Tattersall, 1974]. In the 20 years since its recognition, MODY has now been subdivided into three rare subtypes [reviewed in Spielman and Nussbaum, 1992; Fajans et al., 1994]. However, as demonstrated earlier, there is at present little need to invoke a true genetic syndrome to explain the observed association.

Carmelli et al. [1994], analyzing data on "syndrome X" similar to that in this paper and derived from the panel of male twin veterans of World War II established under the auspices of the National Research Council, as described by Jablon et al. [1967] and Hrubec and Neel [1978], stated: "Multivariate genetic modeling of the correlation in liabilities to develop these conditions suggested the presence of a common latent factor mediating the clustering of hypertension, diabetes and obesity in this twin sample. This common factor was influenced by both genetic and environmental effects (59% genetic, 41% environmental)." The analysis was based on a total of 2,508 Caucasoid twin pairs of known zygosity, of whom 1,236 pairs (2,473 persons) were dizygous, and the remainder monozygous. We note that in their data, for both the monozygous and dizygous twins, there was no excess over random expectation of individuals concordant for hypertension, diabetes, and obesity. Thus, from the population standpoint, these data provide no evidence for a syndrome X. Hong et al. [1997], in a study in Swedish twins with IRS (the definition including hypertension), endorse the concept that "all of the five principal metabolic components contained in IRS are more or less influenced by a single latent genetic factor," but then note, "systolic blood pressure was related to IRS, albeit weakly, only through genetic effects." Their data are not presented in a fashion such that the question of an excess in that population of IRS (including hypertension) over random expectation can be tested.

On the other hand, Mitchell et al. [1996], in a family-based study of the IRS which included hypertension as a component, find that "the genetic correlations of insulin levels with systolic and diastolic blood pressures were low." These observations of Mitchell et al. [1996], plus Hong et al. [1997], together with the data of this paper, suggest that the terms IRS and syndrome X should not be used interchangeably. Hypertension is not an integral aspect of the IRS, although it is often encountered in persons with the IRS. Should, further, our findings be confirmed in other but more complete studies of total populations, then the justification for recognizing a syndrome X disappears, and it would seem appropriate to discontinue the use of the term.

In these two data sets, the greater strength of the association between BMI ≥27 and hypertension than between BMI ≥27 and NIDDM is noteworthy. This is not the stereotypical view, but further discussion would be premature until data are available permitting the subdivision of persons with BMI ≥27 or ≥30, and the analyses, into android and non-android types of obesity [for population data see Cassano et al., 1992; Haffner et al., 1987; Hartz et al., 1984; Iso et al., 1991; Ohlson et al., 1985; Williams et al., 1987]. However, we question whether an analysis based on breaking the subset with android obesity out of the more general category of obesity could reverse the relative strengths of these two associations or, for that matter, together with data on dyslipidemia and insulin resistance, reveal a sufficient association of hypertension, NIDDM, and android obesity to establish the concept of syndrome X as a major, uniquely determined genetic entity.

Thus, our findings lead us to consider that "syndrome X" is very predominantly the result of an overlap among the distributions of multifactorial etiologies underlying each of three common diseases. The genetic analyses of these multifactorial diseases present the most difficult research challenge facing human geneticists today. For the purposes of understanding both etiology and prediction, it is particularly relevant to recognize that variation in many disease susceptibilities among individu-

als in the population at large is a consequence of the intersection of exposures and genetically permissive factors. As we gain more information about the molecular biology of the metabolic systems involved in the common diseases and identify more causal factors, we are faced with the realization that fewer and fewer cases of the common diseases will be associated with a specific etiology, i.e., an interaction between a particular genotype and a particular set of environmental exposures [Sing et al., 1996]. This is particularly true in the case of an individual with multiple common diseases such as syndrome X. Few studies of common multifactorial diseases recognize this reality.

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