Diagnostic efficacy of screening tests for hereditary hemochromatosis

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Hereditary hemochromatosis is transmitted as an autosomal recessive trait. Analyses of pedigrees suggest that the frequency of disease (proportion of homozygous individuals) in the general population is approximately 0.3% and that approximately 11% of the population are heterozygous. The genotype of 194 persons in 38 pedigrees was determined by HLA-A and HLA-B haplotyping. Likelihood analysis was then used to appraise the transferrin saturation test when used alone and in combination with the serum ferritin test to detect homozygosity and heterozygosity in these pedigrees. A single cut-off point of 55% for transferrin saturation and a cut-off point at the 90th percentile for the serum ferritin level were adequate for the detection of hemochromatosis if homozygosity was considered to be present when the results of one or both tests were positive. To further assess the value of the transferrin saturation test the percentages were stratified into five intervals. A percentage transferrin saturation of 75 or greater and a serum ferritin level above the 90th percentile ruled in homozygosity, whereas a percentage transferrin saturation of less than 55 and a serum ferritin level at or below the 90th percentile ruled it out with confidence. The probability of heterozygosity rose to 90% when the percentage transferrin saturation was between 35 and 55 and the serum ferritin level was at or below the 90th percentile. The use of five cut-off points allowed the probability of homozygosity and heterozygosity in a pedigree to be estimated for all values of transferrin saturation. Although these screening tests are not recommended for use in the general population, they may be worth while in selected groups of patients.

L'hémochromatose héréditaire se transmet sur le mode récessif autosomique. L'analyse génétique donne une fréquence probable de la maladie (c'est-à-dire la proportion d'individus homozygotes) dans la population générale de quelque 0,3% et des porteurs hétérozygotes d'environ 11%. Les auteurs établissent d'abord le génotype de 194 sujets répartis en 38 arbres généalogiques par la détermination des haplotypes HLA-A et HLA-B. Ils recherchent ensuite comment les résultats de l'épreuve de saturation de la transferrine, seule ou en rapport avec la ferritinémie, permettent de donner la probabilité de l'état homozygote ou hétérozygote dans ces arbres. Des points critiques à 55% pour la saturation de la transferrine et au 90e centile pour la ferritinémie suffisent à déceler l'hémochromatose, dans la mesure où l'on considère que la positivité de l'un ou de l'autre de ces examens démontre l'état homozygote. Afin d'évaluer davantage la valeur de l'examen de saturation de la transferrine, on répartit les pourcentages en cinq strates. On affirme l'état homozygote devant une saturation de la transferrine d'au moins 75% et une ferritinémie dépassant le 90e centile. Mais on peut l'exclure en toute confiance si la saturation est inférieure à 55% et que la ferritinémie ne dépasse pas le 90e centile. La probabilité de l'état hétérozygote atteint 90% devant une saturation de la transferrine se situant entre 35% et 55% et une ferritinémie ne dépassant pas le 90e centile. L'emploi de cinq points critiques permet d'établir la probabilité de l'homozygotie et de l'hétérozygotie dans un arbre généalogique pour tout pourcentage de saturation de la transferrine. Bien que ces examens ne conviennent pas au dépistage dans la population générale, ils peuvent être fort utiles dans l'étude de sujets choisis.

Hereditary hemochromatosis is transmitted as a recessive trait. From an analysis of 19 pedigrees we estimated that the frequencies of homozygosity and heterozygosity in a reference population in Ontario and Quebec were 0.3% and 11%.[1] Similar rates have been found in the United States.[2] Although hemochromatosis is present from the time of conception, the clinical symptoms develop in homozygous individuals later in life, when sufficient iron has accumulated in the body. Once iron overload is detected, phlebotomies must be done regularly to arrest tissue damage. Therefore, as soon as a proband has been identified it is essential that other family members be screened for homozygosity before iron loading leads to serious complications.

The hemochromatosis allele is linked to the HLA locus, and typing for HLA-A and HLA-B haplotypes can identify the genotypes in a pedigree once homozygosity has been identified.[1,2] However, this technique is expensive and not generally used as a screening test. The transferrin saturation test is widely used to screen family members. A percentage transferrin saturation greater than 80, in the absence of other diseases associated with such a high level, suggests homozygosity for the hemochromatosis allele.[2] However, the percentage transferrin saturation is between 50 and 80 with either homozygosity or heterozygosity for the abnormal gene. The serum ferritin test serves as a reliable indicator of the amount of iron accumulated in the body, but it lacks sensitivity in the early stages of the disease and in homozygous females during the reproductive period.

We performed a likelihood analysis to appraise the transferrin saturation test when used alone and in combination with the serum ferritin test to detect

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hemochromatosis. With HLA-A and HLA-B typing we classified the family members of 38 pedigrees with hemochromatosis as being homozygous, heterozygous or normal. Then, using strategies developed by the Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ont.[3-6] for interpreting the results of diagnostic tests, we determined (a) the most appropriate single cut-off point for the percentage transferrin saturation when used alone or in combination with the serum ferritin level to identify homozygosity and (b) several cut-off points based on stratification of the percentage transferrin saturation into five intervals used alone or in combination with the serum ferritin level to identify homozygous and heterozygous individuals. Finally, the likelihood ratios for each interval of the percentage transferrin saturation, along with those for the serum ferritin levels, were applied to case-finding in a general population.

Subjects and methods

Pedigree subjects

The study sample consisted of 194 persons who were derived from 38 pedigrees with hereditary hemochromatosis. The 38 probands were identified on the basis of having more than 5 g of exchangeable body iron and were classified as homozygous. The remaining 12 homozygous family members had HLA-A and HLA-B haplotypes identical to those of the respective proband. The 108 heterozygous members had one HLA-A and HLA-B haplotype in common with the respective proband, whereas the 36 normal individuals had none of these haplotypes in common with the proband. It is unlikely that all of the persons classified as normal were genotypically normal, as three had a high percentage transferrin saturation; in one this was due to chromosome recombination (cross-over of HLA-A and HLA-B alleles), and in the other two it was probably due to the introduction of new hemochromatosis alleles from spouses. The frequency of homozygosity, heterozygosity and "normality" among the family members was 26%, 55% and 19% respectively. Details of 19 of the pedigrees have been published elsewhere.[1] Persons with diseases that produce an increase in the percentage transferrin saturation or the serum ferritin level disproportionate to the size of the body iron stores were not excluded.

Normal control subjects

A random sample of 1013 persons aged 1 to 90 years who had participated in the Nutrition Canada Survey[7] served as normal controls. Of the 1013, 200 were selected at random from those aged 20 years of age and older to determine crossings of frequency distributions of percentage transferrin saturation among the genotypes. The entire group was used to assess the application of likelihood ratios to case-finding in the general population.

Methods

The serum iron concentration and total iron-binding capacity were measured with a diagnostic kit from Hoffmann-La Roche Limited. A blood sample was obtained from the subjects in the morning, usually after they had fasted overnight. The results were expressed as a ratio of the serum iron concentration to the total iron-binding capacity. Although two or more blood samples have been advocated for screening because of the day-to-day fluctuations in the serum iron level,[8] it was not practical to do so in this study because many of the families lived far from London.

The serum ferritin level was measured by radioimmunoassay.[9] The upper limits of normal, which vary with age, were based on the 90th percentiles for the serum ferritin levels in Canadians who participated in the Nutrition Canada Survey:[7] 50 μg/L at 5 to 10 years, 100 μg/L at 11 to 20 years and 350 μg/L at more than 20 years for males, and 40 μg/L at 5 to 20 years, 65 μg/L at 21 to 30 years, 80 μg/L at 31 to 40 years, 100 μg/L at 41 to 50 years and 200 μg/L at more than 50 years for females.

To evaluate the usefulness of the transferrin saturation and serum ferritin tests in predicting the genotype of the family members we calculated the sensitivity, specificity and predictive value of the results.[3-5] The likelihood ratio of a positive test result was calculated as sensitivity/1 − specificity or the true-positive rate/the false-positive rate.[6] This ratio can easily be applied to several cut-off points that encompass the entire range of test results.

Results

Distribution of percentage transferrin saturation

The frequency distribution of percentage transferrin saturation among the homozygous, heterozygous and normal family members, as well as the 200 normal controls, is shown in Fig. 1. The frequency distribution crosses at 55% for the homozygous and heterozygous members and at 35% for the heterozygous members and either the normal members or the controls.

Sensitivity and specificity of transferrin saturation test

To determine the best cut-off point for the percentage transferrin saturation we calculated the true-positive and true-negative values using different cut-off points.[5] The maximum true-positive and true-negative rates for distinguishing between homozygous and nonhomozygous individuals were obtained with a cut-off point of 55% (Fig. 2); these rates were both 92%. When the cut-off point was 50%, 4% more homozygous individuals were detected; however, 11% more of the nonhomozygous individuals were incorrectly labelled as homozygous. The probability of homozygosity in our control group increased from 26% before the test to 81% when the percentage transferrin saturation was above 55 and to 75% when it was above 50; when the value was less than 55% or 50% the post-test probability of homozygosity was only 3% or 2% respectively.

Sensitivity and specificity of transferrin saturation test combined with serum ferritin test

When the identification of homozygosity required

that the results of both tests exceed the cut-off points (percentage transferrin saturation 55 or greater and serum ferritin level above the 90th percentile for age and sex) the sensitivity was only 71%, but the specificity was 98%. Although few of the heterozygous or normal individuals were incorrectly labelled with this approach, nearly 30% of the homozygous individuals were missed. When only one of the cut-off points had to be exceeded the sensitivity jumped to 98%; however, the specificity fell to 86%. This approach thus provided better sensitivity than using the percentage transferrin saturation alone with a cut-off point of either 50 or 55.

Likelihood ratios

The likelihood ratios for several intervals of percentage transferrin saturation are given in Table I. An advantage of the likelihood ratio is that it considers both sensitivity and specificity.[6] The results show that a percentage transferrin saturation of 75 or greater is 37 times as likely to come from a homozygous individual as from people with the other two genotypes, whereas a value between 35 and 54 is only 3.7 times as likely to come from a heterozygous individual, and a value of 15 to 34 is only 2.5 times as likely to come from a normal individual as from people with the other genotypes.

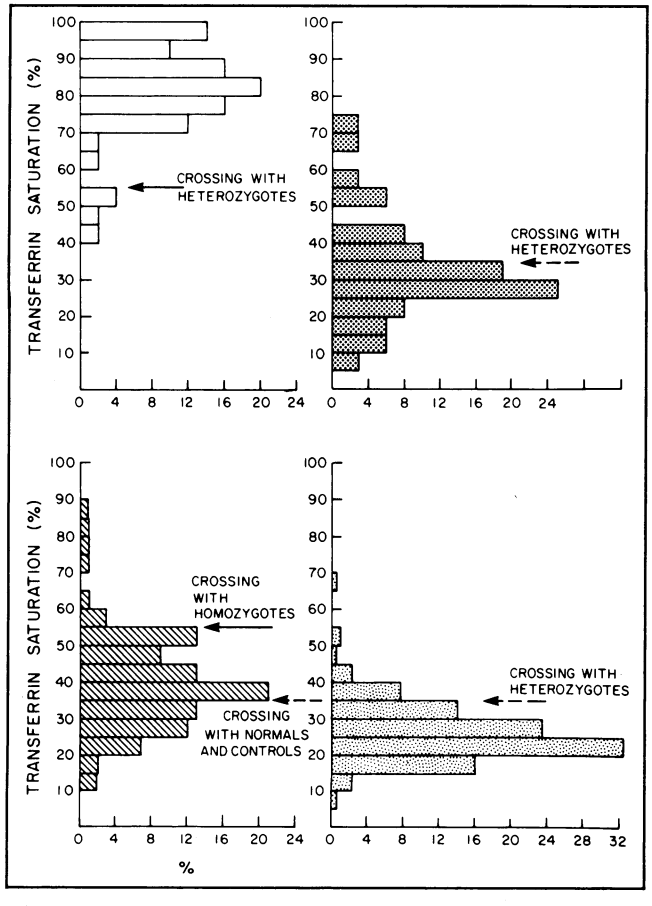

Fig. 1—Frequency distribution of percentage transferrin saturation among 50 homozygous (top left), 108 heterozygous (bottom left) and 36 normal family members (top right) and 200 normal adult controls (bottom right). Crossing of two frequency distributions is point above which distribution with higher mean has higher proportion of cases in each category than distribution with lower mean.

Table II shows that a serum ferritin level above the 90th percentile for age and sex is 10 times as likely to come from a homozygous as from a nonhomozygous individual. A level at or below the 90th percentile, however, is only 2.0 times as likely to come from a heterozygous individual as from people with the other two genotypes.

Application to screening of families with hemochromatosis: In the families that we studied the pretest probability of homozygosity was 26%. The post-test probabilities for the five intervals of percentage transferrin saturation and a single cut-off point for the serum ferritin level were determined from the pretest probability and the likelihood ratios with a nomogram, described

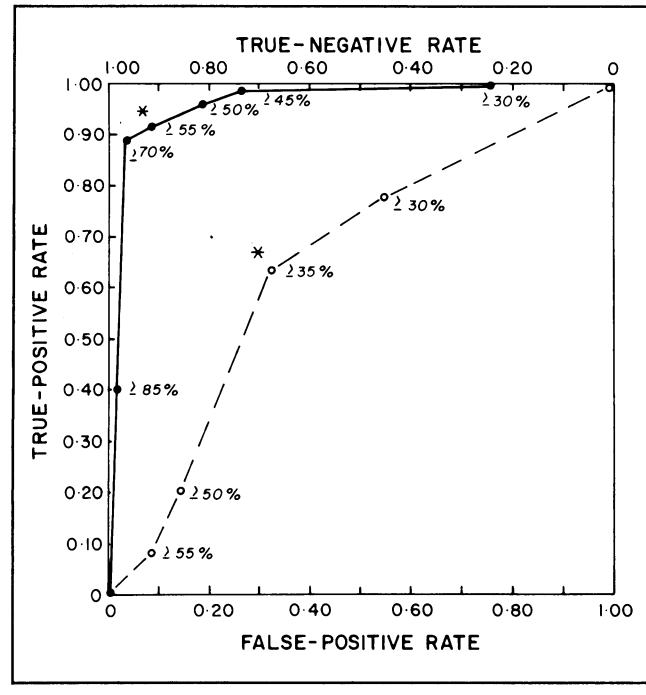

Fig. 2—ROC (receiver-operating characteristic) curve, showing percentage transferrin saturation in family members heterozygous (broken line) or homozygous (solid line) for hemochromatosis allele. Asterisks indicate cut-off points with best combination of sensitivity (true-positive rate) and specificity (true-negative rate).

Table I—Likelihood ratios for several intervals of percentage transferrin saturation

Percentage transferrin saturation	Genotype; ratio		
	Homozygous	Heterozygous	Normal
≥ 75	37	0.1	0
55–74	3	0.4	1.0*
35–54	0.2	3.7	0.6*
15–34	0	1.4	2.5
< 15	0	0.6	6.2

***Spuriously high due to the inclusion of three persons who were classified as normal on the basis of the results of HLA typing; abnormalities in iron metabolism were due to chromosome recombination in one and probably to the introduction of new hemochromatosis alleles in two.**

elsewhere.[6] Fig. 3 depicts the change in probability when the percentage transferrin saturation was considered and then the serum ferritin level was examined. When the percentage transferrin saturation was between 55 and 74 the probability of homozygosity jumped from 26% to 51%. When the serum ferritin level was above the 90th percentile the probability rose further, to 91%, but when the level was at or below the 90th percentile the probability fell to 9%. This tandem approach was most discriminating when the percentage transferrin saturation was between 55 and 74.

The crossing of the percentage transferrin saturation at 35 for the heterozygous and normal individuals suggests that this cut-off point may be helpful in distinguishing between these groups, assuming that homozygous individuals have already been excluded. Fig. 4 depicts the usefulness of the same tandem approach to analysis of the percentage transferrin saturation and the serum ferritin level in determining the probability of heterozygosity. A percentage transferrin saturation between 35 and 55 increased the probability from 55% before the test to 82%. A serum ferritin level at or below the 90th percentile further increased the probability, to 90%, whereas a high level reduced the probability to 47%.

The pretest probability that a person in one of the families was genetically normal was 19%. A percentage transferrin saturation less than 15 increased the probability to 60%; a serum ferritin level at or below the 90th percentile increased the probability further, to 66%, whereas a higher level reduced the probability to 28% (Fig. 5).

Application to case-finding in the general population: In a previous study we estimated that the frequency of homozygosity for hemochromatosis in a reference population was 0.3% and the frequency of heterozygosity

Table II—Likelihood ratios for serum ferritin level

Serum ferritin level	Genotype; ratio		
	Homozygous	Heterozygous	Normal
> 90th percentile	10	0.2	0.3
≤ 90th percentile	0.1	2.0	1.4

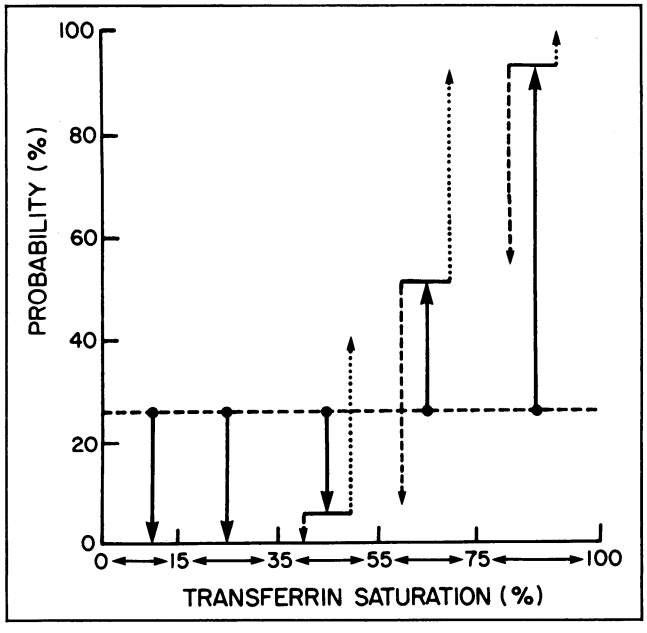

Fig. 3—Change in probability of homozygous hemochromatosis in pedigrees with known proband when analysis of percentage transferrin saturation is followed by analysis of serum ferritin level. Horizontal broken line indicates pretest probability, solid lines indicate effect of first analysis, and remaining lines indicate effect of second analysis; dotted lines represent effect of serum ferritin level above 90th percentile, broken lines effect of lower level. In remaining three figures lines have same meaning.

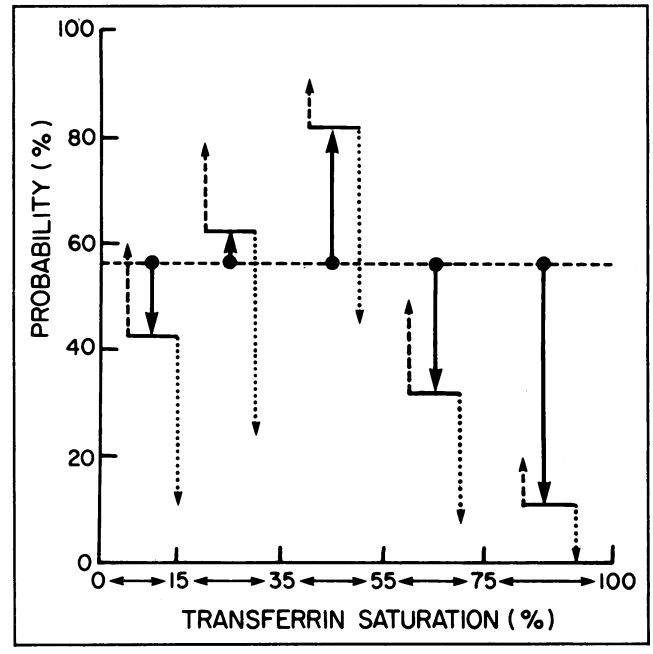

Fig. 4—Change in probability of heterozygous hemochromatosis with same tandem analysis as in Fig. 3.

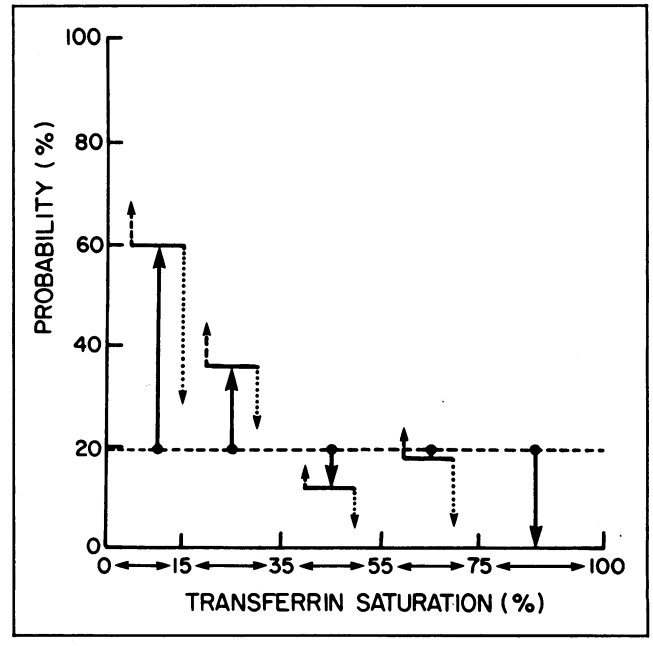

Fig. 5—Change in probability of genetic normality with same tandem analysis as in Fig. 3.

11%.[1] The results of applying the likelihood ratios in Tables I and II to these pretest probabilities are shown in Fig. 6. We found that the transferrin saturation test alone was of little help in detecting homozygosity; however, a percentage transferrin saturation of 75 or greater combined with a serum ferritin level above the 90th percentile increased the probability of homozygosity from 0.3% to 52%. A percentage transferrin saturation between 35 and 54 combined with a serum ferritin level at or below the 90th percentile increased the probability of heterozygosity to 47%.

Using the same approach with a random sample of 1013 persons who had participated in the Nutrition Canada survey[7] (Table III) we found a 47% probability that the 62 with a percentage transferrin saturation between 35 and 54 and a serum ferritin level at or below the 90th percentile were heterozygous, and a 52% probability that the 1 person with a percentage transferrin saturation of 75 or greater and a high serum ferritin level was homozygous.

Discussion

The transferrin saturation test is a good indicator of homozygous individuals who are at risk of iron overload.[1,2,10] In our study of 38 pedigrees with hemochromatosis a single cut-off point of 55 for percentage transferrin saturation provided the best statistical combination of true-positive and true-negative results. Values above this cut-off point increased the likelihood of homozygosity from 26% to 81%. In a previous study of 19 pedigrees with hereditary hemochromatosis, discriminant function analysis indicated that the transferrin saturation test was 3.3 times as important as the serum ferritin test in distinguishing homozygous from normal individuals.[1] Nevertheless, the serum ferritin test was also important. When both tests were used in our study and the results were considered positive if one or both tests gave abnormal results the sensitivity, 98%, exceeded that when either test was used alone, and the specificity fell to 86%. O'Leary and Block,[11] in a retrospective analysis of reports in the literature, also concluded that the transferrin saturation test was slightly more discriminating in identifying persons with excess hepatic iron stores when used in combination with the serum ferritin test than when used alone. Thus, a single cut-off point for both tests was efficacious in identifying homozygous members of families with a known proband.

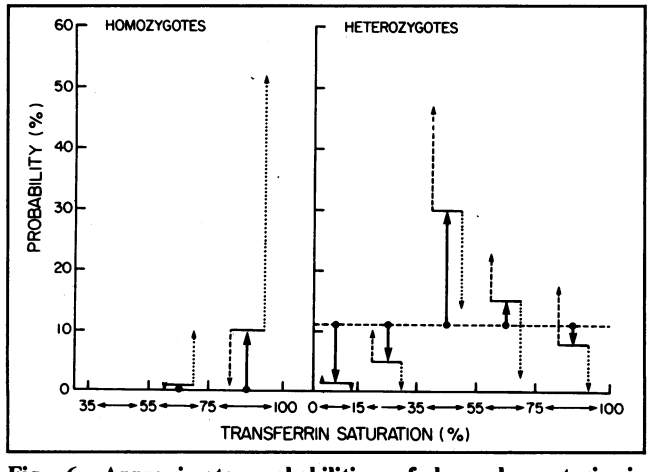

Fig. 6—Approximate probabilities of hemochromatosis in general population after same tandem analysis as in Fig. 3. Pretest probability of homozygosity 0.3% and of heterozygosity 11%.[1]

The stratification of percentage transferrin saturation into five intervals and selective application of the cut-off points to pedigrees with hemochromatosis showed that values in the interval of 75% to 100% were more discriminating than those in the interval of 55% to 74% for the homozygous form of the disease. The likelihood ratio proved to be a convenient, easily calculated measure with which we could determine the post-test probabilities for results falling into each interval. Moreover, it permitted the calculation of the post-test probability for the serum ferritin test when this test was used with the transferrin saturation test. The post-test probability for the transferrin saturation test served as the pretest probability for the serum ferritin test. Likelihood ratios consider both sensitivity and specificity, and they are more stable with changes in prevalence than either sensitivity or specificity.

A percentage transferrin saturation of less than 35 ruled out homozygosity. A percentage transferrin saturation between 55 and 74 was not discriminatory; however, when it was combined with the serum ferritin level, it was possible to predict that the probability of homozygosity was either very low (9%), if the level was at or below the 90th percentile, or very high (91%), if the level was above this percentile. A percentage transferrin saturation of 35 to 54 had to be combined with a serum ferritin level at or below the 90th percentile to rule out homozygosity. A percentage

Table III—Percentage transferrin saturation and serum ferritin levels in a random sample of the Canadian population

Variable	Value				
Transferrin saturation (%)	≤ 34	35–54	55–74	55–74	≥ 75
Serum ferritin level (percentile)	≤ 90	≤ 90	≤ 90	> 90	> 90
	No. (and %) of persons				
Age (yr)					
1–19 (n = 408)	390 (95.6)	18 (4.4)	0	0	0
20–90 (n = 605)	553 (91.4)	46 (7.6)	3 (0.5)	2 (0.3)	1 (0.2)
Total (n = 1013)	945 (93.3)	62 (6.1)	3 (0.3)	2 (0.2)	1 (0.1)

transferrin saturation of 75 or greater combined with a high serum ferritin level was sufficient to rule in homozygosity with confidence. A potential limiting factor is that the transferrin saturation and serum ferritin tests are convergent; that is, the serum ferritin level is more likely to be high when the percentage transferrin saturation is high.[6] Consequently, the post-test likelihoods given in Fig. 3 tend to overestimate, probably by 10% to 20%, a person's true likelihood of having hemochromatosis alleles.

Edwards and colleagues[2] observed that the frequency distribution of percentage transferrin saturation for heterozygous individuals was skewed toward higher values when the results were compared with those in normal subjects. In the families that we studied, the frequency distribution identified a crossing at 35% between the heterozygous and normal individuals. Likelihood analysis indicated that a percentage transferrin saturation of 35 to 54 was 3.7 times as likely in a heterozygous individual as in people with the other two genotypes. The pretest probability of heterozygosity, 55%, increased to 81% when the percentage transferrin saturation fell to between 35 and 54 and jumped to 90% when the serum ferritin level was at or below the 90th percentile. The use of the serum ferritin test in addition to the transferrin saturation test was helpful over the entire range of percentages of transferrin saturation in identifying heterozygosity, but it was especially discriminatory when the percentage transferrin saturation was between 35 and 74. It is important to distinguish heterozygous from homozygous individuals because the former do not require phlebotomy. Our results suggest that a high proportion of heterozygous individuals have values that approach the upper limit of "normal" for percentage transferrin saturation. Previous reports on the biochemical expression of hemochromatosis, which considered 50 or 55 to be the upper limit of normal for percentage transferrin saturation, underestimated the prevalence of abnormalities in iron metabolism in heterozygous individuals.[1,2]

While transferrin saturation and serum ferritin tests are helpful in identifying homozygosity in families once a proband has been identified, they are of limited value in screening the general population for hemochromatosis. Our calculations, which were based on an estimated prevalence of homozygosity of 0.3%, suggest that the selected use of the interval of 75 to 100 for percentage transferrin saturation combined with a serum ferritin level above the 90th percentile is the only approach of any value in detecting homozygosity in the general population. The probability that these results came from a homozygous individual was about 50%. When this approach was applied to a sample of 1013 participants in the Nutrition Canada Survey,[7] however, only one person was found to have a percentage transferrin saturation of 75 or greater and a high serum ferritin level. A cut-off point of 55 for percentage transferrin saturation would have yielded an additional two persons with a serum ferritin level above the 90th percentile. The probability that these results came from heterozygous individuals in this population was only 10%. Therefore, the yield is too small to support screening for homozygosity in the general population. Using the transferrin saturation test as an indicator of iron overload, Olsson and associates[12] found that 9 of 1311 blood donors had a percentage transferrin saturation greater than 70. Three males (0.23% of the entire group) were subsequently found to have hereditary hemochromatosis, and some of their relatives were found to be homozygous. Hence, if cut-off points for percentage transferrin saturation and serum ferritin levels are set to identify all of the homozygous individuals in the general population it would be a formidable task to follow up all those with false-positive results. This screening approach is not recommended for use in the general population, but it may be worth while in selected groups of patients with comparatively high pretest possibilities of hereditary hemochromatosis (e.g., those with diabetes or arthropathy due to pseudogout). However, a sensitive, noninvasive technique is needed for determining the hepatic iron content.

At present there is no test for detecting heterozygosity in the general population. Our results suggest that there is a 47% probability that a person is heterozygous if the percentage transferrin saturation is between 35 and 54 and the serum ferritin level is at or below the 90th percentile. Six percent of the random sample of participants in the Nutrition Canada Survey[7] fulfilled these criteria. Again, however, the post-test probability of 47% is not high enough to suggest that these tests be used for screening for heterozygosity in the general population.

In conclusion, the best approach to screening family members for hemochromatosis is to use the transferrin saturation and serum ferritin tests in tandem and then to estimate the probability that a person is homozygous with likelihood ratios. A percentage transferrin saturation lower than 55 and a serum ferritin level at or below the 90th percentile rule out homozygous hemochromatosis with confidence; on the other hand, a percentage transferrin saturation greater than 75 and a serum ferritin level above the 90th percentile rule it in. Persons with a percentage transferrin saturation between 55 and 74 can be classified as having a very high (91%) or very low (9%) probability of homozygosity depending on the serum ferritin level. In these cases a definitive diagnosis of homozygosity will require direct measurement of hepatic iron stores by percutaneous liver biopsy or HLA typing if the haplotypes of the proband are known.

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