Associations of Iron Overload in Africa With Hepatocellular Carcinoma and Tuberculosis: Strachan’s 1929 Thesis Revisited

By V.R. Gordeuk, C.E. McLaren, A.P. MacPhail, G. Deichsel, and T.H. Bothwell

We analyzed data from the first study of iron overload in Africans, conducted between 1925 and 1928, to determine whether this common condition is associated with death from hepatocellular carcinoma and/or tuberculosis. In the original study, necropsies were performed on 714 adult blacks from southern Africa. Hepatic and splenic iron levels were measured semiquantitatively in 604 subjects and one of five iron grades was assigned. We examined death from hepatocellular carcinoma or from tuberculosis and the variables of age, sex, the presence of cirrhosis or other diagnoses that might be influenced by iron status, and tissue iron grades. Nineteen percent of men and 16% of women had the highest grade of hepatic iron. After adjustment for the presence of cirrhosis, hepatic iron grade was the variable most significantly associated with death from hepatocellular carcinoma (P < .021). The odds of death from hepatocellular carcinoma in subjects with the highest grade of hepatic iron was 23.5 (95% confidence interval, 2.1 to 225) times the odds in subjects with the three lowest grades. Splenic iron was the variable most significantly associated with death from tuberculosis (P < .0001). The odds of death from tuberculosis with the highest grade of splenic iron was 16.9 (4.8 to 59.9) times the odds with the two lowest grades. These findings suggest that iron overload in black Africans may be a risk factor for death from hepatocellular carcinoma and for death from tuberculosis.

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Iron overload in southern African blacks was first described by A.S. (Archie) Strachan,1 who was a pupil of the renowned Scottish pathologist, Robert Muir. In 1926, he was appointed the first Professor of Pathology at the newly created Medical School of the University of the Witwatersrand in Johannesburg. Six years after taking up his post, he was awarded an MD by the University of Glasgow for a thesis entitled “Haemosiderosis and Haemochromatosis in South African Natives with a Comment on the Etiology of Haemochromatosis.” The thesis was based on a necropsy study of 876 individuals from several parts of southern and central Africa who died in Johannesburg, South Africa from 1925 to 1928. Strachan concluded that “haemochromatosis is a not uncommon disease in the South African native; the chief factor in its production appears to be the diet...”

The development of the complete picture of bronzed changes in the drinking habits of urban black South Africans; as a result, a steady decline in the prevalence and severity of iron overload occurred in the cities.10 However, interest in the condition was revived in the 1980s when it was shown that iron overload remains prevalent in rural populations in southern Africa.11,12 In addition, there is now evidence that the condition may be caused by an interaction between the amount of dietary iron and a gene distinct from the HLA linked iron-loading locus responsible for hereditary hemochromatosis.21

The recognition that iron overload is an important contemporary problem in Africa has led us to question whether this condition might have an overlooked association with two other important diseases in that part of the world, namely hepatocellular carcinoma and tuberculosis. No association of iron overload in black Africans with hepatocellular carcinoma has previously been noted,2 although this malignancy occurs frequently in southern Africa3,24 and is a well-recognized complication of the hemochromatosis associated with the HLA-related iron-loading gene in whites.23 Iron overload has not been reported as a risk factor for active tuberculosis,26 an infection that is highly prevalent in southern Africa,27 although macrophage antimicrobial function is important in the body’s defense against tuberculosis28 and laboratory studies indicate that excess iron may impair macrophage cytotoxic activity against a variety of microorganisms.29-35 Including mycobacteria. The present study was performed to...
test the hypotheses that iron overload in Africa may be a risk factor for hepatocellular carcinoma and/or tuberculosis. Strachan’s thesis was used as the data base because it provided clinical information on a large number of adult subjects whose iron status varied from normal to severely iron-loaded.

SUBJECTS AND METHODS

Study population. A total of 876 black Africans of all ages were examined postmortem at the General Hospital in Johannesburg, South Africa from January 1925 to September 1928. Of these subjects, 714 were >20 years of age, but in the earlier cases, systematic measurement of tissue iron was not performed. A total of 604 of the adults had iron measurements performed and these subjects served as the basis for the present study. As summarized in Table 1, the study subjects were from 18 different ethnic groups of southern and central Africa and there was a 4 to 1 preponderance of men over women. These demographic features reflect the migration from many parts of the subcontinent of predominantly black men to seek employment in the Johannesburg area at that time. There was no apparent selection bias in performing the autopsies.

Strachan’s methodology. Dr Strachan reported the age, sex, presence of cirrhosis, cause of death, and grades of liver and spleen iron. Cirrhosis was defined on the basis of gross changes that were visible macroscopically. The cause of death was determined by necropsy examination. The measurement of iron was semiquantitative: a piece of tissue was placed in a cold 1:1 mixture of 4% potassium ferrocyanide and 4% hydrochloric acid and the degree of Prussian blue reaction was graded as negative, trace, slight but definite, marked, and very marked to marked. By using a necropsy series of whites for comparison, Strachan defined a reaction of greater than slight but definite as being above the normal range. Strachan did not perform statistical analyses for possible relationships between the causes of death and the degree of tissue iron.

<table>
<thead>
<tr>
<th>Ethnic Group</th>
<th>Modern Country</th>
<th>Males</th>
<th>Females</th>
<th>Total</th>
</tr>
</thead>
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<td>43</td>
<td>182</td>
</tr>
<tr>
<td>Mauitu</td>
<td>South Africa</td>
<td>144</td>
<td>34</td>
<td>178</td>
</tr>
<tr>
<td>Xhosa</td>
<td>South Africa</td>
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<td>18</td>
<td>76</td>
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<td>Shangaen</td>
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<td>5</td>
<td>51</td>
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<tr>
<td>Fingo</td>
<td>South Africa</td>
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<td>5</td>
<td>25</td>
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<td>14</td>
</tr>
<tr>
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<td>Swaziland</td>
<td>12</td>
<td>2</td>
<td>14</td>
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<tr>
<td>Katanga</td>
<td>Zaire</td>
<td>12</td>
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<td>13</td>
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<tr>
<td>Pondo</td>
<td>South Africa</td>
<td>9</td>
<td>2</td>
<td>11</td>
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<tr>
<td>Ndebele</td>
<td>South Africa, Zimbabwe</td>
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<td>1</td>
<td>9</td>
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<tr>
<td>Morolong</td>
<td>Botswana</td>
<td>4</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Baca</td>
<td>South Africa</td>
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<td>1</td>
<td>5</td>
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<td>Basuto</td>
<td>Lesotho</td>
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<td>4</td>
</tr>
<tr>
<td>Tonga</td>
<td>Zambia, Zimbabwe</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>*</td>
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<td>Tembu</td>
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<td>2</td>
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<td>Swahili</td>
<td>East Africa</td>
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<td>1</td>
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<tr>
<td>*</td>
<td>Malawi</td>
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<td>1</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>481</td>
<td>123</td>
<td>604</td>
</tr>
</tbody>
</table>

Table 1. Ethnicity, Geographic Derivation, and Gender of Study Subjects

* Ethnic group not given.

Statistical analysis of Strachan’s data. We examined the relationships between tissue iron grades and deaths from hepatocellular carcinoma and from tuberculosis. In conducting this study, we considered the spectrum of diagnostic categories that are present in this necropsy series (Table 2) and also the substantial body of knowledge that has accumulated regarding the clinical consequences of iron overload and of iron deficiency since the 1920s. First, it was important to consider any statistical associations that might exist between iron overload and the comparison diseases. Second, it was important to consider subjects with blood loss or high iron requirements in whom any association of iron overload with a disease category might tend to be masked. In terms of the first consideration, associations between iron overload in Africa and the following diagnostic categories of Table 2 have been described: cirrhosis,18,19 scurvy,18-20 and possibly cardiomyopathy and esophageal carcinoma.20 As described in the next paragraph, we considered these diagnoses in our statistical analysis of the relationships between tissue iron grades and deaths from hepatocellular carcinoma and tuberculosis. In terms of the second consideration, 99 women were of childbearing age and may have had increased blood loss and high iron requirements related to menstruation and childbearing and 15 subjects across the diagnostic categories had hemorrhage or conditions prone to bleeding. We took sex and age into account to adjust for the effects of the presence of women of childbearing age in the statistical analysis, and we also considered an added category of individuals we judged to be prone to blood loss based on the autopsy findings. To avoid potential bias that might occur in favor of our hypotheses, no adjustment was made for the association between tuberculosis and increased grades of iron in the analysis of death from hepatocellular carcinoma. Similarly, no adjustment was made for the association between hepatocellular carcinoma and increased iron grades in the analysis of death from tuberculosis.

Analysis of variance and the Bonferroni multiple comparisons procedure were used to examine the mean ages of all subjects with respect to hepatic iron grade and to splenic iron grade. Contingency table analysis was used to test for a relationship between sex and the different grades of tissue iron. Logistic regression was used to test for associations between tissue iron grades and cirrhosis, scurvy, myocardopathies, esophageal carcinoma, and a category of blood loss. Logistic regression was used to examine the relationship between death from hepatocellular carcinoma and the finding of cirrho-
sis. Stepwise multivariate logistic regression and hierarchical logistic modelling was used to find the best fitting and most parsimonious models to describe the relationship between death from hepatocellular carcinoma and the lower three liver iron categories (negative, trace, and slight but definite) combined because of the sparse occurrence of hepatocellular carcinoma in these categories. Likewise, in analyses of death from tuberculosis the lower two categories (negative and trace) of splenic iron were combined because of the sparse occurrence of tuberculosis in these categories. Models were compared with the iron grade considered as a categorical variable, being coded as equidistant scores or as nonequidistant standardized mean scores for each grade. To estimate standardized mean iron scores, we examined the shift in the distribution of iron for those who died from hepatocellular carcinoma or tuberculosis when compared with death from all other diseases by fitting the proportional odds model. A logistic distribution for the logarithm of iron was assumed. Thresholds separating ordered categories, the shift parameter modelling iron increase in disease, and standardized mean iron values within categories were estimated. Subgroup analyses were performed on a data set of 565 subjects from which members of the following categories had been removed: cardiomyopathy (n = 13), scurvy (n = 8), esophageal carcinoma (n = 3), and blood loss (n = 15).

RESULTS

Tissue iron grade, age, and sex. Sex and age according to grades of hepatic iron for 604 adult black Africans are given in Table 3. Significant relationships were found between sex and hepatic iron grades (Pearson $\chi^2 = 59.9$; degrees of freedom [df] = 4; $P < .0001$) and between age and hepatic iron grades (Welch test $F = 63.8$; df = 4 and 112; $P < .0001$). Significant relationships were also found between sex and splenic iron grades (Pearson $\chi^2 = 43.9$; df = 4; $P < .0001$) and between age and splenic iron grades (Welch test $F = 35.5$; df = 4 and 90; $P < .0001$). Larger proportions of men than women had the higher grades of iron; for both sexes, mean ages tended to increase with higher iron grades.

Relationships of tissue iron grade with cirrhosis, cardiomyopathy, scurvy, esophageal carcinoma, and blood loss. Logistic regression showed that the presence of cirrhosis (n = 31) was strongly associated with increased grades of hepatic iron (likelihood ratio $\chi^2 = 21.42$; df = 2; $P < .0001$) and splenic iron (likelihood ratio $\chi^2 = 13.41$; df = 1; $P = .0003$). A significant positive association also existed between scurvy (n = 8) and hepatic iron grade ($P = .028$) as well as a significant negative association between the category of blood loss (n = 15) and hepatic iron grade ($P = .034$). No significant associations were found between scurvy or the category of blood loss and splenic iron grade or between myocardopathy or esophageal carcinoma and tissue iron grades ($P > .05$ for all).

Tissue iron grade and death from hepatocellular carcinoma. Hepatocellular carcinoma was the cause of death in 15 subjects. As shown in Table 4, the findings of the highest grades of hepatic and splenic iron were more common in the subjects with hepatocellular carcinoma than in the subjects with other diagnoses. Logistic regression showed a strong association between increased grade of hepatic iron and hepatocellular carcinoma (likelihood ratio $\chi^2 = 17.31$; df = 2; $P = .0002$) as well as between increased grade of splenic iron and hepatocellular carcinoma (likelihood ratio $\chi^2 = 7.81$; df = 2; $P = .02$). The finding of gross, macroscopic cirrhosis was strongly associated with death from hepatocellular carcinoma (likelihood ratio $\chi^2 = 29.5$; df = 1; $P < .0001$) and also with increased grades of hepatic iron. Using stepwise and hierarchical modelling we found that, after adjustment for the presence of cirrhosis, the grade of liver iron was the variable most significantly associated with death from hepatocellular carcinoma (likelihood ratio $\chi^2 = 7.68$; df = 1; $P = .021$). After adjustment for age, sex, and the presence of cirrhosis, the estimated odds of death from hepatocellular carcinoma in subjects with very marked to marked liver iron was 5.6 (95% confidence interval, 1.5 to 21.4) times that of subjects with marked hepatic iron and 23.5 (2.1 to 225) times that of subjects with negative to slight but definite iron grades. Although scurvy and the category of blood loss were significantly related to hepatic iron grade, these categories were not included as explanatory variables in logistic regression analyses because no cases occurred coincident with hepatocellular carcinoma.

Additional analyses were performed in which the ordinal nature of the liver iron grades was taken into account. Models in which liver iron grades were coded as equidistant scores (1 = negative, trace, or slight but definite; 2 = marked; 3 = very marked to marked) or as nonequidistant standardized mean scores confirmed the stability of the regression coefficients for the covariates of age, sex, and the presence of cirrhosis and confirmed that the probability of...
iron overload in africa, hepatoma, and TB

death from hepatocellular carcinoma increased with increasing amounts of hepatic iron. As shown in Fig 1, the mean of the distribution of hepatic iron was increased for subjects with hepatocellular carcinoma when compared with subjects with all other diseases. This increase was statistically significant (likelihood ratio $\chi^2 = 17.01; df = 1; P = .0001$). The observed and estimated proportions (0.67 and 0.66, respectively) of subjects dying from hepatocellular carcinoma who had very marked to marked liver iron grade were increased when compared with the proportion (0.18) of subjects dying of all other diseases who had this highest grade of liver iron.

Using logistic regression, a subgroup analysis was performed on a data set in which all subjects in the categories of myocardiopathy, scurvy, esophageal carcinoma, and blood loss had been removed. For this subgroup, the estimated odds of death from hepatocellular carcinoma for subjects with very marked to marked liver iron was 5.0 (1.4 to 20.2) times that for subjects with marked hepatic iron and 18.2 (1.8 to 186) times that of subjects with negative to slight but definite iron grades, adjusted for age, sex, and presence of cirrhosis.

**Tissue iron grade and death from tuberculosis.** Tuberculosis was the cause of death in 196 subjects. As shown in Table 5, the findings of the highest grades of hepatic and splenic iron were more common in the subjects with tuberculosis as a cause of death than in the subjects with other diagnoses. Logistic regression showed a strong association between death by tuberculosis and increased grade of splenic iron (likelihood ratio $\chi^2 = 47.89; df = 3; P = .0001$) as well as increased grade of hepatic iron (likelihood ratio $\chi^2 = 32.99; df = 3; P = .0001$). There was no significant association between death from tuberculosis and the presence of scurvy. Stepwise multivariate logistic regression and hierarchical logistic modelling indicated that splenic iron was the variable most significantly associated with death from tuberculosis. After adjustment for age, sex, and presence of cirrhosis, the estimated odds of death from tuberculosis for subjects with very marked to marked splenic iron was 1.5 (95% confidence interval, 1.0 to 2.4) times the odds with marked splenic iron, 4.5 (2.3 to 9.1) times the odds with slight but definite splenic iron, and 16.9 (4.8 to 59.9) times the odds with negative and trace splenic iron.

Additional analyses were performed taking into account the ordinal nature of splenic iron grades. Models formed considering splenic iron grades coded as equidistant scores (1 = negative and trace; 2 = slight but definite; 3 = marked; 4 = very marked to marked) or as nonequidistant standardized mean scores confirmed that the probability of tuberculosis increased with increasing amounts of splenic iron after adjustment for age and sex. Figure 2 shows that the mean of the distribution of splenic iron was increased for subjects

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**Table 5. Proportions With the Highest Grades of Tissue Iron According to Deaths From Tuberculosis or All Other Causes**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>N</th>
<th>Very Marked to Marked Hepatic Iron</th>
<th>Very Marked to Marked Splenic Iron</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculosis</td>
<td>196</td>
<td>43</td>
<td>48</td>
</tr>
<tr>
<td>Noncirrhotic</td>
<td>192</td>
<td>39</td>
<td>44</td>
</tr>
<tr>
<td>Cirrhotic</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Other diagnoses</td>
<td>408</td>
<td>71</td>
<td>66</td>
</tr>
<tr>
<td>Noncirrhotic</td>
<td>381</td>
<td>58</td>
<td>55</td>
</tr>
<tr>
<td>Cirrhotic</td>
<td>27</td>
<td>13</td>
<td>11</td>
</tr>
</tbody>
</table>
with tuberculosis when compared with subjects with all other diseases. This increase was significant (likelihood ratio $\chi^2 = 29.2; df = 1; P = .0001$). The observed and estimated proportions (0.25 and 0.28, respectively) of subjects dying from tuberculosis who had the very marked to marked splenic iron grade was increased when compared with the observed and estimated proportions (0.16 and 0.14) of subjects dying of all other diseases who had this highest grade of splenic iron.

Using logistic regression, a subgroup analysis was performed on a data set in which all subjects in the categories of myocardiopathy, scurvy, esophageal carcinoma, and blood loss had been removed. For this subgroup, the estimated odds of death from tuberculosis for subjects with very marked to marked splenic iron was 1.5 (0.9 to 2.4) times that for subjects with marked splenic iron, 4.2 (2.1 to 8.5) times that of subjects with slight but definite iron grades, and 16.6 (4.7 to 59.2) times that of subjects with negative and trace splenic iron, adjusted for age, sex, and presence of cirrhosis.

**DISCUSSION**

A.S. Strachan found a high prevalence of iron overload in his autopsy series of blacks from across southern and central Africa who died in Johannesburg in the 1920s: 19% of the subjects had the highest grade of very marked to marked iron deposition in the liver and in the spleen.\(^1\) Although the condition is under-recognized or even not known by many health care providers today, iron overload still approaches a similarly high prevalence in many areas of Africa.\(^6\) For example, an autopsy series of 427 adults dying in Baragwanath Hospital in Johannesburg in 1976 showed that 18.3% had hepatic iron concentrations greater than 180 $\mu$mol/g dry weight, levels that are more than six times the upper limit of normal and that are comparable to homozygous HLA-linked hemochromatosis in Europeans.\(^10^,\!4^0\) Furthermore, a survey in rural Zimbabwe in 1985 found evidence for iron overload in 11.7% of 307 men from the community on the basis of markedly elevated transferrin saturations and serum ferritins.\(^11\) Similar results were obtained in the survey of a rural South African community reported in 1990.\(^12\) Finally, 14 of 29 (48.2%) of adults undergoing diagnostic liver biopsy in a hospital in Swaziland in the late 1980s had hepatic iron concentrations of greater than 180 $\mu$mol/g dry weight.\(^12\) These contemporary results underscore the fact that iron overload remains an important health problem in Africa and suggest that a fresh analysis of Strachan’s data set might have important implications for the health of Africans today.

Hepatocellular carcinoma and tuberculosis are currently important causes of morbidity and mortality in much of Africa.\(^23^,\!2^7\) Advances are urgently needed in understanding the pathogenesis of these disorders so that improvements in measures for prevention and treatment can be developed. We examined Strachan’s data, assembled more than 65 years ago,\(^1\) to test the hypotheses that iron overload in Africa may be an etiologic factor for hepatocellular carcinoma and for tuberculosis. Three major points emerged from the analysis. First, we found an association between iron overload and cirrhosis in southern African blacks, a finding compatible with results in subsequent studies.\(^5^,\!6^,\!6^\) Two other observations have not previously been recognized, namely an association between iron overload in black Africans and hepatocellular carcinoma and an association of iron overload with tuberculosis. In evaluating the importance of the associations that we are reporting here, it may be helpful to consider the criteria for causation of Sir Austin Bradford Hill.\(^4^\) The criterion of temporality would specify that iron overload
must precede the development of hepatocellular carcinoma or tuberculosis for causality to be a possibility. It was the opinion of Strachan himself regarding the present series "that the iron pigmentation had been the primary condition and that tuberculosis had been superimposed" because of the appearance of the pathologic specimens and because of the fact that similar types of tuberculosis are found in African children and in Europeans without accompanying siderosis. Our statistical analysis is consistent with the criteria of strength of association and of biologic gradient as evidenced by the rather robust and increasing estimated odds for death from hepatocellular carcinoma or tuberculosis in subjects with the highest grades of tissue iron compared with progressively lower grades. Sir Hill's criteria of plausibility, coherence, experiment, and analogy are touched on in the following paragraphs, as are some of the limitations of our study. With regard to the criterion of consistency, further prospective studies are needed to confirm the etiologic importance of the associations we have observed.

Hepatocellular carcinoma and tissue iron. Chronic infection with hepatitis B virus is recognized as the most common etiologic factor for hepatocellular carcinoma in southern Africa, with exposure to aflatoxins as a postulated cofactor. Infection with hepatitis C also plays an etiologic role. Other factors, some of them as yet unidentified, must also be of importance in pathogenesis. In HLA-linked hemochromatosis, affected individuals with cirrhosis have a risk of developing hepatocellular carcinoma that is 200-fold that of the general population. In contrast, iron overload in Africans has not been considered as a cause of this complication. The present analysis of Strachan's data raises the possibility that such a conclusion is not correct and that iron overload may be an important and overlooked factor in southern African blacks. A limitation to the present study is that the data set did not permit the analysis of the presence or absence of exposure to hepatitis B or C or other putative etiologic factors for hepatocellular carcinoma. Furthermore, it was not possible to determine whether the possible relationship between tissue iron grade and hepatocellular carcinoma is direct or whether iron overload may indirectly increase the risk of hepatocellular carcinoma by acting as a cofactor to other etiologies such as viral hepatitis and alcohol.

Tuberculosis and tissue iron. In the present analysis of Strachan's data, we found a possible relationship between death from tuberculosis and both hepatic and splenic iron overload, with increased splenic iron having the stronger association. This observation is of some interest, because heavy involvement of the mononuclear-macrophage system is a striking feature of iron overload in southern African blacks. Macrophages are critical for the body's defense against tuberculosis and recent laboratory studies indicate that iron-loading of macrophages impairs the ability of these cells to inhibit the growth of intracellular mycobacteria and other organisms.

It is not possible to prove causality between iron overload and tuberculosis from the present study. For example, alcoholism is a potential confounding factor. The excess iron in African subjects with iron overload is largely derived from an alcoholic beverage, albeit with a low alcohol content, and alcoholism is itself associated with an increased risk of tuberculosis. Furthermore, alcoholic liver disease can be associated with moderate accumulation of iron, but not to the degree often found in Africans. Chronic infectious and inflammatory conditions are also associated with the accumulation of increased macrophage iron, but not to the massive extent found in many Africans with iron overload. Despite these reservations, we point out that the degree of iron-loading in established African iron overload is more than can be explained on the basis of alcohol or inflammation and that therefore the present findings raise the possibility that iron overload may be an independent risk factor for tuberculosis. These results may have special relevance to the current situation in southern Africa, where infection with human immunodeficiency virus is widespread and where active tuberculosis is a common manifestation of the development of acquired immunodeficiency syndrome in affected subjects. It seems possible that iron-loaded subjects may be particularly vulnerable to such a complication and that tuberculosis might be expected to develop sooner than in subjects with normal iron stores.

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