Although preliminary, the results suggest that L.A.I. in microtome plates is comparable to L.A.I. in glass tubes. The plates are easier to use and require less extract. Counting non-adherent cells by a counter is faster and possibly more objective than microscopic examination. Our observation that with breast carcinoma extracts L.A.I. was positive in 3 of 7 patients with fibrocystic disease and 14 of 16 patients (88%) with confirmed breast cancer but none of 20 patients with other gynecological malignancies may indicate cross-reactivity between benign and neoplastic breast-tissue antigens. One tumour patient reacted to extracts from her own tumour and several other breast carcinomas suggesting cross-reactivity between tumours of the same histological type. Further work with purified extracts is needed to establish the validity of the L.A.I. phenomenon for tumour-specific diagnosis.

We thank Miss G. Fedra for technical assistance. This work is supported by grant from the Deutsche Forschungsgemeinschaft (SFB 136, Heidelberg).

D. FRITZE
C. SCHULTE-ÜNTROP
M. KAUFMANN

HÉMOCHROMATOSIS AND SUPEROXIDE METABOLISM: FREE-RADICAL INFLUENCED IRON STORAGE?

Sir,—The letter from Dr Moldow and Dr Bloomfield (July 15, p. 154) focuses on a possible role for stored iron in potentiating superoxide-ion-induced tissue damage. I suggest that alterations in superoxide ion (O2) metabolism may contribute to the genetic aetiology of “idiopathic” hæmochromatosis.

Studies on iron transfer between proteins in vitro show that the ferrous state is required; dietary studies have demonstrated that deficiency of ascorbic acid, usually considered a reducing agent, accelerates iron accumulation. It seems likely that a decreased capacity for intracellular movement of iron between the many proteins involved in its metabolism would lead to increased ferritin accumulation followed by lysosomal degradation to hemosiderin. Drugs such as streptokinase, daunomycin, doxorubicin, and porphyrin compounds are predicted to increase O2 levels and could hinder iron reduction.

The association if idiopathic hæmochromatosis with the A3 and B14 HLA antigens and the linkage of the disease to the HLA locus even in the absence of these antigens could possibly be related to altered metabolism of O2. The structural locus for mitochondrial superoxide dismutase, the enzyme which is responsible for inactivation of O2, is located on chromosome 6 with HLA. A mutant with decreased levels of superoxide dismutase could be in linkage disequilibrium with HLA (although the map distance seems too great unless there is cross-over suppression) and lead to hæmochromatosis. In man, where the major histocomparability locus (H2) shares almost all the known features of the HLA locus, a locus controlling a catalase-modifying enzyme is closely linked to H2. Since catalase functions to remove the hydrogen peroxide produced by superoxide dismutase, altered catalase activities could also affect iron reduction. The hypothesis of an HLA-linked locus affecting O2 metabolism and, thus, hæmochromatosis can be tested by studying these enzymes and HLA antigens in an accessible tissue (perhaps lymphocytes or fibroblasts) from individuals in families segregating for hæmochromatosis. The possible role of xanthine oxidase, an O2 producing enzyme, in the mobilisation of iron needs to be clarified.

There are alternative hypotheses to explain the HLA-association of hæmochromatosis. Since HLA antigen glycoproteins are major components of the plasma membrane, they may have effects on membrane transport of iron. The catalase-modifying enzyme in mice may be the same as one which modifies the lysosomal enzyme α-mannosidase. If an analogous locus exists in man, altered lysosomal metabolism of iron-containing compounds is a possibility.

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ROBERT P. ERICKSON

BENEFICIAL EFFECT OF D.D.A.V.P. ON BLEEDING-TIME IN VON WILLEBRAND'S DISEASE

Sir,—A major advance in the management of hemophilia and von Willebrand's disease has been the introduction of 1-deamino-8-D-arginine vasopressin (D.D.A.V.P.) which enables surgery to be done without the attendant hazards and expense of blood-product transfusion. A rise in factor-VIII-related antigen (VIII Ag), von Willebrand's factor, and factor VIII coagulant activity after intravenous D.D.A.V.P. infusion has been recorded.1,2 We have recently observed shortening of the bleeding-time (as measured by the template method) on repeated occasions in two young women who were having dental extraction. The results are summarised in the table. The time interval between the doses of D.D.A.V.P. (given in 30 ml of saline over a 10 min period) was 12 h and the effect on bleeding-time lasted less than 12 h and was less apparent on the second occasion.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Bleeding-time (min)</th>
<th>VIII coagulant activity (%)</th>
<th>VIII Ag (%)</th>
<th>D.D.A.V.P. μg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pre 5</td>
<td>Post* 3.5</td>
<td>Pre 20</td>
<td>Post* &gt; 100</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>7</td>
<td>28</td>
<td>&gt; 100</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>9</td>
<td>24</td>
<td>68</td>
</tr>
</tbody>
</table>

* "Post" levels taken 1 h after infusion.

The quality of the clot formed and the rate of healing of the sockets both appeared entirely normal in contrast to the slower healing usually experienced in similar patients treated with cryoprecipitate, antifibrinolytic agents, and antibiotics, as noted in a previous paper on D.D.A.V.P. treatment.3 There were no problems with fluid retention or increase in blood-pressure in our patients, the only side-effect being severe burning pain along the course of the vein during the third of the three injections given to one of the women.

In von Willebrand's disease, giving blood products raises factor-VIII coagulant activity but often does not correct the bleeding-time. Blood-product replacement during surgery is often monitored by the factor-VIII coagulant activity.1–4

11. 1-deamino-8-D-arginine vasopressin (D.D.A.V.P.) which enables surgery to be done without the attendant hazards and expense of blood-product transfusion. A rise in factor-VIII-related antigen (VIII Ag), von Willebrand's factor, and factor VIII coagulant activity after intravenous D.D.A.V.P. infusion has been recorded.1,2 We have recently observed shortening of the bleeding-time (as measured by the template method) on repeated occasions in two young women who were having dental extraction. The results are summarised in the table. The time interval between the doses of D.D.A.V.P. (given in 30 ml of saline over a 10 min period) was 12 h and the effect on bleeding-time lasted less than 12 h and was less apparent on the second occasion.

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