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CO-DERGOCRINE

SIR,—In their paper on the risk-benefit ratio of flunarizine and cinnarizine, Dr Laporte and Dr Capella (Oct 11, p 853) state that drugs with a similar spectrum of indication, such as co-dergocrine, are useless and may not be safe. With respect to co-dergocrine this statement is inappropriate. In contrast to flunarizine and cinnarizine, which both possess antihistaminic and antidopaminergic activities, co-dergocrine is a dopaminergic agonist.[1] Thus, co-dergocrine clearly differs from the other two drugs in its mode of action. The clinical efficacy of co-dergocrine has been established in at least fifteen placebo-controlled trials in senile decline.[2] Furthermore, clinical experience over 30 years clearly indicates that long-term treatment with co-dergocrine does not involve a serious risk; this has been confirmed in a controlled long-term study.[3] It is, therefore, not surprising that regulatory authorities including the US Food and Drug Administration, which recently evaluated this drug, concluded that co-dergocrine has proven clinical efficacy[4] and a favourable risk-benefit ratio.

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BIOLOGICAL BASIS FOR HIGH-VOLTAGE-SHOCK TREATMENT FOR SNAKEBITE

SIR,—Dr Guderian and colleagues (July 26, p 229) propose high-voltage shock as a treatment for snakebites. 20–25 kV direct current shocks of less than 1 mA to the site of the bite led to early relief of pain and diminished local toxic and inflammatory tissue reactions. Not one of thirty-four patients had signs of systemic envenomation. Guderian et al speculate that shutdown of local vessels by electrospasm would prevent the rapid distribution of snake venom.

Snake venoms contain a complex mixture of enzymes, neurotoxic proteins, polypeptides devoid of enzymatic activity, and low-molecular-weight compounds such as peptides, nucleosides, and metal ions.[1] Of at least twenty-six enzymes that have been detected in snake venoms twelve are found in all venoms (eg, phospholipase A and hyaluronidase[2]). A second major group of proteins and polypeptides responsible for the toxicity of the snake venom is characterised by an overall net positive charge (eg, cardiotoxin, cytotoxin, and direct lytic factor). These compounds act on membranes, disturbing their organisation and function.[3] An electrostatic interaction between the basic compounds and the negative charged surface of the membrane is presumed to be essential to their cytotoxic action on leucocytes and nerve and muscle cells. Most of these membrane-active polypeptides can potentiate the action of phospholipase A.[4]

Like snake venoms hymenopteran venom contains very similar constituents (eg, phospholipase A, hyaluronidase, and positively charged polypeptides[5]). Melittin, for instance, the main constituent of honeybee venom represents the correspondent basic polypeptide. Synergism between melittin and phospholipase A results in an enhanced toxic effect on target tissue.[6]

As we know from unpublished experiments with purified bee venom, a high-voltage current applied in vitro decreases the histamine-releasing activity of phospholipase A and melittin on purified peritoneal mast cells from the rat. We conclude that electrical current may directly modify the toxicity of animal venoms. Three different mechanisms seem to be responsible:

(1) The current will influence the hydrogen bonds of the enzymes, destroying their secondary and tertiary structure.

(2) The high voltage, low amperage current applied will reduce metal ions and zinc, copper, magnesium, iron, or calcium ions are firmly bound to some venom enzymes and are mandatory cofactors for these enzymes.[2]

The electric particles interfere with the membrane as well as the positive charged polypeptides decreasing their cytotoxic properties.[7] Taken together the protective high-voltage treatment for venomous snake bites is at least in part due to a direct action of the electrical current on the venom itself.

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RETINOBLASTOMA, MELANOMA, AND PANCREATIC CANCER

SIR,—Your Sept 13 editorial indicated a relation between hereditary melanoma and carcinoma of the pancreas. This was based on a survey of hereditary malignant melanoma in the Netherlands.[1] We have done a similar survey of hereditary retinoblastoma. One result was that hereditary retinoblastoma appeared to be related to both hereditary melanoma and pancreatic malignancy.

Patients were drawn from the national retinoblastoma register of the Royal Netherlands Eye Hospital, Utrecht. This register started in 1862 and has covered the entire Netherlands population for more than a century. All but 1 of 142 patients with bilateral and/or unilateral familial disease registered between 1945 and 1970 were studied. Among 122 survivors of the eye tumour 17 second non-ocular malignancies were found; and 12 of these patients died from this second malignancy. The cumulative incidence was 19% (95% confidence interval 11–29%) at the age of 35 years. No deaths due to second malignancies were observed in 252 patients with unilateral non-familial disease. Most of the second malignancies were sarcomas (4 osteosarcomas, 9 soft-tissue sarcomas). 2 malignant melanomas were found in siblings.

Cancer in the parents was studied in 103 hereditary cases without a family history of the disease. In the fathers an excess of cancer cases was found compared with the general Netherlands population. This excess was due to pancreatic cancer in 3 fathers (expected 0·4; relative risk 8·3, the 95% confidence interval 1·5–20·8).

Two pairs of mutations at two pairs of loci are probably involved in oncogenesis.[2] One pair of loci may be 13q14 since this is involved in both retinoblastoma[3] and osteosarcoma.[4] The other pair may be located on chromosome 3 since this chromosome seems involved in malignant melanoma[5] and in retinoblastoma.[6] We suggest that a pair of loci on chromosome 3 and a pair of loci on chromosome 13 are involved in retinoblastoma, and that the pair of loci on chromosome 3 is involved in retinoblastoma, malignant melanoma, and pancreatic cancer.

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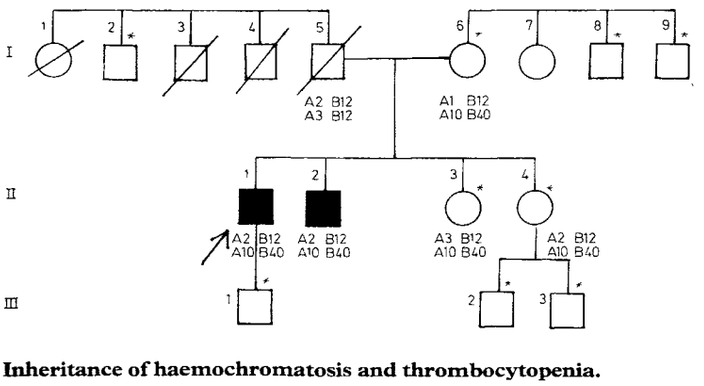
GENETIC HAEMOCHROMATOSIS AND THROMBOCYTOPENIA

SIR,—Thrombocytopenia in a patient with genetic haemochromatosis suggests hepatic cirrhosis, excessive alcohol intake,[1] or folate deficiency—or, more rarely, disseminated intravascular coagulation[2] (DIC) or autoimmune mechanisms.[3] We describe a family in whom both the haemochromatosis and the thrombocytopenia were probably genetic in origin.

The proband (II-1) was first seen in 1983 at the age of 29 because of severe bruising after a fall. He has bruised easily since childhood. He felt well, was taking no drugs, but had been drinking about 16 pints of beer weekly. He had skin pigmentation below the knees. His platelet count was 50×10^9/l although the platelets were normal by light microscopy. Otherwise haematological values were normal. Bone-marrow biopsy specimens contained reduced numbers of megakaryocytes, half of which had large immature nuclei and an excess of siderocytes and sideroblasts. Iron stores were increased with a transferrin saturation of 100% and serum ferritin 1200 µg/l (2·5 times normal). Aspartate aminotransferase (AAT) was 63 IU/l (upper limit of normal 35 IU/l). Other biochemical values, serum vitamin B_{12} and folate, prothrombin time, and other liver function and immunological tests were normal. No IgG autoantibodies to platelets were detected. Haemochromatosis was confirmed by massively increased parenchymal hepatic iron (grade 4)[4] on liver biopsy with no cirrhosis. Despite venesection and reduction of alcohol intake he remains thrombocytopenic with megakaryocytopenia on repeat trephine biopsy.

Because haemochromatosis is an autosomal recessive trait and treatment of precirrhotic cases improves prognosis,[5] the first-degree relatives were examined.[6] The locus is closely linked to the histocompatibility antigen (HLA) complex[7] so HLA class I antigens were identified (see figure). A younger brother (II-2) also bruised easily although his general health was good and took no drugs. He drank 50 pints of beer weekly. In 1977 a hernia operation was complicated by a scrotal haematoma. He had numerous bruises, Dupuytren's contractures, and pigmentation over the shins. His platelet count was reduced to 65×10^9/l although the platelets were normal by light and electron microscopy. A trephine bone biopsy specimen showed megakaryocytopenia. Transferrin saturation was 92% and serum ferritin 3176 µg/l. AAT was 37% above normal at 48 IU/l but otherwise biochemical, haematological, and immunological values were normal. Liver biopsy demonstrated grade 3 iron deposition in hepatocytes but no cirrhosis. Histological examination of the palmar aponeurosis after surgery for Dupuytren's contracture showed heavy iron staining.



Inheritance of haemochromatosis and thrombocytopenia.

Shaded boxes are affected brothers; asterisk indicates screened individuals with normal platelet count; A and B antigens of HLA haplotype shown below males (□) and females (○).

A sister (II-4) aged 32 has an HLA genotype similar to her two brothers and is therefore almost certainly homozygous for haemochromatosis. She is well and pregnant. Her transferrin saturation was 17·6% and serum ferritin 14·0 µg/l with a normal platelet count. Three boys aged 2, 4, and 5 in the third generation are not thrombocytopenic. In 1981 the proband's father (I-5) began intermittent chemotherapy for acute lymphoblastic leakaemia. At presentation he had pancytopenia and a serum iron saturation of 45%. He remained thrombocytopenic with few megakaryocytes in the bone marrow even in remission. No autoantibodies to platelets were detected. An aunt (I-1) developed acute myeloblastic leukaemia at age 56. A sternal marrow examination showed blast cells as 27% of all cellular elements with depressed myeloid series and a marked megakaryocytopenia.

The two brothers with haemochromatosis do not have hepatic cirrhosis, splenomegaly, folate deficiency, evidence of clinically significant DIC or autoimmune platelet destruction which might account for their thrombocytopenia. Alcohol excess can depress the platelet count. However, both brothers have had a bruising tendency since childhood, and, in the proband, thrombocytopenia has persisted for 3 years despite reduced alcohol consumption. We therefore suggest that the thrombocytopenia is an inherited disorder related to megakaryocyte failure. Descriptions of isolated congenital thrombocytopenia with megakaryocytopenia are few and the prognosis is usually grave.[8] Two members of the previous generation had thrombocytopenia but the clinical significance of this is weakened by their leukaemia and its treatment. The inheritance of thrombocytopenia in this pedigree is therefore uncertain. It is consistent with an autosomal recessive condition but HLA linkage is unlikely as the sister (II-4) is not thrombocytopenic. An autosomal dominant thrombocytopenia not linked to the HLA system and with reduced numbers of megakaryocytes has been described.[9] Sex-linked thrombocytopenias of the Wiskott-Aldrich syndrome and its variants[10] have associated features not seen in this family.

Clinicians should be aware of this previously unreported disorder of haemochromatosis and thrombocytopenia which we believe to be genetic.

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