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HAEMOPHILIC ARTHROPATHY: IMMUNOLOGICAL MECHANISMS AND SYNOVITIS.
F. Störkel (1), I. Scharrer (1), L. Hovy (2), J. Rüdigier (3) and S. Störkel (4). Department of Internal Medicine (1), Orthopaedic Clinic Friedrichsheim (2), University Hospital, Frankfurt, West Germany and Department of Accident Surgery (3), Department of Pathology (4), University Hospital, Mainz, West Germany

Up to now questions of pathogenisis in hemophilic arthropathy are still remaining, i.e. humoral mediated immunological mechanisms (type II/III reactions) are supposed to play an important role (Arnold and Hilgartner (1977), Rippey (1978)). Therefore we investigated synovial tissue by immunohistologic technique using antibodies against IgG, IgA, IgM, C1q, C3, fibrinogen and α_1-ACT.
First we examined synovial membrane biopsies (n=7; non-haemophilic) following acute traumatic joint bleeding, to study the first and acute bleeding/absorption phase. Light microscopy showed typical changes as described before by Roy et al. 1967. Immunohistological results revealed negativity for immunoglobulins and complement components in general, whereas fibrinogen and α_1-ACT showed marked intensity of fluorescence.
Secondly synovial membrane biopsies (n=7) of haemophiliacs who have had recurrent joint bleedings were examined in the same way. In light microscopy we found typical synovial alterations as described by Mohr (1984). Immunohistology showed negativity for immunoglobulins and complement components and the intensity of fluorescence of fibrinogen and α_1-ACT was lower as in patients with acute traumatic joint bleeding.
At last synovial tissue specimens (n=2) of patients with pigmented villonodular synovitis were investigated. Light microscopy was in aquaintance with findings of Faßbender (1976). The immunohistological results were similar to those aforementioned.
Conclusions: 1) There is no evidence that acute or chronic joint bleeding causes a humoral mediated immune reaction in synovial membrane. 2) In the contrary the inflammatory reaction leeds to detritus-synovialitis, supported by recurrent bleeding episodes. Concequences for clinical management: a) prevention of joint bleeding b) joint-punction in cause of bleeding, to reduce the intraarticular haematoma c) synovectomy to prevent the progress of arthropathy.

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LONG TERM, FREQUENT PLASMA EXCHANGE DONATION OF CRYOPRECIPITATE.
B. McLeod (1), R. Sassetti (1), E. Cole (1), P. Scott (2). Rush Medical Center (1) and Children's Memorial Hospital (2), Chicago, IL, USA

In plasma exchange donation (PED), several liters of fresh plasma are removed from a donor with a pheresis instrument as a source of cryoprecipitate, and replaced with autologous cryoprecipitate-supernatant from the previous donation. Repetitive PED can produce large quantities of factor VIII from individual donors over time, with a favorable impact on donor exposure for factor VIII recipients. To clarify the implications for donor safety, we report our experience with several donors who have undergone multiple PEDs. Detailed observations are presented for one donor who has undergone PED 101 times between 5/83 and 1/87, and has provided all the factor VIII needed by his son (now age 14) with severe hemophilia A during this period. Exchange volume was gradually increased while donation frequency was gradually decreased. There were 23 exchanges of 2 L, 52 of 2.5 L, and 26 of 3 L for a total of 254 L plasma exchanged. Desmopressin (20 mcg IV) was given before 45 more recent donations to augment factor VIII yield. A total of 343,274 IU factor VIII have been collected; the mean (±SD) yield from a 3 L, desmopressin-stimulated PED is 5598 ± 899 IU. The donor has remained in good health; he has noted no adverse effects from any PED, and none have been found in laboratory monitoring. Prior to the 100th donation the following were within normal limits: CBC, platelet count, urinalysis, SMA-18, protein electrophoresis, IgG, IgA, IgM, hemolytic complement, C3, C4, fibronectin, prothrombin time, partial thromboplastin time, thrombin time, factor VIII:C (140%), factor VIII:Ag (134%), von Willebrand factor (86%) and fibrinogen (215 mg/dL). In another family, the father has donated 40 times since 1981 and the paternal grandmother has donated 31 times since 1984 with no untoward effects detected in clinical or laboratory monitoring. They have supported two moderately affected patients now ages 7 and 9. Extensive experience with these donors suggests that repeated PED is safe, and that a highly motivated donor can sometimes provide single donor support, even for a severe hemophiliac.

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LIFE-EXPECTANCY OF DUTCH HEMOPHILIACS, 1972-1985
F. Rosendaal (1), C. Smit (1,2), I. Varekamp (3), A. Bröcker-Vriends (4), T. Suurmeijer (3) and E. Briët (1). Dept. of Hematology, Leiden University Hospital (1), Dutch Hemophilia Society (2), Dept. of Medical Sociology, State University Groningen (3), Clinical Genetics Center Leiden (4); The Netherlands.

The life-expectancy of hemophiliacs has risen during the last decades from (for severe hemophilia) a mere 16 yrs in 1940, 23 yrs in 1964 to almost normal after coagulation factor preparations became available. Still, many hemophiliacs encounter ratings or refusals when applying for life-insurance.

We carried out three mail surveys (1972, 1978, 1985) among Dutch hemophiliacs to establish excess mortality caused by hemophilia. Follow-up for non-respondents was carried out with help from the municipal authorities, while information on the deceased was obtained from the hemophilia treatment centers. To compare mortality with the general population, we constructed Kaplan-Meier reference curves for population groups with the same age and sex distribution, using national death tables. Pending completion of the follow-up for the 1972-1985 interval, this abstract supplies the results for the 1978-1985 period.

The 1978 cohort included 578 individuals, with a mean age of 26 yrs (general male population: 33 yrs). None were lost to follow-up, 22 (3.8%) had died during the 7½ yrs of observation. In the reference group 1.9% mortality would have been expected. So, overall relative mortality is increased twofold compared to the general male population (95% confidence interval 1.3-3.0). Patients with an inhibitor excluded, excess mortality did not differ much for severe, moderate and mild hemophilia (relative mortality: 2.3, 1.8, 1.5). In 11 cases hemorrhage was the cause of death, but in 6 cases this was associated with an underlying lethal disorder. In 9 cases the cause of death was not related to hemophilia and in 2 it remained unknown. An inhibitor was present in 4 (18%) of these 22 patients, but in only 4% of the total group of 578. In the 1972 survey 43% of the respondents who had applied for a life-insurance (n=199) reported a rating or a refusal, in 1978 47% of 227 and in 1985 53% of 676.

The excess mortality caused by hemophilia is small and similar to that due to smoking cigarettes. Moreover, the excess may be caused in part by a carry-over effect from the time before modern treatment was introduced.

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THE BENEFITS OF MODERN SUBSTITUTION THERAPY IN HEMOPHILIA
C. Smit (1,2), I. Varekamp (3), F. Rosendaal (1), A. Bröcker-Vriends (4), T. Suurmeijer (3) and E. Briët (1). Dept. of Hematology, University Hospital Leiden (1), Dutch Hemophilia Society (2), Dept. of Medical Sociology, State University Groningen (3), Clinical Genetics Center Leiden (4); The Netherlands

Coagulation factor preparations became available in the treatment of hemophilia about twenty years ago, followed by the introduction of prophylactic therapy and home-treatment. The purpose of our longitudinal study was to quantify the impact of these treatment modalities on the medical and social situation of hemophiliacs.
We carried out three mail surveys (1972, 1978 and 1985) among Dutch hemophiliacs. In 1985 we sent questionnaires to 1162 of the estimated total of 1300 patients with a response of 81%.
Eighty-six percent of the respondents had hemophilia A, 14% hemophilia B; 41% had severe hemophilia (<1%), 19% moderately-severe (1-5%) and 40% mild hemophilia (>5%). Growth of prophylactic therapy and home-treatment for severe hemophilia was :

	1972 (n = 255) %	1978 (n = 244) %	1985 (n = 384) %
Prophylaxis	30	40	48
Home-treatment	5	30	67

The mean age increased from 21 yrs in 1972 (n=435) to 29 yrs in 1985 (n=935)(general male population: 34 yrs). The number of manifest bleedings decreased from 25 in 1972 to 15 in 1985, with a corresponding decrease in the number of transfusions for acute bleedings. Hospitalization per 100 patients with severe hemophilia decreased from more than 2100 days in 1972 to 440 days in 1985. Non-attendance at school caused by hemophilia dropped from 6 to 2 weeks per year, and sickleave from work from 35 to 15 days per year, so that it now equals sickleave among the general male population. Unemployment figures for hemophiliacs were similar to those for the general population, but disability figures are still higher. Our study shows in a quantitative way that the benefits of modern hemophilia treatment are impressive and that its costs are more than justified.