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29 September, 1986

Eingegangen am:
2. Okt. 1986
REGISTRIERUNG

Mrs. Henninger,
Immuno AG.

Dear Mrs. Henninger,

Please find enclosed an article on heat treated Factor VIII concentrates from the 6 September issue of The Lancet.

As you will see there is a reference to some work by Longo which gives pharmacokinetic data for Kryobulin TIM3. It seems as though this may be relevant for our submission.

Also enclosed is an extract from the 13 September Lancet relating to a new statement from the WHO in relation to HTLV-III transmission and Immunoglobulins.

Finally, last week when we discussed the amendment to the Bovine Sensitisation paper by Professor Schlag, a figure of 1200 times was agreed for the differences in aprotinin dosage. If you actually do the sum it comes out to greater than 1300 times and I have therefore amended our copy accordingly.

Kind regards.

Yours sincerely,
for IMMUNO LTD.,

GRO-C: Robert Nicholson

R. Nicholson, M.Sc.,
Marketing Manager

Encs.

Eingegangen am:
2. Okt. 1986
REGISTRIERUNG

practitioner is in a unique position to discuss with the patient any sexual difficulties he or she may perceive (most commonly, reduced desire in women and erectile dysfunction in men), so long as the physician is able to discuss such matters within the emotional context of a relationship rather than as mechanical breakdown. Specialist psychosexual training is not necessary, simply basic counselling techniques. The report notes that few family planning organisations in Europe offer any psychosexual counselling. Sexuality is generally treated as entirely separate from family planning. Nevertheless, most heterosexual women will concur with the following observation: "It can be said that family planning means to live for almost a lifetime with the contradiction between the necessity to plan rationally and the desire to experience sexuality irrationally. The contradiction is complicated further if choice of method is considered. Some methods, eg, the pill, make it easier to live with the contradiction. Others may put an extra burden on it, eg, the use of the diaphragm."

SAFETY OF IMMUNOGLOBULIN PRODUCTS IN RELATION TO AIDS

CONCERN that immunoglobulin preparations may transmit the human immunodeficiency virus (HIV) (eg, *Lancet* March 15, p 581 and May 10, p 1090) may not have been dispelled by reports on the safety of these preparations in relation to the acquired immunodeficiency syndrome (eg, *Lancet* May 10, p 1090, May 24, p 1217, and June 7, p 1327). However, a group of experts convened by the World Health Organisation to discuss the safety of blood and blood products with respect to AIDS[1] have concluded that when fractionation is carried out according to the Cohn-Oncley method a safe immunoglobulin product can be expected even when it contains antibodies to HIV. Under those circumstances, the immunoglobulin recipients have a transient positive antibody test due to the passive transfer of immunoglobulin but this is not an indication of infection.

AN AIDS JOURNAL

AT the latest count[2] there were at least nine periodical publications, most of them of the newsletter/abstract type, on the acquired immunodeficiency syndrome (AIDS). Besides the official AIDS weekly surveillance reports from the US Centers for Disease Control there are, for example, *CDC AIDS Weekly* published out of Atlanta, Georgia, and the *AIDS and Retroviruses Update* service from the Bureau of Hygiene and Tropical Diseases in London. A bimonthly journal, *AIDS*, planned for 1987, will publish original clinical and scientific research on AIDS, besides reviews, rapid communications, and correspondence.

AIDS is to be published by Gower Academic Journals, 34–42 Cleveland Street, London W1P 5FP, at the following subscription rates (if paid before Oct 31, 1986): £50 ($75) for individuals and £66 ($100) for institutions. Papers may be sent to the London office or to Gower Medical Publishing, 101 Fifth Avenue, New York, NY 10003, USA.

Protecting Children from Misuse of Drugs

The Health Education Council and the Teachers' Advisory Council on Alcohol and Drug Education has compiled a drug education programme for use in primary schools. The aim of the programme, which has been tested in schools in Merseyside, is to create awareness among pupils, teachers, and parents of the potential danger of all drugs, including over-the-counter remedies, cigarettes and alcohol, and illicit drugs. The Health Education Council admits the possibility of creating an attraction to drugs by introducing lessons on the subject, but warns that children are already exposed to information about drugs from many sources, much of it inaccurate and open to misinterpretation. Drug education in primary schools is believed to be an essential preventive measure. The pack of materials, which includes detailed information, slides, and exercises, may be purchased by schools (£33.95) from TACADE, Furness House, Trafford Road, Salford M5 2XJ.

1. Acquired immunodeficiency syndrome: WHO meeting and consultation on the safety of blood and blood products. *WHO Wkly Epidem Rec* 1986; 18: 138–40.
2. Anon. Publications exclusively covering AIDS. *CDC AIDS Weekly* 1986 (Sept 1): 4.

Reducing Industrially Caused Lung Cancer

A 5-point plan[1] has been drawn up by the Health and Safety Commission to reduce the risk of lung cancer in foundry workers. Measurement of levels of dust and fumes in foundries should determine exposure levels in particular environments. Hazardous materials and processes should then be replaced wherever possible; dust and fumes should be contained; exhaust ventilation should be efficient; the use of respiratory protection equipment should be required; and high standards of general cleanliness should be maintained.

1. Reducing the Risk of Lung Cancer in the Iron and Steel Foundries. Available (free) from Health and Safety Executive area offices (01-221 0870).

Cancer Research Campaign

Dr J. A. Wyke, head of the Imperial Cancer Research Fund Laboratories, St Bartholomew's Hospital, London, has been appointed director of the Beatson Institute for Cancer Research, Glasgow, which receives £1·5 million from the Cancer Research Campaign. Dr Wyke succeeds Dr John Paul on Oct 1.

A 2-day meeting entitled **Trace Elements and Human Health** is to take place at University of Edinburgh on Sept 24–25: Dr J. L. Clapperton, Hannah Research Institute, Ayr KA6 5HL.

A one-day conference on **Soil Fertility and Human Health** will be held at the Ninewells Hospital and Medical School, Dundee, on Saturday, Oct 4: Mrs C. Wade, Secretary, McCarrison Society, 36 Norwood, Newport-on-Tay, Fife DD6 8DW (0382 543136).

A one-day meeting entitled **Promotion of Continence in Later Life** is to be held at the University of Lancaster on Wednesday, Oct 8: British Association for Service to the Elderly, 119 Hassell Street, Newcastle under Lyme, Staffordshire ST5 1AX (0782 661033).

A course of 10 lectures and group discussions on **Counselling Before and After Bereavement** will take place at the Manchester Business School on Wednesdays, Oct 8–Dec 10: Cruse House, 126 Sheen Road, Richmond, Surrey TW9 1UR (01-940 4818/9047).

A 4-day course in two 2-day blocks, entitled **Co-counselling Training**, is to be held at the British Postgraduate Medical Federation, London WC1, on Oct 9–10 and Oct 23–24: Mrs Elva Macklin, Education Department, British Postgraduate Medical Federation, 33 Millman Street, London WC1N 3EJ (01-831 6222).

A one-day meeting on **Public Perception of Radiation** will be held at the City Conference Centre, London, on Tuesday, Oct 14: Professor J. H. Martin, Department of Medical Biophysics, Building 15, Park Wynd, University of Dundee, Dundee DD1 4HN (0382 23181 ext 4438).

An evening meeting, including the presidential address on **Clinical Observations and Other Aspects of an Area Service from 1852 to Present Day** is to take place at the Royal Society of Medicine, London W1, on Tuesday, Oct 14: Miss N. Aaron, Sections Office, The Royal Society of Medicine, 1 Wimpole Street, London W1M 8AE (01-408 2119).

Diary of the Week

SEPT 14 TO 20

Monday, 15th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London WC2A 3PN

5 pm Dr David Gadian: Magnetic Resonance Imaging and Spectroscopy.

Tuesday, 16th

INSTITUTE OF PSYCHIATRY, De Crespigny Park, Denmark Hill, London SE5 8AF

5.30 pm Prof E. Strömgren (Risskov): The Recent History of European Psychiatry: Ideas, Developments and Personalities.

Thursday, 18th

ROYAL COLLEGE OF SURGEONS OF ENGLAND

12 pm (Music Hall, Assembly Rooms Building, George Street, Edinburgh) Mr Adrian Flatt (Dallas): The Hand as a Mechanism.

Friday, 19th

INSTITUTE OF NEUROLOGY, National Hospital, Queen Square, London WC1N 3BG

1 pm Dr Charles M. Poser (Boston): The Pathogenesis of Multiple Sclerosis.

with horseradish peroxidase and the developed colour was read in a spectrophotometer. This procedure ought to reduce the risk of non-specificity, a consistent problem with IgM antibody research methods.

For confirmation of IgM ELISA positivity we incubated serum (1 in 25) with nitrocellulose strips containing HIV-specific proteins (Biotech Research Laboratories) for 18 ± 2 h at 4°C at a pH and with a molar concentration and ionic strength suitable for buffering. The strips were washed and incubated with an anti-human IgM goat-immunoglobulin biotin conjugate and a 4-chloronaphthol substrate. As a further confirmatory test an indirect immunofluorescence method was also used (J.L.C. Scientific, Alaman, Switzerland).

Among the 65 HIV IgG seronegative addicts attending the drug centre we detected 5 IgM positives (8%) confirmed by IgM western blot and IFA. 4 switched from IgM to IgG after 1, 14, 23, and 38 weeks, and the switch was always accompanied by a modification in the band pattern on western blot. Of the other 60 drug addicts who were HIV IgM and IgG seronegative when first tested 24 have been followed up for 1–12 months (7 months on average); 1 other had seroconverted to IgG 42 weeks after the first test without our being able to detect any possible IgM phase.

Among the 135 addicts who were in hospital for hepatitis and were HIV IgG negative we found 8 confirmed IgM positives (6%). We have followed up 4 of these; 1 switched from IgM to IgG after 41 weeks. The other 3 have not convertd to IgG. All 13 addicts are still anti-HIV positive (table).

SEROLOGICAL PATTERNS IN THIRTEEN INITIALLY HIV SERONEGATIVE (IGM AND IGG) DRUG ADDICTS WHO CONVERTED TO IGM SEROPOSITIVITY

Case	IgM pattern detected	Follow-up post IgM	Switch to IgG	Latest pattern
1			Yes (1 wk)	
2			Yes (14 wk)	
3			Yes (23 wk)	
4			Yes (38 wk)	
5	p15,17, p24	8 wk	No	
6			Yes (8 wk)	
7	p15,17, p24	9 wk	No	
8	p15,17, p24	9 wk	No	
9	p15,17, p24	74 wk	No	
10		ND		
11		ND		
12		ND		
13		ND		

Thus in some instances HIV IgM may be the only serological sign of infection and this may be a prelude to IgG seropositivity. However, IgM seropositivity may also persist for several months without a switch to IgG. The specificity of the HIV IgM ELISA described has been confirmed not only by western blotting but also by the switch to IgG and by the lowering and/or disappearance of IgM that accompanied this switch. Our findings, if confirmed in a larger population, would lead to a reassessment of screening procedures, especially of blood donors.

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Immunchaematology Service, Ospedale di Tradate, Varese

E. MAGNI

1. Aiuti F, Rossi P, Sirianni MC, et al. IgM and IgG antibodies to human T cell lymphotropic retrovirus (HTLV III) in lymphoadenopathy syndrome and subjects at risk for AIDS in Italy. *Br Med J* 1985; 291: 165.
2. Alter HJ, Eichberg JW, Masur H, et al. Transmission of HTLV III infection from human plasma to chimpanzees; an animal model for AIDS. *Science* 1984; 226: 549.
3. Melioli G, Varnier CE, Merli A, Schito G. Detection of specific anti-LAV/HTLV III IgM antibodies during seroconversion using enzyme-linked immunosorbent assay. International Symposium on AIDS and Blood Transfusion (Turin, June, 1985).

HALF-LIFE AND IN-VIVO RECOVERY OF HEATED FACTOR VIII CONCENTRATES

SIR,—To assess the effect of heat treatment on factor VIII (FVIII) Barrowcliffe et al[1] did experiments based on Weinstein's method[2] and found that the peptide distribution of heated concentrates was altered. This suggested that heat treatment degrades FVIII:C protein, with formation of low-molecular-weight peptides.

Since all concentrates show degradation of FVIII relative to plasma, Barrowcliffe et al analysed one brand and found no difference in peptide distribution before and after heat treatment; on the other hand, a comparison of wet and dry heated products suggested that degradation after wet treatment was more extensive. Barrowcliffe et al concede that the contribution of heat treatment to the degradation of FVIII:C is uncertain and call for in-vivo evaluations of the recovery and half-life of heated products.

At least two such clinical studies have already been done. In 1985 Matucci et al[3] demonstrated that the half-life of 'Hemofil T' (Travenol), an FVIII concentrate prepared by dry heat treatment, was nearly identical (11·4 h) to that of two FVIII unheated concentrates (10·1 h for 'Kryobulin' [Immuno] and 12·3 h for 'Koate' [Cutter]). Hemofil T had a volume of distribution (a pharmacokinetic index highly correlated with in-vivo recovery) virtually identical to that of the unheated products. In 1986, Longo et al[4] showed that the mean residence times and volumes of distribution (15·8 h and 55·6 ml/kg, respectively) of kryobulin TIM3, a steam-treated concentrate, were similar to the values (13·2 h, 53·9 ml/kg) calculated for the unheated predecessor kryobulin. In both studies the one-stage method was used to assay FVIII:C activity. Thus our in-vivo data[3,4] suggest that FVIII derangement is not enhanced in heated products or that, if present, it does not alter the recovery and half-life of FVIII.

We have used material stored in our laboratory to evaluate one hypothesis put forward by Barrowcliffe et al. In one of the seven brands tested Barrowcliffe et al found a low-molecular-weight peptide pattern consistent with increased thrombin proteolysis of FVIII:C due to heat treatment. Thrombin activation increases one-stage activity compared with the two-stage activity, and higher in-vitro values of FVIII activity by one-stage than by two-stage assays were found by Barrowcliffe et al for this brand (average ratio of 1·49). This finding contrasts with data for unheated concentrates[5-7] showing significantly greater in-vitro potency by two-stage than by one-stage as well as slightly higher post-infusion FVIII:C in-vivo levels assayed by two-stage than by one-stage assays. This body of data suggests that though thrombin proteolysis may be increased in some heated concentrates, the loss of FVIII:C might be offset in vitro by the increase in one-stage activity resulting from thrombin activation.

We have tested plasma samples collected after infusion of heated concentrates in haemophiliacs, comparing ex-vivo data with Barrowcliffe's in-vitro findings. We reassayed, by one-stage[3,4] and two-stage (Immuno kits) methods, 42 of the 96 plasma samples collected in Longo's 1986 study[4] after infusion of kryobulin TIM3. The 42 samples were the ones that had been kept at −70°C. The mean one-stage/two-stage ratio was 1·12 (SD 0·24, range 0·70–1·55), indicating a tendency for the one-stage assay to give higher results after infusion of heated concentrates ($p < 0·02$, Wilcoxon's test). This preliminary result is interesting because in studies on unheated concentrates[6,7] the two-stage values invariably exceeded the one-stage values, typically by 10–20%. The one-stage values that we found are very similar to the values found during the original clinical study, where the mean ratio was 1·19 (SD 0·11, range 0·95–1·38), demonstrating negligible loss of FVIII activity since the collection of plasma samples.

Barrowcliffe's hypothesis of increased thrombin activation in heated concentrates cannot be excluded by our in-vivo and in-vitro data. Only by comparing the peptide distributions of several FVIII

concentrates before and after heat treatment can we reach firm conclusions about the effects of heat treatment on the FVIII molecule.

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1. Barrowcliffe TW, Edwards SJ, Kemball-Cook G, Thomas DP. Factor VIII degradation products in heated concentrates. *Lancet* 1986; i: 1448–49.
2. Weinstein MJ, Chute LE, Deykin D. Analysis of factor VIII coagulant antigen in normal thrombin-treated and hemophilic plasma. *Proc Natl Acad Sci USA* 1981; 78: 5137–41.
3. Matucci M, Messori A, Donati-Cori G, et al. Kinetic evaluation of four factor VIII concentrates by model-independent methods. *Scand J Haematol* 1985; 34: 22–28.
4. Longo G, Matucci M, Messori A, Morfini M, Rossi-Ferrini P. Pharmacokinetics of a new heat-treated concentrate of factor VIII estimated by model-independent methods. *Thromb Res* 1986; 42: 471–76.
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TORSADE DE POINTES WITH PRENYLAMINE: DO WE STILL NEED THE DRUG?

SIR,—We have treated a 55-year-old woman who experienced syncope 2 weeks after starting treatment with prenylamine of 60 mg three times a day prescribed for vague symptoms of ill-health. The admission electrocardiogram revealed QT prolongation (QT_c = 0·67 s). She was also taking bendrofluazide 5 mg daily, and her serum potassium was 3·1 mmol/l. Monitoring demonstrated frequent brief episodes of torsade de pointes ventricular tachycardia. These episodes and the QT prolongation persisted after correction of the hypokalaemia. One episode caused cardiorespiratory arrest but she was resuscitated. The QT interval returned to normal within one week of her stopping prenylamine. She remains well.

Prenylamine is a calcium antagonist which also depletes sympathetic nerve terminals of noradrenaline.[1,2] It was introduced for the treatment of angina about 25 years ago and this remains its sole indication. However, it produces only a modest reduction in the frequency of angina without increasing effort tolerance.[3,4]

We have found forty-eight published case-reports since 1970 of torsade de pointes complicating prenylamine therapy.* Four patients died. The incidence of this life-threatening arrhythmia in patients taking prenylamine is unknown, but it can occur after many years of apparently safe administration.[5] In a prospective study of QT changes, Oakley and colleagues[6] found no serious arrhythmias but they excluded patients in whom the drug was stopped because of marked QT prolongation. This is recognised as a contraindication to continued treatment, as is hypokalaemia, but our experience confirms that prenylamine is still being prescribed without the necessary monitoring. Therapeutic problems can also arise if torsade is not suspected as the cause of syncope, because its treatment (by overdrive pacing and by drugs that shorten the QT interval[7]) differs from that for other types of ventricular tachycardia.

Safer and more effective drugs are now available for the treatment of angina. Since there no longer seems to be any need for prenylamine it should be withdrawn.

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A. G. FRASER
S. IKRAM

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*Additional references may be obtained from *The Lancet*.—ED. L.

FREQUENCY OF *Xba*I POLYMORPHISM IN MYOCARDIAL INFARCT SURVIVORS

SIR,—Dr Law et al (June 7, p 1301) report an association between a common restriction fragment length polymorphism (RFLP) of the apoprotein B gene and raised serum triglyceride levels in Caucasians. They go on to suggest the possibility of an association between this particular RFLP and coronary artery disease.

We have recently used an apoprotein B cDNA probe[1] to investigate the frequency distribution of the *Xba*I polymorphism in a group of Caucasian myocardial infarction survivors and in a group of healthy controls from a health screening centre. The results of our study are summarised in the table.

Our preliminary data do not suggest any direct aetiological relation between the *Xba*I polymorphism and premature coronary heart disease. Nor does there seem to be linkage disequilibrium between the alleles characterised by the *Xba*I polymorphism and other putative atherogenic alleles. The genotype distributions were similar in both groups of subjects, and the allelic frequencies were very similar to those reported by Law et al. This apparent lack of disease association contrasts with the association between an allelic variant of the apoprotein AI-CIII-AIV gene cluster (the S2 allele) and premature coronary heart disease previously demonstrated in similar patient and control groups.[2]

SERUM LIPID LEVELS AND FREQUENCY DISTRIBUTION OF *Xba*I POLYMORPHISM IN MYOCARDIAL INFARCT SURVIVORS AND CONTROLS

Group	Post-infarct (n = 52)	Normotriglyceridaemic post-infarct (n = 34)	Normotriglyceridaemic controls (n = 33)
Mean age (yr) (± SD)	53·8 ± 6·9†	53·0 ± 6·8†	43·8 ± 8·8
Mean serum triglyceride (mmol/l) (± SEM)	1·98 ± 0·13‡	1·44 ± 0·06	1·41 ± 0·09
Mean serum cholesterol (mmol/l) (± SD)	5·9 ± 1·51	5·7 ± 1·60	6·2 ± 0·94
Mean plasma HDL (mmol/l) (± SD)	1·20 ± 0·42	1·17 ± 0·40	1·26 ± 0·40
ApoB genotype frequency (%)			
X1X1	15 (29)	9 (26)	10 (30)
X1X2	21 (40) *	14 (41) *	17 (52)
X2X2	16 (31)	11 (32)	6 (18)
Allelic frequencies			
X1	0·49	0·47	0·56
X2	0·51	0·53	0·44

*$p > 0.05$ when compared in a 3 × 2 contingency table and a χ^2 test applied.
†$p < 0.001$ compared with normotriglyceridaemic controls by use of an unpaired t test.
‡$p < 0.01$ compared with normotriglyceridaemic controls by use of a Mann-Whitney U test.

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