contaminated surfaces is the most likely explanation for positive cultures of the finished product.

In culture surveys of retail poultry *L monocytogenes* has been isolated from 15% to 80% of specimens depending on the sampling method.[25] Undercooked chicken has been recognised as a risk factor for outbreaks of *Salmonella* and *Campylobacter* infections;[27,28] it has also been implicated in a population-based study of sporadic *Campylobacter* infection.[29] This study suggests that contaminated chicken is also a vehicle for listeriosis if cooked insufficiently to kill the organism.

Since the estimate of risk attributable to uncooked hot dogs and undercooked chicken was only 20% of the total risk of listeriosis, four-fifths of the risk of sporadic infection remains to be explained. Because of non-differential misclassification the risk attributed to the implicated food items may be underestimated and, in conjunction with the small sample size, may have resulted in our not identifying other foods associated with listeriosis. Additionally, a portion of the unattributed risk may be due to products not included on the questionnaire—such as shellfish. A further possibility is that not all sporadic listeriosis is foodborne, although our study did not identify any non-dietary risk factors.

Our results add to a growing body of evidence that consumption of contaminated food is a risk factor for listeriosis. Although our findings need to be replicated, they suggest that undercooked poultry and uncooked hot dogs need to be added to a list of foods associated with listeriosis—a list that already includes vegetables and dairy products. These results suggest that listeriosis may occur when a contaminated product is improperly prepared and eaten by a susceptible host. Whether systemic infection results directly from the exposure, or carriage is established with eventual dissemination, cannot be determined by the epidemiology alone. The association of both sporadic and epidemic listeriosis with food products emphasises the need for industry and regulatory agencies to work together to elminate *L monocytogenes* from food products—especially ready-to-eat foods. Consumers, especially pregnant women and those who are immunosuppressed, should be aware of the risk of listeriosis and could decrease their risk by preparing foods properly and avoiding uncooked food products that have been implicated as risk factors for listeriosis.

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References continued at foot of next column

Occasional Survey

VIRUCIDAL TREATMENT OF CLOTTING FACTOR CONCENTRATES

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HEPATITIS B virus (HBV), hepatitis non-A, non-B (NANB) virus, and the human immunodeficiency virus (HIV) are important causes of morbidity and mortality in haemophilic patients, who can become infected after transfusion with clotting factor concentrates made from large plasma pools. Manufacturers have tried to inactivate the viruses in concentrates by several methods (table 1). The first method was to expose whole plasma to ultraviolet irradiation and beta-propiolactone, a denaturing agent. This method can be applied to concentrates of the stable factor IX but not to concentrates of labile factor VIII. Manufacturers then attempted to inactivate viruses without substantial loss of factor VIII activity by heating lyophilised concentrates (dry heating) or concentrates resuspended in the organic solvent n-heptane. Factor VIII and factor IX concentrates have also been heated in solution (pasteurisation) and the moist bulk product has been heated with hot vapour. All methods based on heating use temperatures between 60°C and 80°C for 30–72 h. Another method has been developed in which the solvent tri-n-butyl-phosphate (TNBP) and

B. SCHWARTZ AND OTHERS: REFERENCES—*continued*

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detergents such as 'Tween-80' or sodium cholate are added to concentrates. Finally, both virus removal and inactivation methods have been applied to factor VIII concentrates produced by immunoadsorption on monoclonal antibodies bound to a solid phase. The chromatographic process itself removes substantial amounts of virus, and the eluate is inactivated (by heating in the lyophilised state at 60°C for 30 h by one manufacturer or by addition of TNBP/'Triton X-100' by another) to destroy residual virus. All these methods effectively inactivate substantial amounts of model viruses added in vitro. However, in-vitro viral inactivation is not necessarily paralled by clinical safety, and clinical trials in haemophiliacs are needed to prove the effectiveness of the inactivation method.

In an international survey, the risk of anti-HIV seroconversion among anti-HIV-negative haemophiliacs who used only treated concentrates made from plasma from donors screened for anti-HIV was extremely small.[1] The few cases of seroconversion that occurred were in patients treated only with lyophilised concentrates heated at temperatures of 60–68°C for 30–72 h. All dry-heated concentrates (including those implicated in cases of roconversion) have now been voluntarily withdrawn from sale by the manufacturers (table I). No case of seroconversion has been reported after treatment with the concentrates now available for haemophiliacs.

Attempts to lower the incidence of hepatitis by use of treated products have met with variable success. The attack rates of hepatitis vary from 0 to 80%, implying that the methods are not all equally effective. Therefore physicians treating haemophiliacs must now choose the methods and concentrates that guarantee greater safety from hepatitis. This choice can be based only on the results of suitable clinical studies in haemophiliacs, which should be carried out as soon as a new concentrate has proved safe in animals, such as chimpanzees.

CLINICAL PROTOCOL FOR STUDIES OF SAFETY FROM HEPATITIS

In 1984, the International Committee on Thrombosis and Haemostasis was so concerned about the lack of a uniform and rational methodological approach for clinical evaluation of the safety from hepatitis of treated concentrates, that it appointed a task force to draw up and recommend uniform criteria for the design and performance of safety studies (Miami, Florida, USA).

TABLE I—VIRAL INACTIVATION PROCEDURES APPLIED TO CLOTTING FACTOR CONCENTRATES

Method	Time (h)	Temperature (°C)	Concentrate state during inactivation	Manufacturer
β-propiolactone + ultraviolet	..	22	Solution	Biotest
Dry heating	30	60	Lyophilised	Armour*
	72	60	Lyophilised	Hyland*
	72	68	Lyophilised	Cutter*
n-heptane plus heating	20	60	Suspended in slurry	Alpha
Dry super-heating	72	80	Lyophilised	UK National Health Service
Vapour heating	10	60	Moisture	Immuno
Pasteurisation	10	60	Solution	Behring, Cutter
TNBP/sodium cholate	4	22	Solution	New York Blood Center
TNBP/tween 80	6	22	Solution	Aima/Biagini
Immunoadsorption + TNBP/Triton X-100	6	22	Solution	Hyland
Immunoadsorption + dry heating	30	60	Lyophilised	Armour

*Recently withdrawn from sale by manufacturers.

The committee recommended that safety studies should be prospective, but without a control group of patients infused with "untreated" concentrates. A control group would not only be unethical, it would be impossible, because untreated concentrates have not been licensed since 1985, when HIV was shown to be highly sensitive to most methods of virus inactivation. To increase the accuracy of safety studies, the committee recommended that only patients who had previously been given no blood or blood products should be enrolled. Previously untreated patients are very susceptible to hepatitis, with an attack rate of 100% when they are first treated with infectious concentrates,[2,3] and safety studies are based on the postulate that the attack rate of 100% in previously untreated haemophiliacs infused with any untreated concentrate serves as a historical control. Despite these recommendations, patients who had been treated a few times in the past with cryoprecipitate or other single-donor blood derivatives but no large-pool concentrate (so-called "infrequently treated" patients) have been enrolled in several safety studies. This practice reduces the sensitivity of such studies, because we do not know whether the attack rate for infrequently treated patients is 100% after exposure to untreated concentrates; some of these patients may not be susceptible to hepatitis. Moreover, these studies did not define what they meant by "infrequently treated" in terms of number of previous transfusions of single-donor fractions. In addition, the incubation periods for hepatitis transmitted by previous transfusions and by the concentrate under study might overlap and interfere with the analysis of the results.

The committee also recommended that haemophiliacs with underlying liver disease and those with serum markers of HBV infection (except for patients vaccinated against HBV) should be excluded, so that the interpretation of rises in aminotransferases due to the treated concentrate under study would not be confused by the presence of previous liver disease.

Since NANB hepatitis may be a biochemically short-lived and clinically attenuated disease after treated concentrates, another recommendation was that blood samples for aminotransferase testing should be taken every 2 weeks for the first 4 months after the first concentrate infusion and then monthly until the 6th month. With longer intervals, short-lived rises in aminotransferases might be missed. That these stringent criteria for blood sampling are important was clearly shown in a prospective study of NANB hepatitis after transfusion of a heated factor VIII concentrate into previously untreated patients.[4] In that study, 3 of 11 episodes of hepatitis would have been missed if blood samples had been taken more than 15 days apart.

Finally, to diagnose NANB hepatitis, the committee decided to adopt the widely accepted criterion of a rise in aminotransferase to more than 2·5 times the upper normal limit on two occasions 15 days apart, between 14 and 180 days after transfusion. This criterion for diagnosing NANB hepatitis is less sensitive than others (ie, a single 4-fold increase above the upper normal limit) but is more specific, since it helps to eliminate transient fluctuations of aminotransferases due to factors other than viral hepatitis (ie, drugs, alcohol, strenuous physical exercise).

STUDIES OF THE CLINICAL SAFETY OF FACTOR VIII CONCENTRATES

The reliability of a safety study's estimation of hepatitis risk after treated concentrates depends greatly on the number of patients enrolled. Obviously, even studies in which no hepatitis occurs do not exclude the possibility that those concentrates might transmit hepatitis. The one-sided 95% confidence intervals around the true risk of hepatitis can be calculated simply by the "rule of three"[5]—dividing three by the number of patients who completed the recommended protocol and follow-up. In a study of 10 patients with no cases of hepatitis, the interval around the true risk of hepatitis would vary from 0% to 30%; for 15 patients, to 20%; for 20 patients, to 15%; for 25 patients, to 12%; for 30 patients, to 10%; and so on. The "acceptable" upper limit of the hepatitis risk is an arbitrary decision. Since increasing the number of these rare patients from 20 to 25 only slightly reduces the hepatitis risk (from 15% to 12%) studies should include 20 patients but need not include more, and we have set 15% as an acceptable risk. On this basis, the results of safety studies (published in full or as an abstract) can be divided into cohorts depending on the number of patients included. For the reasons mentioned above, only studies including previously untreated haemophilic patients are considered in this analysis.

So far, only two studies have included more than 20 patients (table II). The only concentrate that produced no recognised case of hepatitis among 26 patients treated with 32 different lots had been pasteurised at 60°C for 10 h; the risk of hepatitis was 0–11%.[6] Note, however, that these risk figures apply only to NANB hepatitis, because 16 patients had been vaccinated, leaving only 10 who were exposed to the risk of hepatitis B; the risk for this infection was therefore as high as 30%. 4 cases of hepatitis B occurred in unvaccinated patients after treatment with a concentrate heated under hot vapour pressure.[7] Since, however, there was no NANB hepatitis among the remaining 24 patients, the risk of this infection from this concentrate was 12%.

TABLE II—PROSPECTIVE SAFETY STUDIES OF AT LEAST 20 PATIENTS

Patients studied (ref)	Manufacturer	Inactivation procedure	No with hepatitis		Hepatitis risk* (95% CI)	Anti-HIV sero-conversion
			B	NANB		
26[6]	Behring	Pasteurisation (60°C, 10 h)	0/10	0/26	0–11%	0/26
28[7]	Immuno	Hot vapour (60°C, 10 h, 1180 mbar)	4/14	0/24	..	0/28

*Values given only for concentrate giving no cases of hepatitis.

TABLE III—PROSPECTIVE SAFETY STUDIES OF 10–20 PATIENTS

Patients studied	Manufacturer	Inactivation procedure	No with hepatitis		Hepatitis risk* (95% CI)	Anti-HIV sero-conversion
			B	NANB		
13[4]	Hyland	Dry heat (60°C, 72 h)	0/12	11/13	..	0/13
16[8]	NHS	Dry heat (80°C, 72 h)	..	0/16	0–19%	0/16
11[9]	Alpha	Heat + heptane (60°C, 20 h)	0/10	3/11	..	0/18
13[12]	Armour	Immuno-adsorption + dry heat (60°C, 30 h)	..	0/13	0–24%	0/13
11[11]	Hyland	Immuno-adsorption + solvent detergent	..	0/11	0–27%	0/11
11[13]	NY Blood Center	Solvent detergent	..	0/12	0–15%	0/12
10[14]	Biotransfusion	Solvent detergent	..	0/10	0–30%	0/10

*Values given only for concentrates giving no cases of hepatitis.

In each remaining study, fewer than 20 patients were enrolled, giving a risk of hepatitis of 19% or more even in studies recording no cases of hepatitis (table III). A lyophilised concentrate heated at 60°C for 72 h was highly infectious; NANB hepatitis developed in 11 of 13 patients.[4] In contrast, a lyophilised concentrate heated at a higher temperature (80°C) produced no post-transfusion hepatitis in 16 haemophiliacs (risk = 19%).[8] We must emphasise, however, that this study[8] did not follow one important recommendation of the committee protocol: for the great majority of patients aminotransferases were tested less frequently than monthly. The safety of a concentrate heated in a suspension containing n-heptane has been evaluated in two independent studies: cases of NANB hepatitis occurred in both groups of patients (3 of 11 in the British study[9] and 2 of 7 in the international study).[10] No hepatitis developed in patients treated with two factor VIII concentrates purified by immunoaffinity chromatography on monoclonal antibodies.[11,12] Although a total of more than 20 patients were studied (13 in one and 11 in the other), we believe that combination of the results for the two studies is not justified, because there are important differences in the fractionation and inactivation processes used to prepare the two monoclonal antibody concentrates. Thus, although the safety of both concentrates looks promising, a larger number of patients must be enrolled in each of the studies still in progress before safety can be established. Finally, no cases of hepatitis developed in two separate studies, evaluating 12 and 10 patients infused with two different brands of factor VIII concentrates treated with solvent and detergent.[13,14] Since one of these studies was published only in abstract, we do not know some important details—eg, whether patients were enrolled and followed up according to the committee's criteria. When more details become available, combination of the results will perhaps be justifiable, giving more statistical power to the safety of this inactivation method.

CLINICAL SAFETY STUDIES OF FACTOR IX CONCENTRATES

There have been fewer studies of the safety of factor IX concentrates than of factor VIII concentrates, probably because of the smaller number of factor-IX-deficient patients available for study. None of 5 non-haemophilic volunteers infused with single doses of factor IX concentrate treated with beta-propiolactone and ultraviolet irradiation showed clinical or laboratory signs of hepatitis during follow-up of 6 months.[15] After that, 6 previously untreated patients with haemophilia B were treated with the same concentrate, and there were no cases of hepatitis.[16] A small study with 6 haemophiliac patients showed no transmission of hepatitis by a factor IX concentrate prepared by hydrophobic interaction chromatography on octano-hydrazide-agarose added to the regular fractionation process.[17] Later, however, hepatitis and even seroconversion to HIV occurred in 4 additional patients treated with this concentrate (I. M. Nilsson, M. Morfini, unpublished); this finding emphasises the risk involved in assuming safety from studies of inadequate numbers of patients. Since then an additional viral inactivation process (heating in the lyophilised state) has been added to increase

the safety of this concentrate. There have been no cases of hepatitis in 6 patients treated with a pasteurised concentrate,[18] whereas 1 case of hepatitis occurred in 5 patients treated with a factor IX concentrate heated in the presence of n-heptane.[10]

CONCLUSIONS

To date published clinical studies indicate that viral inactivation by pasteurisation and, to a lesser extent, by vapour heating definitely improve the safety from hepatitis of factor VIII concentrates over that of unheated concentrates and concentrates heated in the lyophilised state at temperatures lower than 80°C. Other methods (such as solvent-detergent, super-heating at 80°C, and monoclonal antibody techniques) might prove to be of equivalent safety, but the small numbers studied and the lack of details allow us, at the moment, only to say "presumed innocent". Despite the limited number of studies available, it appears that factor IX concentrates are also becoming safer, because the viral inactivation procedures used for them can be more vigorous than those used for the more labile clotting factor VIII.

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International Physicians for the Prevention of Nuclear War

NUCLEAR WINTER

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DESPITE several years of study and debate, the atmospheric and climatic effects of an unlimited nuclear war remain a matter of controversy. Particularly debatable is the theory of a nuclear winter postulated by some scientists who believe that, after a nuclear war, exploded debris in the atmosphere would cause a dramatic drop in the earth's surface temperature, with devastating biological consequences. This issue has been hotly debated in both scientific and political literature.

THE TTAPS STUDY

Shortly after Crutzen and Birks[1] first advanced the theory, a group of atmospheric scientists, in association with the astronomer Carl Saga, published, in 1983 the TTAPS study[2] (an acronym formed by the initials of its authors). This study, which gave widespread recognition and credibility to the concept of nuclear winter, is based on projections indicating that, in the event of a significant ground-burst explosion, millions of tons of dust and soot would spew into the earth's atmosphere. The dust particles would absorb much of the sun's heat and energy and the heated dust particles would rise in the earth's atmosphere. A cooling of the earth's surface would create a large temperature shift from the lower to the higher atmospheres. Ordinarily, rain would clear the atmosphere of smoke and soot, but this heated mass would rise above the rain clouds and persist for longer than usual. The TTAPS estimates indicate that the earth's surface would be in near total darkness after a large nuclear conflict. This blackout would inhibit photosynthesis and disrupt the food chain.

Using a computer model to estimate the effects of a 5000-megaton exchange, multiple scenarios were applied to estimate the amount of dust and smoke generated and how much sunlight would be absorbed. Temperature changes on the earth's surface, wind factors, and their effects on the spread of smoke and soot were also studied. The TTAPS study concluded that the earth would be plunged into near total darkness within one week after a large nuclear conflict. Subfreezing temperatures, possibly as low as −25°C, have been forecast. Lakes and rivers would freeze, killing plant life and most farm animals. Consequently, human survivors would face starvation. Because oceans would not freeze, the coastal land masses would be protected from the dire cooling effects seen inland. Widespread devastation and death would spread rapidly, even to non-combatant nations. Tropical areas would be devastated because they are more sensitive to even minor changes in temperatures. It is generally agreed that the ozone layer would be signfiicantly depleted as a direct result of the release of oxides of nitrogen into the atmosphere by large-scale nuclear explosions. Initially, dust particles injected into the earth's atmosphere would absorb ultraviolet rays, but, after the dust cleared, UVB doses 1·6 times greater than normal would be transmitted to the earth's surface, possibly resulting in a large increase in cancer among survivors of a nuclear war.