part of another study (unpublished because the original objectives were not achieved). What impressed me most at the time was that pharmacologically massive doses of atropine sulfate do not act at all like one would conclude from standard textbooks. In this context the footnoted editorial comment seems quite inappropriate.

Why there should be such a remarkable change in the toxicology of atropine at these levels (15+ mg) is something I do not understand, but I do know that over this extensive series of cases there were no deaths due to therapy and all side effects were easily managed with simple procedures.

Also, in contrast to the Polish work, there was no effort to terminate coma by the use of antidotes. Arousal was spontaneous in 8 to 12 hours.

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Hepatitis and Clotting-Factor Concentrates

To the Editor.—Recent reports[1-3] have aroused alarm about the danger of hepatitis after infusion of clotting-factor concentrates prepared from the pooled plasma of many donors. We have, therefore, reviewed the incidence of clinical hepatitis among 482 hemophiliacs treated here in the last ten years (Table 1). The peak incidence occurred in 1968 in hemophilia A and in 1971 in hemophilia B. Concentrate became the predominant mode of therapy in hemophilia A in late 1967 and in hemophilia B in mid-1969.

A total of 343 patients with hemophilia have been observed here during the six months following their first infusion of concentrate. The incidence of hepatitis in that period is listed in Table 2. Clinical hepatitis was rare in babies. In older patients, hepatitis frequently followed the first exposure to concentrate if prior blood and plasma infusions were few. In patients with many previous transfusions, the incidence of hepatitis was much lower.

Table 1.—Incidence of Hepatitis Among Patients With Hemophilia

Year	Ratio of Cases of Hepatitis to No. of Patients Treated: Hemophilia A	Hemophilia B	Other
1962	0/137	0/31	0/1
1963	0/137	0/27	0/2
1964	2/130	0/24	0/2
1965	3/138	0/33	0/2
1966	5/151	0/31	1/4
1967	2/161	0/32	0/4
1968	8/175	0/45	0/7
1969	4/220	0/52	0/10
1970	0/216	0/58	0/17
1971	1/237	3/66	1/12

Table 2.—Hepatitis Within Six Months of First Infusion of Concentrate*

	No. of Prior Infusions†: <10		>10	
	Age <4 yr	Age ≥4 yr	Age <4 yr	Age ≥4 yr
Factor IX concentrate	0/6	3/10 (30%)	0/2	0/47
Factor VIII concentrate	1/24	4/13 (31%)	0/4	4/237 (2%)

*In a ratio of cases of hepatitis to the number of patients.
†Blood or plasma.

Three patients developed hepatitis after the first dose of factor IX concentrate; two had never had a previous blood-product infusion and one had had seven plasma infusions. None received any other type of blood product after the initial dose of concentrate.

Nine patients developed hepatitis within six months of the first dose of factor VIII concentrate. Six of these patients received only concentrate in the six months before hepatitis; three patients had between one and ten previous blood or plasma infusions, and three had more infusions. Three patients received a dose of cryoprecipitate or plasma in addition to their first dose of concentrate in the six months prior to hepatitis.

Sixteen of the 29 patients who had hepatitis in the ten-year period had either never received concentrate or had received it more than six months before the onset of hepatitis. Thirteen of these patients had had more than 50 infusions of blood products before the six-month period preceding hepatitis. Extensive blood-product exposure evidently does not guarantee immunity.

We conclude that older children and adults who have had little exposure to blood products are at a high risk of developing clinical hepatitis after introduction of clotting-factor concentrates. In such patients, especially those with mild hemophilia, single-donor products are preferable. On the other hand, patients with severe hemophilia who have had many blood and plasma infusions have no increased risk of hepatitis if concentrates are introduced. Concentrates have greatly improved the effectiveness and convenience of management of severe hemophilia and should not be denied to appropriate patients.

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Incontinence With Doxepin

To the Editor.—Two recent notices in the THE JOURNAL report urinary incontinence with thioridazine. I would like to add a somewhat similar effect with doxepin hydrochloride (Sinequan).

The patient, an elderly white woman, was hospitalized about two years ago for a cerebrovascular accident which caused right-sided hemiplegia with aphasia. An indwelling catheter was installed because of incontinence. She became depressed and was given doxepin hydrochloride, with good results.

In a nursing home, I continued the doxepin hydrochloride, 25 mg four times a day since she was doing well emotionally. Because of recurrent urinary infection, the indwelling catheter was removed, with subsequent fair urinary control, but she had to void about every hour, which complicated the nursing care, especially at night. Frequent urinary infection continued. Her condition continued unchanged for about a year, at which time an itching rash appeared over the thighs and buttocks and did not respond to soothing lotions. As "rash" is listed as an occasional reaction to doxepin, the drug was discontinued, and the rash cleared in a few days. However, we were surprised to find that the frequency of urination also disappeared, and within about two days she was voiding naturally about every four hours. She has had no recurrence of frequency of urination or urinary infection—possibly symptoms of urinary retention—and it is now almost ten months since therapy with doxepin hydrochloride was discontinued.

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