

## REACTIONS IN MAN FROM INFUSION WITH DEXTRAN\* †

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DEXTRAN, a polysaccharide produced by the fermentation of sucrose by the microorganism, *Leuconostoc mesenteroides*, has been used both in Sweden (1,2) and in Britain (3) as a plasma volume expander. It is now under investigation in this country.

According to various reports (1-11, 17) dextran, as commercially produced by Pharmacia, Ltd. of Sweden (macrodex®), is effective clinically in combating operative and nonoperative shock of moderate severity. Thorsen (10) reported an incidence of reactions of an allergic type in man of 0.4 per cent in a questionnaire survey in the Scandinavian countries. Over 25,000 patients who were given infusions were surveyed. Some investigators in the United States also have reported low reaction rates (12, 13) and others have reported much higher rates for this material (14, 15, 16).

Dextran was given as an infusion to a number of military and veteran patient-volunteers in the course of the investigation of plasma volume expanders by the Surgical Research Unit, Brooke Army Hospital, Fort Sam Houston, Texas.

A careful history of allergies, a physical examination and laboratory examinations preceded the test. A total of 109 volunteers were infused with Swedish "macrodex®," 9 volunteers with dextran made in England and called "dextran-saline," and 97 volunteers with dextran manufactured in the United States by the Commercial Solvents Corporation. All equipment used was sterilized and tested for freedom from pyrogens. The infusion tubing was of the "throw away" variety and used only once. Patients were given the infusions both in the operating room under anesthesia and in the unanesthetized state. The speed of infusion varied from ten minutes to sixty-five minutes. The amount infused was usually 500 cc., but several patients were given

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TABLE 1

Type of Dextran	State of Subject	Lot Number	Number of Patients	Reactions		Type of Reaction
				Number	Per cent	
Swedish (Pharmacia, I.t.d.)	Anesthetized	Y 5328 A	45	4	8.8	1 moderate 3 mild
	Unanesthetized	Y 5328 A	11	6	54.5	2 severe 3 moderate 1 mild
		Y 5056 A	12	4	33.3	4 severe
		Y 5740 A	25	13	52.0	6 severe 4 moderate 3 mild
		Y 5402 A	11	8	72.7	3 severe 2 moderate 3 mild
		Z 6932 A	5	2	40.0	2 moderate
	Total unanesthetized		64	33	51.5	
Total Swedish			109	37	33.9	

1,000 cc. The incidence and character of allergic reactions was noted by a team of observers.

Observed symptoms and signs were: headache, chills, flushing, urticaria, angioneurotic edema, wheezing or choking or both, abdominal pain, nausea or vomiting or both, cramps, chest pain, vasomotor

TABLE 2

Type of Dextran	State of Subject	Lot Number	Number Reactions	Number Patients	Per Cent Reactions	Type of Reaction
American (Commercial Solvents Corp.)	Anesthetized	84512 A	0	5	0	
		84519 A	0	1	0	
		84684 A	2	21	9.52	1 severe 1 mild
	Unanesthetized	84512 A	1	5	20.0	1 mild
		84519 A	0	11	0	
		84681 A	1	14	7.14	1 mild
		84684 A	4	32	12.5	1 moderate 3 mild
		84686 A	0	8	0	
	Total unanesthetized		6	70	8.56	
	Total American			8	97	8.24

TABLE 3

Type of Dextran	State of Subject	Lot Number	Number Patients	Reactions		Type of Reaction
				Number	Per cent	
English (East Anglia Chem. Company)	Unanesthe- tized	50074	9	4	44.4	1 severe 1 moderate 2 mild

rhinitis, hypotension or syncope on standing, delayed pain in the joints and swelling of the extremities.

Reactions were graded as mild, moderate or severe, depending on the complexity, severity and duration of the phenomena.

The findings with dextran from three sources are shown in tables 1, 2 and 3.

The following case reports are representative examples of reactions.

#### *Severe Reaction*

*Case 1.*—(Fig. 1.) A man who was convalescing from an appendectomy performed two days previously had a history of allergy to dust, animals, ragweed, goldenrod and hay. On October 18 he was



FIG. 1. Case 1.

given 500 cc. of Swedish "macrodex<sup>®</sup>" in twenty minutes; he had not been given premedicants or anesthetics. Ten minutes after administration was started the patient's face became red, his breath became "catchy" and his nose ran profusely. Fifteen minutes after administration, urticaria of both arms, chest and abdomen, and edema of the upper lids were noted. He was unable to talk well because of laryngeal edema, and he coughed severely (dangerous because of the appendectomy). Twenty minutes after the drug was administered, helium and oxygen inhalation was given to relieve the dyspnea. Benadryl, 30 mg., was given intravenously. The itching stopped immediately but the patient's face remained red and he continued to have difficulty in breathing. Within two hours the urticaria had receded, but his feet began to swell. On October 19, the feet were swollen slightly and a mild degree of edema of the eyes was still present.

The laboratory findings were as follows: specific gravity of the urine could not be determined before infusion because of insufficient sample; one hour after infusion it was 1.056 and twenty-four hours after infusion, 1.008. One hour after infusion the urine contained sugar, 4 plus; it was negative for sugar twenty-four hours after infusion. The urine contained albumin, 1 plus, one hour after infusion and a trace twenty-four hours later.

*Case 2.*—This patient was convalescing from pilonidal sinus infection. There was no history of allergic reactions. On October 17, 1,000 cc. of macrodex<sup>®</sup> was given in forty-seven minutes; the patient had not been given premedicants or anesthetic drugs. Twenty-four minutes after administration was begun, the patient's face was flushed and his head felt heavy. Twenty-nine minutes after beginning administration, his lips began to swell. Forty-four minutes after the infusion was begun, urticaria of the back was noted; the chest felt tight and the patient was coughing; dizziness was noted. The blood pressure readings and pulse rate, taken after the patient was asked to stand by the side of the bed, were as follows: standing, 62 mm. systolic and 50 mm. diastolic, pulse 88; sitting, 56 mm. systolic and 50 mm. diastolic, pulse 100; after lying down for one minute, 104 mm. systolic and 70 mm. diastolic, pulse 76. Following this test the patient became nauseated. Ninety-nine minutes after infusion was begun the blood pressure when the patient was standing was still 60 mm. systolic and 50 mm. diastolic; 119 minutes after the infusion was started, the blood pressure was normal and there was no vasomotor instability. Ten hours later swelling of the hands and pain in the joints of the hands were noted.

October 19 operation was performed under spinal anesthesia. Swelling and pain in the hands were present but improved.

The laboratory findings were as follows: The urine contained a trace of sugar one hour after infusion; twenty-four hours later it contained sugar, 4 plus, and albumin, 2 plus.

*Case 3.*—(Fig. 2.) A woman who had a history of allergic reactions to ragweed and dust in the autumn and spring of the year had a biopsy of the breast performed under pentothal-nitrous oxide-oxygen anesthesia. An infusion of 500 cc. of dextran ¶ was given in twenty minutes; the patient had been given both premedicants and anesthetic drugs. Forty-five minutes after the infusion was started and twenty-five minutes after its completion, flushing of the face and neck and swelling of the right eyelid and conjunctiva were noted by the anesthetist while the patient was still anesthetized. As she recovered from the anesthetic



FIG. 2. Case 3.

she complained of persistent cough and nasal congestion and obstruction. A skin rash appeared and increased so that it covered the entire neck and anterior portion of the chest. At that time, a skin wheal with 0.1 cc. of the remaining dextran revealed no local reaction. Three hours and forty-five minutes after the infusion was started, 25 mg. of benadryl was administered intravenously, which gave some relief of the nasal congestion and persistent cough. Within forty-eight hours of the infusion, edema of the eyelid had disappeared.

Six days later, the patient consented to another infusion of dextran of the same lot number. Within fifteen minutes, after 200 cc. had been

¶ Commercial Solvents Corporation (American).

given, she complained of nasal congestion, a choking sensation in the chest and a rash over the anterior portion of the neck and chest wall. The infusion was stopped. Sixty minutes after the infusion was begun, the rash had completely disappeared and puffiness and itching of the eyes were relieved without treatment.

Twenty-four hours after this second infusion the remaining 300 cc. from the same bottle was given to another patient who was under spinal anesthesia for stripping of varicose veins. No reaction occurred.

#### *Moderate Reaction*

*Case 4.*—A man who was convalescing from fistulectomy performed for anal fistula had no history of allergic manifestations. An infusion of Swedish "macrodex<sup>®</sup>" was begun; he had not been given premedicants or anesthetic drugs. Thirty minutes later, when only 250 cc. had been administered, pruritus and urticaria were noted on the arm on the side in which the infusion was being given. The pruritus and urticaria spread to the other arm and over the entire body. The arms and ears became edematous. Within two hours all signs disappeared without medication and the patient became asymptomatic.

#### *Mild Reaction*

*Case 5.*—A man who was convalescing from a gunshot wound of the right tibia had no history of allergic manifestations. An infusion of 500 cc. of Swedish "macrodex<sup>®</sup>" was given in nineteen minutes; the patient was not premedicated or anesthetized. No effects were noted immediately, but mild swelling of both feet began in three hours and became more severe nineteen hours after the infusion. (The patient was seen by Dr. Gunnar Thorsen, of Sweden, who was visting for the purpose of observing reactions.) The swelling persisted for two days and then gradually disappeared.

*Case 6.*—A man who was convalescing from a gunshot wound of the right arm had no history of allergic reactions. An infusion of 540 cc. of English dextran was given in seventy-nine minutes; the patient was not premedicated or anesthetized. Thirty-nine minutes after the infusion was started, generalized itching of the trunk and arms and hives at the site of the injection were noted. Fifty-four minutes after the infusion was begun, hives of the left shoulder and abdomen and itching of the pubic area and left thigh were noted and the patient's face was flushed. Ninety-nine minutes after the infusion was begun itching of the right leg and hives of both thighs, the lower legs and buttocks were noted. Four hours later all signs and symptoms had disappeared spontaneously.

#### COMMENT

The high incidence of reactions in unanesthetized individuals (51.5 per cent) in this series attending infusion of Swedish dextran is in agreement with the findings of Turner *et al.* (16) who noted that 10 of

30 subjects had reactions after administration of a similar Swedish product. More recent reports (17) indicate that in Sweden the incidence of severe reactions is 3 per cent.

The number of reactions in unanesthetized individuals with one batch of British dextran was about the same as with the Swedish product.

The Commercial Solvents Corporation product in a comparable series gave a reaction rate of 8.2 per cent. Of the reactions in 97 volunteers, 2 occurred in the same person. The first reaction occurred in this subject while she was under anesthesia. A second infusion was given with the same lot of dextran (with no previous medication or anesthesia) and she reacted once again. The remainder of the dextran solution causing the second reaction was given to another patient under spinal anesthesia without untoward effects.

In severe and persisting reactions, our impression was that symptoms were ameliorated by antihistaminics administered intravenously. However, the course of the reactions did not appear to be consistently affected.

Mild, untreated reactions largely subsided in from twelve to twenty-four hours. Pre-infusion medication with antihistaminics, morphine or ACTH did not appear to limit the incidence or severity of reactions.

#### SUMMARY

A high incidence of reactions of an allergic nature in unanesthetized or anesthetized patients followed infusion of Swedish dextran (macro-dex<sup>®</sup>) and British dextran-saline. American dextran (Commercial Solvents Corp.) produced fewer reactions.

The incidence of reactions was lower in anesthetized patients than in unanesthetized patients even though the anesthesia used was spinal and the patients were awake.

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Course No.	Title	Instructor
M35-T35	"The Academic and Clinical Aspects of Shock and Its Treatment"	Donald H. Hale, M.D.
M57	"Management of Chronic Pain"	Frederick Haugen, M.D.
M66-T66	"Anesthetic Management for Intracardiac Surgery"	Kenneth Keown, M.D.
M17-T16	"Pediatric Anesthesia"	M. Digby Leigh, M.D.
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T31	"Transsacral Anesthesia"	John S. Lundy, M.D.
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T42	"Pharmacology of Local Anesthetic Agents"	Elton L. McCawley, M.D.
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T13	"Carbon Dioxide in Anesthesia"	Lucien E. Morris, M.D.
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T54	"Vasopressor Agents"	Nevin Rupp, M.D.
T24	"Public Relations and the Anesthesiologist"	B. B. Sankey, M.D.
T34	"Water and Electrolyte Balance in Pediatric Anesthesia"	Robert M. Smith, M.D.
M34	"Postanesthetic Observation Room"	Scott M. Smith, M.D.
M27	"Hypotensive Anesthesia"	Ranald J. M. Steven, M.D.
M46-T46	"Plasma Substitutes"	Lt. Col. Arthur Tarrow
M25-T25	"Explosion Hazards and Their Control"	George J. Thomas, M.D.
M45-T45	"Continuous Spinal Anesthesia"	Edward B. Tuohy, M.D.
T61	"Anesthesiologist in Care of Tetanus and Polio Cases"	F. H. Van Bergen, M.D.
M22-T22	"Physiology of Circulation"	Robert W. Virtue, M.D.
M26-T26	"Anesthesia for Thoracic Surgery"	P. P. Volpitto, M.D.
M14-T14	"Cyclopropane Anesthesia"	Clayton Wangeman, M.D.
M32-T32	"Physiology of Respiration"	Willis G. Watrous, M.D.
M44-T44	"Continuous Caudal and Peridural Anesthesia"	C. Wycoff, M.D.