Effects of Intravenous Infusion of Experimental "Instant" Fat Emulsion Into Volunteer Subjects.* (22183)

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At the first *ad hoc* conference held by the National Research Council dealing with intravenous fat emulsions the stability and toxicity of such newly developed preparations were discussed(1). Except for variations in the type of fat (coconut oil, corn oil, sesame oil, etc.) and the character of the emulsifier ionic or nonionic, all investigators employed practically the same methods of preparation (2,3). The accepted procedure involved a high speed premix of constituents oil, emulsifier and water to form a crude blend after which followed mechanical pressure homogenization and finally sterilization by autoclaving. While these freshly prepared emulsions were well tolerated intravenously, administration of emulsions aged more than a month was correlated with a significant increase in reactions believed to be due to lipolysis, hydrolytic rancidity or physical alterations in particle size(1).

The present investigation was undertaken with a new type of intravenous fat emulsion prepared by means of special emulsifiers which make possible "instant" or spontaneous emulsification of oil and water mixtures for immediate intravenous administration. By this method the effects of aging on the emulsion with resultant toxic degradation products seemingly would be obviated. This study is concerned with the use of one such "instant" fat emulsion tested intravenously in experimental animals and in volunteer human subjects.

Method of study. The emulsion was prepared as follows. Fifteen g of sterile distilled whole coconut oil and 1 g of special emulsifier were placed in small intravenous bottles (250 ml). The emulsifier known as Drew #535 consisted of glycerol and polyglycerols partially esterified with mixed hydrogenated and unhydrogenated soy bean fatty acids. After addition of oil and emulsifier the bottles were capped with transfusion type rubber stoppers and autoclaved at 20 lb pressure for 35 minutes. After sterilization, these bottles were stored at room temperature. Before each infusion a bottle of the oil mixture was warmed and 10 ml of absolute alcohol was added under sterile conditions through the inflow hole. An almost clear solution formed upon mixing. Finally 125 ml of sterile 5% glucose in water was added to yield, after moderate shaking, an opaque emulsion. The latter was administered promptly by venoclysis through transfusion equipment containing a strainer-filter. The "instant" emulsion appeared uniformly white, flowed freely and remained stable for almost 5 hours. Occasional shaking prevented any tendency for separation. Caloric value approximated 230 calories for 150 ml. Microscopic examination with ocular micrometer under dark field illumination revealed active Brownian movement with 70% of the particles about 1 μ and the remainder up to 5 μ in size. The pH of emulsion was 7.35, refractive index 1.345, and dispersion a narrow spectrum band. The "instant" fat emulsion was first administered into a group of 10 dogs. Each animal received daily an infusion of 75 ml of the emulsion administered usually at the rate of 40 drops (2 ml) per minute. Observations were limited to temperature changes recorded at hourly intervals and to such visible reactions as vomiting, chills, etc. Following the animal studies, the same kind of emulsion was tested in a group of volunteer hospital patients. With each subject in the postabsorptive state, 150 ml of the emulsion was infused 20 to 30 drops (1 ml to 1.5 ml) per minute. The temperature, pulse, respirations and blood pressure were taken at hourly

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TABLE I. Reactions of Dogs and Human Subjects to Intravenous Infusion of "Instant" Fat Emulsion. 15 infusions in 10 dogs; 148 infusions in 46 humans.

Reactions	Animal	Humans
	%	
Minimum temp. 0-1°F	43	63
Moderate " 1-2°F	33	32
Maximum " 2°F	20	5
Vomiting	26	8
Chills	13	6
Diarrhea	20	2
Excessive salivation	13	—
Headache	—	9
Dyspnea	7	2
Sweating	—	6
Back pain	—	10
Chest pain	—	1

intervals for the first 12 postinfusion hours of a 24-hour study. Complete blood counts, sedimentation rates, hematocrits and standard urinalyses were performed by the usual technics at regular intervals. In several subjects lipid chemistry of blood was determined quantitatively for rate of clearance of fat from the circulation(4).

Results. Five dogs received single infusions of 50-75 ml; while 5 other dogs received 100 ml emulsion divided into 2 daily doses. The results have been recorded in Table I.

A total of 148 intravenous infusions of the fat emulsions were administered into human subjects. In this group of 46 volunteers, 28 received single infusions while 3 or more infusions were given to other 18 volunteers. The temperature changes associated with these injections and other reactions have also been incorporated in Table I.

Temperature elevations following animal and human infusions were always of a temporary nature and subsided rapidly to preinfusion level. Where multi infusions were given, temperature response varied from maximum elevation to moderate or minimal reaction with each infusion test. Constitutional reactions, when considered singly, totalled 44% but actually averaged 28% because in many cases these untoward effects were multiple in character; *viz.* vomiting, chills, etc. Changes in blood pressure during infusion and in the postinfusion phase were variable and showed no significant trend. Red blood cell counts, hematocrit cell volumes and sedimentation rates did not deviate markedly from normal. In 40% of white blood counts, the first postinfusion blood sample indicated a leukocytosis which averaged 19000 white blood cells after which there was a rapid return to preinfusion level which averaged 10200 white blood cells. Chylomicron counts increased markedly during infusion and then declined rapidly, usually within 4-5 hours after completion of infusion in a manner similar to the chylomicron pattern observed with other fat emulsions. Total blood lipids and partition fractions showed no characteristic trends (Table II). Postinfusion urine samples failed to reveal abnormal excretion of fat or other pathologic changes referable to the use of the emulsion.

Discussion. Considerable data have been reported on effects of "standard" type of fat emulsion but there has been no report with the present preparation. Our data have shown that infusions of the "standard" 10% fat emulsion in units of 1 liter were well tolerated in 77% of recipients when adminis-

TABLE II. Laboratory Data Pertaining to the Single Infusion of 125 ml of 15% "Instant" Fat Emulsion into Subject, A.S.

Infusion	Temp., °F	Blood pressure, mm Hg	Pulse rate, min.	R.B.C. count (million)	W.B.C. count (thous.)	Hematocrit, %	Sedimentation time, mm/hr	Chylomicron count	Total lipids, g/%	Phospholipids, mg/%	Total cholesterol, mg/%	Cholesterol esters, mg/%	Neutral fat, mg/%
Pre	98.8	140/88	86	4.26	9.8	46	28	4	.63	160	123	83	84
End of	99.0	160/88	98	4.24	11.0	40	36	108	.88	180	150	114	273
2 hr	102.8	160/90	110	4.41	11.2	40	36	86	.83	190	152	106	211
5 "	101.2	148/90	100	4.38	10.6	44	30	52	.75	190	157	119	123
7 "	100.6	145/90	94	4.29	10.6	44	34	58	.71	173	144	105	120
18 "	99.0	150/88	94	4.32	10.8	46	34	20	.79	165	152	106	196
24 "	99.0	154/80	90	4.38	10.2	48	20	6	.48	170	140	100	80

tered as a freshly made preparation but toleration declined to 69% when emulsions were 5 to 10 weeks old. A significant rise in concentration of free fatty acids and unstable peroxides or increase in size of fat particles up to 25 μ has been described as characteristic of aging emulsion. Accumulation of any of the latter products might be related to toxicity and thermogenicity of the emulsion when used for intravenous alimentation. These reactions may be compared to toxic effects produced experimentally by injection of free short chain fatty acids(5) or to pulmonary and pyrogenic effects associated with trapping of particulate matter in the lungs(6). Stability of an artificial emulsion should be considered to be a function of time during which physical alterations in size of fat particles and chemical interactions between water and fat may occur. A technic for rapid emulsification of oil and water mixtures with elimination of the factor of aging would therefore be warranted. Although the present "instant" fat emulsion cannot now be considered to be a suitable preparation for general clinical use, investigations along the lines described in this report have been continued.

Summary. An "instant" fat emulsion prepared by manual mixing of oil, emulsifier, alcohol and water was developed and tested. This type of emulsion obviated high pressure homogenization and was freshly prepared for each infusion. A total of 63% of the infusions were fairly well tolerated while in the other 37% reactions were observed.

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Modification of Tumor-Response to Rous Sarcoma Virus (RSV) by Hydrocortisone.* (22184)

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It is well known(1) that cortisone and hydrocortisone usually depress resistance of laboratory animals to viral infection and that effective doses of these steroids are frequently associated with evidence of increased multiplication of the virus. On the other hand, cortisone and several related steroids beneficially affect certain transplanted lymphosarcomas and leukemias in mice(2). However, rabbits injected with cortisone developed much larger tumors upon inoculation with rabbit fibroma virus although tumor size was not appreciably affected if injections of cortisone were delayed until appearance of the tumor(3). Data presented here show that (a) when Rous sarcoma virus (RSV) was inoculated into chicks pretreated with large doses of hydrocortisone, tumors appeared later and were greatly altered in appearance; (b) when hydrocortisone was discontinued the altered tumors promptly reverted to typical invasive type; and (c) when lower doses of hydrocortisone were employed or when injections of hydrocortisone were delayed until 2 days after in-

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