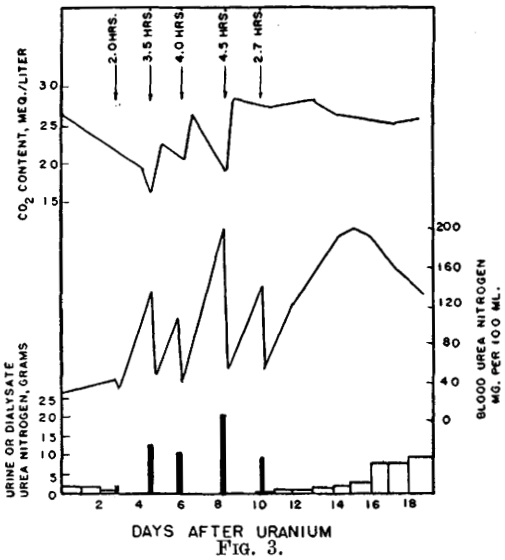

FIG. 3.

The effect of treatment with the artificial kidney on the blood urea nitrogen and the CO_2 content of plasma of a dog given a dose of uranium nitrate (5 mg per kg) which is usually lethal. The arrows represent dialyses of the durations indicated. Note the restoration of the blood urea nitrogen to almost normal levels and the elevation of the CO_2 content towards normal. The solid black bars at the bottom of the chart represent the urea nitrogen removed from the animal by the artificial kidney. This animal recovered.

thal.(20,21) The data on one of these animals are presented in Fig. 3. Three days after the injection of the uranium, the animal became anuric. At this time treatment was instituted and a total of 5 dialyses at 1-2 day intervals were successfully accomplished. The blood urea nitrogen was restored to nearly normal levels by each dialysis. A total of 57 g of urea nitrogen were recovered in the dialyzing solution. The ability of the artificial kidney to regulate acid-base balance is illustrated by the fact that the CO_2 content of the plasma which was decreased as a result of the inadequate renal function was repeatedly elevated toward normal levels. Chloride, sodium, and potassium remained within normal limits. Following the fifth dialysis, 10 days after the dose of uranium, the dog began to excrete urine and survived without further treatment.

Summary. An improved type of continuous dialyzer specifically designed for use as an artificial kidney has been described. A thin film of blood is made to flow between 2 sheets of cellophane supported between rubber pads which are grooved to allow passage of a dialyzing solution. Details of its operation are given and its application in the treatment of acute renal insufficiency in dogs is described.

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Intravenous Infusions of Concentrated Combined Fat Emulsions into Human Subjects.* (17492)

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The successful development of a method for the preparation of a 10% combined fat emulsion and the results after clinical investigation of this emulsion as reported by us warranted further studies in the preparation and administration of more concentrated fat emulsions.(1) The advantages to be derived from the more concentrated intravenous fat preparations, increased caloric potential in reduced volume, would constitute a further advance in the field of parenteral fat nutrition. The present report is devoted to the method of preparation of two combined fat emulsions with fat in 15 and 20% concentrations and a study of the effect of their intravenous infusion on human subjects.

Preparation of Concentrated Fat Emulsions.

* Aided by a grant from the Ben Lewis Fund in Experimental Surgery.

1. Shafiroff, B. G. P., Mulholland, J. H., Roth, E., and Baron, H. C., PROC. SOC. EXP. BIOL. AND MED., 1949, **v70, 343.**

TABLE I.
Composition of 15% and 20% Concentrated Combined Fat Emulsions.

Conc. fat emulsion	% composition				G fat per liter	Calories per liter
	Coconut oil	Gelatin	Glucose	Amigen		
15%	15.5	2.20	5.4	3.6	155.0	1720
20%	20.2	2.66	5.5	2.2	202.0	2100

The successful preparation of the 15% and 20% combined fat emulsions was accomplished by adequate and thorough homogenization and emulsification procedures as described in our previous report on the 10% combined fat emulsion, whereby the homogenizer apparatus adapted to medical usage and the technic of manufacture of sterile emulsions were presented in detail.(1)

The constituents of the emulsions are solutions of 10% protein hydrolysate, 50% glucose, 6% intravenous gelatin (Knox-P-20) and refined coconut oils. All except the latter are available as sterile non-pyrogenic solutions in sealed flasks. The refined coconut oil is autoclaved before mixture with the other emulsion ingredients. In the present studies 15% and 20% concentrations of fatty oil were obtained in the preparation of the combined fat emulsions resulting in caloric values of approximately 1720 and 2100 calories respectively per liter of emulsion. The percentage composition of the various ingredients which make up the emulsions are listed in Table I with fat as the prime contributing factor to the increased caloric value of each preparation.

Intravenous gelatin was used exclusively as the emulsifying agent requiring between 2 and 3% for thorough emulsification of the 15% and 20% concentrations of fatty oil. The stability of both combined fat emulsions has been observed for a period of more than 7 months without "creaming" or "oiling out". The particle size of the emulsions was within the one micron range and active Brownian movement was exhibited on microscopic examination.

Method of Study. The combined fat emulsions were administered without selectivity to hospital patients who were being treated for a variety of surgical conditions. Several of these patients ran a chronic low grade fever. The studies were started in the morning with the subject in the postabsorptive state after a fasting period of 14 hours. Before the infusion was started a sample of blood was taken, the morning urine was obtained, and temperature, pulse, respirations and blood pressure were noted. The infusion was then given intravenously at a specific rate ranging from 20 to 80 drops per minute and varying in different patients. In every case the amount infused was 500 ml of either emulsion. In several subjects a second infusion was also given in the late afternoon. During the course of the infusion and throughout the post-infusion phase until the next morning, blood and urine samples were taken and the above mentioned clinical notations were made at regular intervals. The following tests were made routinely on the blood; hemoglobin, red cell count, white cell count with differential, sedimentation time, chylomicron count and specific gravity. Clinically, subjective and objective constitutional reactions relative to the infusion were studied. X-rays of the lungs were taken in series for any lesions due to fatty infiltration, pulmonary irritation or pulmonary emboli. Final check examinations were made 2 weeks after completion of the infusions for hemolytic anemia and for possible liver or kidney damage. Surgical liver and lung biopsies were obtained from several subjects who received the emulsion. These specimens were prepared for microscopic analysis by staining with osmic acid, Sudan IV and hematoxylin-eosin.

Results. The 15% and 20% combined fat emulsions were administered intravenously into 25 human subjects for a total of 51 infusion studies. Details relative to the method of administration, volume infused, temperature response and constitutional reactions are supplied in Table II. Temperature changes were computed according to the degree of

TABLE II.
Immediate Effects from Infusions of Concentrated Fat Emulsions into Human Subjects.

Emulsion	Volumes infused (ml)	g fat infused	No. of patients infused	No. of infusions given	Reactions. Temperature rise <1°	1°-1.9°	2°-2.9°	>3°	Chill	Vomiting
15%	500 to 600	77.5 to 93.0	14	23	8	3	5	7	7	2
	700 to 900	108.5 to 139.5	2	9	3	0	3	3	2	0
	1000	155.0	2	7	1	1	2	3	1	0
20%	500 to 600	101.0 to 121.2	7	12	4	4	3	1	4	1
Totals			25	51	16	8	13	14	14	3

elevation above the initial pre-infusion temperature but were not corrected for changes due to the disease of the patient. The incidence of chills totalled 14 of all infusions given. Of the latter the occurrence of 7 cases of chills were correlative with high temperature and the administration of the emulsion at the rate of 80 drops per minute. Upon reduction of the rate of infusion these same subjects on other occasions did not repeat the chill when re-infused with the fat emulsion. Chills were the severest type of reaction encountered in the present series. Upon the administration of 50 mg of either pyribenzamine or benadryl the latter reaction was considerably reduced. Vomiting, headache and dizziness occurred in 4 instances and were in association with a chill. Other reactions such as coughs, allergies and fatty taste did not occur in this series. There were also no fatalities. (Table II).

The values for hemoglobin, hematocrit cell volume and red and white cells tended to fall below their initial values during the infusion phase of the emulsion and returned to their original levels shortly before or after the termination of the infusion. The erythrocyte sedimentation rate showed an increase in rapidity of sedimentation which average 25% to 35% greater than the pre-infusion sedimentation time. It also returned to its initial level. The differential white count was not indicative of any trend. The specific gravities of blood and plasma showed a temporary dilution effect due to the infusions followed by a return to normal limits (Table III).

Changes of blood pressure in response to the injection were variable. During the infusion period there was generally a slight elevation of blood pressure followed by a moderate fall which persisted for 2 hours after completion of the infusion. The elevation of systolic pressure did not exceed 20 mm Hg and the fall in systolic pressure ranged from 10 mm to 25 mm Hg. The diastolic pressure tended to fall towards the end of the infusion but also returned to its normal level. There were no falls in blood pressure which indicated any tendencies toward the development of shock.

Counts of chylomicrons were made from peripheral venous blood under dark field illumination with a net micrometer in the eyepiece of the microscope. In the post absorptive state the pre-infusion count varied from zero to 10 chylomicrons. After the infusion was started there was a rapid rise in the number of chylomicrons to a peak. At about the mid-point of the infusion the chylomicrons began to decrease in number and return slowly to the initial level.

Consecutive urine studies were made in 25 infusion tests. In no case was a positive test for blood or urobilinogen obtained which was attributable to the fat emulsion. Chemical tests for fat in the urine were negative. Dark field examination of the urine for chylo-

TABLE III.

Effects of Intravenous Infusions of Combined Fat Emulsions into 2 Subjects. A—Received 15% combined fat emulsion. B—Received 20% Combined fat emulsion.

Time (min.)	Amount infused	Subject	Temp.	Pulse	Blood pressure	Hemoglobin	R.B.C. count (million)	W.B.C. count (thousand)	Hematocrit	Sedimentation time	Chylomicron count	Urine acetone
0	0	A	98.4	60	130/80	13.5	3.95	5.8	42	26	12	neg.
		B	98.8	74	160/92	14.6	4.75	7.0	46	23	0	"
60	100	A	98.4	60	130/80	14.0	4.20	6.2	42	23	150	neg.
		B	99.0	78	168/92	14.8	4.75	6.8	41	23	100	"
120	225	A	98.6	68	154/78	15.0	3.80	6.4	40	38	350	1+
		B	99.0	80	184/88	14.6	4.68	5.0	39	34	400	neg.
180	350	A	99.0	76	130/88	14.0	3.70	6.4	38	41	300	1+
		B	100.0	86	186/74	14.0	4.70	5.6	41	34	400	2+
240	500	A	102.4	100	126/84	14.5	3.65	6.6	41	45	260	3+
		B	102.0	104	178/78	13.8	4.90	5.7	45	34	200	1+
360	—	A	100.6	84	130/88	14.5	3.68	5.8	43	27	100	neg.
		B	102.6	106	182/90	14.0	4.10	6.0	46	30	80	1+
480	—	A	100.0	100	156/70	14.5	3.95	5.6	43	30	100	neg.
		B	102.0	94	188/74	14.2	5.00	6.6	40	28	50	"
600	—	A	100.4	96	132/88	15.0	3.45	6.0	42	36	20	neg.
		B	100.0	92	160/80	14.4	4.92	6.8	46	30	60	"
720	—	A	100.0	88	110/80	14.8	3.90	6.2	40	34	50	neg.
		B	98.4	84	174/88	14.6	4.80	7.4	48	28	0	"
24 hr	—	A	98.8	72	116/80	14.8	3.95	5.2	43	30	0	neg.
			98.6		178/96	13.8	5.00	7.8	40	27	8	"

microns showed a moderate elevation in the number of fat particles. In 4 infusion studies with the 15% fat emulsion and in 3 with the 20% fat emulsion, positive reactions were obtained for acetone varying from 1+ to 2+ in 2 or 3 of the intermediate urine specimens examined during the course of the infusion. During the post-infusion phase the tests for acetone occasionally showed a faint trace and remained negative thereafter. There were no positive tests for diacetic acid. There were no indications by these tests of any greater acetone spillage occurring in recipients of the 20% fat emulsion as compared with recipients of the 15% fat emulsion.

Follow-up studies for hematologic complications in subjects who received either single or multiple infusions showed no signs of hemolytic anemia. Likewise x-rays of the lungs gave no evidence of fatty emboli or pulmonary irritation. Liver and lung biopsy specimens failed to show any organic lesions which could be attributed to the intravenous infusion of fat. Liver and kidney function studies showed no pathologic alterations which were attributable to the emulsions.

Comment. The effects of the intravenous infusion of either the 15% or 20% combined fat emulsions were in many respects similar to those noted in our clinical studies on the infusion of the 10% combined fat emulsion.(1) These pertained particularly to hematologic changes, blood pressure response and follow-up observations on liver, lung and kidney function. Constitutional reactions such as high temperatures or chills averaged 27% as compared with 9% with the more dilute fat emulsion. About 50% of the reactions encountered in this series were found to be due to the speed with which the emulsion was administered, the fast infusions being associated with the chill reaction. The temperature elevations could be accounted for on the basis of a sudden plethora of fat. In any case the concentrated fat emulsions required cautious careful administration.

Summary. Two types of combined fat emulsions, one containing 15% fat and the other 20% fat, were infused into 25 human subjects. A total of 51 of these concentrated fat emulsions were administered intravenously. The incidence of constitutional reactions was 27%. A variety of laboratory and clinical observations were made in conjunction with these infusions.

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Malignant Lymphoid Tumors in Orchidectomized Mice Receiving Hypophyseal and Ovarian Grafts at Various Ages.* (17493)

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While studying the effects of anterior hypophyseal and ovarian transplants on mammary growth in male castrate mice of strain A, we noted the occurrence of lymphoid leukemia and lymphosarcoma in a number of animals bearing these grafts.(1) The present report deals with the incidence of these tumors in the various experimental groups.

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1. Silberberg, R., and Silberberg, M., PROC. SOC. EXP. BIOL. AND MED., 1949, v70, 510.

Material and methods. The experiments have been described in detail in a previous paper.(1) Briefly, 161 male mice of the closely inbred strain A kept on a standard diet of Purina Laboratory Chow and water were castrated at the age of 3 weeks. The animals were divided into two age groups: *I. Younger age group* grafted at the age of one month: Twenty-eight castrates received four anterior hypophyses each; 26 received 2 or 4 ovaries each; 25 received a combination of 4 hypophyses and ovaries. *II. Older age group* grafted at the age of 7 months: Twenty-eight