INHERITED FATTY ACID OXIDATION DISORDERS (FOD) include de-
fects of the cell membrane carnitine transporter, the "carnitine cycle" (CPT I, translocase, CPT II), or the mitochondrial β-
oxidation spiral. The most common disorders of β-
oxidation affect very-long-chain acyl-CoA dehydrogenase, mitochon-
drial trifunctional protein, isolated long-chain hydroxyacyl-
CoA dehydrogenase, and medium- and short-chain acyl-CoA
dehydrogenase. Patients with long-chain FOD commonly
present with recurrent hypoketotic hypoglycemia, hypertrophic
dilated cardiomyopathy, cardiac arrhythmias, rhabdomyol-
ysis, muscle weakness, and hypotonia, (for a review, see Ref.
21). There is considerable phenotypic variation associated with
nearly all of these disorders.

The classical chronic treatment of long-chain FOD involves
frequent feeding with a diet adjusted so as to lower long-chain
fat intake from the usual 30–35% of total kilocalories to
~20%, including essential fatty acids. The decrease in energy
from long-chain fats is partly compensated by an increase in
carbohydrates, often with cornstarch at bed time. In addition,
even carbon medium-chain triglycerides (trioctanoin/tride-
canoin) are added to the diet. This is because fatty acids with
8–10 carbons enter the mitochondrion as carboxylates, which,
after activation, require only those β-oxidative enzymes with
medium- and short-chain length specificity. The dietary treat-
ment with medium-chain triglycerides is obviously restricted
to long-chain disorders and is contraindicated for medium-
and short-chain deficiencies.

A new strategy was recently conceived for the dietary
treatment of long-chain FOD, i.e., providing about one-third of
the calories as triheptanoin (22). The catabolism of heptanoate
yields anaplerotic propionyl-CoA in addition to acetyl-CoA. It
was hypothesized that part of the energy deficit in FOD
patients results from a decrease in the concentration of citric
acid cycle intermediates in muscle and heart cells. These
intermediates carry the carbons of acetyl groups as they are
oxidized. The treatment with triheptanoin resulted in a rapid
improvement of muscle and cardiac function in the three
long-chain FOD patients described in Ref. 22, as well as in
other patients who are presently involved in clinical trials (Roe
CR, unpublished observations). Also, treatment with trihep-
tanoin improved for 6 mo the condition of a patient with almost
complete deficiency of liver pyruvate carboxylase (a major
contributor to hepatic anaplerosis) before she succumbed to an
acute episode of gastroenteritis (17).

In the liver, propionyl-CoA derived from heptanoate oxida-
tion has two main fates. First, it is gluconeogenic via succinyl-
CoA and part of the citric acid cycle reactions. Second, it is
collected to the C5-ketone bodies β-ketopantoate (BKP) and
β-hydroxybutyrate (BHB) via the hydroxy-methylglutaryl
(HMG)-CoA cycle. The C5-ketone bodies are analogs of the C4
acetoacetate (AcAc) and β-hydroxybutyrate (BHB). In periph-
eral tissues, the C5-ketone bodies are converted to acetyl-CoA
and anaplerotic propionyl-CoA by the combined action of
β-β-hydroxybutyrate dehydrogenase, 3-oxoacid-CoA trans-
ferase, and acetoacetyl-CoA thiolase. Thus, after administra-
tion of heptanoate, propionyl-CoA and acetyl-CoA are formed
in peripheral tissues by 1) β-oxidation of heptanoate and 2) 
utilization of C5-ketone bodies formed in the liver.

The goal of the present study was to test in normal rats the
metabolism of a triheptanoin preparation that might be used in
the future for the treatment of acute long-chain FOD decompensa-
tion, via either intravenous or enteral infusion. An emul-
sion of triheptanoin was infused intravenously (iv) or intraduodenally (id), the latter to delineate the role of first-pass metabolism of the substrate through the portal drainage system. Our data show that the route of administration has a major impact on the distribution of triheptanoin metabolites in systemic blood.

**MATERIALS AND METHODS**

**Materials**

\[
\begin{align*}
[U-^{13}C_6]glucose, [6,6-^{2}H_2]glucose, [^{3}H_8]glycerol, [U-^{13}C_1]glycerol, \\
[\omega-^{1}H]heptanoic, \text{H}_2\text{O}, \text{NaH}^3\text{O}, \text{NaOH, sodium borodeuteride (NaB}^2\text{H}_4), \\
\text{and general chemicals were purchased from Isotec/Sigma-Aldrich. Pentafluorobenzyl bromide was purchased from Pierce. An internal standard of R, S, S-\beta-hydroxy-[^{3}H_3]pentanoate was prepared by incubating ethyl } \beta-\text{ketopentanoate in } \text{H}_2\text{O plus NaH}^3\text{O, followed by reducing R, S, S-\beta-keto-[^{3}H_3]pentanoate with sodium borodeuteride (16). A 10% sterile emulsion of triheptanoin was kindly donated by Sasol Germany. As per Sasol’s quality control data, the heptanoic acid used to synthesize triheptanoin contained } 99.5\% \text{ heptanoic acid, with traces of hexanoic, octanoic, and decanoic acids. The triheptanoin used to prepare the emulsion contained } 97.5\% \text{ triheptanoin, with the remaining } 2.5\% \text{ being monoester and diester. The emulsion was stabilized with 1% InWitor 2020 (Sasol), a food-approved emulsifier prepared by interesterification of a mixture of compounds with the following weight composition: } 14\% \text{ glycerol, } 18.5\% \text{ tartaric acid, } 15.0\% \text{ acetic acid, } 4.5\% \text{ palmitic acid, } 2.2\% \text{ stearic acid, } 14.5\% \text{ oleic acid, } 28.2\% \text{ linoleic acid, and } 3.1\% \text{ linolenic acid. The emulsifier meets the specifications of the Food Chemical Codex (3rd ed.) (3a).}
\end{align*}
\]

**Animal Experiments**

The animal experiments were approved by the Institutional Animal Care and Utilization Committee of the Case School of Medicine.

**Preparation of rats.** Male Sprague-Dawley rats were fed ad libitum with Harlan Teklad rat chow. After an overnight fast, rats (235–317 g) were anesthetized with intraperitoneal pentobarbital (5.8 mg/h) were infused into the jugular vein until the placement of catheters, saline (3.5 ml/h) and a maintenance dose of BKP. Glucose and glycerol, samples were divided prior to the addition of sulfosalicylic acid and HCl by transferring 0.2 ml of solution to a separate tube. The glucose and glycerol tubes were then acidified with HCl, whereas sulfosalicylic acid was added to the remaining tubes. Samples were stored at −20°C until assayed.

**Assay of heptanoate and C5- and C3-ketone bodies.** After treatment with sulfosalicylic acid, the slurry was acidified with HCl and extracted with 3 × 4 ml of diethyl ether. The combined extract was dried over NaSO4, evaporated down to ~50 μl, and sonicated for 1 h with 3.5 μl of pentafluorobenzyl bromide, 10 μl of pyridine, and 37.5 μl of acetonitrile. After extraction with 3 ml of hexane, drying the extract over NaSO4, and evaporating the solvent, the residue was reacted with 15 μl of of acetic anhydride and 30 μl of pyridine in 285 μl of ethyl acetate at room temperature overnight. This procedure converts 1 fatty acids to pentafluorobenzyl derivatives and 2 hydroxyacids to acetyl-pentafluorobenzyl derivatives. After extracting with diethyl ether, drying over NaSO4 and evaporating with solvent, the residue was dissolved in 40 μl of ethyl acetate and 2 μl injected into an Agilent gas chromatograph linked to a 5973 MSD mass spectrometer. The chromatograph was equipped with a 30-m 77-025 capillary column (Quadrex). The carrier gas was helium (30 ml/min), and the injection mode was splitless. The GC injector temperature was set at 190°C, and the transfer line was held at 280°C. The column temperature was increased from 100°C by 5°C/min to 235°C and held for 20 min. The mass spectrometer was operated under ammonia negative chemical ionization with the source pressure adjusted to obtain the maximal signal. The retention times and ions monitored were as follows: heptanoate (16 min, m/z 129, 132); BHB (20 min, m/z 145, 146, 151); BHP (21 min, m/z 159, 160, 164).

**Assay of glucose and glycerol.** After the addition of 1 drop of 12 N HCl, the solution was evaporated under nitrogen. The residue was reacted with 150 μl of acetic anhydride and 300 μl of pyridine, heated for 5 min at 100°C, and then left overnight at room temperature. The next day, samples were extracted with ethyl ether, and the extract was then dissolved over NaSO4 before evaporation. The residue was dissolved in 40 μl of ethyl acetate and either 2 μl (glucose assay) or 0.2 μl (glycerol assay) injected into the same chromatograph as above. The injection mode was either splitless (glucose) or split (glycerol). The column temperature was increased from 100°C by 20°C/min to 190°C, by 5°C/min from 190 to 220°C, and then by 20°C/min from 220 to 235°C, where it was held for 45 min. The mass spectrometer was operated under ammonia positive chemical ionization with the source pressure adjusted to obtain the maximal signal. The retention times and ions monitored were as follows: glycerol (8 min, m/z 236, 237, 238, 239, 241), glucose converted to sorbitol (31 min, m/z 453, 454, 455, 456, 459).

**Data Analysis and Calculations**

Total C3-ketone bodies were calculated as the sum of BHB plus AcAc, whereas total C5-ketone bodies were the sum of BHP plus BKP. Glucose and glycerol rates of appearance (Ra) were calculated (15) according to the steady-state equation:

\[
Ra = \left(IE_{\text{infusate}}IE_{\text{blood}} - 1\right) \times (\text{INF})
\]

where IE_{\text{infusate}} is the isotopic enrichment of the tracer infused, IE_{\text{blood}} is the isotopic enrichment of blood, and INF is the rate of the tracer infusion (μmol·min⁻¹·kg⁻¹). To calculate endogenous glycerol Rg from parenteral infusion of triheptanoin, glycerol Rg was
considered significant.

The protocols could be conducted on 70 micro-analytical techniques so that all the assays required in the small sample of blood that we were able to obtain from each rat, blood concentrations of triheptanoin were not obtained.

The blood concentration of C₃-ketone bodies (BKP + BHP; Fig. 2) was not detectable in basal samples or in the blood of saline-infused rats but increased with the rate of intravenous triheptanoin infusion. However, the highest concentration of C₃-ketone bodies was achieved during the intraduodenal infusion at 40% of the caloric requirement (~0.22 mM; Fig. 2, top curve).

The basal blood concentrations of C₅-ketone bodies (BHB + AcAc; Fig. 3) ranged from 0.7 to 1.1 mM. As a result of the anesthesia, the concentration of physiological C₃-ketone bodies increased from the usual concentration of ~0.1 mM in conscious overnight-fasted rats to ~1 mM (25). The high basal concentration of C₃-ketone bodies continued to increase significantly in saline-infused rats (P < 0.05), again presumably as a result of the prolonged fasting and anesthesia, but decreased significantly during the intravenous infusion of triheptanoin at 30 and 40% of the caloric requirement (P < 0.001).

In the second study (protocol 2), anesthetized rats were infused for 2 h with either saline iv, triheptanoin at 40% of the caloric requirement iv, or triheptanoin at 40% of the caloric requirement id. All rats were infused with [U-13C₃]glycerol and [6,6-²H₂]glucose. Tracer glycerol was used instead of a tracer fatty acid, because the measurement of lipolysis with tracer glycerol is less subject to analytic artifacts than the measurement of the total glycerol concentration in the triheptanoin emulsion after alkaline hydrolysis.

Additional calculations were conducted to compute the isotopic data concentration in the triheptanoin emulsion after alkaline hydrolysis.

RESULTS

A major component of this study was the development of micro-analytical techniques so that all the assays required in the protocols could be conducted on 70 μl of whole blood. Pentafluorobenzyl derivatives of carboxylic acids can be assayed using high-sensitivity ammonia negative chemical ionization mass spectrometry (11). Immediate treatment of the samples with sodium borodeuteride allowed stabilization of unstable AcAc and BKP by conversion to stable monodeuterated BHK and BHP (4, 16). These monodeuterated analytes were distinguished by mass spectrometric analysis from the corresponding undeuterated analytes. As a result of the use of sodium borodeuteride during sample processing, glucose was assayed as sorbitol. All of the calibration curves were linear with substrate concentration (not shown). The assays were conducted on whole blood because orientation experiments revealed that the concentration of heptanoate in whole blood was 48–74% of the concentration in plasma. This probably results from the partial equilibration of heptanoate concentration between plasma and erythrocytes.

In the first study (protocol 1), we infused the triheptanoin emulsion for 90 min at 1) 0–40% of the caloric requirement intravenously or 2) 40% of the caloric requirement intraduodenally. Figure 1 shows that the intravenous infusion of triheptanoin (at 10–40% of caloric requirement) resulted in fairly stable blood heptanoate concentrations ranging from ~0.07 to 0.5 mM. In contrast, the intraduodenal infusion of triheptanoin at 40% of the caloric requirement resulted in a very low blood heptanoate concentration, i.e., ~0.02 mM. The blood heptanoate concentrations were undetectable (P < 0.005 mM) in basal samples and in samples from saline-infused rats. Because of the small sample of blood that we were able to obtain from each rat, blood concentrations of triheptanoin were not obtained.

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measurement with tracer fatty acids. Steady-state concentrations of both heptanoate and C₅-ketone bodies were virtually identical to those observed (Figs. 1 and 2) in the first set of experiments despite the 30-min longer infusion period of triheptanoin (not shown). The redox indicator ratio [BKP]/[BHP] stabilized at 1.5–2.0 after 90 min (not shown). Similar to the dose-response experiments, the greatest decrease in steady-state C₄-ketone bodies occurred with intravenous infusion of triheptanoin (from 0.75 ± 0.07 down to 0.51 ± 0.05 mM, P < 0.001), whereas intraduodenal infusion of triheptanoin resulted in an attenuation of this decrease (from 1.05 ± 0.06 down to 0.89 ± 0.06 mM, P < 0.05).

The blood glucose concentration (Fig. 4A) was not significantly affected by the intravenous or intraduodenal infusion of triheptanoin except at 100 min, when glucose concentration was higher with intraduodenal triheptanoin infusion than with intravenous infusion (P < 0.05). However, the rate of glucose appearance (glucose Ra; Fig. 4B) was significantly increased by about one-half by the intraduodenal infusion of triheptanoin (P < 0.05).

The basal blood glycerol concentrations in all four groups were elevated (0.42 ± 0.06 mM) compared with values from nonanesthetized animals (~0.15 mM (20)). This most likely resulted from the stress of the anesthesia and surgery, which stimulates lipolysis (5, 6). These effects are presumably mediated via increased concentrations of catecholamines and cortisol.

Table 1 shows the detail of the calculations of the Ra of glycerol in the four groups of rats of protocol 2. In saline-infused control rats, the glycerol Ra (21.7 μmol·min⁻¹·kg⁻¹) was similar to data from the literature (1). The intravenous infusion of triheptanoin tripled the arterial blood glycerol concentration (Fig. 4C) and about doubled the endogenous glycerol Ra (group 2; Table 1) compared with the saline control. In contrast, the intraduodenal infusion of triheptanoin did not affect the arterial blood glycerol concentration (Fig. 4C). This suggests that, during the intraduodenal infusion of triheptanoin, the glycerol derived from the intestinal hydrolysis of triheptanoin was cleared by the liver. Therefore, to calculate the endogenous glycerol Ra, one should not deduct from the total glycerol Ra (endogenous + exogenous, 25.4 μmol·min⁻¹·kg⁻¹) the amount of glycerol infused intraduodenally as part of the triheptanoin emulsion. So, the endogenous Ra of glycerol of 25.4 μmol·min⁻¹·kg⁻¹ is a reasonable first approximation of peripheral lipolysis during the intraduodenal infusion of triheptanoin. A small correction to this Ra will be added below.

In the group of rats infused intraduodenally with triheptanoin and the glycerol tracer (Table 1, bottom row), the value of the total glycerol Ra (endogenous + exogenous) calculated from the rate of tracer infusion and the enrichment of glycerol in arterial blood (238 μmol·min⁻¹·kg⁻¹) is meaningless. This is because most of the labeled glycerol was taken up by the liver and could not mix with the glycerol derived from peripheral lipolysis. Indeed, the arterial enrichment of glycerol when [U-¹³C₃]glycerol was infused intraduodenally was about one-fifth of the arterial enrichment of glycerol when the tracer was infused intravenously (compare rows 3 and 4 of Table 1). Thus, for the two experiments where triheptanoin was infused intraduodenally, taking into account the rates of tracer infusion and the arterial enrichments of glycerol, one can calculate the fraction of the intraduodenally infused glycerol tracer that escaped uptake by the liver. This fraction is equal to the ratio...
of enrichments of blood glycerol (2.3/12.6) normalized for equal rates of tracer glycerol infusion, i.e., (2.3/12.6) × (3.4/3.9) = 0.16. Thus 16% of the intraduodenally infused glycerol tracer escaped uptake by the liver. This percentage will now be used to calculate the peripheral $R_a$ of glycerol in the two experiments where triheptanoin was infused intraduodenally.

First, in experiments with intraduodenal infusion of triheptanoin and intravenous infusion of tracer glycerol (group 2; Table 1), from the total glycerol $R_a$ (25.4 μmol·min⁻¹·kg⁻¹), one deducts 16% of the rate of glycerol administration via triheptanoin:

$$\text{endogenous } R_a, (\text{group } 3) = 25.4 - (0.16 \times 26.1)$$

$$= 21.2 \mu\text{mol} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$$

Second, in experiments with intraduodenal infusions of both triheptanoin and tracer glycerol (group 4; Table 1), the rate of glycerol tracer infusion that escaped liver uptake was 3.9 × 0.16 = 0.62 μmol·min⁻¹·kg⁻¹. Therefore, the rate of peripheral lipolysis in these experiments was calculated using the classical steady-state equation

$$\text{endogenous glycerol } R_a, (\text{group } 4) = \left[\frac{1}{0.023} - 1\right](0.62)$$

$$= 26.3 \mu\text{mol} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$$

To summarize the data of Table 1, peripheral lipolysis (expressed as glycerol $R_a$) was not substantially affected by the intraduodenal infusion of triheptanoin (groups 3 and 4) but was about doubled by the intravenous infusion of triheptanoin (group 2).

**DISCUSSION**

The initial clinical trial of FOD patients with triheptanoin involved mixing the triglyceride with baby formula or with semisolid foodstuffs (22). However, emulsions of triheptanoin might be used in the future for the treatment of patients with long-chain FOD, either enterally or intravenously, for those who are going through acute decomposition. The latter patients are often comatose or confused and require treatment via intravenous or nasogastric administration. Temporary malabsorption syndromes such as gastroenteritis in long-chain FOD patients could also necessitate the use of intravenous administration. This is why we conducted this study on anesthetized rats receiving triheptanoin either intravenously or intraduodenally. A constant level of anesthesia and adequate hydration were imposed by infusing a low dose of sodium pentobarbital dissolved in saline.

Figures 1 and 2 show that, during the intraduodenal infusion of triheptanoin, virtually no heptanoate derived from triheptanoin hydrolysis escaped uptake by the liver. This is consistent with reports of essentially complete hepatic clearance of enterally administered medium-chain triglycerides (2, 9). It appears that a large fraction of the heptanoate reaching the liver is oxidized to BKP-CoA, which is partly converted to the C5-ketone body BKP in the HMG-CoA cycle. BKP then equilibrates with BHP via a reaction catalyzed by BHP dehydrogenase. Indeed, standard solutions of unlabeled and labeled BHP and BKP are assayed with BHB dehydrogenase (16).

The total concentration of C4- and C5-ketone bodies (Figs. 2 and 3) did not exceed 1.2 mM in any group. Thus the intravenous infusion of triheptanoin at up to 40% of the caloric requirement did not induce a toxic ketosis.

The decrease in the concentration of C4- and C5-ketone bodies during the intravenous infusion of triheptanoin at 30 or 40% of the caloric requirement was quite puzzling, especially in view of the reported increase in C4-ketone bodies during infusion of even-chain triglycerides (medium- or long-chain) (3, 19, 23, 24). Because the heptanoate molecule has two acetyl moieties, these were expected to contribute somewhat to the production of C4-ketone bodies. We considered the possibility that the intravenous infusion of triheptanoin could result in an inhibition of peripheral lipolysis, with a subsequent decrease in C4-ketogenesis. We thus decided to assess the effect of triheptanoin on lipolysis in another series of experiments by measuring the $R_a$ of glucose and glycerol. The glucose $R_a$ was significantly increased by about one-half by the intraduodenal infusion of triheptanoin ($P < 0.05$; Fig. 4B). The increase in glucose $R_a$ (~10 μmol·min⁻¹·kg⁻¹) was only about one-third of the potential glucose equivalent of the triheptanoin infused (glycerol + propionyl-CoA moieties). This is because part of the propionyl-CoA moiety of heptanoate was converted to C5-ketone bodies (Fig. 2). During the intravenous infusion of triheptanoin, the glucose $R_a$ was not significantly increased (Fig. 4B), because a large fraction of the heptanoate derived from triheptanoin hydrolysis in blood was presumably taken up by nongluconeogenic peripheral tissues. In contrast, during the intraduodenal infusion, all the glycerol and heptanoate derived from triheptanoin hydrolysis in the gut reached the liver, the main gluconeogenic organ.

The activation of lipolysis during the intravenous infusion of triheptanoin might result from the activation of lipoprotein lipase by the infused triglyceride. Karpe et al. (14) showed that intravenous infusion of long-chain triglycerides in humans
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leads to an up to ninefold activation of lipoprotein lipase in arterialized blood. Nordestrom et al. (18) demonstrated a similar increase when a combination medium-chain/long-chain triglyceride infusion was infused, with greater lipoprotein lipase activities noted with the medium-chain/long-chain infusion than with long-chain infusion alone. In this latter set of experiments, there was a significant correlation (r = 0.77) between plasma triglyceride concentrations and lipoprotein lipase activity during triglyceride infusion.

In our experiments where triheptanoin was infused intraduodenally (groups 3 and 4; Table 1), there was no increase in endogenous glycerol Ra, presumably because triglyceride particles did not enter the vascular bed and thus did not activate lipoprotein lipase.

During the intravenous infusion of triheptanoin, the activation of lipolysis presumably led to the release of long-chain fatty acids from adipose tissue. However, the arterial concentration of C4-ketone bodies decreased. This is an apparent contradiction, as an increase in the supply of long-chain fatty acids to the liver would be expected to result in enhanced C4-ketogenesis. We suggest that the bulk of the long-chain fatty acids released by lipolysis was reesterified, whereas heptanoate was preferentially oxidized. Preferential oxidation of heptanoate would be favored because 1) it does not accumulate in adipose tissue (26) and 2) its oxidation bypasses the carnitine palmitoyltransferase system. Reesterification of long-chain fatty acids occurs partly in the liver, where the glycerol moiety of triheptanoin is activated to α-glycerophosphate, an intermediate of triglyceride synthesis. However, there are other sites of reesterification (13), in particular, muscle, which uses plasma glycerol for triglyceride synthesis (10) and which is a site of triglyceride storage (8, 12). Reesterification of long-chain fatty acids in muscle was probably promoted by 1) the tripling in glycerol concentration during the intravenous infusion of triheptanoin (Fig. 4C) and 2) the supply of energy substrates in the form of heptanoate and C5-ketone bodies. The increase in glucose Ra and the slight hyperglycemia induced by heptanoate is presumably because triglyceride particles did not enter the vascular bed and thus did not activate lipoprotein lipase.

The data of this translational physiology study have a number of clinical implications for the potential use of triheptanoin emulsion in the treatment of long-chain FOD decompensation. Currently, only the enteral form of triheptanoin is available for beneficial to these patients. In mild cases of FOD decompensation, enteral administration of triheptanoin emulsion would be preferred, in the absence of diarrhea.

We want to stress that we do not imply that this study, conducted in anesthetized cats, clears the way for the utilization of triheptanoin emulsion for the treatment of uncomplicated patients with long-chain FOD. This will require additional studies in larger animals with metabolic rates per kilogram closer to those of humans. Although heptanoate does not accumulate in tissue glycerides (26), detailed studies on the regulation of triheptanoin infusion on the profile and kinetics of plasma lipids, including the concentration of plasma triheptanoin, will need to be conducted in various species, including in genetically engineered mice with FOD.

Grants

This work was supported by the National Institute of Diabetes and Digestive and Kidney Diseases (Research Grants DK-035543 to H. Brunengraber and DK-007319 training fellowship to R. P. Kinman) and the Cleveland Mt. Sinai Health Care Foundation.

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