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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

Insulin to glucagon (I/G) ratios were found to be higher in portal than in peripheral blood in human subjects in the postabsorptive state and after injections of glucose or alanine. This reflects greater removal of insulin than of glucagon by the liver. Nevertheless, peripheral I/G ratio provides an index of the portal ratio since there is good correlation between the two.

Studies are in progress of the effects of total parenteral nutrition on transport of glucose, amino acids, fatty acids and other substrates between

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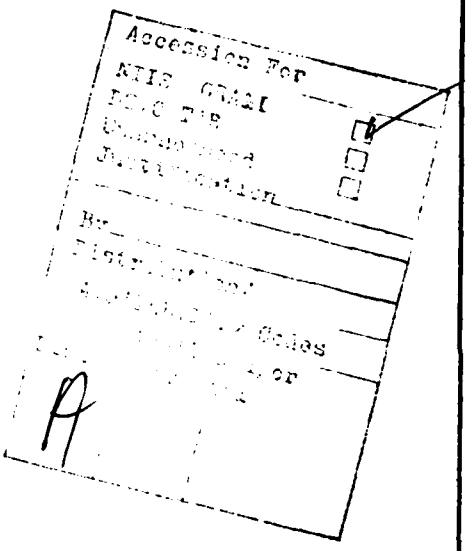
liver and leg in depleted or septic human subjects. Coterminous measurements are also made of nitrogen and energy balance and hormone concentrations.

We plan to initiate studies of oxidation and clearance in human subjects of intravenous fat emulsions labelled with ^{14}C.



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INVESTIGATION OF INTERMEDIARY METABOLISM AND ENERGY EXCHANGE FOLLOWING HUMAN TRAUMA

Annual Summary Report

John M. Kinney, M.D.

October 7, 1976

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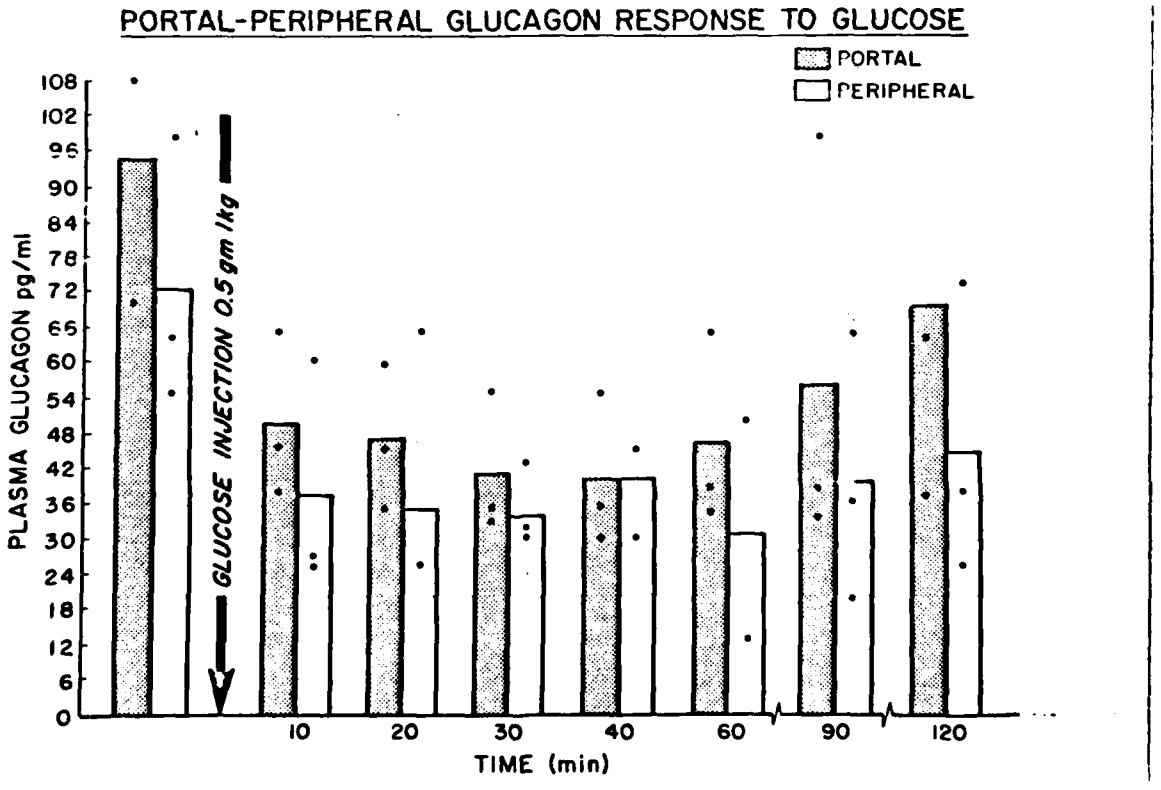
I. REGIONAL SUBSTRATE UTILIZATION IN HUMAN INJURY AND INFECTION

A. PORTAL AND PERIPHERAL INSULIN AND GLUCAGON

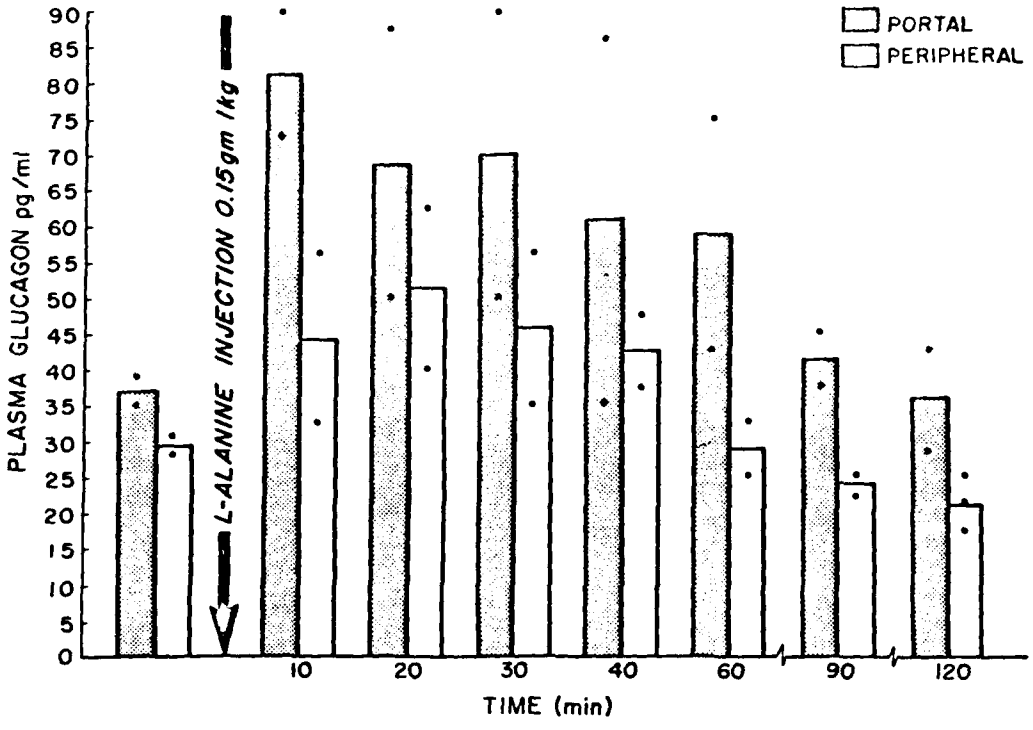
Gump, F. E., Gusberg, R. J. and Kinney, J. M.
(In collaboration with Dr. P. Felig,
Dept. of Medicine, Yale University)

Studies designed to evaluate substrate utilization have continued during the past year. We have also utilized the molar-ratio between insulin and glucagon (I:G ratio) in an effort to better define the balance between catabolism and anabolism in patients being fed by intravenous techniques. However, the IG ratio in peripheral blood has not been as useful in assessing the nutrition state of patients on total parenteral nutrition (TPN) as originally hoped. Since the effects of glucagon are primarily hepatic the IG ratio of portal as well as peripheral blood requires study.

The portal vein was catheterized via the obliterated umbilical vein in 5 patients during minor upper abdominal operations. The catheter was kept patent by saline infusion and studies were performed on the 5th postoperative day at which time the patients were afebrile, ambulatory and on a regular diet. Simultaneous determinations of portal and peripheral levels of glucose, insulin and glucagon were made in the post absorptive state as in our previous studies and also after peripheral injections of glucose (0.5g/kg) or L-alanine (0.15g/kg).



PORTAL-PERIPHERAL GLUCAGON RESPONSE TO ALANINE



In all subjects the baseline I/G ratios were higher in portal than in peripheral blood (2.5 ± 1.0 vs. 1.1 ± 0.3, $p < .05$). Following the injection of glucose the I/G ratio increased as anticipated but this was far more marked in portal than in peripheral blood (+1285% vs 853%). In the 2 patients receiving alanine, the peripheral I/G ratio showed *no* significant increase while the portal ratio increased by 60%.

The I:G ratios in portal and peripheral blood following injection of glucose are shown in Fig. 1. Fig. 2 shows the same ratios following the injection of alanine.

It is clear from these studies that the post absorptive I:G ratio in portal blood is higher than in peripheral blood. In other words, even though the effect of glucagon on carbohydrate metabolism is hepatic rather than peripheral, this is not because of hepatic trapping of the hormone. In fact, glucagon passes through the liver more readily than does insulin. After substrate infusion the portal I:G ratio is more responsive than the peripheral ratio. This become evident after alanine injection which resulted in a significant increase of the ratio in portal but not in peripheral blood. However, the portal-pheripheral gradient for glucagon was reasonably consistent with a mean value of 1.3 ± 0.1. The portal peripheral ratio for insulin was 2.5 ± 0.3 and this is why the I:G ratio was higher in portal than in peripheral blood. However, despite the higher portal I:G ratio, a significant direct linear correlation was observed between portal and peripheral I:G ratios so the peripheral ratio does reflect events in portal blood.

B. HEPATIC AND PERIPHERAL SUBSTRATE UTILIZATION

Gump, F.E., Elwyn, D.H. and Gusberg, R.J.

We are currently extending these studies of substrate infusion with studies of patients on TPN. The protocol calls for a least 13 days of TPN and patients are selected for study only if they fall into one of three categories. The first consists of acutely injured patients and this includes both traumatic and elective surgical (greater than 5 on a scale of 10) injury. All studies have to be started within 1 week of the injury, and there should be no evidence of significant infection. Furthermore, the patients have to be in a normal nutritional state prior to operation or injury. The second category would be septic patients. We defined this as patients with significant infections but not necessarily associated with positive blood culture. All patients will be febrile with an elevated resting metabolic rate (greater than 20% above the predicted normal value).

The third category consists of nutritionally depleted patients that are afebrile with normal or below normal resting metabolic expenditure. Depletion will be defined as weight loss of greater than 15% form the patient's normal or preinjury weight.

Patients will be selected for the study because they are candidates for TPN. For this reason no normal controls can be included although data for comparison will be available from similar studies to be carried out in normal volunteers.

Initial studies are designed to provide quantitative information on the movement of specific substrates between the periphery (leg) and the splanchnic bed in the three categories of patients listed above.

Prior to the actual study the patient will be on calorie and nitrogen balance and be placed in the gas exchange canopy for indirect calorimetry. After an overnight fast, hepatic, femoral vein and femoral arterial catheterization will be carried out. The hepatic vein catheter will be passed through a small right antecubital cutdown and passed into a major hepatic vein using a portable image intensifier. Splanchnic blood flow (ESBF) will be determined by the indirect Fick technique using ICG. Extremity blood flow will be estimated by an impedance technique. Calibration is imperfect but changes in flow in the same patient would be readily detectable with this method and even though more precise techniques have been described, we feel that this represents a reasonable approach in this clinical study. In some instances blood flow across a leg will be measured by dilution of ICG. The flow measurements will be combined with splanchnic and extremity arterio-venous differences of glucose, lactate, pyruvate, glycerol, amino acids, non-esterified fatty acids, ketone bodies and urea.

Approximately 15 ml of blood will be required for each sample from each catheter. Hematocrits will be measured and aliquots of whole blood, plasma or red cells will be taken immediately for the following determinations:

Amino Acids will be determined in picric acid or sulfosalicylic acid extracts of whole blood, plasma, or red cells. An automated amino acid analyzer will be used, modified from that previously described. A single column (Durrum DC-6, resin, 30 x 0.9 cm) is eluted with lithium citrate buffers. Output from two photocolorimeters is converted to digital form, punched on paper tape and processed on a digital computer using a Fortran program. The instrument can analyze 4 Samples per day. Reproducibility (coefficient of variation is 5% or less for most amino acids. The extract from 1 ml of plasma or blood is sufficient for duplicate determinations.

Glucose will be determined in plasma or whole blood by a glucose oxidase procedure (Glucostat, Worthington Biochemicals).

Glycerol will be determined by an enzymatic procedure in plasma. Lactate and pyruvate will be determined colorimetrically in perchloric acid extracts of whole blood by microenzymatic procedures.

Non-esterified fatty acids will be measured by titration of heptane extracts of plasma according to the method of Dole.

Acetoacetate and B-hydroxybutrate will be determined enzymatically by the methods of Williamson and Mellanby.

Urea will be determined using an automated colorimetric procedure for the Technicon Auto Analyzer.

Arterial and hepatic venous levels of insulin and glucagon, arterial levels of growth hormone and cortisol, and urinary excretion of catecholamines will be determined.

Three sets (arterial, femoral venous and hepatic venous) of bloods will be sampled over a 30 minute baseline period and then TPN will be initiated at a rate of 2000 calories and 12 grams of nitrogen/24 hours. Blood sampling from the 3 catheters will be continued at hourly intervals for 4-6 hours after which the catheters will be removed.

Arterial and femoral vein samples will then be taken at 1,2,4,8, and 14 days and weekly thereafter and analyzed for the same substrates and hormones. An effort will be made to study all patients for at least two weeks.

In selected patients a second hepatic vein catheterization will be performed after the first week of TPN. In this way the serial determination of lower extremity uptake or release of substrates can be correlated with the splanchnic data at 3 points: prior to TPN, at the time of initiation of TPN and after one week on TPN.

These measurements will provide a quantitative pattern of hepatic (splanchnic and extremity uptake and release of the substrates mentioned in three categories of surgical catabolism. In addition the associated splanchnic secretory pattern of insulin and glucaton in Units/minute can be calculated.

Significance of the Work

Major research efforts have been devoted to characterizing the metabolic response to starvation, injury and sepsis and to develop a rationale for treatment programs based on this characterization. The studies described above should advance these efforts in several ways: Combination of whole body calorie and nitrogen balance studies with quantitative exchange of substrates between skeletal muscle and the splanchnic bed. While these are primarily descriptive studies, they represent work that has yet to be carried out in a systematic fashion in injured or septic man. Of equal importance is the fact that the patients will be characterized so that differences

(if present) between acute injury, major sepsis and chronic depletion will be apparent.

The splanchnic output of insulin and glucagon, the hormones concerned with nutrient homeostasis, can be determined by hepatic vein catheterization techniques.

The long term significance of this work relates to the hypothesis that the release of amino acid from muscle is actually desirable because it provides the hepatotropic factors necessary for production of acute phase proteins needed following injury. Quantitation of substrate movements and the associated changes in hormone levels and splanchnic output represents the first step. The effect of exogenous hormones and a quantitative approach to the role of the liver in providing the various circulating proteins and enzymes necessary for a favorable response to injury should make it possible to test this hypothesis.

II. TRACER STUDIES OF SUBSTRATE UTILIZATION

A. 14C-INTRALIPID - CLEARANCE VS OXIDATION

Kinney, J.M., King, T.C. and Gump, F.E.

Introduction

The metabolic response to injury and infection commonly involves hypermetabolism, hyperglycemia, increased nitrogen loss associated with shrinkage of muscle tissue, and variable degrees of weight loss. During the past decade there has been a growing awareness of the importance of providing intravenous nutrients to offset the depletion which develops during this acute catabolic state.

The European experience with an intravenous fat preparation has been confirmed by many countries as being beneficial but no intravenous fat preparation is currently available in the United States. The effective utilization of this material in acute surgical conditions seems well established, however the details of altered fat metabolism in acute catabolic states are poorly understood. We propose to use small amounts of ^{14}C-Intralipid as a test material to assay the severity of change in specific reactions that are thought to be sensitive to catabolic influences.

Basic Assumptions:

1. The clearance of chylomicra from the blood stream of experimental animals (dogs) follows a predictable and reproducible pattern. (1)

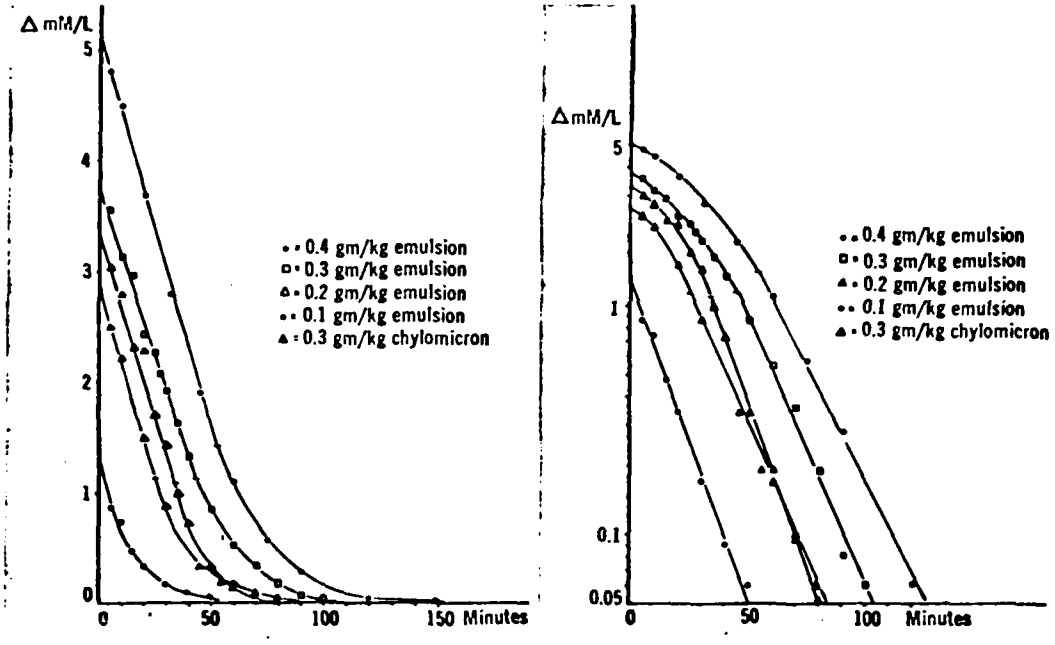


FIGURE 1. Elimination from the bloodstream of various amounts of fat emulsions (single injections) and chylomicrons in the dog. Triglyceride concentration is given for whole blood and represents the increase above the basal level. *Left:* A linear graph. *Right:* A semi-logarithmic scale.

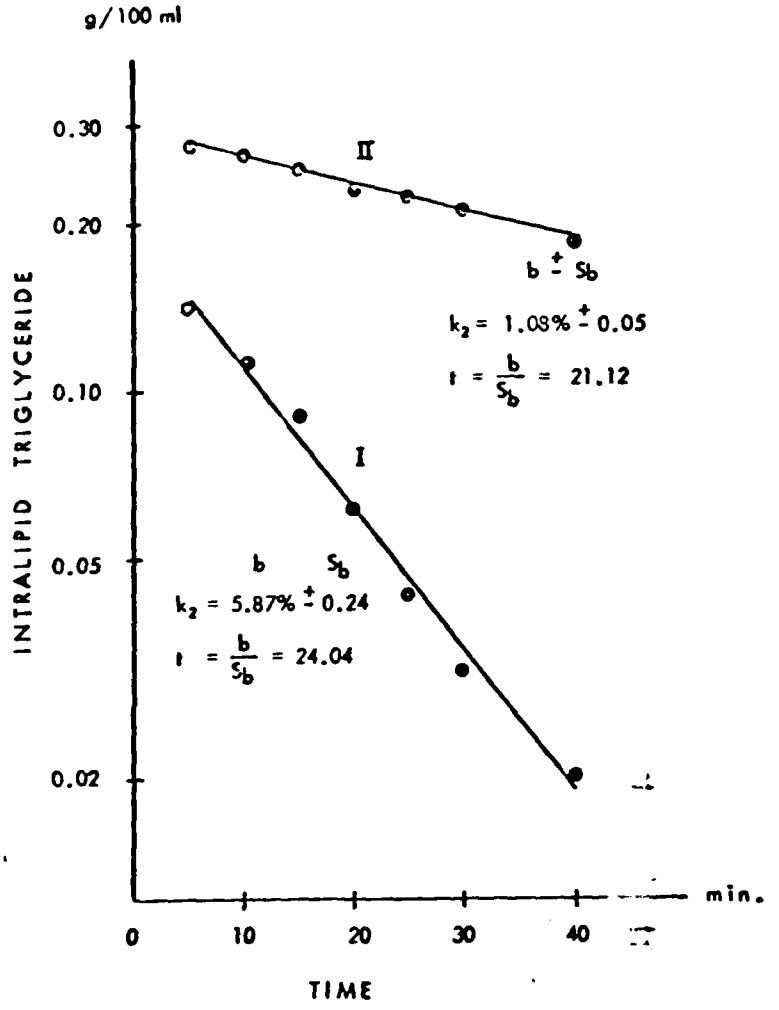


Fig. 2. Disappearance curves of 10% Intralipid[R] in a healthy volunteer (I) and in a patient with hyperlipidaemia (II). The respective figures for the exponential elimination rate $k_2 \pm$ S.E.M. and Student's t-value are given.

2. With some identifiable alterations, similar characteristic decay curves are observed in humans. (2)

3. Trauma increases the clearance rate in man. (3,4)

4. An exogenous infusion of an emulsion of soybean triglyceride (Intralipid) has clearance characteristics which, for practical purposes, are identical with the chylomicra. (1,4)

5. Analysis of the clearance characteristics of ^{14}C-labelled Intralipid will allow a rapid and reasonably accurate indicator of the decay curve of the Intralipid, hence chylomicra, in various injured states.

6. The implications of accelerated clearance of chylomicra from the bloodstream are quite different if the rate of oxidation is also accelerated than if this is not true.

Proposed Research:

We propose to admit surgical patients in one of the following four categories for study.

1) Postoperative uncomplicated

2) Major skeletal trauma

3) Major sepsis

4) Depletion (loss of over 15% body wt.)

The studies will be performed in our Surgical Metabolism Unit and related laboratories. The study of tracers doses of (40 uc) ^{14}C-Intralipid will include measures of expired $^{14}CO_2/^{12}CO_2$, as well as isolation and counting of serial samples of blood, chylomira, glucose and perhaps fatty acids or other circulating lipid materials if the degree of labelling permits.

Questions for Investigation:

1. In what ways can the changing slope of the clearance rate curve be correlated with varying types and extent of trauma?

2. Do changes in slope of the clearance curves reflect other changes in catabolic states: oxygen consumption, nitrogen excretion, etc?

3. Can the ratio of the transfer of label from fatty acid to expired CO_2 and perhaps to circulating glucose be used as an indication of the severity of catabolism?

4. Can the turnover of glycerol in the plasma and transfer of label from glyceride labelled intralipid into circulating glucose be used as a measure of the catabolic influence?

5. Is the transfer of carbon from glycerol labelled triglyceride to glucose increased whenever gluconeogenesis is accelerated from amino acids (at times of increased urea systhesis and excretion)?

Ultimate Objectives:

A large body of experimental and clinical data has been developed by Wretlind, Hellberg and associates which support the concept that a soybean

emulsion (Intralipid) can provide an effective calorie source for intravenous nutrition. However, there is general lack of information concerning the optimum intake of calories with nitrogen to treat or offset the protein breakdown in severe catabolic states. There is the additional need to establish what differences exist between carbohydrate and fat in improving a negative N balance.

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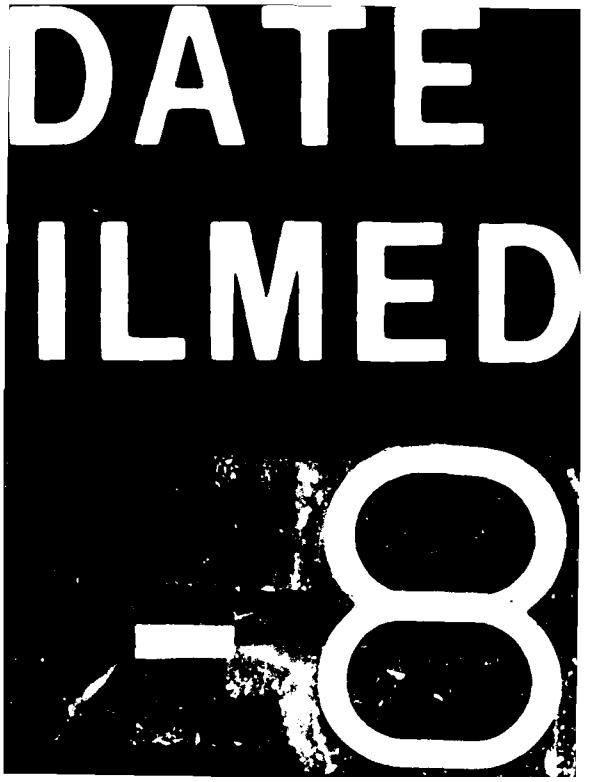
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