BILIARY EXCRETION OF ^{99m}Tc-ALBUMIN MICROAGGREGATE DEGRADATION PRODUCTS (A METHOD FOR MEASURING KUPFFER CELL DIGESTIVE FUNCTION?)

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The rapid metabolism of radioactive albumin colloids used for liver-spleen-bone marrow scanning reduces radiation exposure to these organs and permits one to study the proteolytic digestive capacity of the reticuloendothial system (RES). The phagocytic function of the RES has been investigated extensively with ^{131}I-albumin aggregates as well as other radiocolloids. Despite its much greater potential clinical value, no practical test procedure has been developed to estimate digestive functions of the RES or more specifically of the liver's Kupffer cells in man.

Previously, small, colloidal-sized (10–20 nm) albumin aggregates were used (*1,2*). These preparations in tracer doses (>0.05 mg/kg) do not tax the enzymatic capacity of the RE cells. Albumin microaggregates, as developed in this laboratory (*3,4*), have a much larger size (1–5 μm) and do have the capability to load the proteolytic enzymatic function of the RE cells.

At an early stage of our search for a way to measure proteolytic RES function with microaggregates, ^{99m}Tc was found inadvertently to be excreted by the biliary system into the gallbladder and small bowel. This observation was surprising in view of the different metabolic pathways of its ^{131}I counterpart (^{131}I-albumin microaggregates) and of ^{99m}Tc-pertechnetate. The present study was then designed to learn more about the biliary excretion of ^{99m}Tc following albumin microaggregate injection and to determine whether its rate and amount of excretion could be used to estimate a proteolytic digestive function of the liver's Kupffer cells.

TEST MATERIALS

Technetium-99m-microaggregate suspensions of human serum albumin were prepared daily in the laboratory by the method of Yamada and Taplin (*4,5*).

Preparation of ^{99m}Tc-albumin microaggregates. Technetium-99m-albumin (*4*) at pH 5.2 in a 0.1 solution is heated at 100°C for 3½ min with shaking. It is then cooled to room temperature and yields a suspension of macroaggregates, measuring 10–15 microns in diam. This suspension is then ultrasonicated for 10 min to reduce the aggregate size to 1–5 microns. The suspension is examined microscopically to ascertain the absence of particles larger than 8 microns which are not suitable for liver scanning. This method of preparation has been used in this laboratory for more than 5 years and has consistently given suspensions with a relatively narrow size range (1–5 microns). As much as 98% of the radioactivity can be removed from the suspensions by centrifugation for 5–10 min at 3,000 rpm.

METHOD

Studies were performed in 59 patients with various disorders. Among them, 15 had no known hepatic, infectious, or hematological diseases. One healthy volunteer also served as a control subject. The main disorders in the other patients included nine with diffuse liver disease (hepatitis, cirrhosis, fatty liver), 14 with infectious diseases (liver abscess, sepsis, pneumonia, empyema, pancreatitis, etc.), 11 with hematological diseases (anemia, hemoglobinopathies, undiagnosed splenomegaly, hypersplenism), and nine with Hodgkin's disease.

After intravenous injection of ^{99m}Tc-microaggregated albumin (2.5 mCi attached to less than 1.0 mg albumin) routine liver-spleen imaging was performed during the first 30 min after injection, using a gamma scintillation camera*. Three hours after

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* Either a Nuclear-Chicago Pho/Gamma or a Picker Dynacamera II.

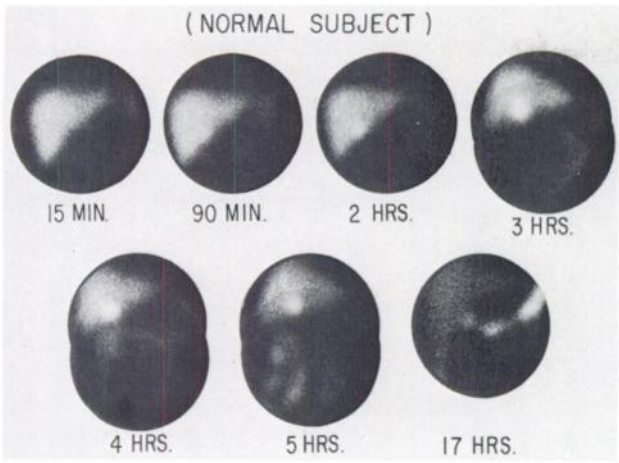

FIG. 1. Sequential liver-abdominal imaging with ^{99m}Tc-albumin microaggregates in healthy 35-year-old male. Radioactivity increases in gallbladder between 2 and 3 hr and later configuration of small intestine is visualized.

injection, anterior views of the liver-spleen and upper abdominal regions were obtained. In selected cases, serial imaging was performed at various intervals during the first 5 hr.

Most patients were given breakfast 2 hr prior to tracer injection, and the studies were completed before lunch. An additional meal was given in 12 patients 2–3 hr after injection to observe its effect on biliary excretion of the tracer.

RESULTS

A representative sequential study in a healthy control subject is shown in Fig. 1. In controls the liver and biliary system images show negligible changes within the first 90 min. Between 2 and 3 hr the gallbladder becomes faintly visible. At 3 hr the gallbladder image becomes distinct. Small amounts of activity also appear in the upper abdominal region and have the configuration of the small intestine. This activity in the small intestine is better appreciated when the image is produced with increased intensity. However, the relative activity in the intestine at 3 hr is normally much less than that in the liver. Small intestinal activity gradually increases, and by 5 hr the small intestinal configuration is readily recognized. However, no activity was found to accumulate either in the stomach or in the large intestine during this period. In five patients with various RES disorders, increased biliary excretion of ^{99m}Tc was seen by 3 hr.

Case 1 was a 59-year-old male with chronic thoracic empyema following pneumococcal pneumonia 10 years ago. The first radioisotope study was done when the patient was under tubal drainage. As shown in Fig. 2A, the gallbladder had a high concentration of radioactivity as early as 90 min after injection and by 3 hr a considerable accumulation of activity was present in the small intestine.

Eight days later, the same procedure was repeated and showed similar findings (Fig. 2B). The same study was repeated 5 months later (after the empyema was completely healed) and revealed intestinal and gallbladder activity in amounts (Fig. 2C) which could not be distinguished from those in control subjects.

Case 2 was a 22-year-old male with Hodgkin's disease, Class IIa. The first serial study (Fig. 3A) showed high radioactivity levels in the gallbladder and small intestine in the camera image taken 3 hr after injection. The 4-hr study showed more activity in the small intestine than that remaining in the liver. This patient was also studied 8 days later to confirm the reproducibility of this observation. The picture taken 2 hr after injection already showed considerable activity in the small intestine, and serial pictures taken between 2.5 and 3 hr showed changing patterns in the upper intestine below the gallbladder and increasing activity levels in the lower part of the small bowel (Fig. 3B).

Case 3 involved hemoglobinopathy with splenomegaly in a 49-year-old male. The patient was admitted because of severe epigastric distress and anemia. The initial clinical impression was hemorrhagic pancreatitis although serum and urinary amylase values were not markedly increased (9,900 units in

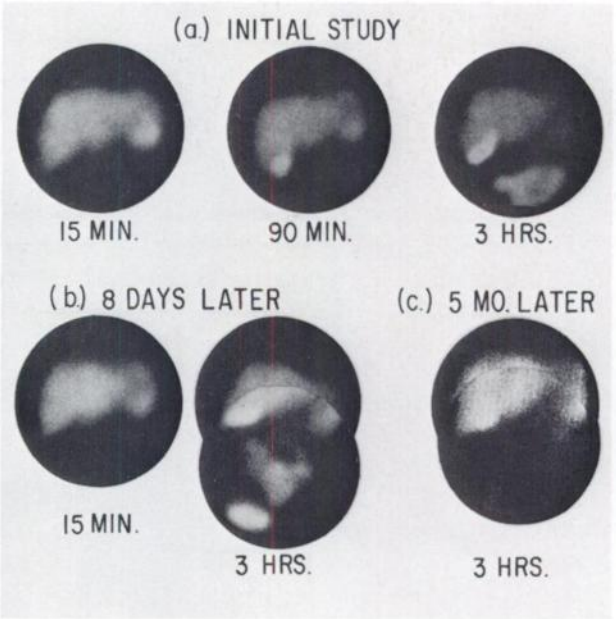

FIG. 2. Case 1. Similar studies in 59-year-old man with chronic thoracic empyema. Initial sequential study (a) shows marked accumulation of activity in gallbladder at 90 min followed by considerable increase of small intestinal activity at 3 hr. Repeated study 8 days later (b) shows again greatly increased activity in small intestine in 3-hr image. Third study (c) performed 5 months later shows biliary excretion of activity in normal amounts at 3 hr.

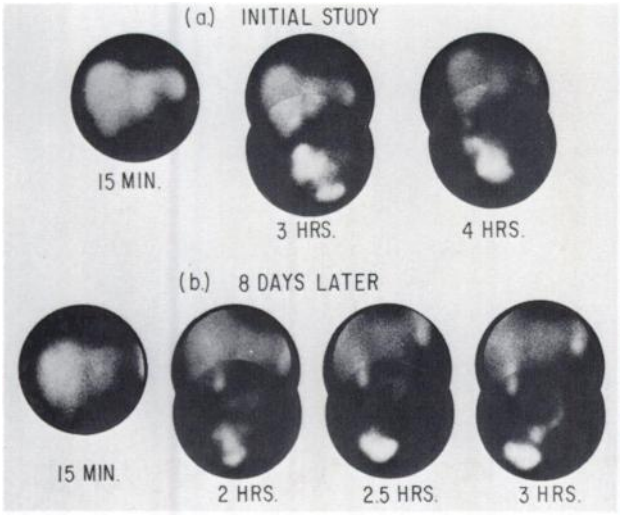

FIG. 3. Case 2. Hodgkin's disease (IIa), 22-year-old male. First examination (a) shows high radioactivity levels in gallbladder and small intestine regions in 3 hr images. Four-hour study shows more activity in small intestine than that remaining in liver. Second study (b) performed 8 days later again shows increased amounts and rapidity of ^{99m}Tc excretion through biliary system.

24-hr urine sample). Eight units of blood transfused in 4 days did not improve the hematocrit in spite of no known source of bleeding.

Soon after the transfusions, the patient began to complain of severe left hypochondral pain. The spleen became larger by palpation, and the enlargement was confirmed by x-ray films of the abdomen taken before and after the transfusions.

The possibility of abnormal splenic sequestration of red blood cells was suspected. The discontinuation of transfusion treatment was followed by immediate clinical improvement, and spleen size began to decrease. The first sequential ^{99m}Tc-albumin microaggregate study was performed at this time. Between 2 and 3 hr, activity in the small intestine became easily visible and progressively increased until 4 hr when the study was stopped (Fig. 4A). The gallbladder was not visualized (oral cholecystography also did not show the gallbladder). One month later, the patient was examined again, and less activity was found in the small intestine than previously. The same patient was followed for 1 year with repeated examinations. In these, the images at 3 hr showed minimal biliary excretion similar to the second study. During this period, however, no episodes of hypersequestration were observed.

Case 4 involved probable mycosis fungoides in a 62-year-old male with a generalized skin disease of 10-years' duration. The dermatologist's clinical impression was mycosis fungoides, but skin biopsy was not confirmatory. His past history included a cholecystectomy 10 years ago and a gastrojejunostomy with subtotal gastrectomy 6 years previously.

The first liver-imaging study showed a considerable accumulation of activity in the upper small intestinal area at 3 hr, and the 4-hr examination showed a faint liver image compared with the much higher intestinal activity (Fig. 4B). Serial pictures taken between 3 and 4 hr showed persistent radioactivity near the liver hilum indicating biliary excretion of ^{99m}Tc. A second study 1 week later showed similar findings.

A similar increase of biliary excretion of ^{99m}Tc was observed in another case during an acute infection (high fever, abdominal pain, and leukocytosis) which subsided promptly after administration of colistin. In this case, successive radioisotope studies after the febrile episode was over showed normal biliary excretion. Excessive biliary excretion of a milder degree was observed in two other patients with Hodgkin's disease and in one young woman with an hemoglobinopathy (SS) and splenomegaly. However, the other 11 patients with bacterial infections did not show this phenomenon, nor was it seen in the other six cases of Hodgkin's disease even though some of them were studied repeatedly. In patient's with diffuse liver disease, the rates and amounts of biliary excretion of pertechnetate were either in the normal range or below (Figs. 5A, B, C).

Among 12 studies in which a second meal was given during the examination, only one showed increased biliary excretion of ^{99m}Tc, the same person (Case 4) who also showed abnormal excretion during his first study.

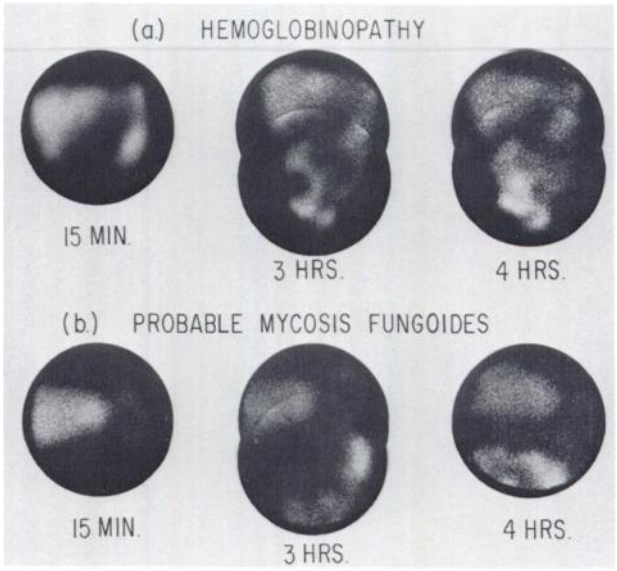

FIG. 4. Cases 3 and 4. Hemoglobinopathy with splenomegaly, 49-year-old female, (a) and probable mycosis fungoides, 62-year-old male (b). Both patients show abnormally increased biliary excretion of ^{99m}Tc in delayed examinations compared with findings in control subjects (Fig. 1).

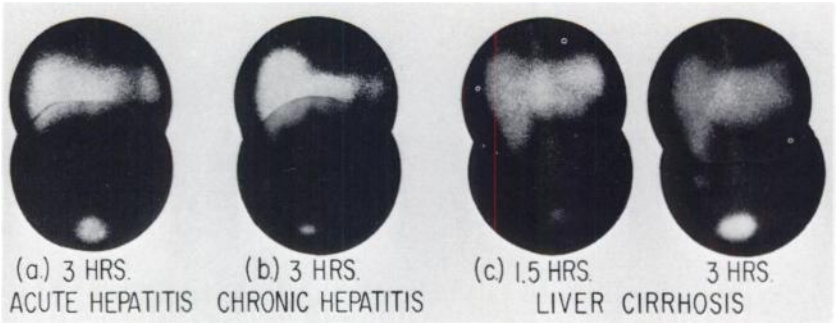

FIG. 5. Acute hepatitis (a), chronic hepatitis (b), and liver cirrhosis (c), all show less biliary excretion of ^{99m}Tc than normally seen.

DISCUSSION

Metabolic pathways. Technetium-99m as pertechnetate was first introduced for human use by Harper in 1964 (*6*). Since then several different preparations of ^{99m}Tc-labeled compounds such as ^{99m}Tc-albumin macroaggregates and sulphur colloids have been widely used. With these preparations, however, no reports concerning their metabolic fates have mentioned *biliary excretion* either in man or animal studies (*6–9*). Among these compounds, ^{99m}Tc-pertechnetate (*7*) is well known to be excreted into the stomach and the large intestine but not through the biliary system. The ^{99m}Tc-iron-ascorbic acid complex, which is present in our albumin microaggregate preparations in small amounts, is almost exclusively excreted by the kidney (*9*). The small amount of activity found in the urinary bladder in the first few hours may be due to the ^{99m}Tc-iron-ascorbic acid complex which is not bound to protein.

Results of the present study clearly demonstrate the presence of a biliary pathway of ^{99m}Tc excretion in man when ^{99m}Tc-albumin microaggregates are administered intravenously. The first question one might raise is, what kind of ^{99m}Tc compound comes through the biliary pathway? To investigate this problem, delayed imaging was performed following injection of ^{99m}Tc-pertechnetate, ^{99m}Tc-albumin, ^{99m}Tc-albumin macroaggregates, and ^{99m}Tc-sulphur colloid. As anticipated, none of these compounds showed scan evidence of biliary excretion during the first 5 hr postinjection. The origin of the ^{99m}Tc in the bile is probably neither a non-protein fraction (iron-ascorbic acid complex) contained in the original radioalbumin microaggregate preparation nor unaggregated (plain) radioalbumin. Most probably, the ^{99m}Tc in the bile is a radioalbumin degradation product released from the liver's Kupffer cells into the hepatobiliary pathway.

Possible biliary excretion mechanisms. The biliary excretion of this ^{99m}Tc compound or albumin degradation product may occur in three steps or by three different physiological mechanisms; initial phagocytosis of particles by the liver's Kupffer cells, a secondary proteolytic digestive phase in the Kupffer cells, and final hepatic cell uptake with subsequent excretion into the biliary tract.

Since the total test dose of albumin ($\sim$1.00 mg) in the microaggregate suspensions used in this study is a trace amount, the blood clearance is solely dependent upon liver blood flow (*1*). It is known from previous work (*10*) that the liver extraction efficiency of this agent is more than 90% and is much higher than that of conventional smaller colloids. Therefore the duration of the Kupffer cell trapping process ($T_{1/2}$ = 2–3 min) is quite constant, except in advanced liver disease (severe cirrhosis) where effective liver blood flow is known to be reduced and peak liver uptake time is grossly delayed.

The final (third) step or hepatobiliary excretion, on the other hand, could be affected by various pathologic conditions. The undetectable amounts of ^{99m}Tc biliary excretion in patients with liver disease may be explained by disturbances involving the hepatic cells *and* the biliary pathway. In these cases a delay in the second step (proteolytic process) may be possible but cannot be proved. In patients without liver disease, and presumably normal hepatobiliary kinetics, the second step (Kupffer cell digestive phase) could then be considered the rate controlling process. Thus in such patients, overactive proteolytic digestive function of the Kupffer cells seems to offer the best explanation for increased rates and amounts of ^{99m}Tc biliary excretion.

RES digestive function measurement. With the administration of loading doses of colloidal albumin aggregates labeled with ^{131}I, Biozzi, et al found rapid decreases of liver activity in mice treated with diethylstilbestrol (*1*). With the same principle, Taplin, et al found rapid liver release rates and secondary rises of activity in the blood in patients with bacterial infections, allergic dermatitis, and Hodgkin's disease (*2*). The rapid turnover of loading doses of albumin particles might be due, as Biozzi admitted, either to an increase of the number of phagocytic cells or to an increase of enzymatic function of individual cells

and cannot be interpreted as direct evidence for the latter. In other words, a simple increase of RE cells, with normal or even somewhat less enzymatic activity, could produce the same results. In addition, proliferation of RE cells with decreased enzymatic activity has been reported by Pisano, et al in glucan treated rats (*11*). Therefore the RE test procedures employed in the past have theoretical limitations for assessing the digestive enzymatic activity of RE cells generally or individually.

Kupffer cell digestive function. Albumin microaggregate suspensions used in the present study have a much larger particle size than conventional albumin colloids. The capacity to load the liver's RE cells has been demonstrated by ^{131}I-labeled microaggregates which have much slower liver release rates than ^{131}I-colloidal albumin administered in the same tracer doses (*4,5,10*). Thus the larger particle size suspensions have greater potential applicability as agents for the qualitative assessment of proteolytic digestive function once an adequate index for their liver release rates is devised.

The method developed in the present study, namely, repeated abdominal imaging following ^{99m}Tc-albumin microaggregate injection to measure biliary excretion and liver release, appears to be practical and adequate for clinical purposes but does not lend itself to precise quantification. Whether or not the patients who showed excessive biliary excretion really had increased digestive function of the Kupffer cells is hard to prove because of the lack of another confirmatory procedure. However, those cases described as examples of increased Kupffer cell function had various disorders known to be associated with increased RES phagocytic function (*2,12–15*). It is conceivable that in some of these disorders the proteolytic digestive function of the Kupffer cells is also enhanced. The negative findings in other cases with similar diseases in this study could be due to associated liver cell damage or to normal or below normal Kupffer cell enzymatic function. A discrepancy between the phagocytic and catabolic functions of the RES has been reported in some disorders (*15*).

Limitations and potential value. The limitations of this procedure are its dependency on biliary kinetics and its qualitative nature which make slight deviations from normal, difficult, or impossible to detect. However, on the positive side, the procedure is relatively simple compared with other methods (*1,2,12*) for estimating digestive function of the RES and can be performed on a routine basis. Its capacity to visualize the gallbladder is clinically helpful for interpreting liver scans, when the cause of a scan indentation by the gallbladder needs confirmation. Further clinical experience with this method is necessary to establish its value as an indicator of Kupffer cell digestive function. The biliary excretion of an unknown ^{99m}Tc compound may have significance in the future for studying hepatobiliary pathophysiology. Once the chemical nature of this compound is elucidated, it might well serve as a valuable adjunct to radio-rose bengal and BSP in the assessment of hepatobiliary function.

CONCLUSIONS

The most important result of this study is the direct observation using scintillation camera imaging of the hepatobiliary excretion of a ^{99m}Tc compound, most probably an albumin degradation product, following the intravenous injection of ^{99m}Tc-albumin in particulate form (1–5-micron microaggregates). This finding has provided the first objective, practical, and potentially useful clinical method to *estimate* a proteolytic digestive function of the liver's Kupffer cells separately as opposed to those of the entire RES.

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