PHAGOCYTIC ACTIVITY OF THE LIVER AS A MEASURE OF HEPATIC CIRCULATION—A COMPARATIVE STUDY USING ^{198}Au AND ^{99m}Tc-SULFUR COLLOID

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The cells of the reticuloendothelial system, which are mainly localized in the liver, spleen, and bone marrow, are known to be capable of eliminating colloid particulate matter from the blood stream. As the colloidal particles are accumulated preferentially in the Kupffer cells of the liver, the disappearance rate of the injected colloid can be used to estimate the blood flow in this organ. It is understood in this case that considerable hepatocellular damage which might lead to Kupffer cell dysfunction does not exist.

Dobson (*1*) was apparently the first to measure the hepatic blood flow using the colloidal chromic phosphate labeled with ^{32}P. Colloidal radioactive gold (^{198}Au) was proposed by Vetter (*2*), the measurements being carried out by means of an external counting technique. Halpern and his group (*3*) advocated the use of heat denatured and labeled (^{131}I) human serum albumin for estimating liver blood flow. Technetium-99m-sulfur colloid, introduced by Harper (*4,5*), was also used to determine hepatic circulation (*6*). The usefulness of these procedures has been well established by comparing the values obtained with those of direct flow measurements (*7,8*).

In recent years, ^{99m}Tc as ^{99m}Tc-sulfur colloid is being used increasingly for clinical applications, especially for scanning purposes (*4–6,9–11*) because of its very favorable physical characteristics [$T_{1/2}$ = 6 hr; E_γ = 140 keV (98.6%); I_γ = 0.70 R/mCi-hr (*4*)]. The purpose of this study is to compare the clearance rates of ^{99m}Tc-sulfur colloid and the commonly used ^{198}Au-colloid in order to examine the validity of the disappearance rate as a characteristic parameter of the liver blood flow as confirmed in the case of ^{198}Au (*7,8,12*).

Both colloidal agents were administered to the same subject simultaneously; after the intravenous injection, the activity of both radionuclides (^{99m}Tc and ^{198}Au) was registered at several sites of the body. Each detector was attached to a dual discriminator which was adjusted to the photopeak of the individual nuclide (^{99m}Tc, 140 keV; ^{198}Au, 411 keV). By using the doses mentioned below, the Compton fraction of ^{198}Au in the ^{99m}Tc channel could be neglected. The digital data were stored in the memory of a multiscaler, processed to eliminate statistical fluctuations, and evaluated with respect to the corresponding rate constants. These studies were performed on normal (n = 27) and diseased (n = 71) subjects to show the disappearance rate in relation to the severity of the vascular impairment. Further clinical results will be published elsewhere (*13*).

After intravenous injection of a radioactive labeled colloid of suitable and uniform size, the elimination of the injected colloidal particles from the blood stream, as in many other physiological clearance processes, follows the equation (*14*):

$$P_t^b = P_0^b \exp(-kt) \qquad (1)$$

in which P_0^b is the number of injected particles, P_t^b the value at any time t, and k the corresponding disappearance constant. This equation is followed as long as the administered dose does not exceed certain limits, i.e. k is independent of P_0^b. With regard to the proportionality between the number of particles P and their externally measurable radioactivity N, this equation can be used to evaluate k and therefore the liver blood flow D (*1,2,15*).

However, the validity of this procedure depends on the following assumptions:

1. The colloidal particles perfusing the liver are removed from the blood stream in a single passage resulting in a clearance coefficient of a = 1.00.
2. The injected colloid is specifically accumulated

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in the liver, and the uptake by other organs can be disregarded.

3. The colloidal particles must be uniform in size and identical with regard to their physical and chemical properties.

4. The injected dose must be kept below a critical value so that the disappearance rate is independent of the amount.

As pointed out by several authors, these assumptions are not strictly valid in any case. Vetter found (*2*) that ^{198}Au is removed from the blood stream by the liver with an efficiency of about 80%, resulting in a clearance coefficient of a = 0.80. Hence it follows that the values calculated for the hepatic circulation were 20% too low compared with the true flow rate.

^{99m}Tc-sulfur and ^{198}Au-colloid are not only accumulated in the liver but also in other parts of the reticuloendothelial system, mainly in spleen and bone marrow (*9–11,16*). In this case, the measured rate constant k_T is the sum of the individual values k_1, k_2 . . . k_i; hence the hepatic flow calculated from the disappearance curve must be overestimated to a greater or less extent. Sometimes, the colloidal particles injected are not uniform with respect to their physical or chemical properties; in this case, the single fractions may be removed from the blood following exponentials of different rate constants k_a, k_b . . . k_z.

Furthermore, it must be pointed out that a multiexponential curve measured externally does not represent unambiguously the biological processes occurring in the organism after intravenous injection of a colloidal substance. The elimination of two different fractions from one compartment (blood) as well as the distribution of a uniformly sized fraction within two compartments, if injected into the one (blood) and penetrating with reduced exchange rate into the other (*15*), may be described by the same equation.

From the accumulation of the colloid in the liver,

$$N_t^1 = N_\infty^1 [1 - \exp(-kt)] + N_0^1 \exp(-kt) \quad (2a)$$

in which N_t^1 is the radioactivity measured above the liver at time t, N_∞^1 the value for $t \to \infty$, and N_0^1 that of the fractional blood volume perfusing the organ ($t \approx 0$). If accumulation also occurs in spleen and bone marrow, this becomes

$$N_t^1 = N_\infty^1 [1 - \exp(-k_T t)] + N_0^1 \exp(-k_T t). \quad (2b)$$

The rate constant k or k_T can be evaluated according to the procedure mentioned below. However, it must be assumed that the colloid is eliminated from the blood at the same rate as accumulated in the organs.

MATERIALS

^{198}Au-colloid. The ^{198}Au-colloid was obtained commercially (Farbwerke Höchst, Frankfurt-Höchst, Germany) as a sterile suspension stabilized with gelatin. The specific activity was about 100 μCi/μg, and the carrier concentration was in the range of 10 μg/ml. The particle size in a typical lot, obtained by electron microscopic measurements, was on the average 275 Å, ranging from 220 to 360 Å*. A dose of 200 μCi of ^{198}Au, corresponding to approximately 2 μg gold carrier, was administered to each subject, taking into account the decay of this radionuclide ($T_{1/2}$ = 2.70 days).

^{99m}Tc-sulfur colloid. The suspension of ^{99m}Tc-sulfur colloid was prepared in our laboratory whenever needed, using a kit available commercially (Farbwerke Höchst, Frankfurt-Höchst, Germany). The suspension used for injection contained about 2 mCi ^{99m}Tc and 50–150 μg colloidal sulfur in 0.5–2.0-ml solution. The size of the colloidal particles, measured by electron microscopy, ranged from 200 to 300 Å*. A determination of size distribution failed because of technical difficulties.

METHODS

These studies were carried out with the multichannel function test device "Mainz". A description of this apparatus and some examples of actual application were given elsewhere in detail (*16,17*).

Both colloidal suspensions were injected intravenously within a few seconds, and the radioactivity was measured continuously as a function of time at several sites of the body (liver, spleen, and forearm; in some cases additionally above heart, head, and left kidney). The digital data were fed into the memory unit operating in multiscaler mode. Each detector is equipped with two independent channels which can be adjusted individually to the photopeak energy of two different radioisotopes. The memory unit is divided into 16 subgroups of 256 storage places each; each subgroup is assigned to one channel of a detector. The pulses in the single channels can be fed into the memory at different counting times. This direct storage mode under preselected standard conditions was advantageous because of the considerable time saving in routine work (*15*).

The activity curve resulting from an elimination process (blood and forearm activity curve, respectively) was read out logarithmically by an x-y plotter. The rate constants k can be evaluated by analyzing

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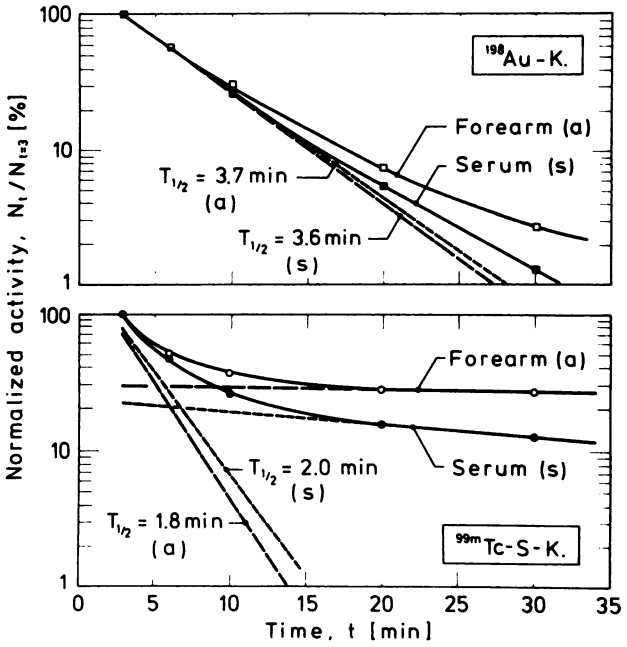

FIG. 1. Top shows disappearance of ^{198}Au-colloid from blood stream measured by withdrawing blood samples (s) and by external counting (a), respectively. Bottom shows disappearance of ^{99m}Tc-sulfur colloid from blood stream measured by withdrawing blood samples (s) and by external counting (a), respectively.

the activity curves in the logarithmic scale. This can be achieved if (A) the single rate constants of a multiexponential curve differ from each other sufficiently and/or (B) the contribution of the slower component can be neglected.

Complementary exponentials, as observed in accumulation processes (liver), are first differentiated electronically, read out logarithmically, and then evaluated as mentioned above. From Eq. 2, which describes the accumulation of activity in the liver and the simultaneous elimination from the fractional blood volume viewed by the detector, one obtains by differentiation

$$\frac{dN^1}{dt} = k \exp(-kt)(N_\infty{}^1 - N_0{}^1). \qquad (3)$$

Placing the detector above the liver properly, $N_0{}^1$ is generally found to be negligible ($N_\infty{}^1 \gg N_0{}^1$).

In practice, the digital data stored on magnetic tape are fed back into the memory of the multiscaler with negative sign, the origin differing from the original stored data for z storage places (*15*). Hereby, instead of the differential quotient (Eq. 3), one obtains the following expressions:

$$\frac{N_{i+z}{}^1 - N_i{}^1}{t_{i+z} - t_i} = z\,k \exp(-kt)(N_\infty{}^1 - N_0{}^1) \quad (4)$$

in which the denominator ($t_{i+z} - t_i$) is made equal to unity for convenience. In both cases, the statistical fluctuations could be minimized by processing the digital data in a suitable manner (*15*).

RESULTS AND DISCUSSION

Measuring the disappearance of gamma-emitting radionuclides from the blood stream, the external counting technique has proven to be most advantageous. Without the necessity of withdrawing several blood samples, the radioactivity of the injected radiocolloid can be measured continuously and evaluated in the usual manner.

However, it must be kept in mind that the region viewed by the detector may be composed of several "subcompartments" in which the colloidal particles behave quite differently. Hereby, complex activity curves may result which cannot be analyzed in any case by means of the usual graphical procedures. To insure that the measured activity curves really represent the biological process under investigation, i.e. the disappearance of the injected colloid from the blood stream, the external counting technique had to be controlled in an appropriate manner.

By measuring the disappearance of both colloids from the peripheral blood using external counting in the forearm and blood sampling at proper intervals following the injection, it could be shown (Fig. 1) that the half-time values in both cases agreed fairly well within the limits of accuracy of the determination.

In the case of the forearm counter measurements (a), the increased contribution of the slower component seemed to indicate that the colloid, especially ^{99m}Tc-sulfur, is retained in the region viewed by the detector to a greater or less extent. Furthermore, it was noticed that 30 min after injection ^{198}Au was eliminated from the blood stream to more than 98% whereas the elimination of ^{99m}Tc-sulfur amounted to 90% maximum in the same interval. The values measured were related to those obtained at 3 min after injection because at this point complete mixing of the colloids within the vascular system should be attained.

The activity curves in a normal case showing elimination and accumulation of ^{198}Au- and ^{99m}Tc-sulfur colloid from peripheral blood and in the liver are compiled in Fig. 2. Whereas the behavior of ^{198}Au in the processes of elimination and accumulation can be described by monoexponential functions, ^{99m}Tc-sulfur appeared to follow a biexponential expression of different rate constants. Since both exponentials occur as well in elimination as in accumulation processes, it follows that this colloid must be composed of at least two fractions which are removed from the blood stream at different rate constants. The complex character of the measured ^{99m}Tc curves may not be brought about by a disturbed perfusion, for the simultaneously applied ^{198}Au behaves as expected.

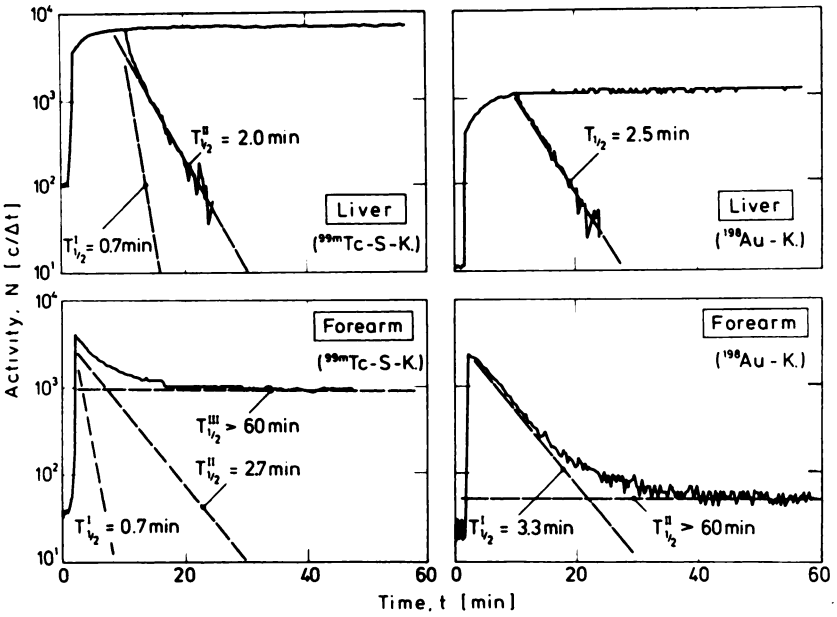

FIG. 2. Comparison of elimination with accumulation of ^{198}Au- and ^{99m}Tc-sulfur colloid, measured above liver and forearm simultaneously by external counting (normal case).

The corresponding curves for both colloids in a diseased subject (cirrhosis) are shown in Fig. 3. This plot appeared to be representative for all studied cases (n = 11) of cirrhotic disease. The significantly increased half-time values both in elimination and accumulation indicates the degree of impairment of hepatic circulation produced by cirrhosis.

Comparing the half-times of both colloids measured in the peripheral blood (forearm), one obtains the correlation shown in Fig. 4. The values obtained were processed by the usual statistical procedures (*18*). The regression line was determined by least-squares fit of the data. The broken lines above and below the main line are the 95% confidence limits.

From this it follows that the main fraction of ^{99m}Tc-sulfur colloid is removed from the blood stream more rapidly than ^{198}Au. This finding, first stated by Haas (*6*), may be explained by assuming an enhanced accumulation of ^{99m}Tc-sulfur colloid in other parts of the reticuloendothelial system, mainly in spleen and bone marrow (*9–11*). By

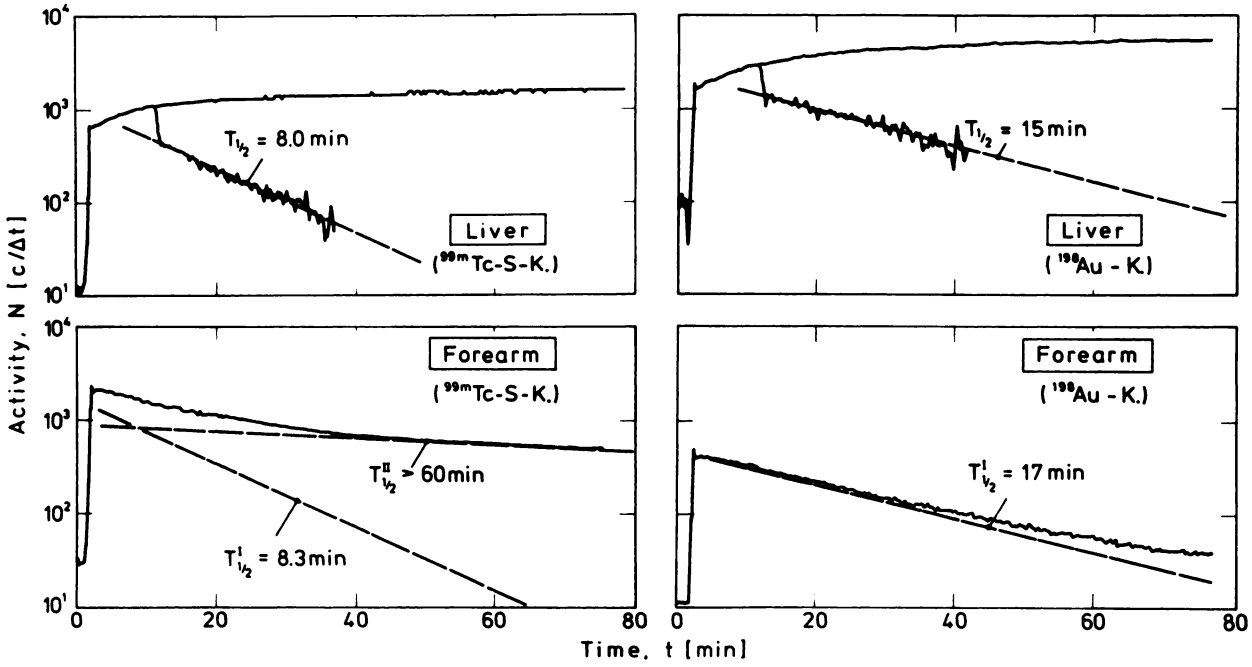

FIG. 3. Comparison of elimination with accumulation of ^{198}Au- and ^{99m}Tc-sulfur colloid measured above liver and forearm simultaneously by external countng (cirrhotic subject). Plot is representative of all studied cases.

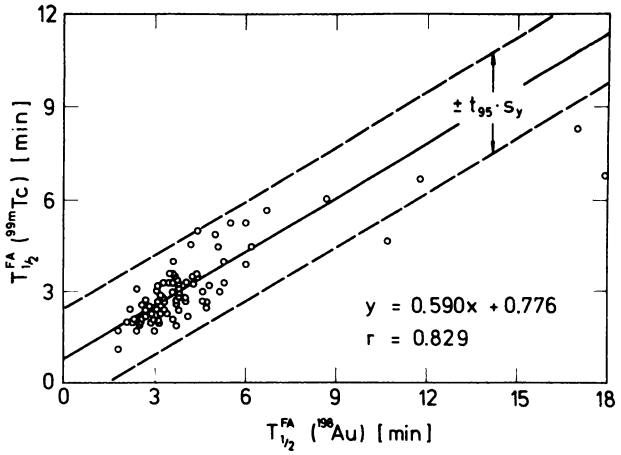

FIG. 4. Correlation of disappearance half-time of ^{198}Au [$T_{1/2}^{FA}$ (^{198}Au)], measured in the peripheral blood (forearm), with that of ^{99m}Tc-sulfur colloid [$T_{1/2}^{FA}$ (^{99m}Tc)], showing regression line and its 95% confidence limits (n = 82).

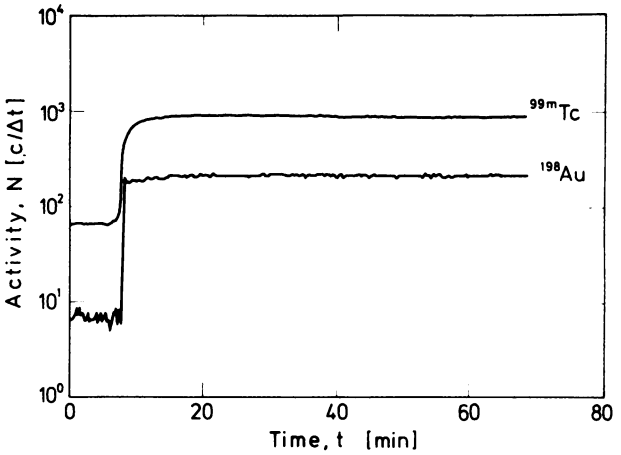

FIG. 5. Splenic uptake of ^{198}Au- and ^{99m}Tc-sulfur colloid, respectively, measured simultaneously by the same detector.

measuring the splenic uptake of both colloids with the same detector simultaneously, this assumption could be confirmed in all cases (Fig. 5); ^{99m}Tc-sulfur colloid was accumulated in the spleen to a greater extent than ^{198}Au-colloid. Hence it follows that ^{99m}Tc-sulfur must be eliminated from the blood stream at an increased rate. The enhanced affinity of the phagocytic cells of spleen and bone marrow towards the ^{99m}Tc-sulfur colloid may also be deduced from the finding that the correlation observed (Fig. 4) seems to fail at high $T_{1/2}^{FA}$ values.

However, ^{198}Au-colloid is also accumulated in the spleen to a greater or less extent (*16*). The constant activity level (Fig. 5) of the ^{198}Au curve over a period of 60 min in which the concentration in the peripheral blood decreased by almost two orders of magnitude (Figs. 1 and 2) indicated an accumulation of the colloid in the spleen. A similar correlation could be found between the half-times $T_{1/2}^{L}$ of both colloids measured above the liver. From least-squares fit computation the regression line obtained was: $y = 0.522 \times +1.005$, with a correlation coefficient of $r = 0.818$.

A comparison of accumulation with elimination of each colloid revealed that both processes proceed at slightly different rate constants. As shown in Fig. 6 for ^{198}Au-colloid, the half-time values measured above the liver (accumulation) are significantly shorter than those obtained in the peripheral blood (elimination). A similar correlation was obtained in the case of ^{99m}Tc-sulfur colloid. By means of least-squares fit computation the observed data could be represented by the regression line, $y = 1.048 \times +0.513$, with a correlation coefficient of $r = 0.858$. There is no reasonable explanation for this observation until now. Perhaps accumulation of the colloid in the liver may occur heterogenously, and the detector viewing only a small region of the total organ measures in this part the accumulation proceeding with relative high speed. On the other hand, a slightly disturbed perfusion in the forearm may also lower the elimination rate to a greater or less extent.

The disappearance of intravenously injected colloidal particles from the blood stream generally follows a first order reaction (Eq. 1), implying that the rate constant k is independent from the administered dose P_0. This assumption holds true as long as P_0 does not exceed a "critical value" P_c (*3,14*). In the case that $P_0 > P_c$, k proved to be strongly dependent on P_0 (*14*). Furthermore, it was found that k only depends on the number of injected particles and not on the size within certain limits (*14*).

To insure the validity of the assumption that the k values obtained in these studies only indicate hepatic circulation, two equally sized doses were injected within a period of 1 hr into the same sub-

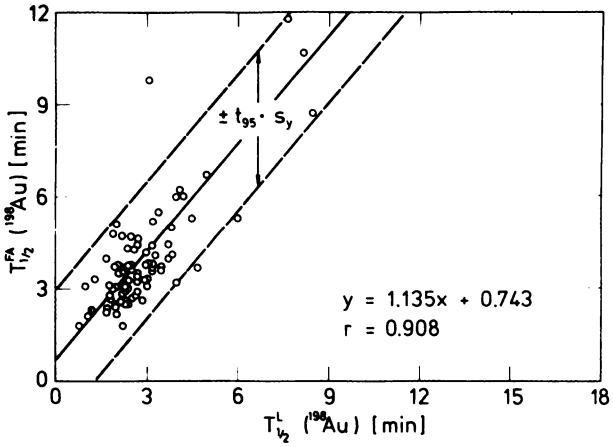

FIG. 6. Correlation of accumulation half-time $T_{1/2}^{L}$ measured above liver, with elimination half-time $T_{1/2}^{FA}$, measured in peripheral blood (forearm), showing regression line with its 95% limits (n = 88).

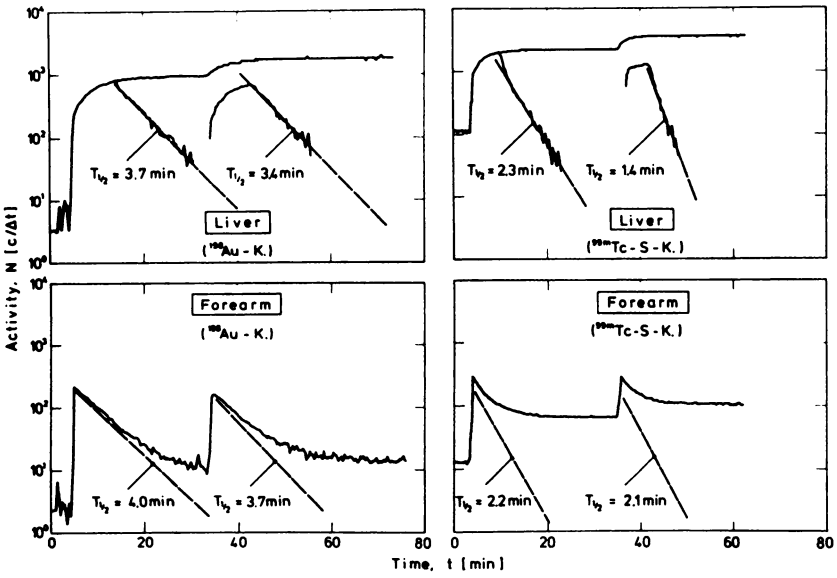

FIG. 7. Examination of reproducibility of half-time values of elimination and accumulation of both colloids, respectively, by repeated administration of equally sized doses.

ject (Fig. 7). The half-times of accumulation and elimination measured above the liver and forearm were determined in both cases and compared with each other by calculating the quotient of the corresponding values.

In the case of ^{198}Au, the measured half-times agreed fairly well within the limits of accuracy of the determination in both repeated injections, yielding a quotient of $T_{1/2}^{(1)}/T_{1/2}^{(2)} = 1.060 \pm 0.022$ ($n = 21$) for peripheral blood and $T_{1/2}^{(1)}/T_{1/2}^{(2)} = 1.067 \pm 0.042$ ($n = 21$) for liver ($\pm$ 1 s.d.). The ratio of the saturation values $N_\infty^{(1)}$ and $N_\infty^{(2)}$ measured above the liver approached very closely $N_\infty^{(2)}/N_\infty^{(1)} = 1.994 \pm 0.019$ ($n = 21$); the theoretical value is $N_\infty^{(2)}/N_\infty^{(1)} = 2.000$. Hence it follows that the dose administered in these studies (about 2 μg) is far below the critical value [about 250 μg (*2*)], and therefore the process of phagocytosis may proceed at a rate which really reflects the situation of hepatic circulation.

In the case of the ^{99m}Tc-sulfur colloid, there is quite a different situation. The ratio of half-times and saturation activities are found to be $T_{1/2}^{(1)}/T_{1/2}^{(2)} = 1.215 \pm 0.049$ ($n = 23$) for peripheral blood and $T_{1/2}^{(1)}/T_{1/2}^{(2)} = 1.408 \pm 0.075$ ($n = 26$) and $N_\infty^{(2)}/N_\infty^{(1)} = 1.514 \pm 0.035$ ($n = 26$) for the liver, respectively. The significantly lowered uptake of the colloid in the liver following the second injection appeared as a result of a partial saturation of the phagocytic cells in th.s organ, for the doses administered amounted to 2 $\times$ 150 μg sulfur carrier maximum. On the other hand, the increased rate constants in the second phase seemed to indicate that phagocytosis within the reticuloendothelial system was stimulated by the preceding injection. There is no reasonable explanation for this principal difference in phagocytosis of both colloidal substances.

To establish the normal range for the clearance of both colloids, 27 adult males ($n = 18$) and females ($n = 9$) without any hepatic disorder were selected. Determining the usual clinical standard tests, GOT, GPT, G1DH, SDH, alkaline phosphatase, bilirubin, proteins by electrophoresis in serum, and urobilinogen and bilirubin in urine, all values appeared to be normal. In the case of the cirrhotic subjects ($n = 11$), the clinical diagnosis was additionally confirmed by liver biopsy, laparoscopy, or section (*13*). The normal values obtained in this study for the half-time $T_{1/2}$ and the rate constant k for the elimination were found to be in the following range (with 95% limits):

^{198}Au-colloid	$T_{1/2} = 1.98 - 4.86$ min
	$k = 0.350 - 0.143$ min^{-1}
^{99m}Tc-sulfur colloid	$T_{1/2} = 1.46 - 4.21$ min
	$k = 0.476 - 0.165$ min^{-1}

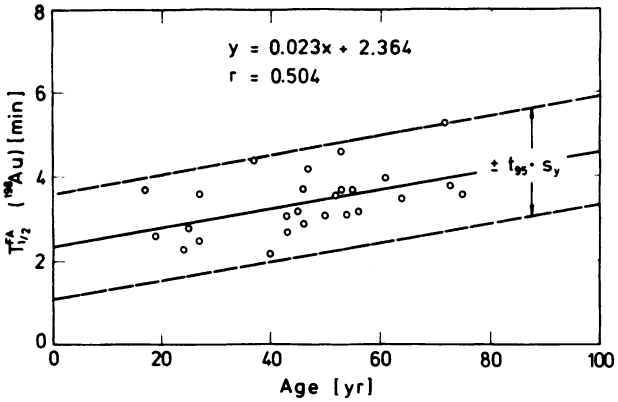

FIG. 8. Correlation of disappearance half-time $T_{1/2}^{FA}$ of ^{198}Au with age of normal subjects, showing regression line with its 95% confidence limits ($n = 27$).

These values agree fairly well with those quoted in the literature (*2,6,19,20*).

By plotting the half-times against the age of the subjects, it could be shown that the colloids are eliminated from the blood stream more rapidly in young people than in aged persons. The regression line for the ^{198}Au-colloid, calculated by least-squares fit with the 95% limits, is shown in Fig. 8. The corresponding correlation for the ^{99m}Tc-sulfur colloid could be described by the equation $y = 0.032 \times +1.502$, with a correlation coefficient of $r = 0.510$.

SUMMARY

A comparative study of the disappearance of ^{198}Au- and ^{99m}Tc-sulfur colloid from the blood stream clearly showed that both agents differ appreciably from each other in their behavior. The most essential points can be summarized as follows:

1. ^{99m}Tc-sulfur colloid is eliminated from the blood stream more rapidly than ^{198}Au-colloid (^{99m}Tc: $k = 0.165–0.476\ min^{-1}$; ^{198}Au: $k = 0.143–0.350\ min^{-1}$). The increased values can be explained by the observation that the ^{99m}Tc-sulfur colloid is accumulated in other parts of the reticuloendothelial system to a greater extent than ^{198}Au. In particular, the splenic uptake of the former exceeds that of the latter significantly as shown by direct, simultaneous measurements (Fig. 5).

2. By measuring elimination and accumulation of the ^{99m}Tc-sulfur colloid simultaneously, the resulting activity curves are often composed of two exponentials, in contrast to the ^{198}Au-colloid (Fig. 2). This finding may be explained by assuming a heterogeneity of the colloid used. In both cases, accumulation in the liver proceeds slightly more rapidly than elimination from the blood stream (Fig. 6).

3. The disappearance of both colloids is slowed down appreciably in cirrhotic subjects indicating that blood flow is reduced by impairment of the vascular system of this organ. The ^{198}Au seemed to be a more sensitive index of hepatic circulation than the ^{99m}Tc-sulfur colloid because the correlation of the $T_{1/2}$ of the latter fails in the region of high values (Figs. 3 and 4).

4. As shown by repeated injections of equally sized doses into the same subject within 60 min, ^{198}Au is eliminated in the second phase at the same rate ($k^{(2)}/k^{(1)} = 1.060$) from the blood stream and accumulated in the liver at the same ratio ($N_\infty^{(2)}/N_\infty^{(1)} = 1.994$). In contrast to this, ^{99m}Tc-sulfur colloid is removed at an increased rate ($k^{(2)}/k^{(1)} = 1.215$) and deposited in liver and spleen to a lowered extent ($N_\infty^{(2)}/N_\infty^{(1)} = 1.514$).

5. The colloids are eliminated from the blood stream more rapidly in young subjects than in aged persons (Fig. 8).

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