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Research Article

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Studies of the Metabolism and Distribution of Fibrinogen in Patients with Hemophilia A*

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Abstract. Using autologous ^{131}I-fibrinogen, we made studies of the metabolism and distribution of fibrinogen in 10 patients with hemophilia A. In two patients simultaneous studies of autologous ^{131}I-fibrinogen and homologous ^{125}I-fibrinogen prepared from healthy donors' plasma were carried out. The average value for the plasma volume was 42.1 ± 8.8 ml/kg; for the plasma fibrinogen concentration, 349 ± 90 mg/100 ml; for the intravascular fibrinogen, 144 ± 32 mg/kg; for the interstitial fibrinogen, 30 ± 11 mg/kg; for the slower half-life of ^{131}I-fibrinogen, 2.34 ± 0.17 days; for the transcapillary transfer rate of fibrinogen, 109 ± 37 mg/kg per day; and for the catabolic and synthetic rates of fibrinogen, 51.7 ± 13.1 mg/kg per day. Comparison of these results with those of the previous study in healthy male subjects showed that in patients with hemophilia A the catabolic and synthetic rates of fibrinogen are markedly increased, whereas the plasma fibrinogen concentration, intravascular and interstitial fibrinogen, and the transcapillary transfer rate of fibrinogen are not significantly different. The simultaneous studies of autologous ^{131}I-fibrinogen and normal homologous ^{125}I-fibrinogen in two subjects revealed that the two preparations behaved very similarly. Based on these findings, we concluded that our present findings are not due to the qualitative difference between the hemophilia A and normal fibrinogens, but that they are due to the difference in the host condition with respect to the fibrinogen metabolism, which is either an increased rate of direct breakdown of fibrinogen or an increased rate of fibrinogen breakdown after fibrin formation, or both.

Introduction

It has been reported that fibrinolytic activity in patients with hemophilia A is increased (1, 2) and that ε-aminocaproic acid is effective in reducing the incidence of hemorrhage (2) and also hemostasis after dental extraction in such patients (3). However, other reports claim that ε-aminocaproic acid is not effective in reducing the incidence or severity of hemorrhage (4). Therefore, it seemed of interest to see whether there is any alteration of fibrinogen metabolism in patients with hemophilia A. We therefore studied the metabolism and distribution of fibrinogen in 10 male patients with hemophilia A, using autologous ^{131}I-fibrinogen in eight patients and autologous ^{131}I-fibrinogen and homologous ^{125}I-fibrinogen simultaneously in two patients.

Methods

The subjects were male patients with hemophilia A who have been under study at Colorado General Hospital for many years. They ranged in age from 10 to 54 yr, and all had a family history of hemophilia A. The general experimental procedure was the same as described previously (5). The preparation of ^{131}I- or ^{125}I-fibrinogen was carried out by the previous methods (5). The clottability of prepared fibrinogen and labeled fibrinogen (6) averaged 96%. At the start of the experiment, 20–30 μc of ^{131}I-fibrinogen prepared from the subjects' own

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plasma was injected intravenously into the subjects, and in two subjects homologous ^{125}I-fibrinogen prepared from the plasma of healthy donors was injected simultaneously. The injected ^{131}I- or ^{125}I-fibrinogen contained about 5 mg fibrinogen. The first blood sample was obtained at 15 min postinjection and subsequent samples were obtained 0.125, 0.25, 1, 2, 3, 4, 5, 6, 7, and sometimes 8 days postinjection. The samples were heparinized. 24-hr urine collections were made daily. The samples were assayed for radioactivity in a well scintillation counter (Nuclear-Chicago Corp., Des Plaines, Ill., model 8725) with spectrometer and a sensitivity of approximately 8×10^5 cpm/μc of ^{131}I above the background of 20 cpm and about the same sensitivity for ^{125}I above the background of 15 cpm. The total radioactivity remaining in the body at any time after initial injection of ^{131}I- or ^{125}I-fibrinogen was measured daily as described elsewhere (5), and in some cases it was doubly checked by whole body counting. The whole body counter was equipped with a 4×9 inch NaI crystal and 512 Channel analyzer (model 120, Nuclear Data Corp.). The counting was done by the State of Colorado Department of Public Health. The plasma volume (5) and the plasma fibrinogen concentration were measured as described previously (6). The microhematocrit and the erythrocyte sedimenattion rate [Wintrobe's method (7)] were measured on all blood samples. Some plasma samples were analyzed for radioactivity unbound to fibrinogen (5) and euglobulin fibrinolysis time (8). In all subjects studied the euglobulin fibrinolysis time was within the normal limit, 2–6 hr. The recalcification time (9), serum prothrombin time, (9) and Lee-White clotting time (9) were also determined by Dr. K. N. von Kaulla and his staff, and in all subjects they were found to be abnormal. The diagnosis of hemophilia A was made by noncorrection of the shorter serum prothrombin time upon addition of normal serum and by its correction upon addition of $BaSO_4$-treated normal plasma. The tracer data were analyzed by the previous methods (10–13).

Results

Table I gives the plasma fibrinogen data. The body weight measured daily showed negligible fluctuations during the study. Analysis showed that the plasma volume is significantly increased ($0.05 > P > 0.02$), whereas the hematocrit is significantly decreased ($0.001 > P$) compared with the values in healthy male subjects (5), but the hematocrit stayed relatively constant in each subject during the study. The plasma fibrinogen concentration was not significantly different ($P > 0.9$), showing negligible fluctuations in each subject during the study. The plasma fibrinogen ($\bar{x}$) showed no significant difference ($0.2 > P > 0.1$). It is also seen in Table I that in subjects M.C. and P.C. the values of plasma volume, plasma fibrinogen concentration, and plasma fibrinogen ($\bar{x}$) obtained simultaneously by autologous ^{131}I-fibrinogen and normal homologous ^{125}I-fibrinogen were in close agreement. The relative constancy of body weight, hematocrit, and the plasma fibrinogen concentration indicates that the subjects were in or near steady state during the study.

The function describing the plasma fibrinogen radioactivity (x) and the cumulative radioactivity (u). The plasma radioactivities of all plasma samples were expressed as fractions of the 15 min

TABLE I

*Plasma fibrinogen data**

Subject	Age	Height	Weight	Plasma vol	Hematocrit	Plasma fibrinogen	Plasma fibrinogen, $\bar{x}$	Reticulocyte count
	yr	*cm*	*kg*	*ml/kg*	%	*mg/100 ml*	*mg/kg*	%
F. K.	30	177	70.4	31.9	48	425	136	1.5
G. L.	13	155	32.5	39.2	41	392	154	2.9
J. L.	54	178	58.6	45.4	39	401	182	1.5
M.C$_a$.	20	169	51.8	39.1	47	282	110	2.6
M.C$_h$.				38.7		285	110	
P.C$_a$.	17	170	46.9	51.0	34	268	137	1.6
P.C$_h$.				50.7	"	278	141	
Q.N.	15	176	72.6	34.3	43	313	107	0.8
D.C.	21	170	46.8	62.2	28	251	156	2.5
W.C.	27	165	54.5	39.9	36	268	107	2.0
D.O.	15	173	49.5	37.8	46	536	203	1.2
P.O.	10	150	25.4	40.5	39	356	144	2.4
Means	22	168	50.9	42.1	40	349	144	1.9
SD				±8.8	±6	±90	±32	±0.6

* In subjects M.C. and P.C. the plasma vol and plasma fibrinogen concentration were measured with both autologous (a) ^{131}I-fibrinogen and normal homologous (h) ^{125}I-fibrinogen, simultaneously.

TABLE II

*Tracer data and calculated rate constants**

Subject	$x = C_1e^{-at} + C_2e^{-bt}$ C_1	a	C_2	b	s^2	$t_{\frac{1}{2}}$ for a, days	j_1 day^{-1}	j_{3p} day^{-1}	j_{3u} day^{-1}
F.K.	0.85 ±0.01	0.297 ±0.006	0.15 ±0.01	5.91 ±1.08	$7X$ 10^{-5}	2.33	0.792	0.347	0.382
G.L.	0.68 ±0.01	0.276 ±0.001	0.32 ±0.01	2.44 ±0.11	$1X$ 10^{-5}	2.51	0.583	0.385	0.411
J.L.	0.87 ±0.01	0.320 ±0.001	0.13 ±0.01	4.00 ±1.00	$2X$ 10^{-5}	2.17	0.470	0.328	0.399
M.C$_a$.	0.89 ±0.01	0.274 ±0.001	0.11 ±0.00	6.00 ±1.71	$3X$ 10^{-5}	2.53	0.599	0.305	0.336
M.C$_h$.	0.86 ±0.01	0.270 ±0.001	0.14 ±0.00	5.80 ±0.10	$3X$ 10^{-5}	2.57	0.732	0.312	0.343
P.C$_a$.	0.86 ±0.01	0.301 ±0.001	0.14 ±0.01	6.70 ±1.70	$1X$ 10^{-4}	2.30	0.850	0.347	0.346
P.C$_h$.	0.83 +0.02	0.299 ±0.001	0.17 ±0.00	5.38 ±1.70	$2X$ 10^{-4}	2.32	0.806	0.356	0.350
Q.N.	0.78 ±0.01	0.269 ±0.005	0.22 ±0.01	3.92 ±0.40	$4X$ 10^{-5}	2.58	0.734	0.338	0.316
D.C.	0.85 ±0.02	0.318 ±0.001	0.15 ±0.02	6.04 ±1.47	$1X$ 10^{-4}	2.18	0.804	0.372	0.337
W.C.	0.76 ±0.02	0.281 ±0.008	0.24 ±0.02	3.78 ±0.60	$1X$ 10^{-4}	2.47	0.758	0.362	0.351
D.O.	0.84 ±0.01	0.309 ±0.006	0.16 ±0.01	6.00 ±1.14	$8X$ 10^{-5}	2.24	0.856	0.364	0.345
P.O.	0.74 ±0.02	0.329 ±0.010	0.26 ±0.02	5.26 ±0.87	$1X$ 10^{-4}	2.11	1.176	0.435	0.420
Means	0.81	0.297	0.19	5.01	$6X$	2.34	0.762	0.358	0.361
SD	±0.01	±0.003	±0.01	±1.01	10^{-5}	±0.17	±0.190	±0.035	±0.033

* x is the function of time (t) describing the behavior of plasma ^{131}I- or ^{125}I-fibrinogen; $t_{\frac{1}{2}}$ is the half-life of the slower component, a, of x. j_1 is the fractional transcapillary transfer rate of plasma fibrinogen per day. j_{3p} and j_{3u} are the fractional catabolic rates of plasma fibrinogen per day. $j_1 = C_1a + C_2b - j_{3p}$ (10), $j_{3p} = (C_1/a + C_2/b)^{-1}$ (10), and $j_{3u} = [u_{2,3}/\xi_{2,3}(t_3 - t_2)] \times [(k_5 - a)/k_5]$ (10), where $u_{2,3}$ is the total radioactivity excreted in the urine during the time interval t_2 to t_3, $\xi_{2,3}$ is the mean plasma fibrinogen radioactivity during the same interval, and k_5 is the daily fractional excretion rate of the breakdown products or ^{131}I- or ^{125}I-fibrinogen per day (13). s^2 is the "variance of the fit" (14). In subjects M.C. and P.C. the data on both autologous (a) ^{131}I-fibrinogen and normal homologous (h) ^{125}I-fibrinogen are given. SD are given where ± signs appear.

sample, and these data were analyzed by the method of least squares (14) with the IBM 7044 digital computer (International Business Machines Corp., New York, N. Y.), which showed that the plasma fibrinogen radioactivity curve is closely described by a two exponential equation of the form, $x = C_1e^{-at} + C_2e^{-bt}$. The closeness of the fit is demonstrated by the small values of the "variance of the fit" (Table II) (14). One of the typical experiments is shown in Fig. 1. The half-life of the slower component of x averaged 2.34 days and is significantly shortened ($0.001 > P$) compared with 3.36 days in healthy male subjects (5). In subjects M.C. and M.P. the behavior of autologous ^{131}I-fibrinogen and normal homologous ^{125}I-fibrinogen were simultaneously studied (Fig. 2). It was found that there was no appreciable difference between the two (Table II). The total amount of radioactivity excreted during the first 24 hr averaged 14.6 ± 1 SD of 3.0% and that excreted by the 7th day was 83.0 ± 1 SD of 3.5%. A typical urinary radioactivity curve is shown in Fig. 1. When 1− the cumulative urinary excretion of radioactivity (u) is

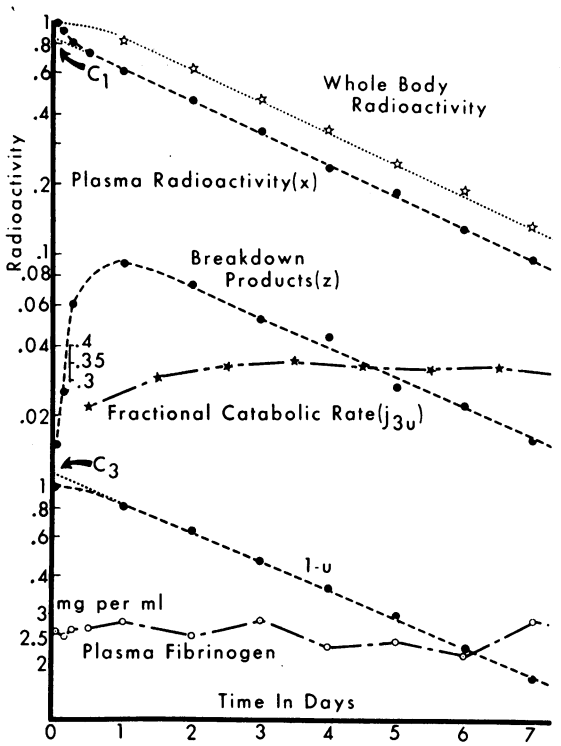

FIG. 1. IN VIVO BEHAVIOR OF I.V. ADMINISTERED AUTOLOGOUS ^{131}I-FIBRINOGEN IN SUBJECT D.C. x, z, and $1-u$ represent the radioactivities of the plasma ^{131}I-fibrinogen, the breakdown products of ^{131}I-fibrinogen in the iodide space, and the total radioactivity remaining in the body at time t, respectively, and are expressed as fractions of the total radioactivity initially injected. C_1 is the intercept of the slower component of x with the ordinate at zero time, and C_3 is the intercept of the $1-u$ curve with the ordinate at zero time. j_{3u} is the fraction of plasma fibrinogen catabolized per day and is calculated from x and u, the cumulative radioactivity excreted in the urine up to time t (10). The ^{131}I-fibrinogen was prepared from the subject's own plasma.

plotted against time, after a day or two in all experiments, $1-u$ is described by the exponential equation $1-u=C_3e^{-a_ut}$. The values of C_3 and a_u were determined by the method of least squares by the IBM 7044 digital computer (14). The average values of C_3 and a_u with their SD were 1.19 ± 1 SD of 0.01 and 0.288 ± 1 SD of 0.002/day, respectively, and the "variance of the fit" averaged 6×10^{-5} (14). In Fig. 2 it is shown that the $1-u$ curve of autologous ^{131}I-fibrinogen and that of normal homologous ^{125}I-fibrinogen were very similar. One of the typical whole body radioactivity curves is shown in Fig. 1, which is in close agreement with the $1-u$ curve, and is parallel with the plasma ^{131}I-fibrinogen radioactivity curve.

The radioactivity not precipitable with trichloroacetic acid (free ^{131}I or ^{125}I) in the body (z). This was obtained as described elsewhere (5, 13). In Fig. 1 a typical z curve shows that after a day or two z is closely described by a function in the form of $z=C_ze^{-a_zt}$. It is also seen in Fig. 2 that the z curves of ^{131}I- and ^{125}I-fibrinogen were closely similar. Mean values for z with their SD in 10 subjects at 0, 0.125, 0.25, 0.5, 1, 2, 3, 4, 5, 6, and 7 days after injection of ^{131}I-fibrinogen were 0.02 ± 0.01, 0.03 ± 0.01, 0.04 ± 0.01, 0.05 ± 0.01, 0.07 ± 0.02, 0.06 ± 0.02, 0.04 ± 0.01, 0.04 ± 0.01, 0.03 ± 0.01, 0.02 ± 0.01, and 0.01 ± 0.01, respectively. Thus, the general behavior of z is similar to that in healthy subjects (5), but its rate of decline appears more rapid than that in healthy subjects (5).

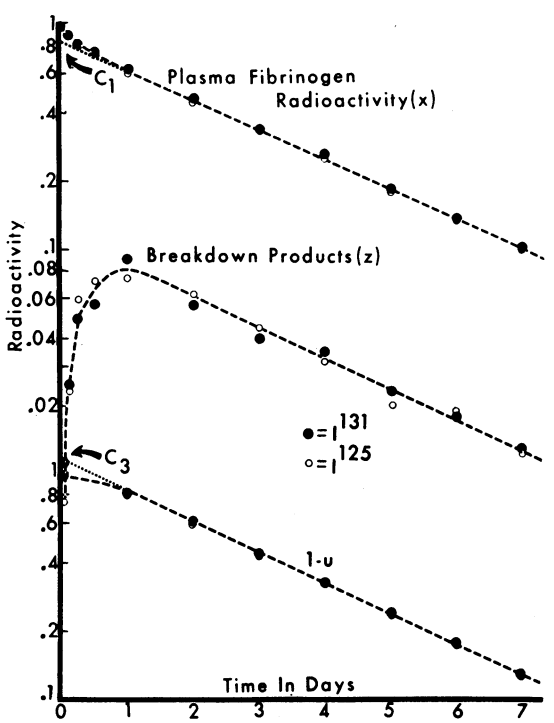

FIG. 2. THE SIMULTANEOUS STUDY OF I.V. ADMINISTERED AUTOLOGOUS ^{131}I-FIBRINOGEN AND NORMAL HOMOLOGOUS ^{125}I-FIBRINOGEN IN SUBJECT P.C. Autologous ^{131}I-fibrinogen and normal homologous ^{125}I-fibrinogen prepared from a healthy donor's plasma were simultaneously injected and their in vivo behavior was compared. It is seen that the curves of x, z, and $1-u$ of ^{131}I- and ^{125}I-fibrinogen are very similar. For x, z, $1-u$, C_1, and C_3 see Fig. 1.

TABLE III

*Fibrinogen fluxes and interstitial fibrinogen**

Subject	$j_1\bar{x}$	$j_{3p}\bar{x}$	$\bar{y}$	$\bar{y}/\bar{x}$	$F(T)=\frac{e^{-dt}}{d}$ day^{-1}
	mg/day per kg		*mg/kg*		
F. K.	108	47.1	21	0.15	5.07
G. L.	90	59.3	51	0.33	1.75
J. L.	85	59.7	24	0.13	3.52
M. C_a.	66	33.6	12	0.11	5.37
M. C_h.	81	34.3	16	0.15	5.02
P. C_a.	116	47.5	20	0.15	5.80
P. C_h.	114	50.2	25	0.17	4.52
Q. N.	79	36.2	34	0.32	3.12
D. C.	125	58.0	30	0.19	5.18
W. C.	81	38.7	36	0.34	2.94
D. O.	174	73.9	34	0.17	5.09
P.O.	169	62.6	42	0.29	3.98
Means	109	51.7	30	0.22	4.18
SD	37	13.1	11	0.09	1.32

*$j_1\bar{x}$ is the amount of intravascular fibrinogen filtered through the capillaries per day. $j_{3p}\bar{x}$ is the amount of intravascular fibrinogen catabolized per day. $\bar{y}$ is the interstitial fibrinogen. $\bar{y}/\bar{x}$ is the ratio of the interstitial to the intravascular fibrinogen. F(T) is the function describing the passage time distribution of interstitial fibrinogen. In subjects M. C. and P. C. the results obtained by both autologous (*a*) ^{131}I-fibrinogen and normal homologous (*h*) ^{125}I-fibrinogen are given.

However, the radioactivity caused by ^{131}I or ^{125}I in the plasma never exceeded 3% of the total plasma fibrinogen radioactivity.

Fractional rates, j_1 and j_3 (j_{3p} and j_{3u}), and their fluxes, $j_1\bar{x}$ and $j_3\bar{x}$. Table II gives the data on the fraction of plasma fibrinogen filtered through the capillaries per day (j_1) and the fraction of plasma fibrinogen catabolized per day j_3(j_{3p} and j_{3u}). Analyses showed that j_1 is not significantly different ($0.1 > P > 0.05$) whereas j_3 is markedly increased ($0.001 > P$), compared with the values in healthy subjects (5). The values of j_{3p} are in close agreement with j_{3u} (Table II). The daily values of j_{3u} are shown in Fig. 1, which stayed nearly constant during the study except for the first 2 days. Table III gives the data on the amount of fibrinogen filtered through the capillaries per day ($j_1\bar{x}$) and the amount of fibrinogen catabolized per day ($j_3\bar{x}$). Analysis showed that $j_1\bar{x}$ is not significantly different ($0.3 > P > 0.2$), but $j_3\bar{x}$ is markedly increased ($0.001 > P$) compared with the values in healthy subjects (5). The catabolic rate ($j_3\bar{x}$) equals the synthetic rate since the subjects were in or near steady state. Therefore, the latter was also increased.

Interstitial fibrinogen ($\bar{y}$) and its passage time distribution through the interstitial fluids [$F(T)$]. Table III gives the data on $\bar{y}$, $\bar{y}/\bar{x}$, and F(T), which were obtained by previous methods (11, 12). Analyses showed that $\bar{y}$ ($0.2 > P > 0.1$), $\bar{y}/\bar{x}$ ($0.3 > P > 0.1$), and F(T) ($0.2 > P > 0.1$) are not significantly different compared with the values in healthy subjects (5).

Discussion

A few studies of ^{131}I-fibrinogen metabolism in patients with hemophilia A have been reported previously (15–17). Thus, Rausen, Cruchaud, McMillan, and Gitlin (15) studied six cases of patients with hemophilia A and reported an average half-life of 3.0 days. By comparing these results with those of other investigators who found a range of 1.5–6.0 days in healthy subjects, Rausen and co-workers concluded that the half-life of fibrinogen in patients with hemophilia A is not prolonged. Hart (16) published a study of fibrinogen metabolism in one case of hemophilia A and concluded that the half-life of fibrinogen in patients with hemophilia A is similar to that in healthy subjects. Blombäck, Carlson, Franzén, and Zetterqvist (17) also did not find significant difference in half-life value between normal and hemophilia A subjects in their studies of two hemophilia A patients. Half-lives alone are insufficient to define fibrinogen metabolism.

The present study shows that in patients with hemophilia A in Denver, plasma fibrinogen concentration and plasma fibrinogen ($\bar{x}$) were not significantly different compared with the values in healthy subjects (5). However, the half-life of plasma ^{131}I-fibrinogen was significantly shorter, and as a result, the fraction of plasma fibrinogen catabolized per day j_3 (j_{3p}, j_{3u}) was significantly increased over the value in healthy subjects (5), whereas the fraction of plasma fibrinogen filtered through the capillaries per day (j_1) was unchanged; because of the increase in j_3 the catabolic flux ($j_3\bar{x}$) was markedly increased (Table III). In the steady state $j_3\bar{x}$ equals the synthetic rate of fibrinogen. Since the subjects were in or near steady state, the latter was also increased. However, the transcapillary flux of fibrinogen ($j_1\bar{x}$) and the interstitial fibrinogen ($\bar{y}$) were not significantly different (Table III). Question may be

raised whether the observed shorter half-life of autologous ^{131}I-fibrinogen and the increased j_3 and $j_3\bar{x}$ (Tables II and III) in patients with hemophilia A might have been due to the difference in the amount of contaminant proteins such as antihemophilic globulin within the labeled preparations. As stated earlier and in the previous report (5) the clottability of the present ^{131}I-fibrinogen prepared from each patient's own plasma and the previous ^{125}I-fibrinogen prepared from each healthy subject's own plasma (5) was 96%. Therefore, the maximum amount of contaminant protein was 4%. Hemophilia A plasma lacks or is deficient in antihemophilic globulin. Therefore, the amount of contaminant antihemophilic globulin within the present ^{131}I-fibrinogen should be less than that in the previous ^{125}I-fibrinogen, since exactly the same method of preparation was used (5). Antihemophilic globulin has been reported to have a half-life of several hours (21, 22). Therefore, a longer half-life should be expected for the present ^{131}I-fibrinogen compared with that of the previous ^{125}I-fibrinogen (5), if the contaminant antihemophilic globulin played a significant part, and the observed shorter half-life of ^{131}I-fibrinogen in hemophilia A patients cannot be explained on this basis. The next question is whether or not there is any physicochemical difference between hemophilia A and normal fibrinogens and if this is responsible for the observed findings (Tables I, II, and III). In an attempt to answer this question at least partially, autologous ^{131}I-fibrinogen prepared from the subject's own plasma and normal homologous ^{125}I-fibrinogen prepared from the plasma of healthy donors were simultaneously studied and their behavior was compared in two hemophilia A patients (Tables I, II, and III). As shown in Fig. 2, their in vivo behavior was closely similar and, as a result, the plasma volume, plasma fibrinogen concentration, $\bar{x}$, j_1, $j_1\bar{x}$, j_3, $j_3\bar{x}$, $\bar{y}$, and F(T) obtained simultaneously by the two preparations were also closely similar. These results prove that the hemophilia and normal fibrinogens are at least metabolically similar and support the earlier report (23) that hemophilia A fibrinogen is not qualitatively different from normal fibrinogen. Another possible criticism is that the observed shorter half-life of autologous ^{131}I-fibrinogen might have been due to a hemorrhage during the study. If it is assumed that the increase in j_3 (Table II) was due entirely to a hemorrhage, then, the subjects must lose about 11% of the total plasma fibrinogen daily ($0.358 - 0.246 = 0.112$ day^{-1}) (Table II) (5), which amounts to about 300 ml plasma daily and should have been large enough to be detected clinically. Furthermore, the relative constancy of hematocrit and plasma fibrinogen concentration during the study speaks against the idea that the observed findings were due to hemorrhagic episodes. Further question may be raised; are the observed difference in fibrinogen metabolism due to the age difference between the normal and hemophilia A subjects or are they due to the seasonal variation in fibrinogen metabolism? Examination of the previous (5) and present data shows that there is no noticeable correlation between plasma fibrinogen concentration or half-life of ^{131}I-fibrinogen and the subject age. The control and present studies were carried out in about the same seasons of the year, and a few studies of healthy subjects during or upon completion of the hemophilia study gave values of fibrinogen metabolism close to the previous results (5). Thus, the only alternative explanation is the abnormal host condition with respect to the fibrinogen metabolism, which is either an increased rate of direct breakdown of fibrinogen or an increased rate of fibrinogen breakdown after fibrin formation, or both (5), although the present study is unable to determine which. Nevertheless, the finding of a faster catabolism of fibrinogen in hemophilia A patients with defective clotting mechanisms suggests an increased rate of direct breakdown of fibrinogen with insignificant fibrin formation.

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