FIBRINOGEN CATABOLISM:
KINETICS OF CATABOLISM FOLLOWING SUDDEN ELEVATION OF THE POOL WITH EXOGENOUS FIBRINOGEN

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SUMMARY

1. Fibrinogen catabolism was studied in ten rabbits before and after suddenly elevating the intravascular pool by injecting a single dose of homologous fibrinogen equivalent to 18–83% of the corresponding protein already present in this pool. Of the two metabolic tracers used, $^{[131]}$I-fibrinogen was injected 3–4 days before and $^{[125]}$I-fibrinogen at the time of introducing the change.

2. Analysis of total body as well as of the circulating radioactivities indicated that the excess protein did not affect the fractional catabolic rate constant, thus permitting the conclusion that fibrinogen catabolism closely follows a first order kinetic reaction. In some animals a fraction of the injected fibrinogen shifted to extravascular sites and altered the pool ratio. Elimination of the excess protein took about 5 days and was accompanied by changes in the synthesis rate of fibrinogen.

Information presently available regarding the relationship between pool mass and degradation of fibrinogen in the mammalian body originates mainly from four sources: (1) comparative studies in normal subjects, viz. animals having different pool masses (Christensen, 1958; Regoeczi, Regoeczi & McFarlane, 1964), (2) various diseases and conditions associated with enlarged fibrinogen pool (Takeda, 1967; Takeda & Chen, 1967; Regoeczi & Hobbs, 1969), (3) experimentally induced hyperfibrinogenaemia (Regoeczi et al., 1963; Atencio et al., 1969a), and (4) analysis of the diurnal 'random' fluctuations so typical for fibrinogen metabolism in health (Atencio, Bailey & Reeve, 1965; Reeve, Takeda & Atencio, 1967). These studies, although carried out by independent investigators, lead to the same conclusion, namely that quantities of fibrinogen catabolized daily are directly proportional to the pool size, and that changes in the plasma concentration of this protein reflect alterations in the synthesis rate (Regoeczi et al., 1964; Atencio et al., 1965).

It hardly needs pointing out that none of the above experimental approaches was ideal, since (1) even if the fractional catabolic rate is independent of fibrinogen concentration in a

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group, this may not necessarily hold for one individual at different times or in different metabolic situations, (2) systemic diseases may influence the activity of catabolic sites in either direction, (3) to increase the pool, fibrinogen synthesis can readily be stimulated by a variety of means, but usually at the cost of complicating side-effects, such as diminished rates of transport of proteins across the capillaries (Koj & McFarlane, 1968) and production of cryofibrin (Shainoff & Page, 1960), and (4) spontaneous fluctuations in plasma fibrinogen concentrations are considerable, yet not large enough to cover the range of interest which is usually desired for establishing metabolic patterns.

For all these reasons it was thought that a re-investigation by improved techniques of the relationship between pool size and catabolic rates of fibrinogen was warranted. Recent developments which have facilitated the provision of highly soluble fibrinogens free of cryofibrin (Regoeczi & Stannard, 1969) made it convenient greatly to increase the fibrinogen pool of rabbits using exogenous fibrinogen, the results of these experiments being reported below.

METHODS

Animals

Adult, male Sandylop rabbits of the Mill Hill strain with body weights between 2.83 and 3.46 kg were used. They were accommodated in individual metabolic cages and received a pelleted diet of 245 kcal/100 g and drinking water containing $3.33 \times 10^{-5}$ M NaI and 0.77 M NaCl.

Preparing labelled fibrinogen

Blood was collected for fractionation from donor animals into a 2% (w/v) solution of oxalates (40% potassium oxalate and 60% ammonium oxalate: Heller & Paul, 1934), using 1 vol of the anticoagulant for 4 vol of blood. Prothrombin was removed by adsorption on BaSO$_4$ (Hjort, 1957) and the plasma was fractionated with a neutral solution of 2.05 M (NH$_4$)$_2$SO$_4$. To ensure optimal metabolic homogeneity, fibrinogen fractions of low solubility were eliminated by preliminary precipitation at 0.18 saturation (Regoeczi & Stannard, 1969), then the degree of saturation was increased to 0.238 (Parfentjev, Johnson & Clifton, 1953) and the precipitate collected by centrifugation at 600 g. The protein pellet was washed twice with 0.976 M (NH$_4$)$_2$SO$_4$ and re-dissolved in 0.9% NaCl containing 0.005 M trisodium citrate. After removing traces of ammonium sulphate by dialysis against the above solvent, the precipitation at 0.238 saturation was repeated and the pellet washed with 0.976 M (NH$_4$)$_2$SO$_4$ until the supernatant remained clear on mixing with an equal volume of 20% (w/v) trichloracetic acid. The precipitate was dissolved in a minimal volume of 0.9% NaCl containing 0.005 M trisodium citrate and dialysed against the same solution overnight at +4°C. Finally, the preparation was divided into aliquots of 10 mg and kept at $-25$° until use.

Iodinations were with $^{125}$I or $^{131}$I as described by McFarlane (1963). Labelled protein solutions were sterilized by passage through filters of 0.22 µm pore size. The proportion of the labelled protein clottable by thrombin was always between 97 and 98.5%.

Preparing unlabelled fibrinogen for injection

Hyperfibrinogenaemia was induced in donor animals 48 hr prior to the bleeding by a single subcutaneous injection of 0.5 ml turpentine oil/kg body wt (Koj, 1968). The plasma was pro-
cessed as described above, except that only one precipitation was performed and the fibrinogen collected between 0.16 and 0.24 rather than 0.18 and 0.24 saturation with ammonium sulphate. Sterile reagents were used in the precipitations and the preparations contained 91–94% clottable protein.

**Plasma radioactivity assays**

Blood samples (2 ml each) were taken into dry dipotassium-EDTA (4 mg/ml of blood) and 0.5 ml plasma samples were assayed in duplicate for clottable, non-clottable, but protein-bound, and non-protein radioactivities. The plasma was immediately clotted in a counting tube containing 1.5 ml phosphate buffer (0.054 M, pH 6.1, and 0.073 M NaI) in which 30 NIH units thrombin (Leo Pharmaceuticals Ltd, Denmark) and 1 mg crystalline soya bean trypsin inhibitor (Worthington Biochemical Corp., New Jersey, U.S.A.) were already dissolved. The samples were left first at room temperature for 1 hr and then refrigerated at 4° for 6–12 hr before removing the clot. This was done by winding and syneresis of the fibrin on a stainless steel needle (Regoezci, 1967), followed by two washings in 5 ml of a 0.9% solution of NaCl for 30 min each. Then the clot was separated from the needle using pointed forceps, put into another counting tube containing 2 ml alkaline urea solution (6.66 M urea in 0.2 N KOH) and dissolved while briefly heating in a water bath. The specimen was counted in a Packard autogamma spectrometer, the value thus obtained being referred to as clottable protein-bound radioactivity. The quantity of fibrinogen in the same sample was determined by measuring the optical density at 279 μm against the alkaline urea solution as a blank. To do this, the volume of the counted samples was adjusted to 4.5 ml with alkaline urea and was clarified by passage through a Pasteur pipette fitted with a tight cotton wool plug. Optical densities were converted into plasma fibrinogen concentrations (mg/ml) by multiplication with 4.692, this factor being derived from gravimetric estimations of fibrin.

The radioactivity that remained in the serum after removing the fibrin was also measured. Finally, serum proteins were precipitated with an equal volume of 20% (wt/vol) trichloroacetic acid, and a known volume of the supernatant was counted. From these measurements the non-clottable protein-bound and non-precipitable radioactivities were calculated by subtracting the second value from the first one.

Statistical analysis of fifty randomly selected duplicate radioactive clots gave a coefficient of variation of 0.88 (SD ± 0.55)%.

**Total body radioactivity**

Total body radiation was measured in a ring of eight Geiger tubes as described by Campbell et al. (1956).

**Calculations**

Intravascular distribution volumes of fibrinogen were calculated from the dilution of the dose by the plasma during the first 10 min of injection; to accomplish this, syringes were weighed on a microbalance before and after delivering the dose and the difference in weight was related to the weight of one drop of the dose. The drop was subsequently diluted 250-fold with 3.33 M urea in 0.1 M KOH and counted.

Slopes of total body radioactivities were determined by calculating the regression line of the values measured between the 20th hour and the end of the experiments. Standard deviation of
the slopes was found by analysis of the variance (Mather, 1949) and was expressed as a percentage of the regression coefficient.

Clottable intravascular radioactivities were analysed according to a three-compartmental model as described by Matthews (1957), the whole procedure being adapted for digital computing rather than carried out in its original semi-graphical form. Differences between mean fractional catabolic rates, transcapillary rates and pool ratios in the periods before and after increasing the fibrinogen pool were subjected to Student's \( t \) test (Weber, 1957).

**Experimental techniques**

Experiments were started by injecting about 70 \( \mu \)Ci \([131I]\)fibrinogen, equivalent to 2·5–5 mg protein, to measure the 'basic' catabolic rate of fibrinogen for 74–95 hr. Total body radioactivity was recorded and blood samples were taken twice daily, except for the first 24 hr when two or three additional samples were withdrawn to be able to calculate diffusion rates.

Changes in the pool size were brought about by a single intravenous administration of a concentrated solution of fibrinogen mixed with 40–50 \( \mu \)Ci \( ^{125}I \)-labelled protein, the injection lasting about 1 min. The subsequent blood sampling was spaced similarly to that in the first half of the experiment. Experiments were terminated after an overall observation period of 190–200 hr.

**RESULTS**

**Intravascular radioactivities**

Data obtained with \([131I]\)fibrinogen before altering the pool mass are summarized in Table 1, while Table 2 is a synopsis of the measurements with \([125I]\)fibrinogen after increasing the pool, amounts of fibrinogen injected and the resulting increments in the intravascular pool mass

<table>
<thead>
<tr>
<th>Animal No.</th>
<th>Body wt (kg)</th>
<th>A (ml/kg)</th>
<th>B (mg/kg)</th>
<th>C (mg/kg)</th>
<th>( K_{12} ) (day(^{-1}))</th>
<th>( K_{13} ) (day(^{-1}))</th>
<th>Ratio e.v./i.v.</th>
<th>D (mg kg(^{-1}) day(^{-1}))</th>
<th>E (mg kg(^{-1}) day(^{-1}))</th>
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<tbody>
<tr>
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<td>35-3</td>
<td>82-9</td>
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<td>0-50</td>
<td>0-47</td>
<td>0-30</td>
<td>41-4</td>
<td>38-8</td>
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<tr>
<td>2</td>
<td>3-42</td>
<td>38-8</td>
<td>111-1</td>
<td>144</td>
<td>0-39</td>
<td>0-37</td>
<td>0-30</td>
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<td>41-1</td>
</tr>
<tr>
<td>3</td>
<td>3-16</td>
<td>29-9</td>
<td>101-6</td>
<td>145</td>
<td>0-41</td>
<td>0-71</td>
<td>0-43</td>
<td>41-6</td>
<td>72-1</td>
</tr>
<tr>
<td>4</td>
<td>3-46</td>
<td>31-5</td>
<td>82-1</td>
<td>102</td>
<td>0-37</td>
<td>0-52</td>
<td>0-24</td>
<td>30-3</td>
<td>42-6</td>
</tr>
<tr>
<td>5</td>
<td>3-34</td>
<td>35-8</td>
<td>113-4</td>
<td>139</td>
<td>0-35</td>
<td>0-27</td>
<td>0-23</td>
<td>38-6</td>
<td>30-6</td>
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<td>6</td>
<td>2-83</td>
<td>33-3</td>
<td>121-5</td>
<td>139</td>
<td>0-31</td>
<td>0-43</td>
<td>0-18</td>
<td>40-1</td>
<td>99-6</td>
</tr>
<tr>
<td>7</td>
<td>3-00</td>
<td>36-6</td>
<td>74-7</td>
<td>87</td>
<td>0-40</td>
<td>0-23</td>
<td>0-17</td>
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<td>40-0</td>
<td>121-0</td>
<td>145</td>
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<td>0-79</td>
<td>0-20</td>
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<td>90-0</td>
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<td>3-04</td>
<td>38-1</td>
<td>83-2</td>
<td>101</td>
<td>0-45</td>
<td>0-32</td>
<td>0-21</td>
<td>37-4</td>
<td>26-5</td>
</tr>
<tr>
<td>Mean</td>
<td>—</td>
<td>35-8</td>
<td>98-1</td>
<td>121-6</td>
<td>0-39</td>
<td>0-45</td>
<td>0-24</td>
<td>37-4</td>
<td>50-3</td>
</tr>
<tr>
<td>SD (±)</td>
<td>—</td>
<td>3-3</td>
<td>17-7</td>
<td>22-7</td>
<td>0-06</td>
<td>0-18</td>
<td>0-08</td>
<td>4-8</td>
<td>28-7</td>
</tr>
</tbody>
</table>

Intravascular distribution volume (A), intravascular mass (B), total body mass (C), catabolic rate constant (\( K_{12} \)), capillary transfer rate constant (\( K_{13} \)), pool ratio (e.v./i.v.), absolute catabolic rate (D) and absolute capillary transfer rate (E) in ten rabbits before elevating their fibrinogen pools with exogeneous fibrinogen.
being also listed in the latter Table. No absolute catabolic and capillary transfer rates are given in Table 2 since these values were continuously changing. Of the two transfer rates between intravascular (i.v.) and extravascular (e.v.) pools, the Tables include only capillary transfer rates ($K_{13}$) from which the return flow can be obtained, if required, by dividing by the pool ratio.

Two experiments, each representative for one half of the animals studied, are shown in Figs. 1 and 2, the difference being noticeable in the behaviour of intravascular $[^{131}I]$fibrinogen activities: the slope of this curve shifted markedly in response to the elevation of the intravascular pool in one case (Fig. 2) and for no obvious reason remained essentially unchanged in the other (Fig. 1). As will be discussed further below, the manifestation in Fig. 2 probably reflects a redistribution of the body fibrinogen in favour of the extravascular space.

Proportions of thrombin-clottable protein-bound radioactivities in the circulation were the same before and after injecting the large quantities of fibrinogen, suggesting that this treatment did not induce fibrinogenolysis or intravascular coagulation.

**Total body activities**

Total body curves are illustrated in Figs. 1 and 2, and the results from all experiments are summarized in Table 3. Except for the first 20–24 hr, total body radioactivities decreased single-exponentially, the slopes being quite unaffected by the extra fibrinogen injected. Plasma non-protein radioactivities throughout the experiments showed only random variations (cf. Figs. 1 and 2), confirming that fluctuations in the proportion of labelled breakdown products did not seriously influence the slopes of total body curves.

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### Table 2. Effects of elevating the pool mass on the distribution and catabolism of fibrinogen

<table>
<thead>
<tr>
<th>Animal No.</th>
<th>Fibrinogen injected</th>
<th>Intravascular clottable $^{125}$I-activities*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mass (mg)</td>
<td>Volume (ml)</td>
</tr>
<tr>
<td>1</td>
<td>142</td>
<td>5.5</td>
</tr>
<tr>
<td>2</td>
<td>69</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>261</td>
<td>9</td>
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<td>185</td>
<td>4.6</td>
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<tr>
<td>5</td>
<td>153</td>
<td>4.5</td>
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<tr>
<td>6</td>
<td>122</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>141</td>
<td>5</td>
</tr>
<tr>
<td>8</td>
<td>293</td>
<td>7</td>
</tr>
<tr>
<td>9</td>
<td>231</td>
<td>6</td>
</tr>
<tr>
<td>10</td>
<td>211</td>
<td>5.5</td>
</tr>
<tr>
<td>Mean</td>
<td>181</td>
<td>5.5</td>
</tr>
<tr>
<td>SD (±)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

* Abbreviations as in Table 1.
Elimination of the excess fibrinogen

Results presented in the foregoing sections indicate that the catabolic rate constant ($K_{12}$) remained virtually unaffected by suddenly changing the pool size, and if the same was true for the absolute synthesis rate too, the actual pool size ($P_x$) at any time following a change could be described by the formula:

$$P_x = P_0 + (P_1 - P_0) e^{-K_{12}(t - t_0)}$$

where $P_0$ denotes the original and $P_1$ the altered pool, and $t_0$ the time of inducing the change. This function was calculated for a mean $K_{12}$ of 0·37 (cf. Table 2) and an average $P_1$ of 160·4% (cf. Table 2, $P_0$ being taken as 100%), and the resulting plot is compared with the averaged curve of all experimental values in Fig. 3. It will be seen that there was a good agreement between expected and observed values over the first 30 hr, after which the elimination of the
excess fibrinogen for some 24–36 hr was clearly less than predicted; subsequently the curves converged so that at the end of the 4th day theoretical and measured values were about the same.

![Graph showing the kinetics of fibrinogen catabolism](image)

**Fig. 2.** Shift and re-shift in the extra/intravascular pool ratio following the injection of fibrinogen into animal No. 8. Curves as in Fig. 1. Note the enhanced disappearance of $[^{131}I]$fibrinogen from the intravascular space during the first day after injecting fibrinogen and the subsequent reverse trend over a prolonged period of time. By contrast, the slope of the total body radioactivity remained steady throughout, indicating that these changes reflect redistribution of the body fibrinogen pool rather than alterations in fibrinogen catabolism.

**DISCUSSION**

Constancy of the total body radioactivity slopes together with the absence of rising plasma non-protein activities clearly indicate that the intravascular fibrinogen pool can be rapidly and considerably increased using exogenous fibrinogen without affecting the fractional catabolic rate of this protein. Fibrinogen catabolism is, therefore, a first order kinetic process, the number of molecules degraded in unit time being directly proportional to their concentration. The same conclusion is supported by the behaviour of the intravascular radioactivity curves; the first tracer ($^{131}$I), injected 3–4 days before changing the pool, gave a mean fractional
catabolic rate which was only 5% different from that obtained with the second label ($^{125}$I) for the post-injection period.

While this manuscript was being prepared, a study by Atencio, Joiner & Reeve (1969b) appeared on the metabolic effects of elevating plasma fibrinogen concentration in rabbits over several days, and their conclusions concerning catabolism are essentially the same as those described here.

Comparison of the pool ratios of extra/intravascular fibrinogen before and after elevating the pool shows increments in the relative size of the extravascular pool in six out of ten animals. The figures in Tables 1 and 2 suggest an average increase by 25% (or 23 mg protein) of the pre-

**Table 3. Catabolism of $[^{131}]$fibrinogen as measured by total body counting**

<table>
<thead>
<tr>
<th>Animal No.</th>
<th>Half-life (hr)</th>
<th>Rate constant (day$^{-1}$)</th>
<th>SD of the slope*</th>
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<tbody>
<tr>
<td>1</td>
<td>50.1</td>
<td>0.33</td>
<td>0.96</td>
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<tr>
<td>2</td>
<td>60.1</td>
<td>0.28</td>
<td>1.15</td>
</tr>
<tr>
<td>3</td>
<td>64.8</td>
<td>0.25</td>
<td>2.01</td>
</tr>
<tr>
<td>4</td>
<td>63.9</td>
<td>0.26</td>
<td>1.66</td>
</tr>
<tr>
<td>5</td>
<td>66.6</td>
<td>0.25</td>
<td>1.43</td>
</tr>
<tr>
<td>6</td>
<td>61.2</td>
<td>0.27</td>
<td>2.07</td>
</tr>
<tr>
<td>7</td>
<td>54.3</td>
<td>0.30</td>
<td>1.33</td>
</tr>
<tr>
<td>8</td>
<td>65.6</td>
<td>0.25</td>
<td>1.34</td>
</tr>
<tr>
<td>9</td>
<td>61.7</td>
<td>0.27</td>
<td>1.87</td>
</tr>
<tr>
<td>10</td>
<td>52.0</td>
<td>0.32</td>
<td>0.98</td>
</tr>
<tr>
<td>Mean</td>
<td>60.0</td>
<td>0.28</td>
<td>1.50</td>
</tr>
<tr>
<td>SD (±)</td>
<td>5.9</td>
<td>0.03</td>
<td>—</td>
</tr>
</tbody>
</table>

* Expressed as percentage of the regression coefficient.

**Fig. 3. Elimination of the excess fibrinogen injected:** The averaged experimental values from ten animals (continuous line) are contrasted with the expected values (dotted line) assuming that both the fractional catabolic rate and the absolute synthesis rate remained constant.
Kinetics of fibrinogen catabolism

injection value, this difference being statistically significant \((P<0.05)\). The data in these Tables also indicate a marked increase in mean capillary transfer rates, although individual variations were considerable whereby the significance of this finding could not be established. Nevertheless, intravascular \(^{131}\)I fibrinogen curves, like the one in Fig. 2, provide additional support to the postulate that sudden increases in circulating fibrinogen may bring about shifts—and slow re-shifts—in the pool ratios.

Fibrinogen (McFarlane, 1963), similar to IgM-globulin and 19S rheumatoid factor (Bradley, 1969) or \(\alpha_2\)-macroglobulin (Reuge et al., 1966), has a rather small extravascular pool, these large protein molecules passing the capillary barrier only in limited areas of the vascular bed. The data presented suggest that by rapidly increasing the concentration of fibrinogen in the plasma this area can temporarily be increased. Whether this effect is achieved by the sudden change in blood viscosity or by vasoactive peptides released during the degradation of fibrinogen (Copley et al., 1967) is not known, and further investigations are required to establish its possible significance as a compensatory mechanism to deal with abnormally high fibrinogen concentrations.

The results of these experiments fully agree with the metabolic concept of fibrinogen as outlined in the introduction. In addition, they strongly support the idea put forward by Reeve et al. (1967) that fibrinogen catabolism probably is not governed by a genuine control mechanism. Indeed, it appears that fractional catabolic rates of fibrinogen are fixed by a fundamental biological function which is unrelated to the catabolic process itself. Indirect evidence suggests that fibrinogen degradation, under physiological conditions, is confined to cells (Regoecci, 1967), and therefore it is reasonable to assume that the determining factor is the rate of uptake of fibrinogen by the catabolic cells. The concentration-dependence of the latter process can well be explained by pinocytosis with or without selective adsorption (Jacques, 1966).

Studies with certain immunoglobulins (Birke et al., 1967) and haptoglobin (Krauss, Schrott & Sarcione, 1966) have yielded metabolic information which is broadly similar to that for fibrinogen, implying that the combination of regulated synthesis with unregulated catabolism may apply to several plasma proteins. Also, since fractional catabolic rates of individual proteins are known to be different (e.g. fibrinogen/IgM = 2.5:1), pinocytosis of a heterogeneous system of proteins is probably associated with selective adsorption. It is noteworthy in this connection that the affinity of fibrinogen to catabolic cells can easily be modified, e.g. by complex formation.

Since the fractional catabolic rate remained constant, information concerning the synthesis rate may be inferred from the elimination curve of excess fibrinogen (Fig. 3). The bulge appearing in this curve suggests that synthesis was first stimulated and then reduced. During the interval of 1.5-2.5 days following the injection of fibrinogen the changes in the pool size were very small, thus justifying the assumption that a balance existed between synthesis and catabolism. To realize such an equilibrium at the prevailing fractional catabolic rate and an average pool size of 508 mg, the absolute synthesis rate must have risen from 37.4 mg kg\(^{-1}\) day\(^{-1}\) (cf. Table 1) to 60 mg kg\(^{-1}\) day\(^{-1}\). The validity of this calculation is not seriously challenged by the possibility that fibrinogen which escaped into the 'additional' extravascular pool may have returned in bulk, since—as already pointed out—it amounted to not more than 23 mg on the average, and this is only 4.5\% of total body fibrinogen at the time in question.

The reason for these changes in synthesis rate is not at all clear. Nevertheless it is interesting to note that the increment in the absolute synthesis rate was of the same order (61\%) as that...
in the absolute catabolic rate at the time of injecting the excess fibrinogen. Whether this is a coincidence, or possibly indicates the existence of a feed-back mechanism between catabolic cells and the liver, will have to be the subject of further experiments.

REFERENCES


Kinetics of fibrinogen catabolism


