For a Drug the Liver Extracts Almost Completely, Blood Flow Sets the Injection and Enzymes Set the Pill

— for a drug with extraction ratio **0.95**, halving the liver's enzyme activity raises exposure to an injection only **1.050000**-fold while exposure to a pill exactly doubles — when liver blood flow falls to **70** per cent the roles reverse — [Paper 591]

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September 2026

— *From thinking to syncing.* —

Abstract

It is said that when the liver weakens, drugs act too strongly.What this paper shows is that the same change in the liver acts differently on an injection and on a pill, and that for a drug the liver removes almost completely (high extraction ratio) the injection is governed by liver blood flow and the pill by the liver's enzyme activity.No new theorem or law is claimed. First, a drug of high extraction ratio barely reaches the body when swallowed——with a liver blood flow of 90 L/h and an extraction ratio of 0.95, only 0.050000 of a swallowed dose passes the liver, so a pill needs 20.000000 times the dose of an injection (Section 2). **Second, and this is the core.When the liver's enzyme activity halves, exposure to the injection rises only 1.050000-fold, while exposure to the pill exactly doubles, 2.000000-fold——the same change in the liver acts almost twice as strongly by one route as by the other** (Section 3). **Third, when liver blood flow falls to 70 per cent, the roles reverse——exposure to the injection rises 1.407143-fold, and exposure to the pill stays at 1.000000, because the pill's exposure is the dose divided by the enzymes' capacity and contains no blood flow** (Section 3). **Fourth, for a drug of extraction ratio 0.05 the two routes agree——when enzyme activity halves, the injection rises 1.950000-fold and the pill 2.000000-fold, both nearly double** (Section 3). **Fifth, solving the equations of two compartments, body and liver, gives the same——eight exposures agree with the closed forms to a relative 5.4×10^{-7}** (Section 4). **Sixth, the separator is whether the extraction ratio is near 1 or near 0——near 1, blood flow holds the injection and enzymes hold the pill; near 0, enzymes hold both** (Section 5). **Keywords**: pharmacokinetics, hepatic extraction ratio, bioavailability, clearance, first-pass effect.

Scope of this paper (scope note): **No new theorem or law is claimed——the well-stirred model of the liver, the extraction ratio, bioavailability, and the relation between exposure (the time integral of blood concentration) and clearance are all standard.Only the simplest model is used——a pill is taken to be completely absorbed; metabolism in the gut wall, elimination outside the liver, return of drug from bile to gut, and changes in protein binding are not included.A liver blood flow of 90 L/h is representative——the two drugs are set by extraction ratios of 0.95 and 0.05, and no drug is named.No dosing is advised——adjusting doses is for physicians and pharmacists; this paper looks only at the form of the equations.Relation to earlier papers**: **Paper 578 showed that what sets a dosing interval is the half-life and the width of the therapeutic window, and set aside in its scope note both absorption (taken as instant) and differences between people in liver function——this paper takes that seat and shows that a change in liver function moves exposure differently by injection and by pill.Paper 300 showed that sharing a root is decidable——exposure to the injection and exposure to the pill come from one formula and share a root; the limits of the extraction ratio separate them.**What is added is **setting out exposure ratios for two drugs and three changes**, **confirming by two routes, closed forms and equations of motion, that the pill's exposure does not depend on blood flow and exactly doubles when enzyme activity halves**, and **placing the separator on the extraction ratio**.

1. Notation and the Question

Setting: **let Q be liver blood flow and C the capacity of the liver's enzymes to process the drug (the intrinsic clearance of the drug not bound to blood proteins).In the well-stirred model of the liver, the rate at which the liver clears the drug from blood (hepatic clearance), the fraction removed in one pass (extraction ratio), and the fraction of a pill that passes the liver to reach the body are**

$$CL_H = \frac{QC}{Q+C}, \qquad E = \frac{C}{Q+C}, \qquad F = \frac{Q}{Q+C}.$$

With a dose D, exposure (the time integral of blood concentration) is D/CL_H for an injection and $FD/CL_H = D/C$ for a pill.

Observation 1.1

it is said that when the liver weakens, drugs act too strongly.The liver clears drugs, so slower clearing leaves more drug——whether that applies equally to injections and pills is another question.

Question: **does the same change in the liver act equally on an injection and on a pill?**

2. Drugs of High and Low Extraction

Computation 2.1: **with liver blood flow 90 L/h, the intrinsic clearance was set to give extraction ratios of 0.95 and 0.05.**

drug	intrinsic clearance (L/h)	hepatic clearance (L/h)	extraction	fraction of pill reaching body
high extraction	**1710.000000**	**85.500000**	**0.950000**	**0.050000**
low extraction	**4.736842**	**4.500000**	**0.050000**	**0.950000**

> **Observation 2.2**
>
> **a drug of high extraction loses 95 per cent in one pass through the liver when swallowed.To act as strongly as an injection, a pill needs 20.000000 times the dose——the liver receives blood from the gut first, so a pill is sieved once before it reaches the circulation.**

3. When the Liver Changes

Computation 3.1: **enzyme activity was halved and doubled, and blood flow reduced to 70 per cent; the table gives exposure relative to the original.**

drug and change	injection	pill	fraction of pill reaching body
high, enzymes halved	**1.050000**	**2.000000**	**0.050000 → 0.095238**
high, flow at **70** per cent	**1.407143**	**1.000000**	**0.050000 → 0.035533**
high, enzymes doubled	**0.975000**	**0.500000**	**0.050000 → 0.025641**
low, enzymes halved	**1.950000**	**2.000000**	**0.950000 → 0.974359**
low, flow at **70** per cent	**1.021429**	**1.000000**	**0.950000 → 0.930070**
low, enzymes doubled	**0.525000**	**0.500000**	**0.950000 → 0.904762**

Observation 3.2

this is the core.For the drug of high extraction, halving enzyme activity raises injection exposure only 1.05-fold but exactly doubles pill exposure——for an injection, the liver was already clearing nearly all the blood that reached it, and with half its enzymes it still clears nearly all. For a pill, the fraction surviving one pass nearly doubles, from 0.050000 to 0.095238.

Observation 3.3

when blood flow falls to 70 per cent, the roles reverse.Injection exposure rises 1.407143-fold and pill exposure stays at 1——pill exposure is D/C and contains no blood flow Q. With less flow, the fraction reaching the body falls to 0.035533, but elimination from the body slows by just as much, and the two cancel exactly.

Observation 3.4

for the drug of low extraction, the two routes respond together.Halving enzyme activity raises the injection 1.950000-fold and the pill 2.000000-fold——the liver clears only a small part of the blood reaching it, so the enzymes' capacity sets the rate of elimination directly.

4. Checking with Two Compartments

Computation 4.1: **as a route separate from the closed forms, two compartments, body and liver, were joined by the liver blood flow, the drug being eliminated in the liver in proportion to the enzymes' capacity, and the equations were solved numerically (Runge--Kutta).Injections entered the body compartment and pills the liver compartment, and the body concentration was integrated over time.The eight exposures, injection and pill for the high-extraction drug at baseline, with enzymes halved and with flow at 70 per cent, and for the low-extraction drug at baseline, agreed with the closed forms to a relative 5.4×10^{-7}.**

Observation 4.2

the compartment equations show directly that pill exposure does not depend on liver blood flow.For the high-extraction drug with flow at 70 per cent, pill exposure was 0.058480, the same as at baseline——a pill is processed by the enzymes at every pass through the liver, and however many passes it makes, the total processed is set by the enzymes' capacity alone.

5. The Separator

Observation 5.1

the separator is whether the extraction ratio is near 1 or near 0.Near 1, blood flow holds injection exposure and enzymes hold pill exposure; near 0, enzymes hold both——"when the liver weakens, drugs act too strongly" is neither right nor wrong until one says which function (flow or enzymes) weakened, by which route (injection or pill), for which drug (extraction ratio).

Observation 5.2

taking the seat left by Paper 578.It showed with a one-compartment model that the dosing interval is set by the half-life and the width of the therapeutic window, and set aside in its scope note absorption and differences between people in liver function——this paper shows that such a difference in liver function acts in different directions by different routes.

Observation 5.3

one root, under Paper 300.Injection exposure and pill exposure come from the same formula——what separates them is only the limit of the extraction ratio.

Observation 5.4

what is not said.No dosing is advised and no drug is named; metabolism in the gut wall and return from bile to gut are not included——what is shown is only the form of the equations: the same change in the liver acts differently by different routes.

6. Roll Call and Closing

1. **a drug of extraction 0.95 reaches the body at 0.050000 as a pill** (Computation 2.1): **20.000000 times the injected dose needed.**
2. **halved enzymes raise the injection 1.050000-fold** (Computation 3.1): **barely moves.**
3. **halved enzymes raise the pill exactly 2.000000-fold** (Observation 3.2): **the core.**
4. **flow at 70 per cent raises the injection 1.407143-fold** (Computation 3.1): **the roles reverse.**
5. **flow at 70 per cent leaves the pill at 1.000000** (Observation 3.3): **exposure is D/C, with no flow in it.**
6. **for extraction 0.05, 1.950000 and 2** (Observation 3.4): **the two routes agree.**
7. **two-compartment equations agree to 5.4×10^{-7}** (Computation 4.1): **two routes.**
8. **the compartments also show the pill independent of flow** (Observation 4.2): **0.058480 unchanged.**
9. **taking the seat left by Paper 578** (Observation 5.2): **differences in liver function.**
10. **the separator is extraction near 1 or near 0** (Observation 5.1): **held by flow or by enzymes.**

Closing: **It is said that when the liver weakens, drugs act too strongly.That depends on which function weakens, and by which route——a drug with extraction ratio 0.95 at a liver blood flow of 90 L/h reaches the body at only 0.050000 when swallowed, so a pill needs 20.000000 times the injected dose. When the liver's enzyme activity halves, injection exposure rises only 1.050000-fold while pill exposure exactly doubles, 2.000000-fold. When liver blood flow falls to 70 per cent the roles reverse: the injection rises 1.407143-fold and the pill does not move, because pill exposure is the dose divided by the enzymes' capacity and contains no blood flow. For a drug of extraction 0.05, halved enzymes raise the injection 1.950000-fold and the pill 2-fold: the two routes agree.Solving the equations of two compartments, body and liver, the eight exposures agreed with the closed forms to a relative 5.4×10^{-7}.The separator is whether the extraction ratio is near 1 or near 0——near 1, flow holds the injection and enzymes hold the pill; under Paper 300 the two come from one formula and share a root.Placed among the earlier papers——this takes the seat that Paper 578 left in its scope note, for differences in liver function and for absorption.To be honest——this is the simplest well-stirred model, with complete absorption and without metabolism in the gut wall, elimination outside the liver, return from bile to gut, or changes in protein binding. The liver blood flow is representative, no drug is named, and no dosing is advised.**

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