

# 会長講演

創薬と医療における薬物動態予測の利用

私の生まれた年の薬物動態と現在、そして  
これからの薬物動態研究

# クロラムフェニコール J Pharmacol Exp Ther, 96. 445 (1949)

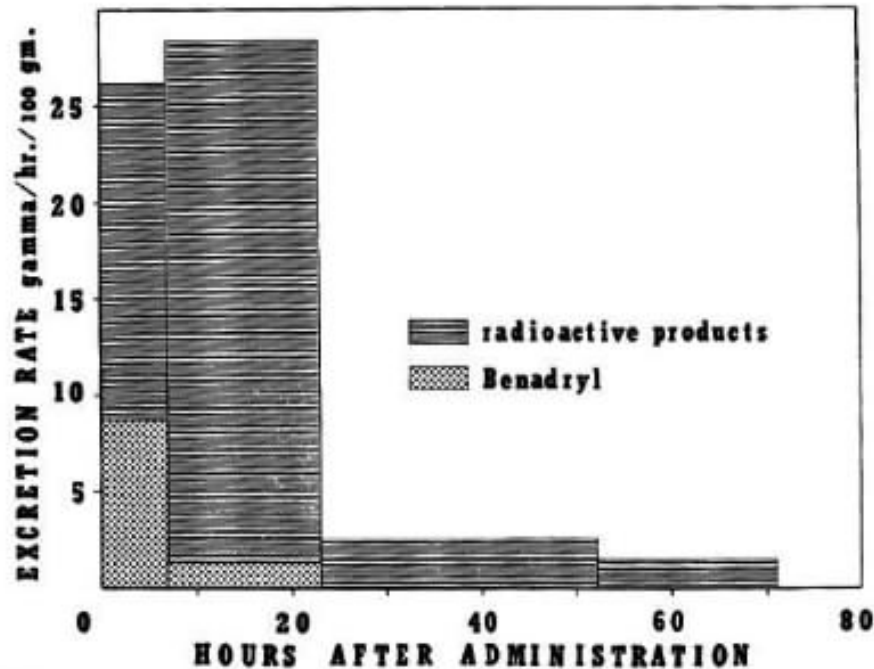
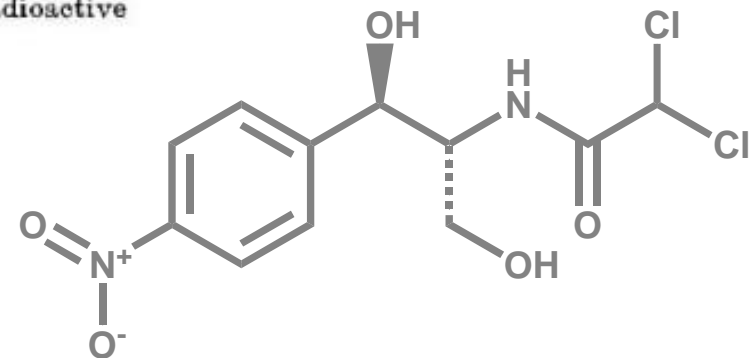
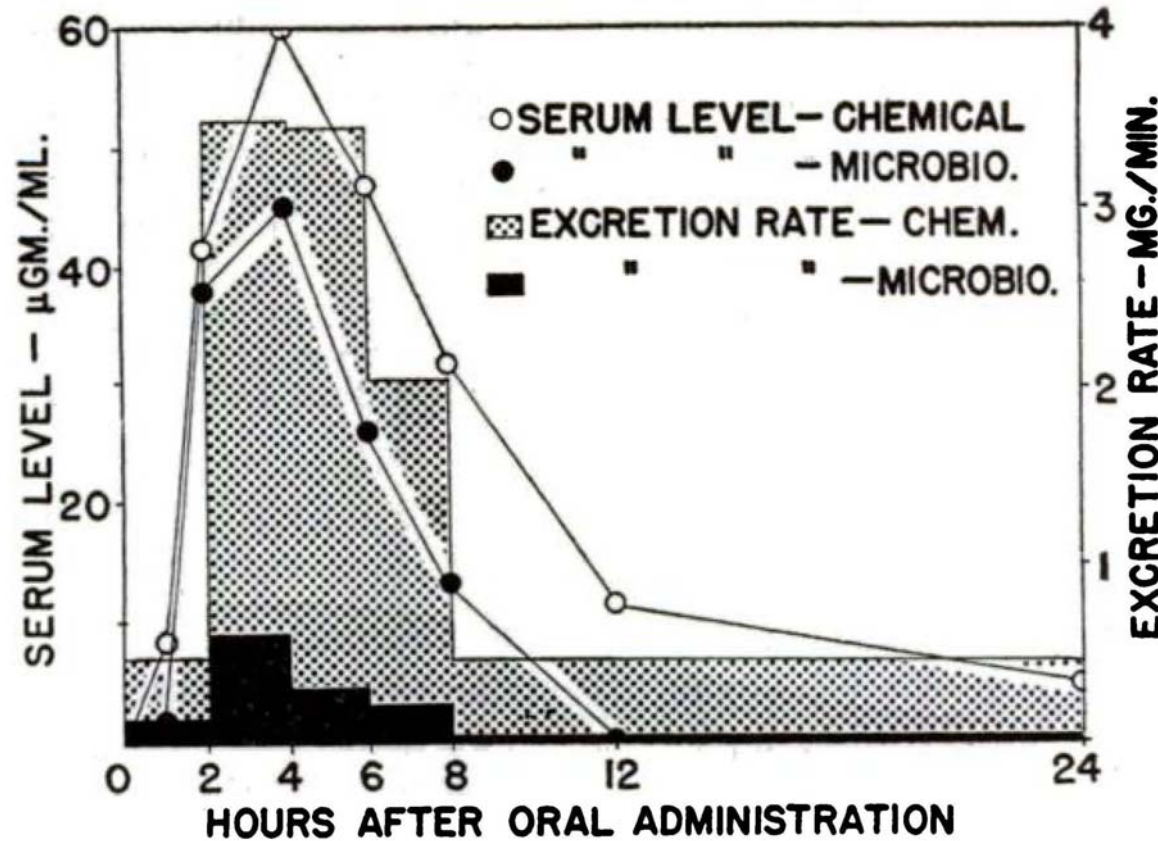


FIG. 1. Urinary excretion rate of free Benadryl and of radioactive metabolic products in the rat. Average excretion rate from three rats given 2 mg. of radioactive Benadryl hydrochloride subcutaneously per 100 gm. of body weight.

UV-VIS spectra  
ヒトで、尿中に  
90%が排泄  
生体内で大部分が  
代謝物に変化



# クロラムフェニコール 2



体内からの消失が代謝に依存

血中動態と活性

FIG. 5. BLOOD LEVELS AND URINARY EXCRETION RATES FOR CHLORAMPHENICOL AND TOTAL NITRO COMPOUNDS IN A DOG GIVEN 150 MG. OF CHLORAMPHENICOL PER KGM. OF BODY WEIGHT BY MOUTH

The amount of chloramphenicol accounted for in 24 hour urinary excretion was 54.7 per cent of the administered dose by the titanium reduction procedure, and 6.3 per cent by microbiological assay.

Kinetics of disposition and activity

# ジフェンヒドラミン J Biol Chem, 179. 409 (1949)

## BIOCHEMICAL STUDIES ON DIPHENHYDRAMINE (BENADRYL\*)

### III. APPLICATION OF RADIOACTIVE CARBON TO METABOLIC STUDIES OF BENADRYL

By ANTHONY J. GLAZKO, D. A. MCGINTY, WESLEY A. DILL, M. L. WILSON,  
AND C. S. WARD

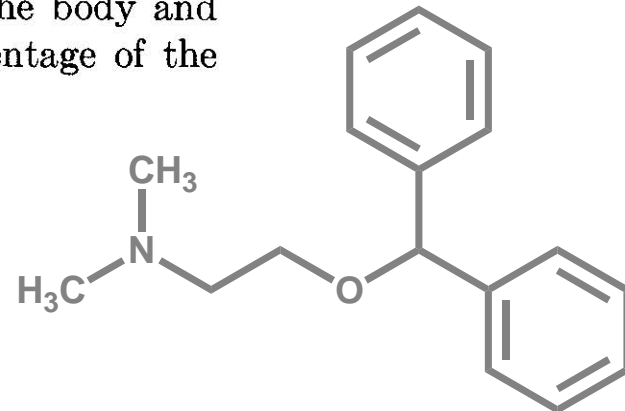
*(From the Research Laboratories, Parke, Davis and Company, Detroit)*

(Received for publication, January 14, 1949)

Biochemical studies on the urinary excretion of Benadryl have generally accounted for 5 to 15 per cent of the administered dose in 24 hours (1-3). Evidence has been obtained for the enzymatic degradation of Benadryl *in vitro*, the products no longer producing color in the analytical procedure for Benadryl (4, 5). The present work with a radioactive tracer demonstrates that metabolic products of Benadryl are formed in the body and excreted in the urine, thereby accounting for a greater percentage of the total dose than that found by chemical analysis.

Detection tools for  
Parent and metabolites

未変化体の  
尿中排泄は  
5-15%  
比色法で  
検出不可  
放射性同位  
元素で標識  
した薬物の  
動態試験



# Colorimetry to Radioactivity

Separation by  
paper  
chromatography

検出感度の向上

クロマト 分離分析

QuickTime<sup>®</sup> C2  
TIFF (LZW) compression  
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# J Biol Chem, 179. 417 (1949)

## BIOCHEMICAL STUDIES ON DIPHENHYDRAMINE (BENADRYL\*)

### IV. DEGRADATION OF BENADRYL BY TISSUE ENZYMES†

BY ANTHONY J. GLAZKO AND WESLEY A. DILL

(From the Research Laboratories, Parke, Davis and Company, Detroit)

(Received for publication, January 14, 1949)

The excretion of unchanged Benadryl accounts for only a small portion of the total administered dose in man (1, 2). Indirect evidence for the presence of degradation products in tissues and urine was obtained with Benadryl labeled with radioactive carbon (3). The experiments reported here show that degradation is produced by tissue enzymes, resulting in a loss of the basic properties of Benadryl as measured by the methyl orange technique (4).

分解する部位

P450はまだ  
見つかっていない

Site of  
Metabolism

#### *Degradation of Benadryl by Various Tissues*

50  $\gamma$  of Benadryl hydrochloride were incubated with 1 gm. of minced tissue in Tyrode's solution for 16 hours, and then analyzed for Benadryl. The amount of degradation is expressed as per cent of Benadryl originally added.

Tissue	Rat	Guinea pig	Rabbit
Liver . . . . .	97	96	99
Lung . . . . .	70	9	14
Kidney . . . . .	25	8	27
Brain . . . . .	6	8	4
Heart . . . . .	6	5	5
Spleen . . . . .	4	2	1
Muscle . . . . .	3	4	13

# 60年前と今

- Chloramphenicol study  
PK-PD(薬効-薬物濃度)
- Diphenhydramine  
Analytical method;  
radioactive probe  
Drug metabolism  
with tissue samples
- 基本的概念が、この頃に誕生している。

# 薬物のサイズ

脂溶性 **小分子**

CYP, transporter



脂溶性 **大分子**

CYP3A4



**タンパク分子**

抗体薬物

吸収性

受容体選択性

標的特異性



# 薬効・安全性と動態

- 薬効マーカー
  - 血中濃度
  - 標的における濃度
    - 受容体占有率(中枢作用薬)
  - Protein drug
    - 直接、あるいは間接的に応答マーカーを検出
- 組織移行と毒性標的
  - 共有結合付加体
  - in vivo生成レベル/臓器特異的な標的
  - 標的タンパクの選択的検出とその修飾を知る

# 分析手法

50-60'	UV
70'	GC,
80'	GCMS Stable isotope LC,
90'	LCMS
00'	AMS Microdose, NMR, Array

分離分析、一齊分析、網羅的解析

These are for small molecules, and what for protein drugs?

# 生体内変換

P450 1955 Omura & Sato

複数分子種 70'

精製、再構成系 Imai

cDNA クローニング 80' Fujii

ヒト分子種

2D6 遺伝的多型 88' Gonzalez, Kimura

Drug metabolism-associated P450 model from  
the crystal 00' Johnson

Prediction methods

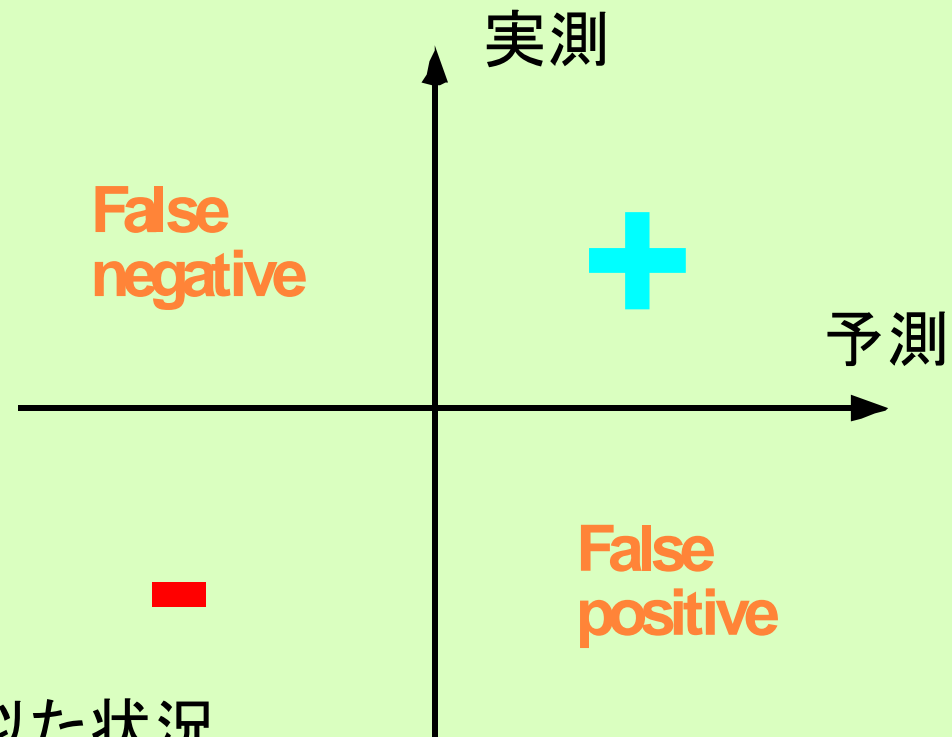
# 機能タンパクの基質特異性

- データベース型
- 酵素モデル

物性依存、  
典型基質を鋳型  
とするDocking model  
では不十分

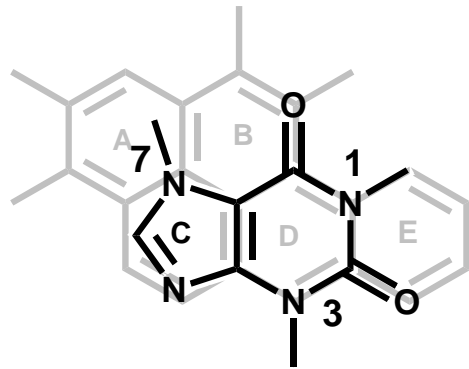
過去の変異原性試験に似た状況

基質構造から活性部位の特性を知る。

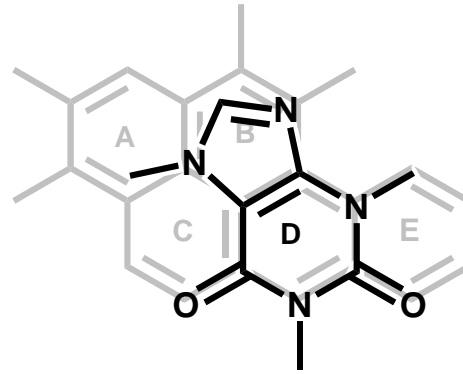


# Predicted interaction with caffeine and theophylline

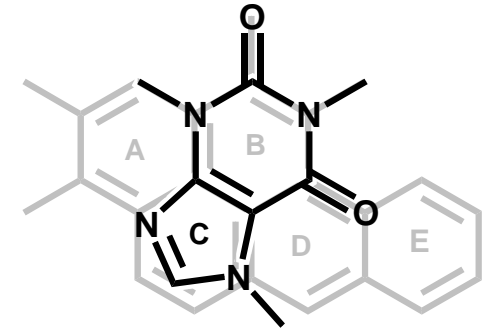
## A Caffeine



3N-demthylation

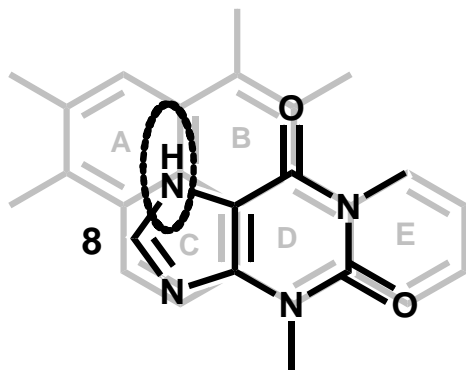


1N-demthylation

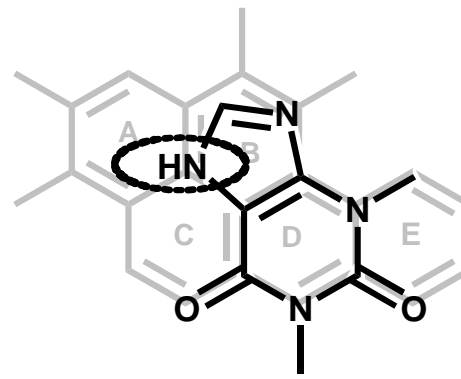


7N-demthylation

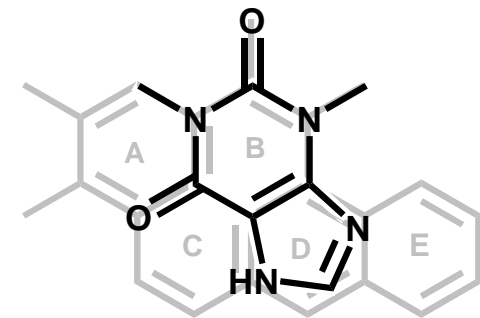
## B Theophylline(7-demethylated caffeine)



3N-demthylation



1N-demthylation



8-hydroxylation

# 今後の薬物動態研究

