

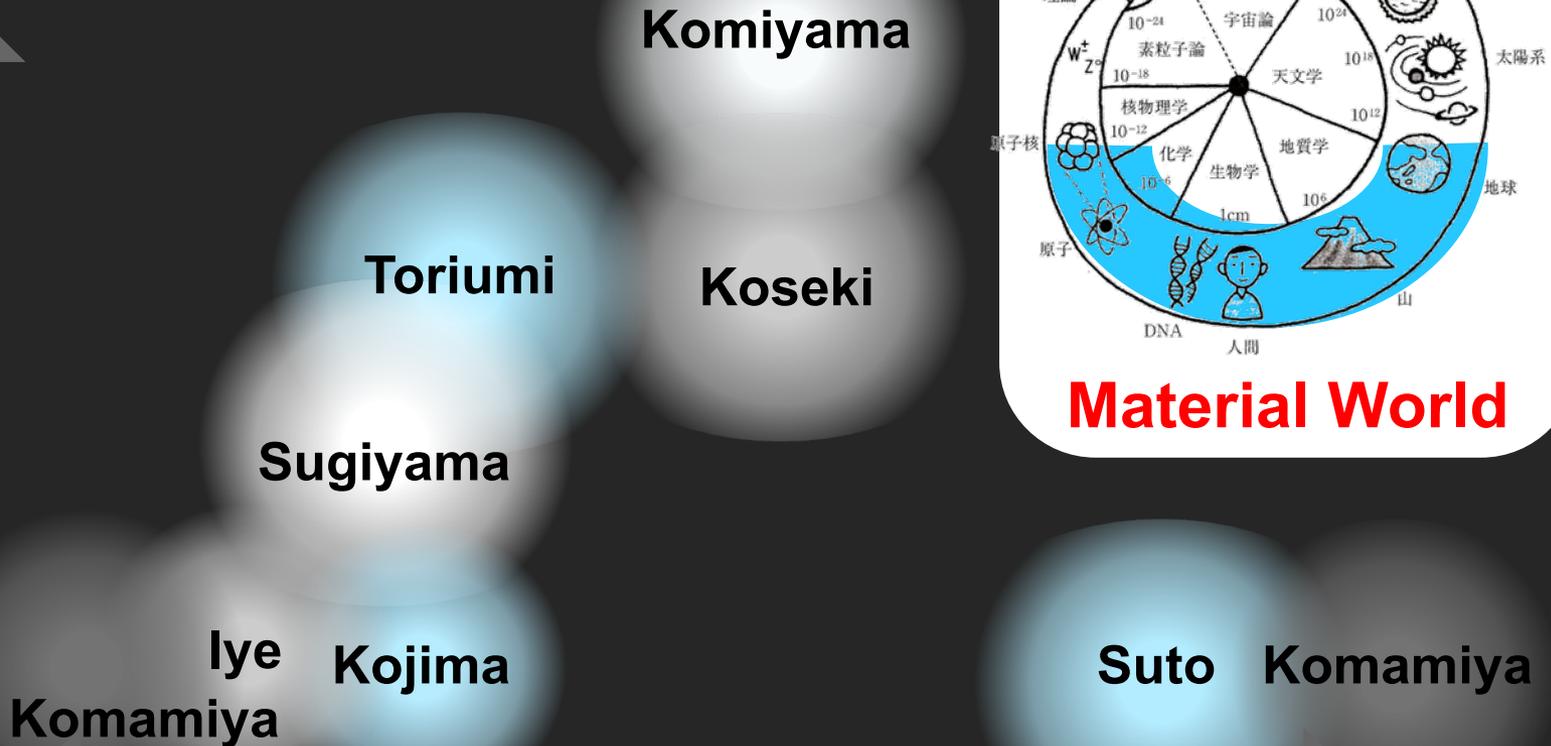
Two-Axis Recognizing Material World

Involvement with human beings and society

Span of Integration-Application

Span of Scientific (Physical-Chemical) Exploration

10^{-10} 10^{-6} 10^{-2} 10^2 10^6 10^{10} (m)
Size



The Search for, and Creation of Matter with Desirable Properties — Discovery from the Field of Pharmaceutical Science

- Why Do Drugs Work?**
- Drug Transporters**
- Drugs and Compatibility with Humans**

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Why do individual difference of sensitivity to drugs occur?



Genetic Factors



Physiological Factors

(Age, Gender, Obesity, Liver function, Kidney function)



Environmental Factors

(Smoking, Drinking, Work environment, Climate, Stress, Food, Regular medication)

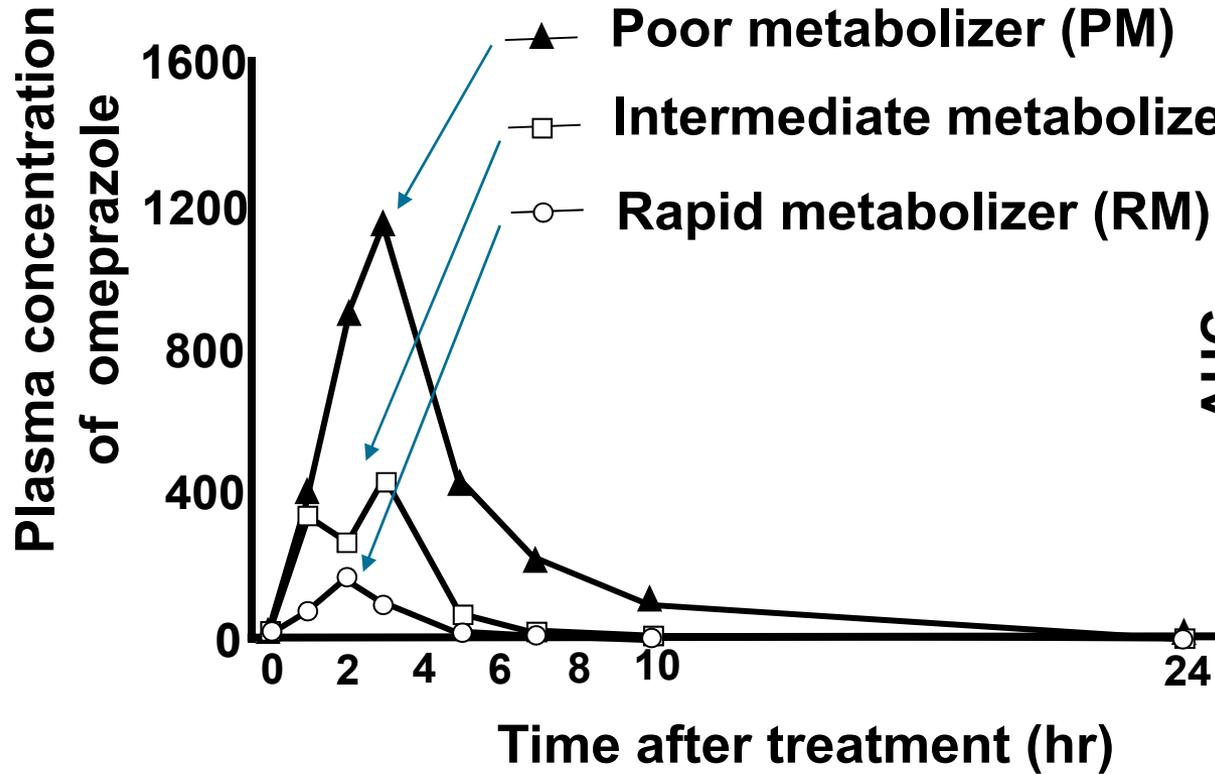
Failure Rate in Achieving Therapeutic Effect in Compliant with Drug Activity Classification

Drug groups	Failure rate in achieving therapeutic effect (%)
β -blockers (antihypertensive)	15—35 %
Angiotensin converting enzyme inhibitors (antihypertensive)	14—37 %
Angiotensin II receptor inhibitors (antihypertensive)	12—29 %
HMG CoA reductase inhibitors (antihyperlipidemia)	11—33 %
5-HT ₁ (antiasthma)	20—45 %
α -Interferon (treatment of hepatitis C)	30—70 %
Anticancer agents	20—80 %

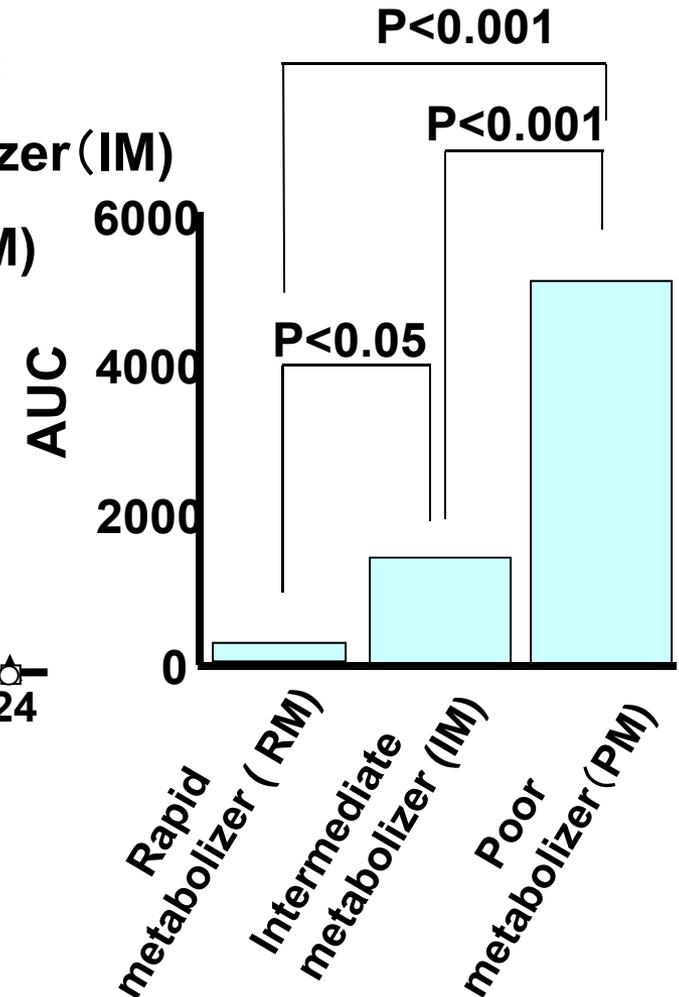
CYP2C19 Genotype and Plasma Omeprazole Concentration

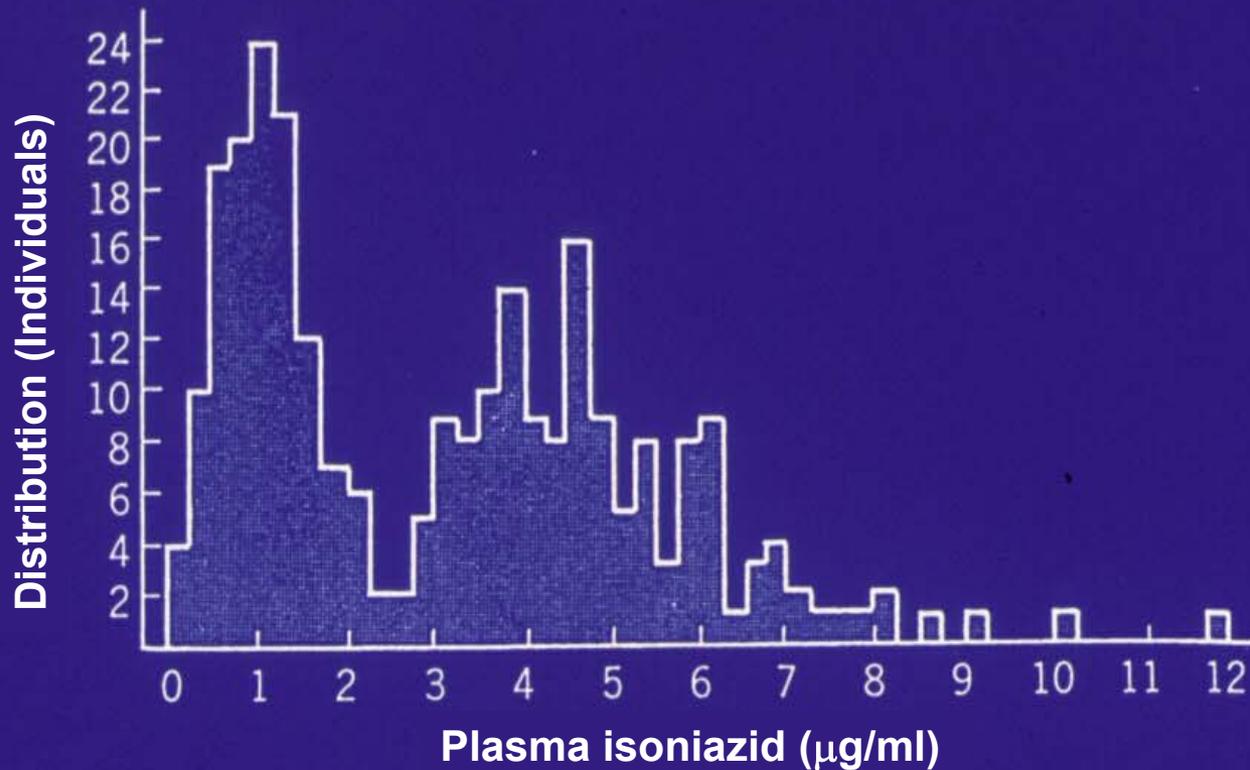
Omeprazole, 20mg treatment

(ng/ml)



Comparison of AUC

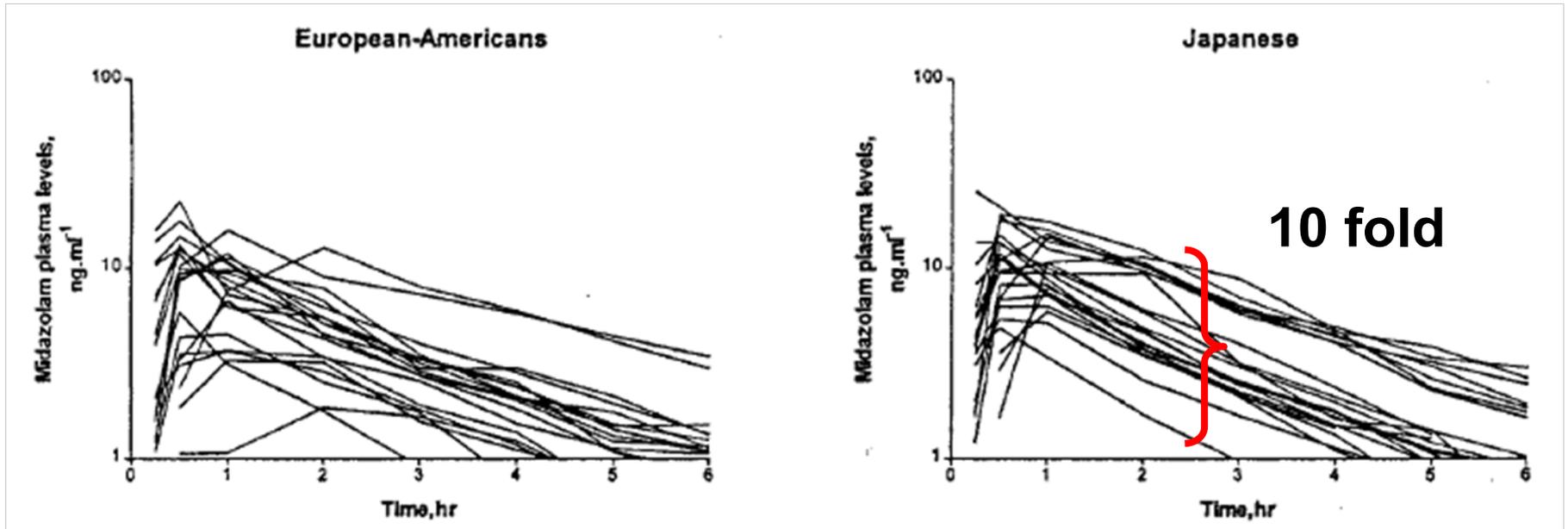




Histogram for Bimodal Distribution of Plasma INH Concentration in 267 Caucasians in 53 families

R. Kato, 'Clinical Pharmacokinetics', Nankodo, Tokyo, 1998

Time Course of Plasma Concentration of Midazolam after 2 mg Oral Administration



Clin Pharmacol Ther. 69, 333, 2001

Approx. 10- fold individual differences are shown in the CYP3A4 substrate without definite gene polymorphism

† Provided by Dr M. Kato (Chugai Pharmaceutical)

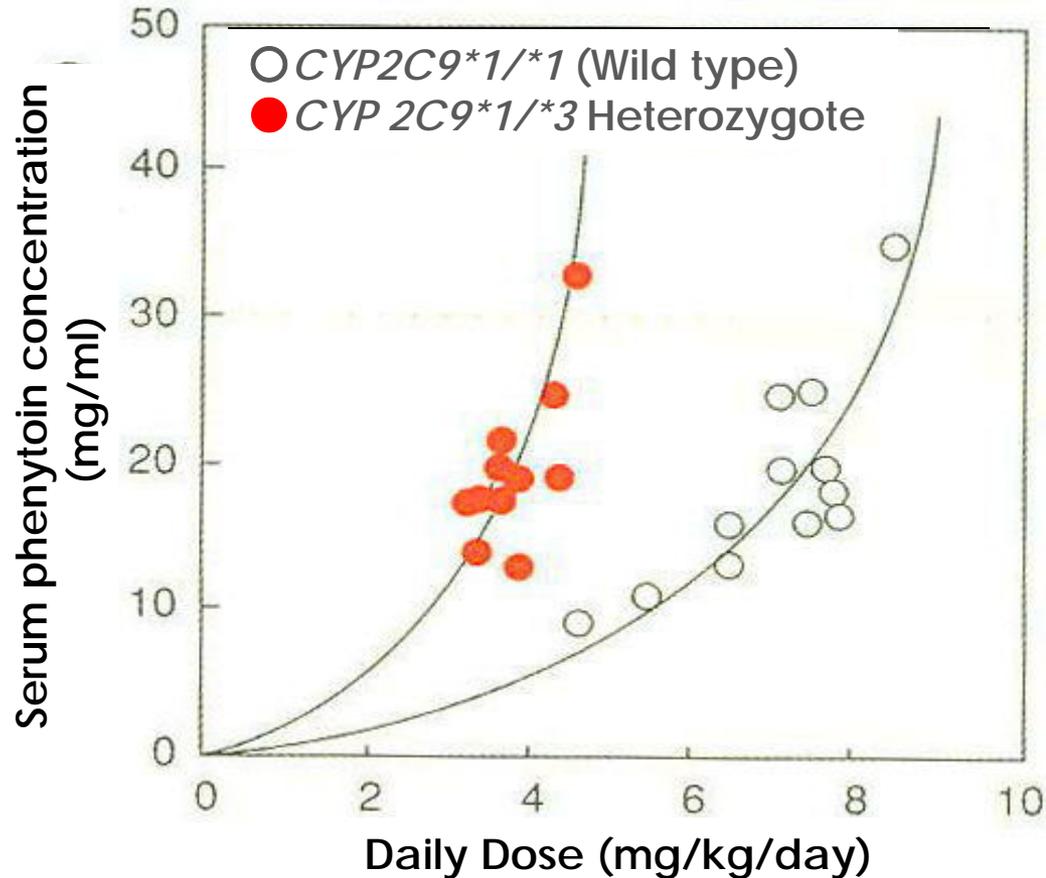
TDM(Therapeutic Drug Monitoring)

- What is TDM

Methodology for Individualization of drug dose so as to fit within the desirable effective blood concentrations (therapeutic window), by measuring the blood drug concentration of individual patients.

It applies to drugs with delicate prescription.

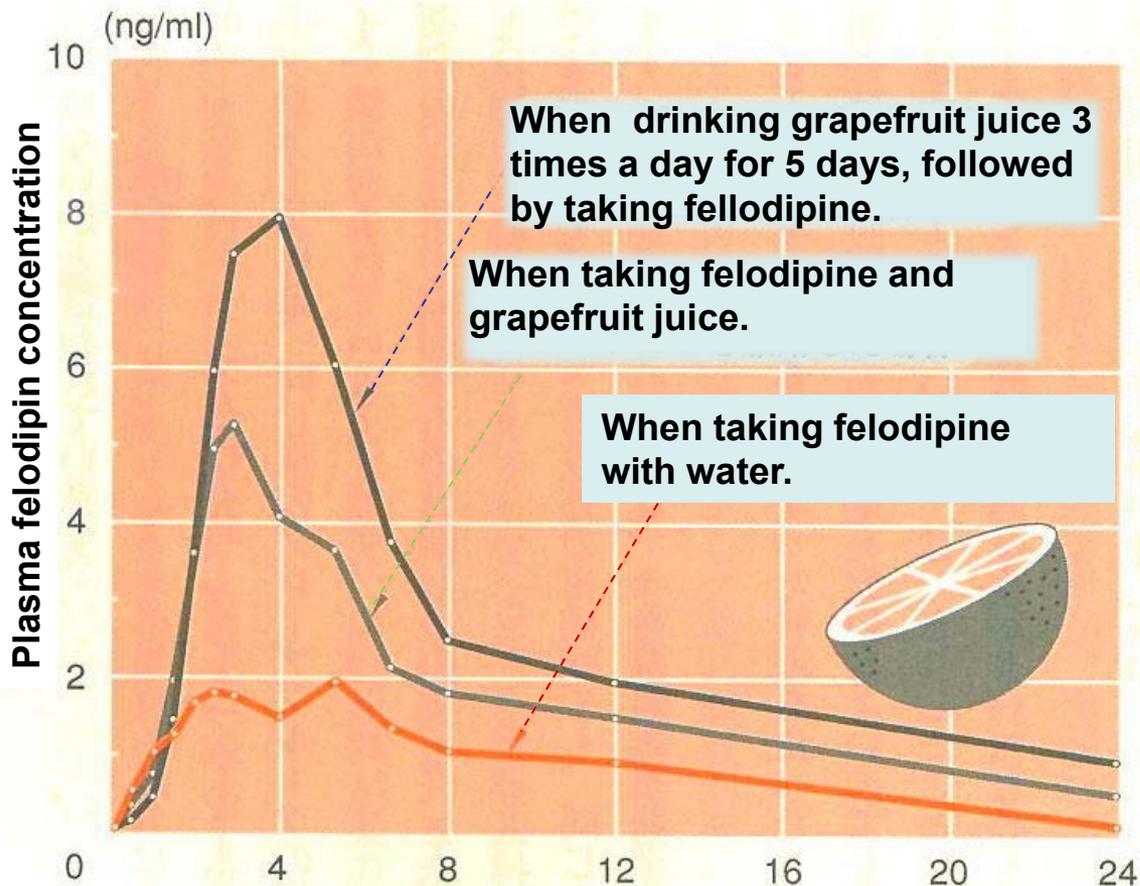
Relationship between Serum Phenytoin Concentration and Gene Polymorphism



† Source: J. Azuma: 「「クスリに弱いヒト」と「困ったクスリ」たち」
(Individual Difference of Reactivity to Drug), Jiho, Inc., Tokyo, 2001

Blood pressure lowered too much with combination of grapefruit and antihypertensive drug!

(Example of Felodipine, 10 mg as an antihypertensive drug.)



When the antihypertensive felodipine is taken with grapefruit, plasma felodipine concentration increased 2-5 fold compared with taking with water to decrease blood pressure too much.

※ Plasma is the liquid component of blood prepared from the blood itself after adding anticoagulant to the collected circulating blood.

Source: K. Takada, 'My Medicine, Your Poison!', HOME-SHA, Tokyo, 2000

Alteration in Clinical Efficacy and Adverse Effect of Drugs by Smoking

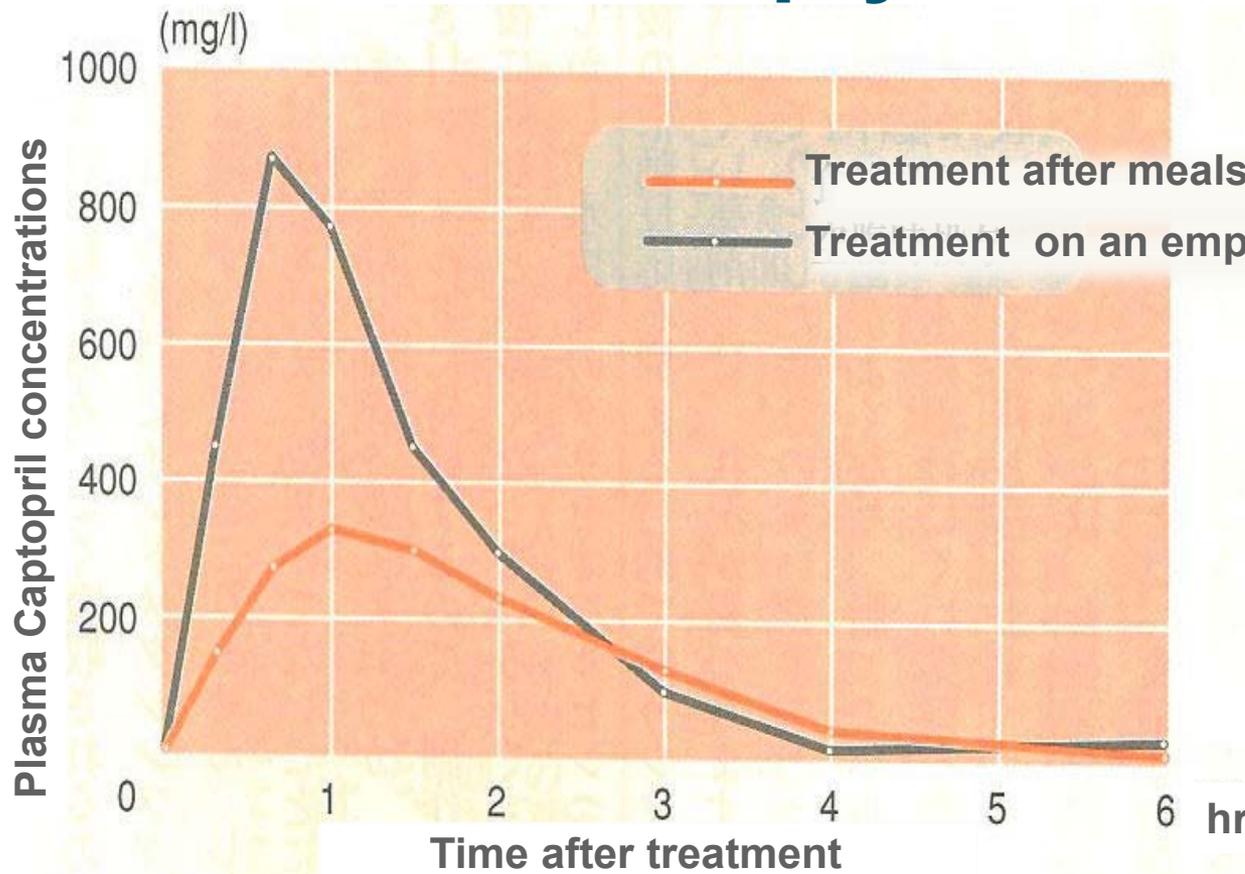
Drugs	Decreased action	Frequency of occurrences, %		
		NS	Light S	Heavy S
Propoxyphenene	Analgesic effect	10.1	15.0	20.3
Chlorpromazine	Sleepiness	16	11	3
Diazepam	Central inhibition	7.9	7.7	2.8
Chlordiazepoxide	Central inhibition	9.7	6.1	3.5
Phenobarbital	Antiepileptic	9.3	5.9	4.8
Theophylline	Adverse effect	12.9	10.8	7.0

R. Kato, 'Clinical Pharmacokinetics', Nankodo, Tokyo, 1998

Male, Aged 50, Self-employed.

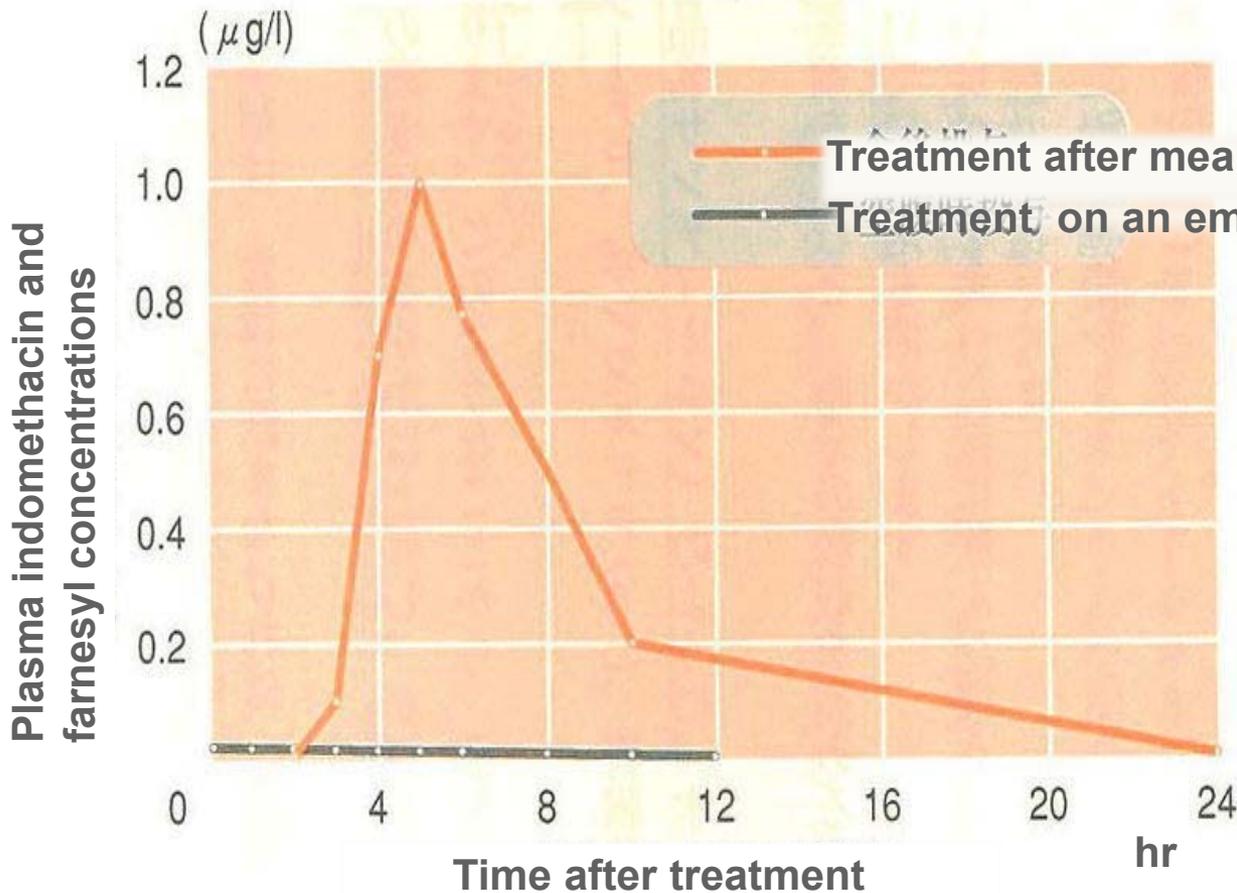
The patient has asthma, and has regularly used thophylline. He began to smoke cigarettes from about the age 20, and has until recently averaged 40 cigarettes a day. The patient decided to stop smoking, resulting in headaches, anorexia, and palpitations.

Characteristics of Drugs Taken on An Empty Stomach

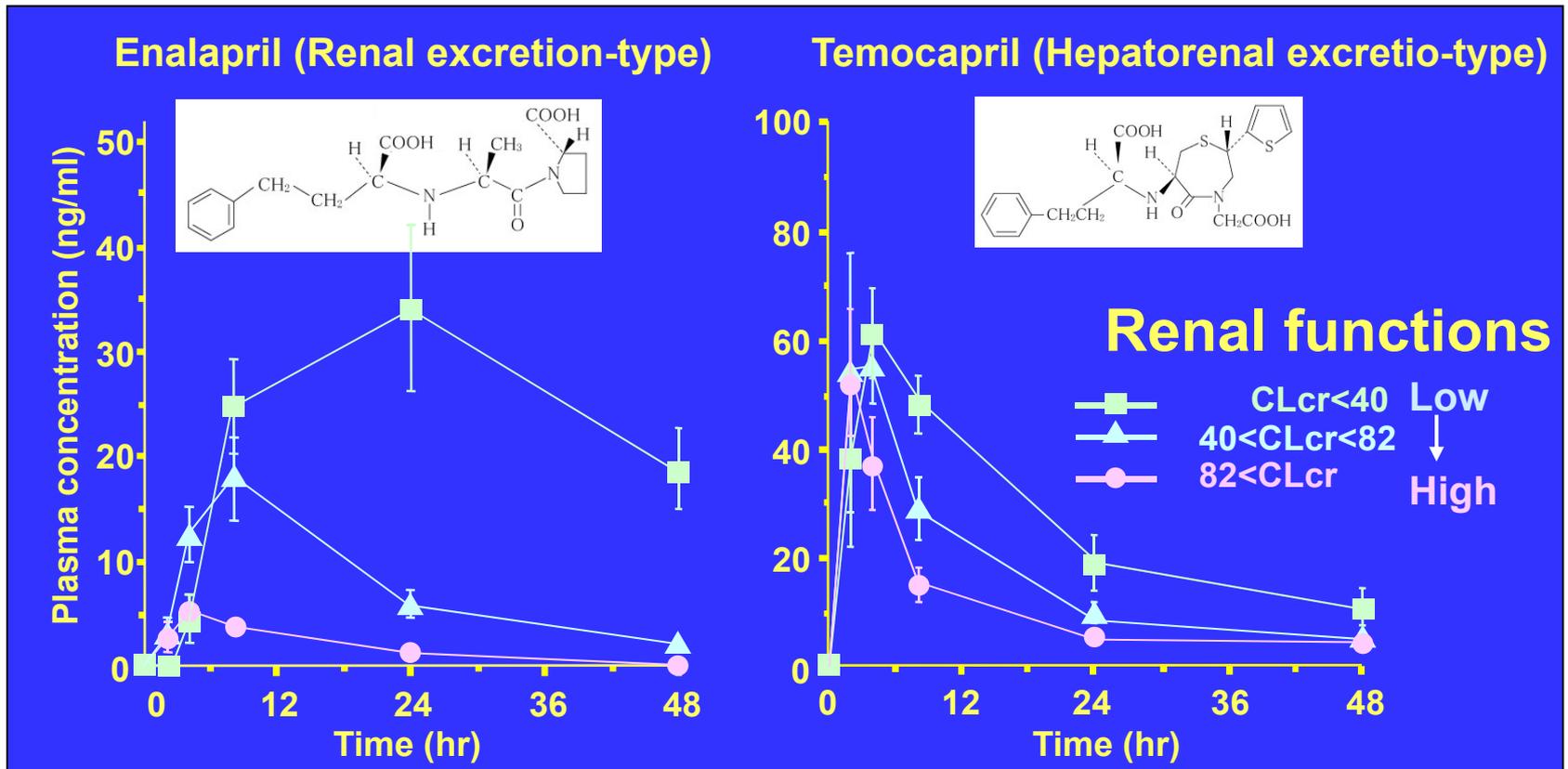
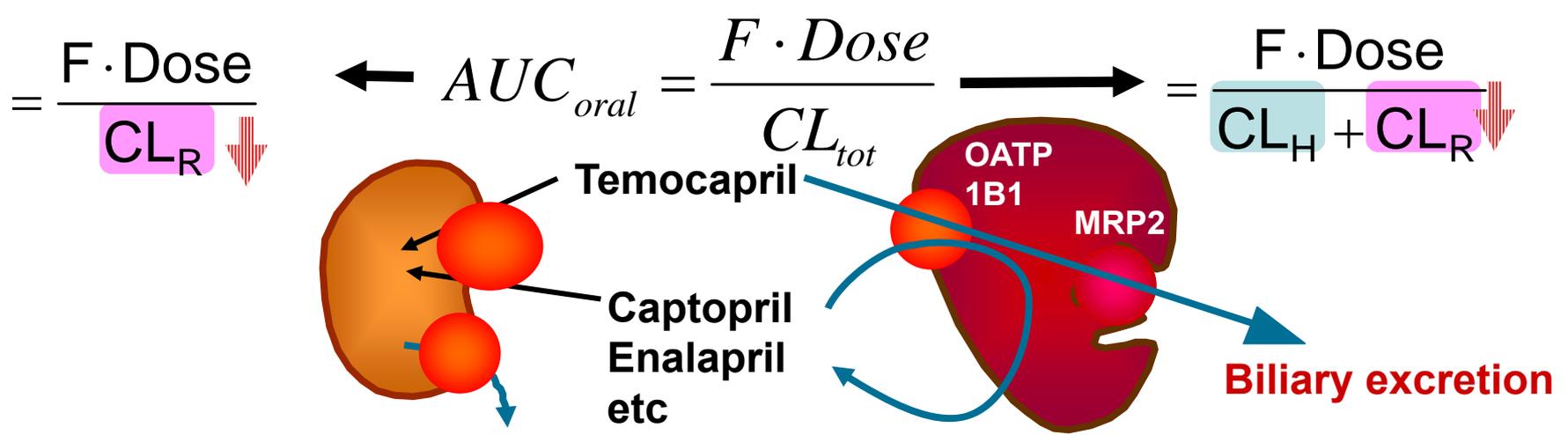


Taking drug on an empty stomach leads to a good absorption of drugs, whereas taking after meals results in less absorption than on an empty stomach. Thus, the drug is taken on an empty stomach.

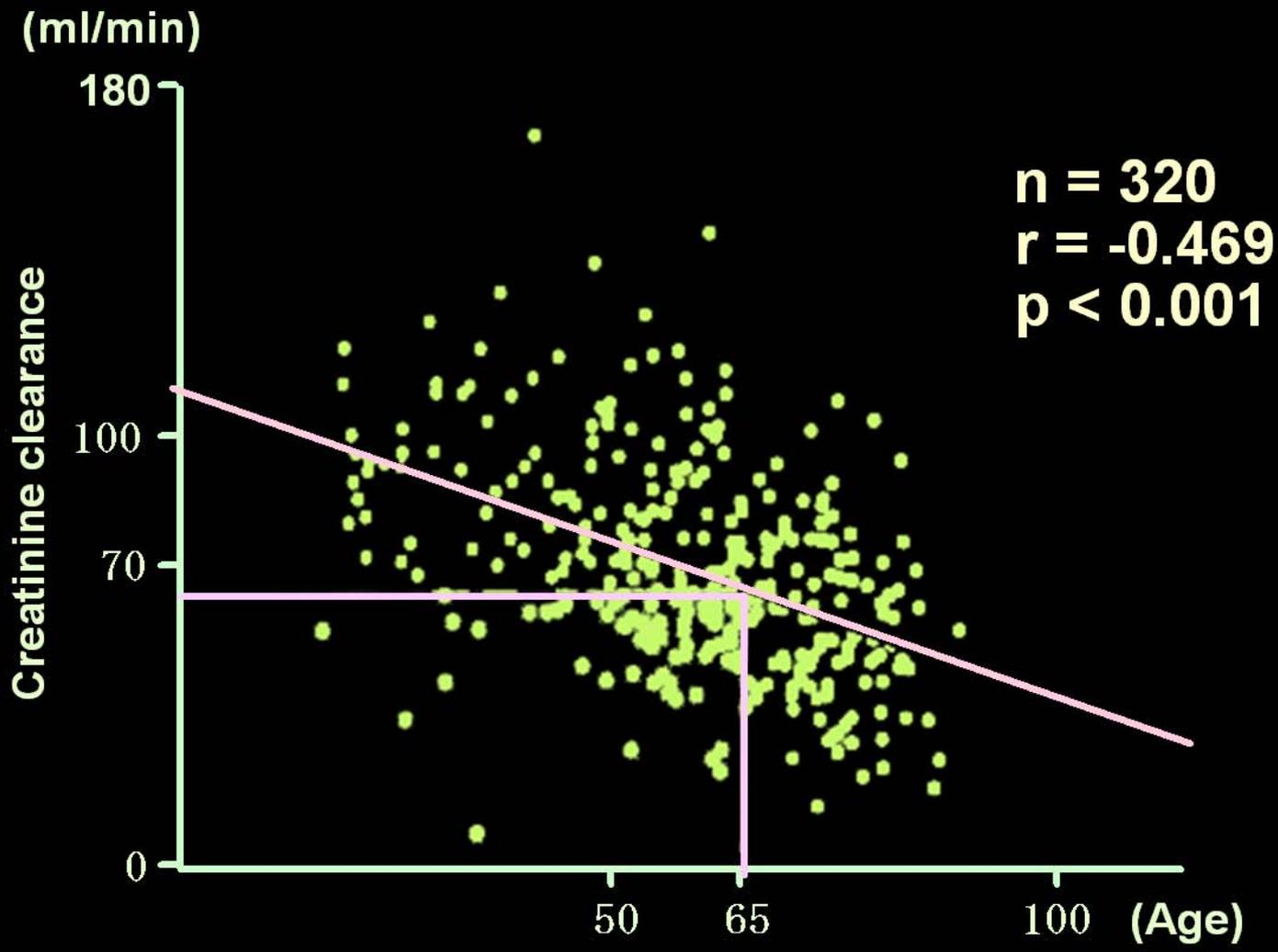
Characteristics of Drugs Taken after Meals



Since taking drugs on an empty stomach resulted in almost no absorption of drugs, no efficacy can be obtained. Taking after meals lead to increase bile excretion and good absorption of the drug. Thus, the drug is taken after meals



‡ Relationship between plasma concentration and renal function in angiotensin converting enzyme inhibitors, “compatibility(Open lecture at UT)” University of Tokyo Press, 2001



Relationship between Aging and Renal function (Japanese)

Summary

- 1) Factors regulating the activities of enzymes and transport carriers are classified as follows:**
 - (a) Genetic factors**
 - (b) Physiological factors (age, obesity, hepatorenal functions etc.)**
 - (c) Environmental factors (smoking, drinking, foods, etc)**
- 2) Care should be exercised in some drugs whose concentrations in blood and adjacent to the receptors, efficacies and adverse effects increase in individuals with low ability of metabolism in the liver and excretion in the kidneys.**

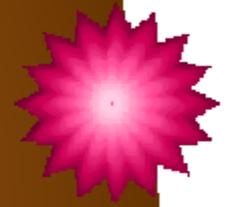
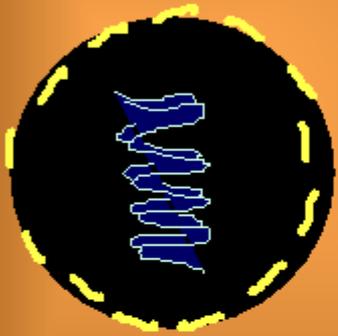
Cell

Nuclear : 0.01 mm

Chromosome: 46

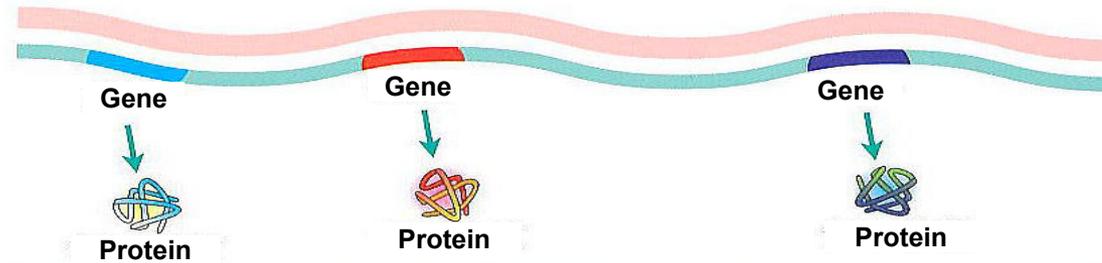
DNA: Placing of all DNA on the 46 chromosomes in a human cell results in 2 m in length. Width of DNA is approx. 10 thousandth of hair in size.

If we replaced DNA with a cassette tape and keep a similar configuration, human 2-m DNA would extend 3000 km in length. Reading proteins from DNA appears to be similar to playing a tape back. If we read the tape with a tape reader, it would take us 2 years.

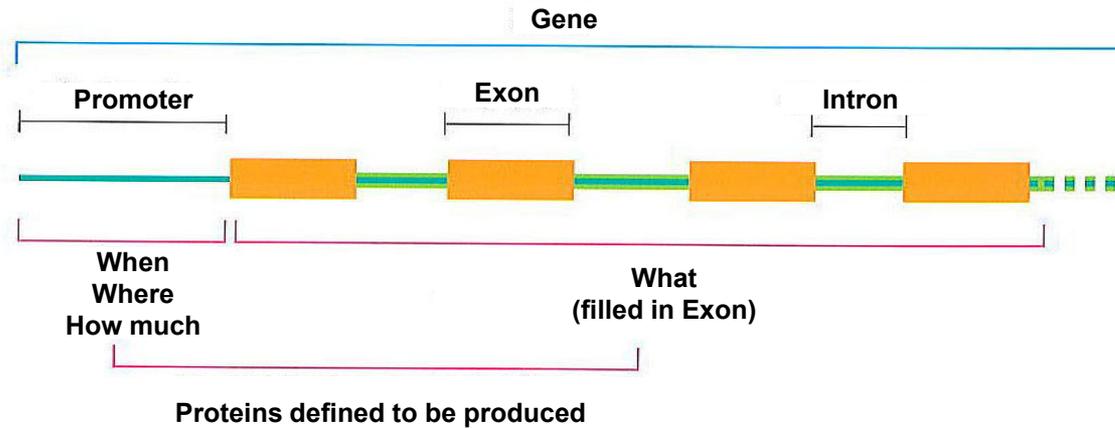


Central Dogma

What is a gene?



Gene has information about When/Where/How much and what characteristics of protein to be produced



† Source: Yusuke Nakamura, Know about Front-line Genomic Medicine, YODOSHA, Tokyo 2002

SNP (Single nucleotide polymorphism)

One SNP in hundreds – thousands base pairs

3 – 10 million SNPs in a human genome

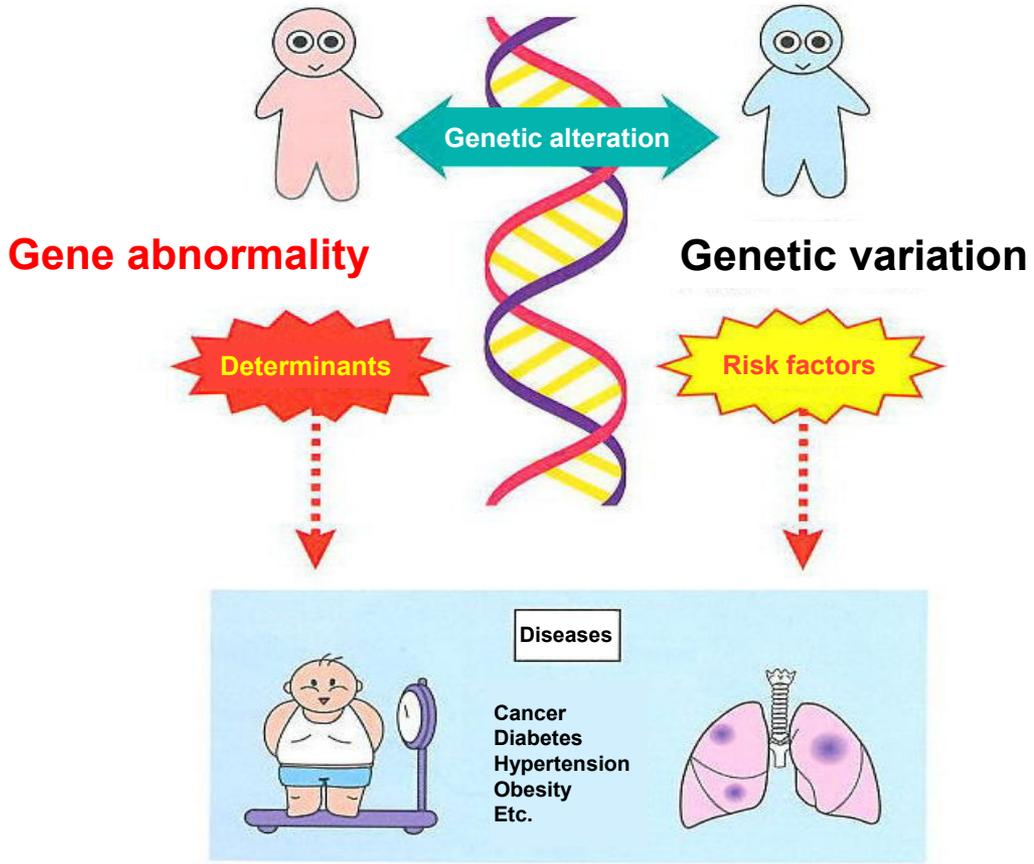
Housewife, Aged 40

On board a plane during a trip abroad, she took a tablet of benzodiazepine, an anti-anxiety drug that her husband had regularly taken, followed by developing dizziness and was unable to have in-flight meal.

(40 min)

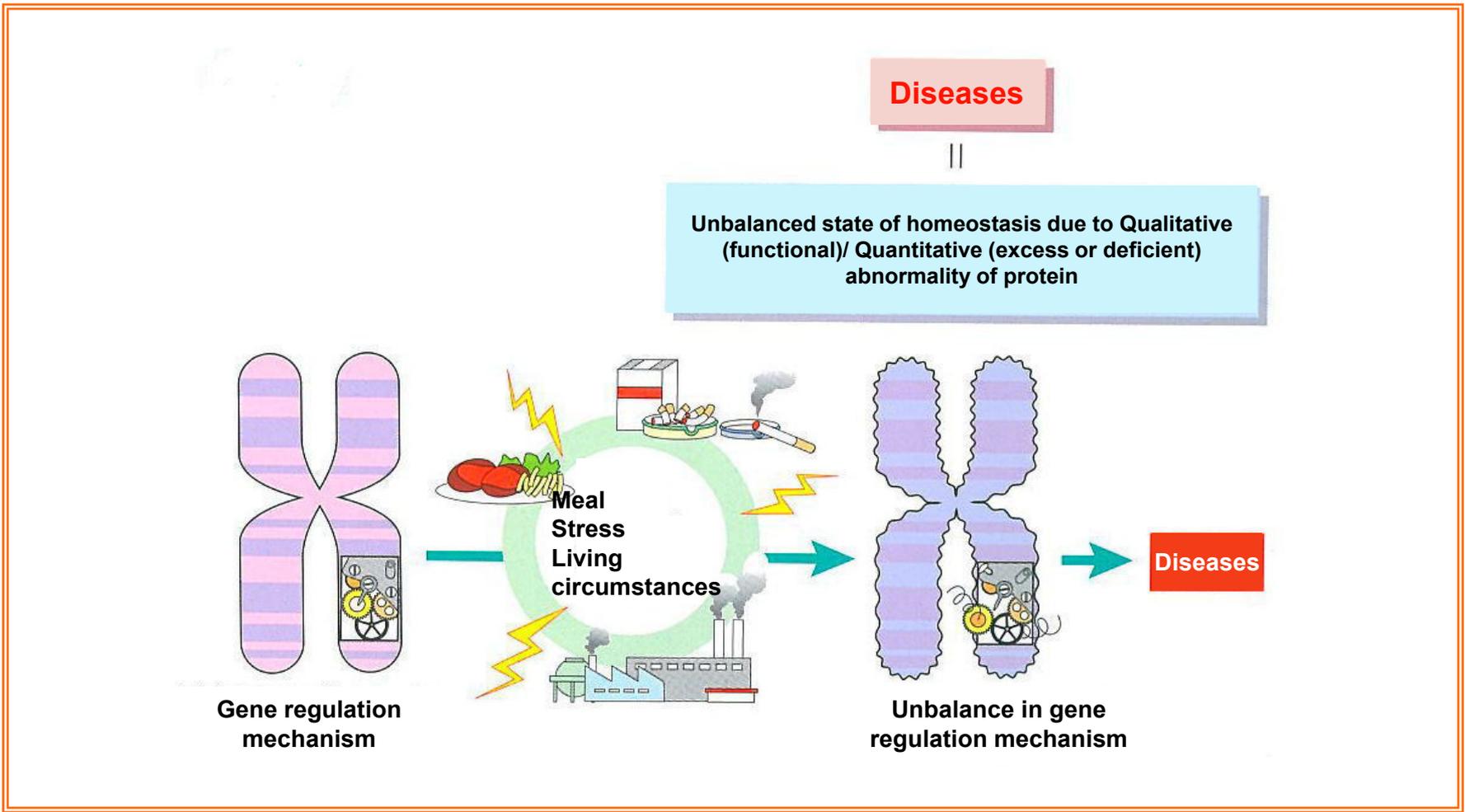
2C19

Disposition of Disease



† Source: Yusuke Nakamura, Know about Front-line Genomic Medicine, YODOSHA, Tokyo 2002

Disease and Gene



† Source: Yusuke Nakamura, Know about Front-line Genomic Medicine, YODOSHA, Tokyo 2002

The elderly man next door had been smoking until he was 100 years old.



‡ Cited from Professor Tetsuya Kamataki, Hokkaido University.

Tailor-Made Medicine

Single gene diseases

Single gene mutation

e.g.

Muscular dystrophy

Familial Alzheimer disease

Cystic fibrosis

Gauche disease

ADA deficiency

Genetic factors

Multi-factor gene diseases

Multiple gene mutations
+
Environmental factors

Hypertension

Diabetes

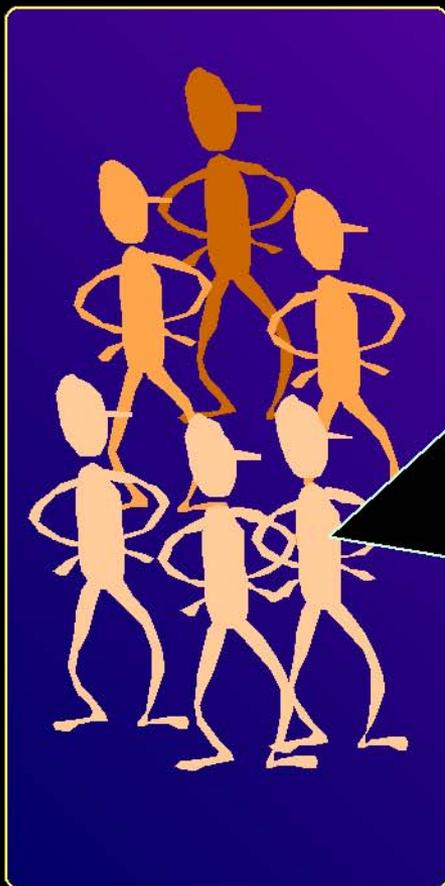
Hyperlipidemia

Ischemic heart disease

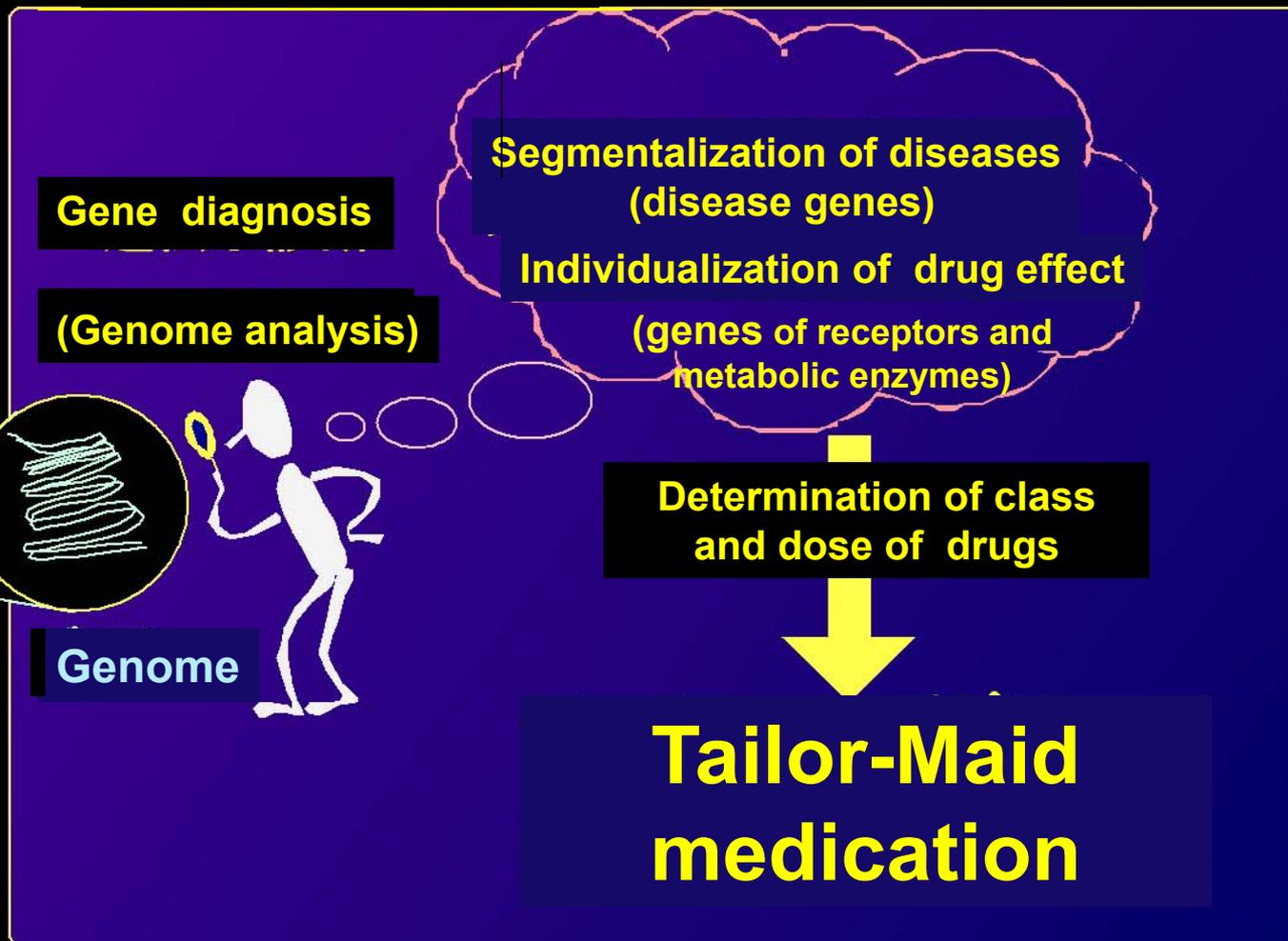
Environmental Factors



Individuals

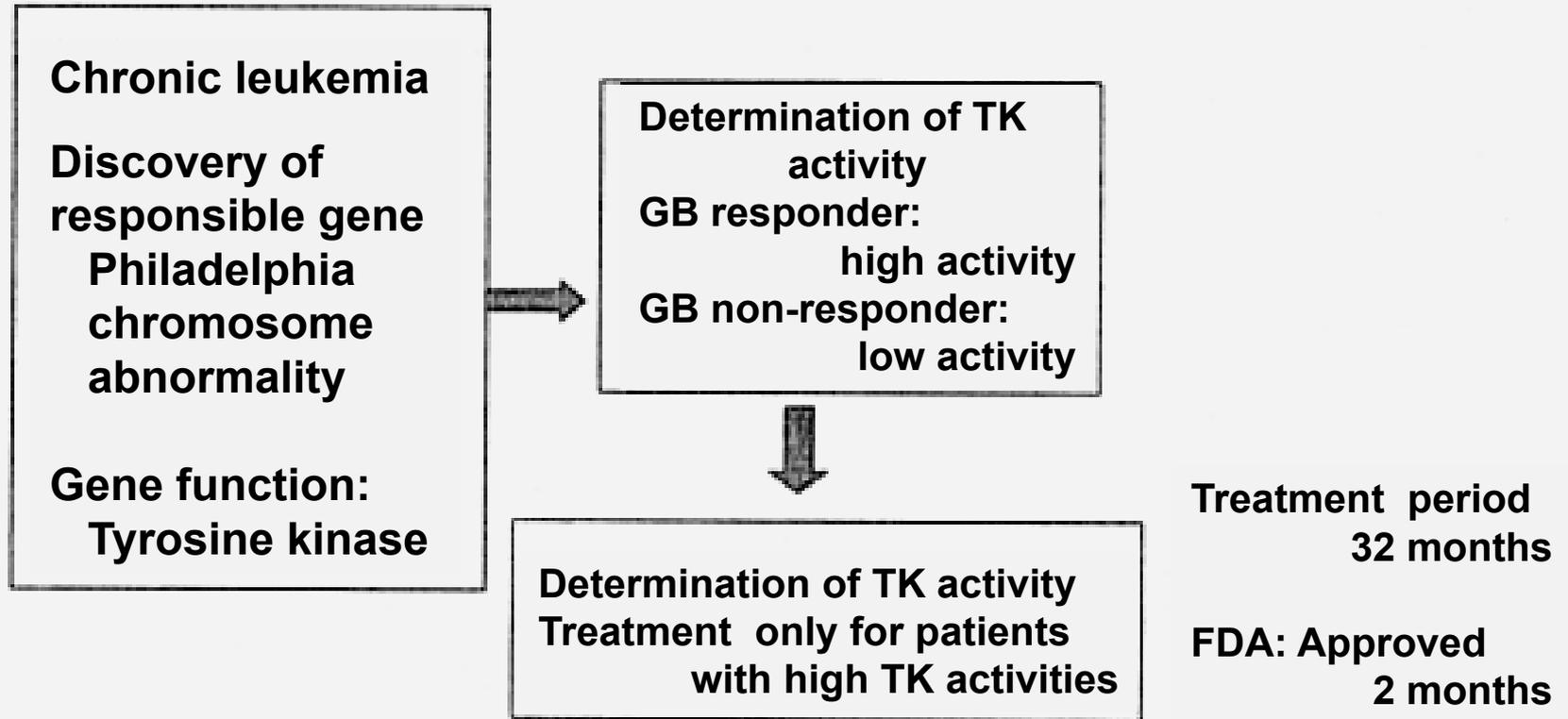


Patients



Genome Analysis and Medication

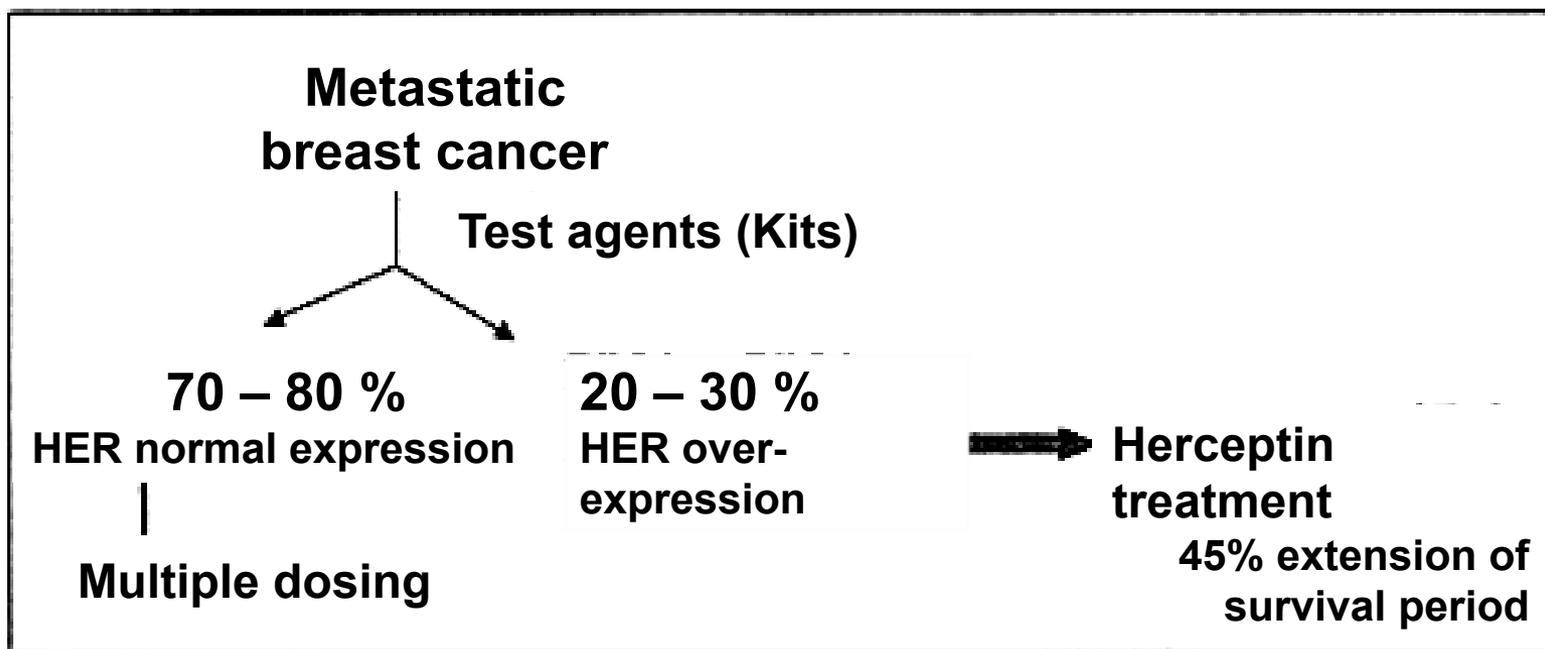
Therapeutic Agent of Chronic Leukemia: Glivec



Herceptin: Therapeutic Agents for Breast Cancer

R&D, Genentech: Sale, Roche

Herceptin: Therapeutic antibody specifically bound to HER 2 (human epidermal growth factor)

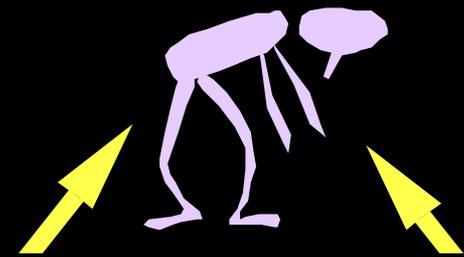


(Herceptin)

‡ HS Report No. 37 (April 2002)

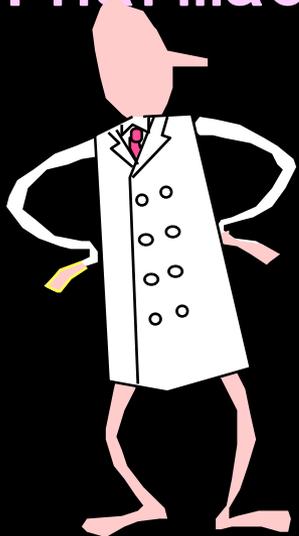
Ideal Medication in Near Future

Patients



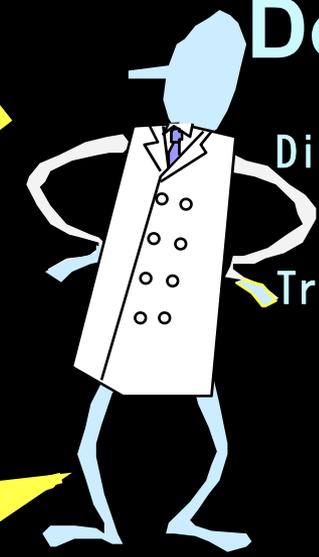
Informed Consent

Pharmacist



TDM
Gene analysis (metabolic enzymes, receptors)
Understanding of pathophysiology
Pharmacokinetic analysis

Doctor



Diagnosis
Treatment

Needs for gene analysis

Discussion about selection of drugs and treatment design

Summary-2

1) Individual sensitivity to drugs depends on gene polymorphism of the metabolic enzymes.

Poor metabolizers

Extensive metabolizers

2) A number of metabolic enzymes including Phase I enzyme (P-450), Phase II enzyme (conjugating enzyme) and others are known to present gene polymorphisms, which have been demonstrated to be responsible for individual difference of drug efficacies and adverse effects.

3) There are also ethnic differences in the frequency of developing gene polymorphisms.

4) Some receptors directly involved in efficacies also present gene polymorphisms.

Conclusion

- 1) In the near future, availabilities of the diagnosis with most genes coding drug metabolizing enzymes as well as transporters and receptors and with genes of disease characteristics might allow us to establish 'Tailor-made medicine', where drugs with high efficacy and less adverse effects and the treatment in optimal dose could be chosen.**
- 2) Furthermore in the future, during the course of drug development, a method for rapid selection of drugs, which work well with anyone, with characteristics of everyone's friend and < a small individual difference > might be developed, then there will be hope for ideal drugs to become available.**

Fork in the Road Session



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**The Controlled Release Society's 33rd Annual Meeting
and Exposition in Vienna, Austria, 22-26 July 2006.**

First Fork;

**Graduate School
Lecture by
Professor S. Awazu**

Second Fork;

**Study under
Professor N.
Kaplowitz (UCLA)**

Fork in the road – Which way?

**Chose a positive way
when you are not able to
make up your mind.**

Nothing to lose

Generalist or Specialist

What you must do is to see how many things that you can learn from experiencing yourself, reading plenty of papers, and thinking them through by yourself. You can keep information stored and sorted inside your head, and you can draw on it when needed, and then actually apply this information to pharmaceutical research and development. In other words this is really a 'capacity of wisdom'. (Wisdom is knowledge plus experience.)

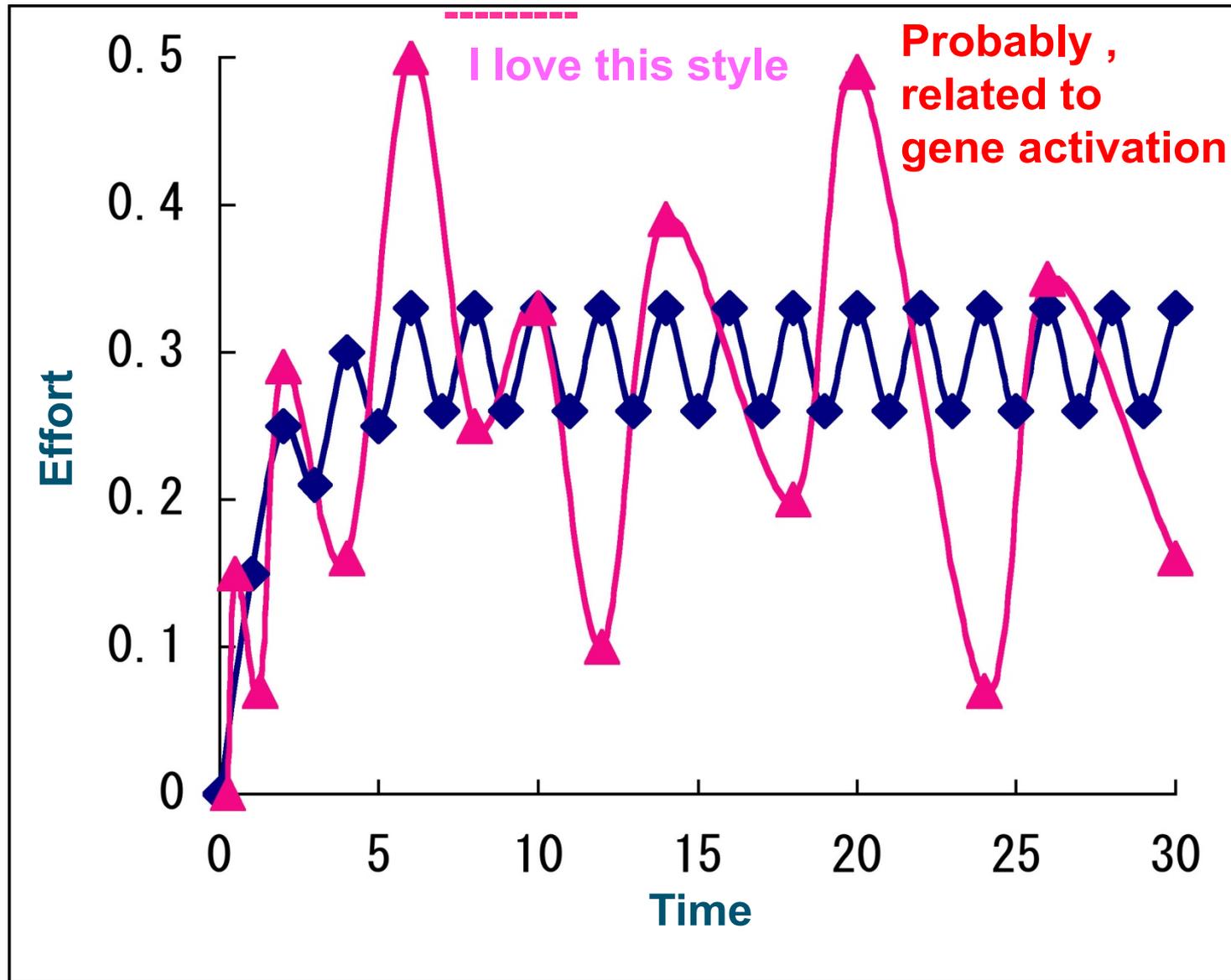
I ask both academic and corporate researchers to be “a researcher capable of taking an integrative, panoramic view of many research fields on deepened scientific basis through high-quality research experiences”.

In other words, “a generalist with specialist experience”.

It is necessary for you to devote yourself to your studies and to make a through-going effort to be a 'specialist' over a period of time (about 5 years).

You will do well to master a specialty until a certain age. Then, having the flexibility to be a generalist without clinging to being a specialist, you will be able to do really good research to contribute to drug development.

Experiences of working to the limit of your ability is essential. → Self confidence



What is important

- **Increase your capacity for wisdom. Increase your 'Vmax'.**
 - **No example? Then, you will be able to make a good example.**
 - **Internationality (English-language ability, human skill / communication).**
 - **Get the hang of enjoying discussion and collaboration.**
 - **For corporate researchers:**
 - **For female researchers:**
 - **Challenge unflinchingly what hasn't been done before and what has real originality.**
- Persistence: You can not expect serendipity without it.**

Philosophy

- I am OK and you are OK
- (Be positive about yourself and others. Be yourself.)
- It flows naturally.
- Tomorrow is another day.
- (Now, do your best. Think if today will not, tomorrow may.)
- 日々是好日: Every day is a good day.

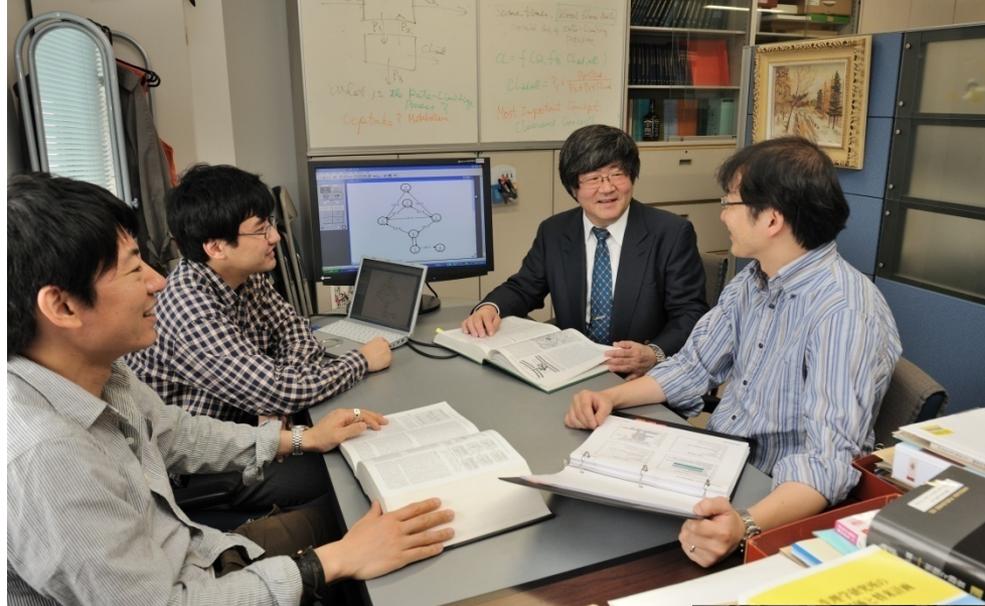
Conclusion

- 1) Have a prophetic research vision in the future (to talk about your ideas and dreams).
 - 2) Be ambitious and persistent to create a sweeping trend for future research by yourself.
 - 3) Be proactive to make collaboration with other research fields.
 - 4) Frequently hold 'brain storming' sessions on both an individual and a group basis.
 - 5) Be an international person with representational power to transmit new concepts to the world and leadership. (English-language skills are extremely important.)
- * Increase capacity for wisdom.
 - * Be devoted maximally to your research to be a 'specialist' for about 5 years!
 - * It is necessary to have experiences of making continuous research efforts at nearly full load. (Self-fulfillment)



‡

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