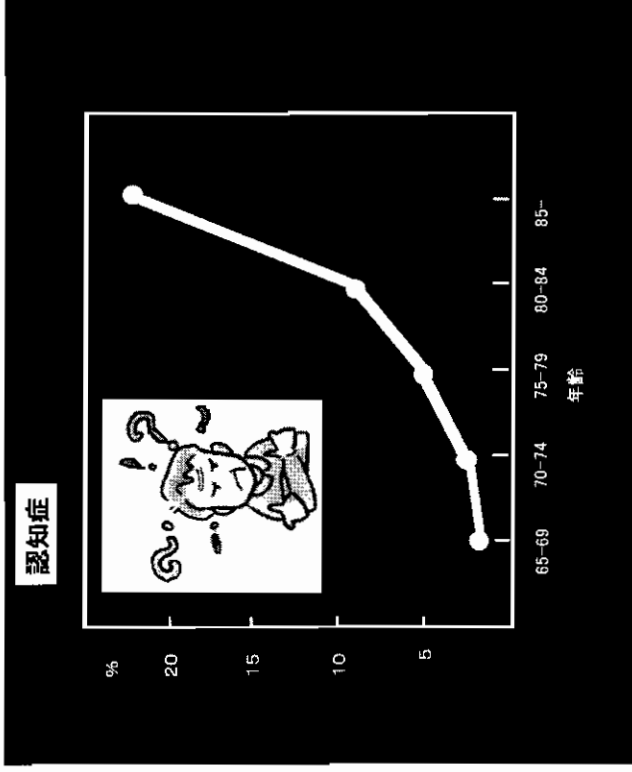


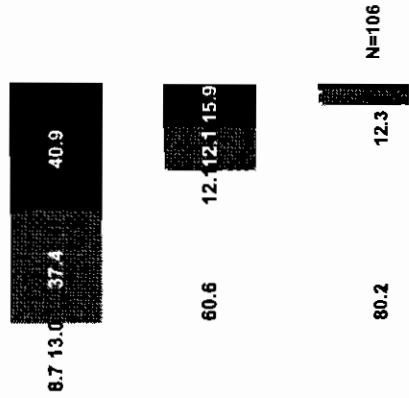
# アルツハイマー病の 治療を考える

同志社大学・生命医科学部設置  
準備室

井原康夫



超高齢者の知的レベル  
(東京都)

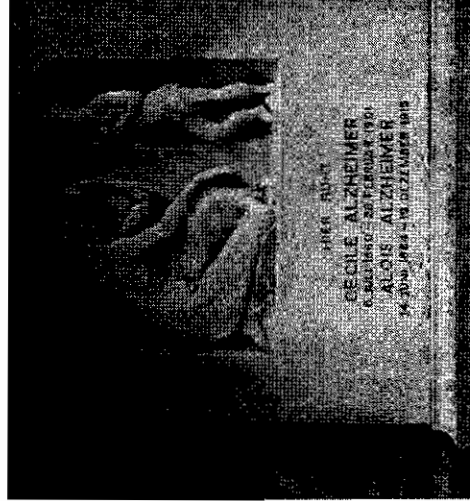


指数関数的上昇の傾向はそのまま続く！  
この大多数がアルツハイマー病

## Alois Alzheimer (1864-1915) 臨床神経病理学の創始者



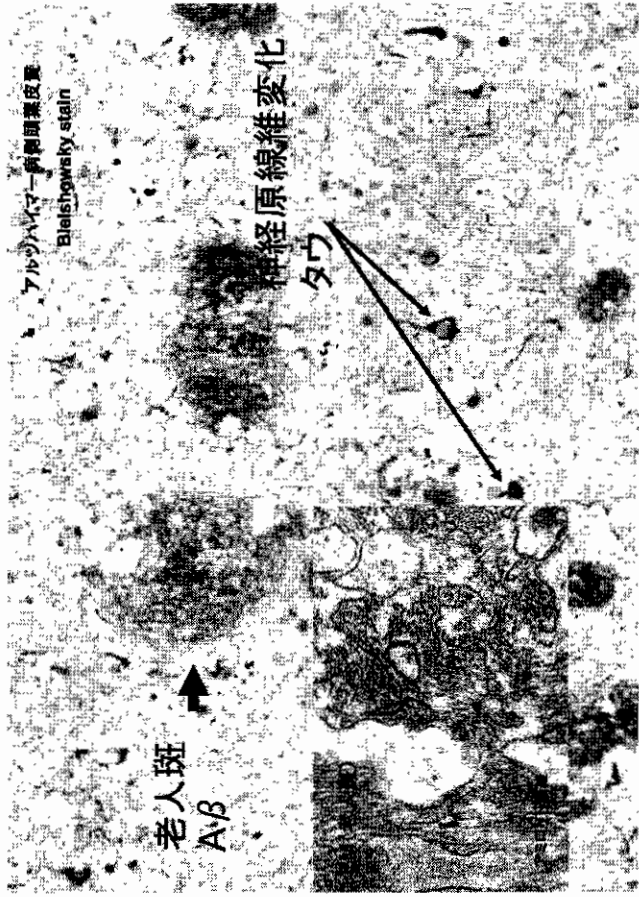
*Alzheimer*  
Alois Alzheimer 1864-1915



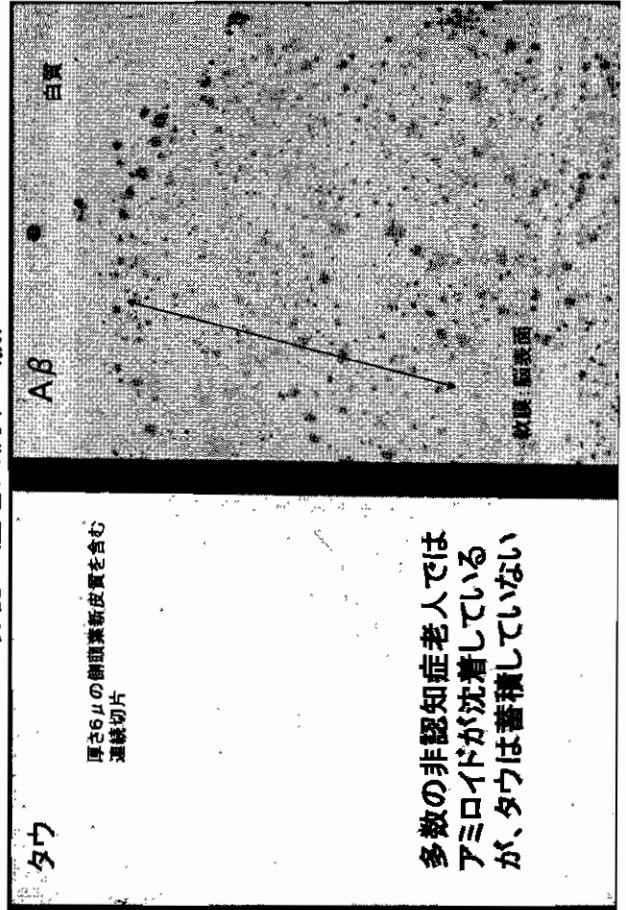
Alzheimer A: Ueber eine eigenartige Erkrankung der Hirnrinde. Zentralblatt fuer die gesamte Neurologie und Psychiatrie 18: 177-179, 1907

# アルツハイマー病の病理

- 神経原線維変化 = タウ
  - 老人斑 = A $\beta$
  - 神経細胞の脱落
- 陽性徴候
- 陰性徴候



非認知症老人例 (75歳)



多数の非認知症老人ではアミロイドが沈着しているが、タウは蓄積していない

## ダウン症 (第21染色体が3つ)

ダウン症患者は、100%の確率でアルツハイマー病の病理を持つようになる。⇒老人斑(A $\beta$ )と神経原線維変化(タウ)の時系列を追うことができる。

Case	Age (years)	senile plaques	neurofibrillary tangles	Angiopathy (p-peterson)	Isletamyloid Tangles
11	6	-	-	-	-
2*	12	-	-	-	-
3*	17	-	-	-	-
4*	18	-	-	-	-
5*	22	-	-	-	-
6*	31	-	-	-	-
7**	31	-	-	-	-
8*	31	++	++	-	-
9**	37	++	++	-	-
10*	38	++	++	-	-
11*	38	++	++	-	-
12*	38	++	++	-	-
13*	39	++	++	-	-
14*	40	++	++	-	-
15*	41	++	++	-	-
16*	42	++	++	-	-
17*	42	++	++	-	-
18*	43	++	++	-	-
19*	46	++	++	-	-
20*	47	++	++	-	-
21*	48	++	++	-	-
22*	49	++	++	-	-
23*	50	++	++	-	-
24-34*	55-71	+++	+++	0 (n=1)	+++ (n=16)
30-41	55-62	++	+++ (n=2)	+	+++ (n=3)
40-6)		++	+++ (n=2)	+	+++ (n=2)
41	55	+++	+++	+	+++

The severity of lesions was rated:  
 (-) Not present  
 (+) Found only after extensive search  
 (++) Substantial numbers of plaques and tangles on several affected vessels, but none

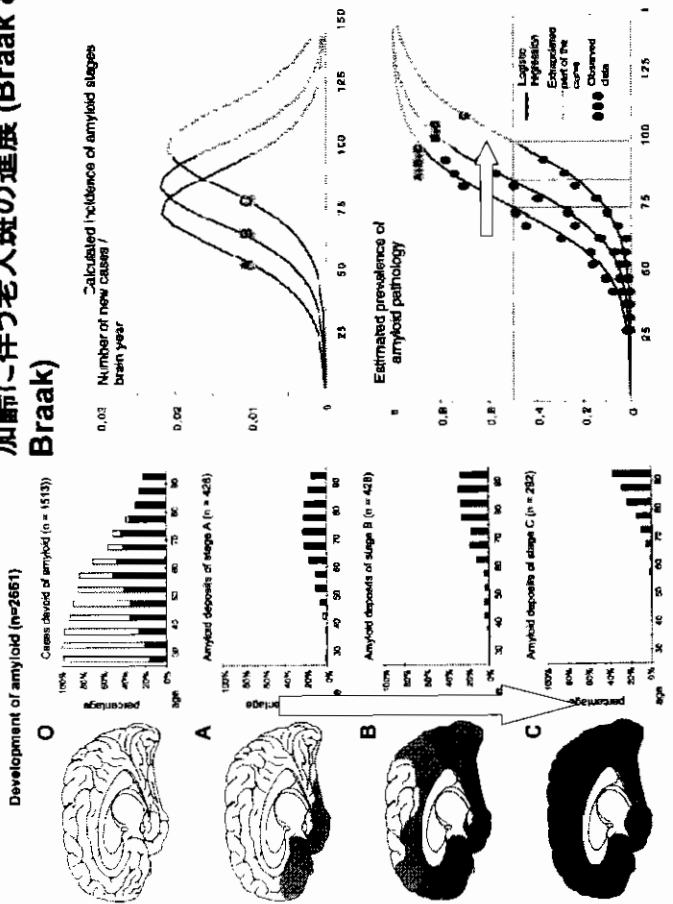
# アルツハイマー病の発症

1期 Aβの蓄積 認知症(-)

2期 タウの蓄積 認知症(+)

# アルツハイマー病 変は誰もがつ

## 加齢に伴う老人斑の進展 (Braak & Braak)



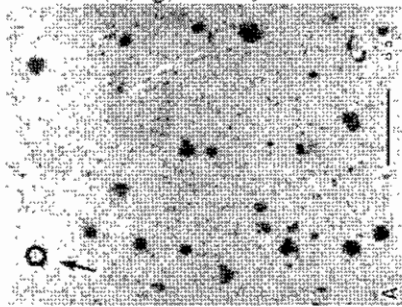
## 老人斑の構成成分: Aβ40 and Aβ42



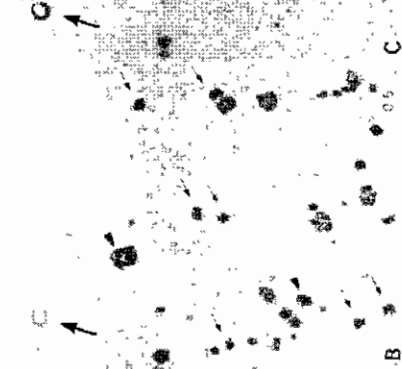
分泌されるAβの90%はAβ40, Aβ42は10%以下  
Aβ42は極めて凝集しやすい!

### Aβ40 and Aβ42: 孤発性アルツハイマー病

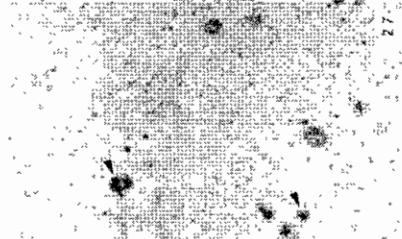
Aβ42+Aβ40



Aβ42



Aβ40



アルツハイマー病側頭葉皮質

### 37歳のダウン症患者の脳: 認知症はない

Aβ40 + 42

Aβ42

Aβ40



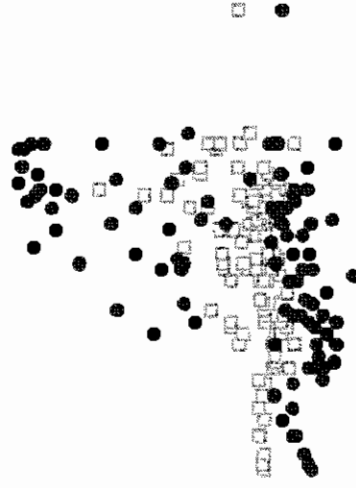
Aβ42は陽性だがAβ40は陰性!

非常に多くのヒトの脳  
に加齢とともにAβが  
蓄積する

Brodman area 9-10



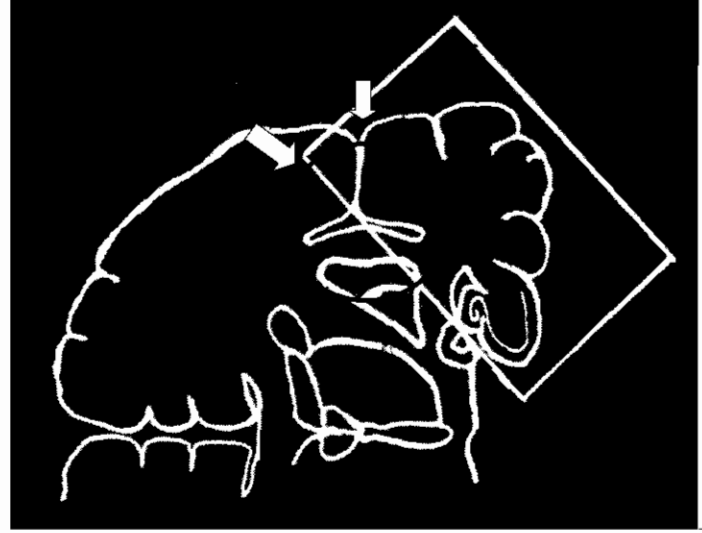
非認知症患者



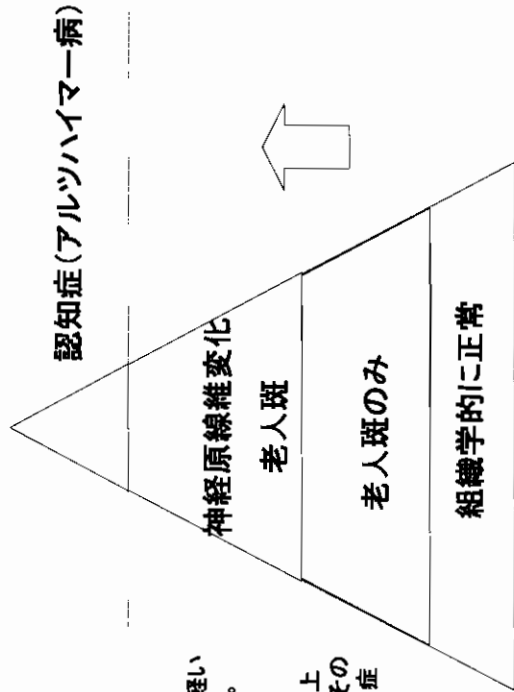
年齢

アルツハイマー病で神経細胞は

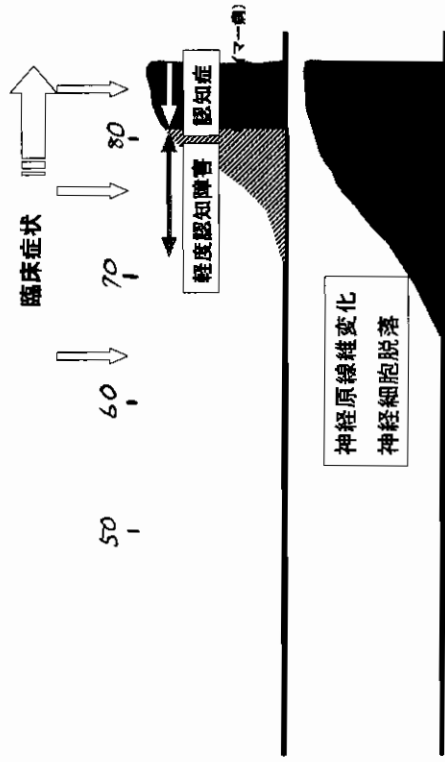
上側頭溝 (STS)の神経細胞を数える



# 氷山の一角



- 1 病理は、程度は軽いが誰でも持っている。
- 2 病理は数十年以上にわたって進行し、その最終結果として認知症になる。



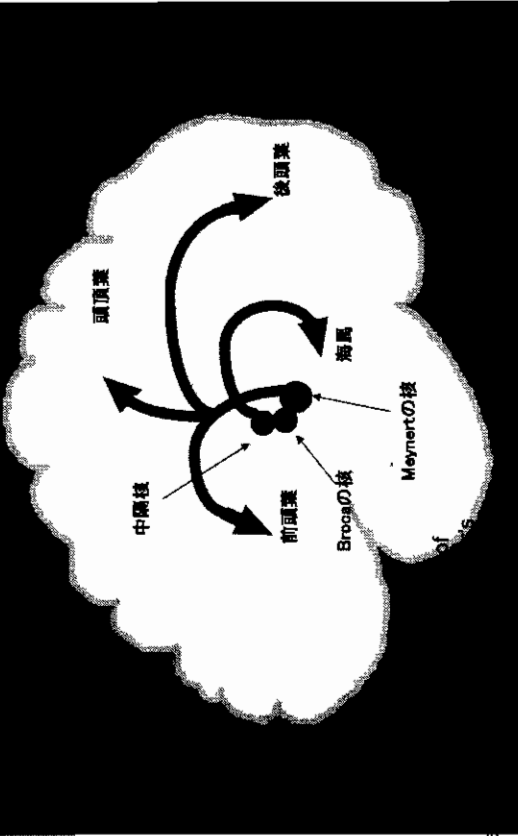
## アミロイドカスケード仮説



- 1 Aβの蓄積
- 2 Aβの蓄積

## 治療法の進歩

アセチルコリン仮説からアミロイド仮説へ

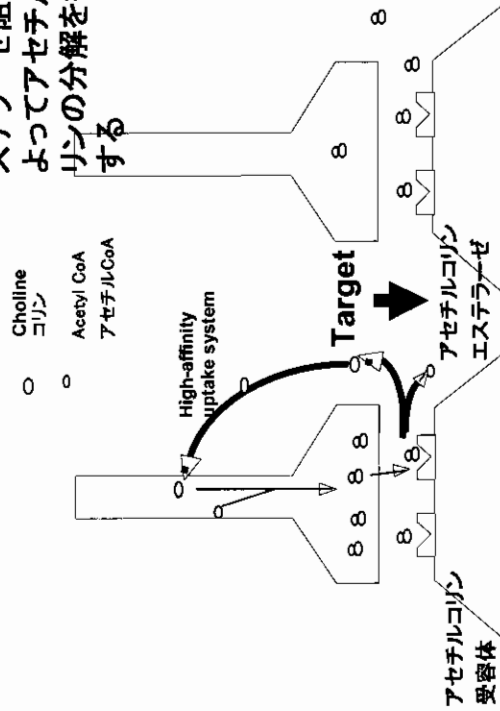


# アセチルコリン仮説に基づく治療法の開発

— 神経回路を補強する —

- アセチルコリン前駆体 (Lethicin) の投与
- アセチルコリンエステラーゼ阻害剤の投与
- アゴニストの開発

## アセチルコリンエステラーゼ阻害剤によってアセチルコリンの分解を抑制する



正常

アルツハイマー病

シナプス前線維は活性化しているが、シナプス後線維は正常

Structure	Drug	Trade name	Efficacy	Side-effects	Comment
<chem>CC1=CC=C(C=C1)N</chem>	Tacrine	Cogeca	Improvements in ADAS cog and NPISE	Hepatotoxicity and gastrointestinal side effects	AChE inhibitor with weak antagonist properties at K <sup>+</sup> channels
<chem>CC1=CC=C(C=C1)N2C=CC(=C2)N</chem>	Donepezil	Alzocip	Improvements in ADAS cog, MMSE, CIBIC and global clinical state	Nausea, vomiting and diarrhoea in some patients from 10 mg/day	Highly selective, reversible inhibitor of AChE with high bioavailability, almost total protein binding and a half life of 70 h
<chem>CC1=CC=C(C=C1)N2C=CC(=C2)N3C=CC(=C3)N</chem>	Rivastigmine	Exelon	Improvements in ADAS cog and global clinical state	Nausea, diarrhoea and anorexia, probably less well tolerated than donepezil	Neurosteroid-inhibitor of AChE
<chem>CC1=CC=C(C=C1)N2C=CC(=C2)N3C=CC(=C3)N4C=CC(=C4)N</chem>	Galehinane	Renuryl	Improvements in ADAS cog, global depression and assessment of daily living	Nausea, diarrhoea and anorexia occurred acutely at higher doses (24-32 mg/day)	Alkaloid extracted from alfalfa buds, in addition to inhibiting AChE, it may also act as a nicotinic acetylcholine receptor, it has a half life of 6 h and is highly inactivable

## アセチルコリンエステラーゼ阻害剤による治療

大脳皮質の後シナプス細胞が存在することが効果の前提



- アルツハイマー病の初期に効果がある。
- 効果は、あったとしても長続きはしない(神経細胞の脱落には効果が無い)。

## ワクチン療法の発想

血液脳関門があるが、

Aβ抗体のごく一部が脳内に入るだけで効果があるのではないか

— Dale Schenk (Elan Pharmaceutical)



## トランスジェニックマウスにAβ42を注射・免疫

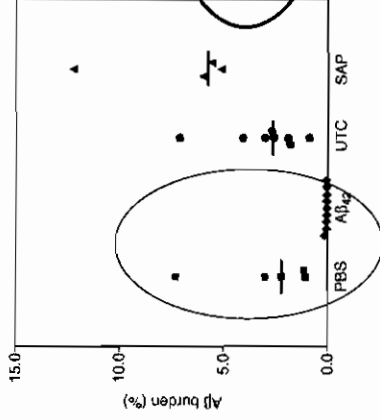
Schenk D, Barbour R, Dunn W, Gordon G, Grajeda H, Guido T, Hu K, Huang J, Johnson-Wood K, Khan K, Kholodenko D, Lee M, Liao Z, Lieberburg I, Motter R, Mutter L, Soriano F, Shopp G, Vasquez N, Vandeventer C, Walker S, Wogulis M, Yednock T, Games D, Seubert P: Immunization with amyloid-β attenuates Alzheimer-disease-like pathology in the PDAPP mouse. Nature 400: 173-177, 1999

## アミロイドカスケード仮説

に基づく治療法 — 神経細胞死を防ぐ—

- 1 ワクチン療法
- 2 γセクレターゼ阻害剤
- 3 非ステロイド性消炎剤(NSAIDs)
- 4 その他

コレステロール  
酸化化剤(ビタミンE等)  
エストロゲン



PDAPP マウスを Aβ42で免疫する



Hippocampal Aβ deposition, neuritic plaque formation and cortical astrogliosis in PBS- and Aβ<sub>42</sub>-injected mice.

12ヶ月齢

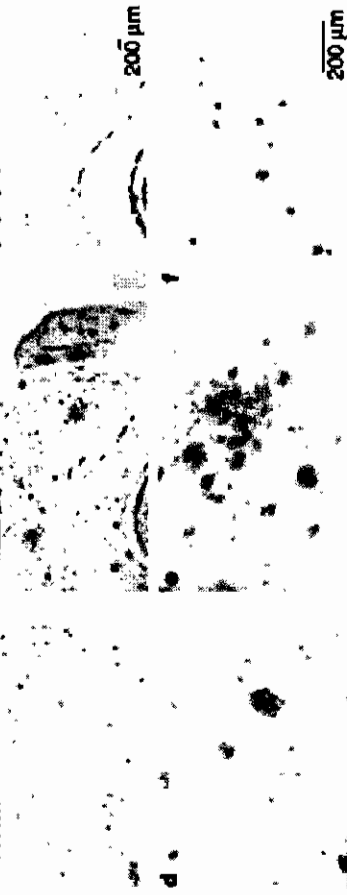
18ヶ月齢

ワクチン接種、18ヶ月齢

● 始点

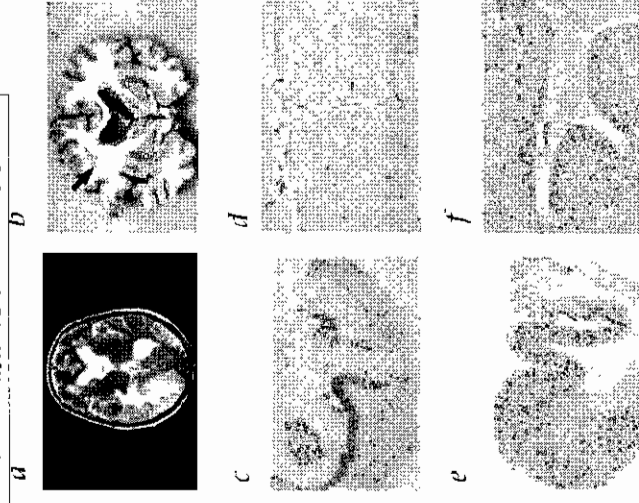
● 生食

● ワクチン



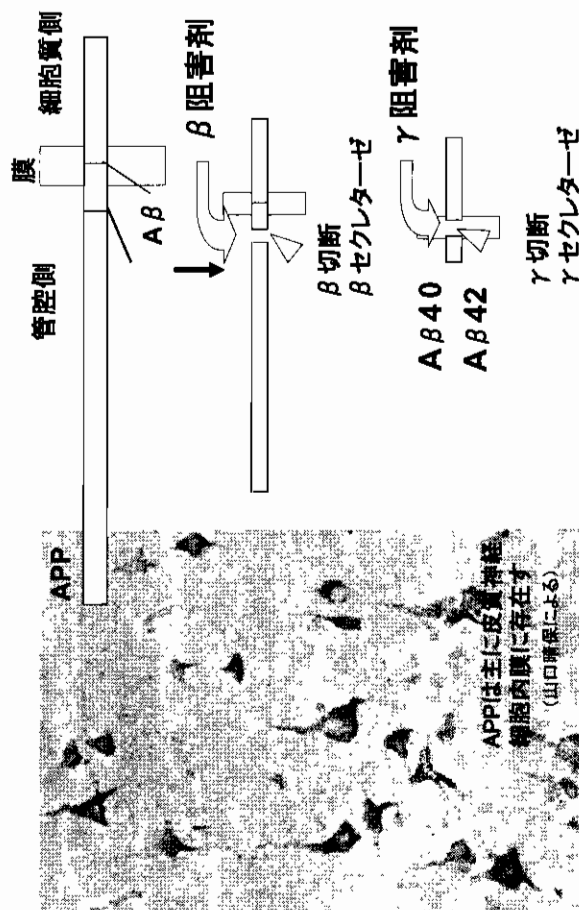
Reduction of cortical A $\beta$  deposition in older PDAPP mice immunized with A $\beta$ 42. A $\beta$  deposits in the brains of 12-month-old untreated PDAPP mice and 18-month-old PBS- and A $\beta$ 42-injected mice with median A $\beta$  burdens representative of their respective treatment groups. a. Distribution of amyloid plaques in the frontal and retrosplenial cortices of a 12-month-old untreated PDAPP mouse, typifying the plaque burden of both PBS- and A $\beta$ 42-injected groups at the start of the study. The plaques are shown at a high magnification in d. Compared with the 18-month PBS controls (b, e), A $\beta$  deposits were significantly decreased in the 18-month A $\beta$ 42-immunized group (c, f). Most of the cortical A $\beta$  in brains of A $\beta$ 42-injected mice was detected in small extracellular or cell-associated deposits (f) compared with the large and numerous extracellular deposits in the PBS group (e). Scale bar in c corresponds to a-c. Scale bar in f corresponds to d-f.

### ワクチン療法後の死亡例



Distribution and quantitation of A $\beta$  pathology. a, MRI scan at the time of acute illness, showing widespread signal alteration in cerebral white matter. b, Corresponding coronal slice of the cerebral hemisphere showing the white matter signal change. c, Immunohistochemistry for A $\beta$  plaques in post-mortem examination. d, Plots of A $\beta$  plaques (mean  $\pm$  SEM) in the cerebral cortex and hippocampus. e, A $\beta$  plaques (mean  $\pm$  SEM) in the cerebral cortex and hippocampus. f, A $\beta$  plaques (mean  $\pm$  SEM) in the cerebral cortex and hippocampus. g, A $\beta$  plaques (mean  $\pm$  SEM) in the cerebral cortex and hippocampus. h, Quantitative image analysis showing plaque density (plaque area/2, 3 and A $\beta$  load/4) for the immunized cases in the medial frontal cortex (a). Values were within the range of unimmunized Alzheimer's disease. In contrast, the plaque density and A $\beta$  load of the immunized case was lower than in unimmunized AD in the cerebral cortex and the inferior, middle, and superior temporal cortex. Immunized case, open squares; 7 individual unimmunized AD cases.

### A $\beta$ の前駆体、APPの分解過程



### γセクレターゼの基質

APP以外にも多数ある

- APP: VIATVIVITLVMLKKK... AICD
- APLP2: AIATVIVISLVMLRKR... AICD
- APLP1: GGGSLIVLSLILRKKK... AICD
- Notch1: VLLFEVGGVLSRKR... NICD
- Notch2: IILFFILLGVIMAKRKR... NICD
- Notch3: VFLLIIFLGVMVARRKRE... NICD
- Notch4: GVLLALGALLVQLIRRRR... NICD
- ErbB-4: LFILVIVGLTFAYVRRK... NICD
- CD44: LLALILAVCIAVNSRRR... NICD
- LRP: LLLLVLVAGVVFVYKRR... NICD
- E-cadherin: ALLILILLFLRRRAVVK... NICD
- N-cadherin: ILLILVLMFVVMKRRDKER... NICD



# 消炎鎮痛剤とアルツハイマー病

関節リウマチ患者では、アルツハイマー病の発症率が有意に低い。

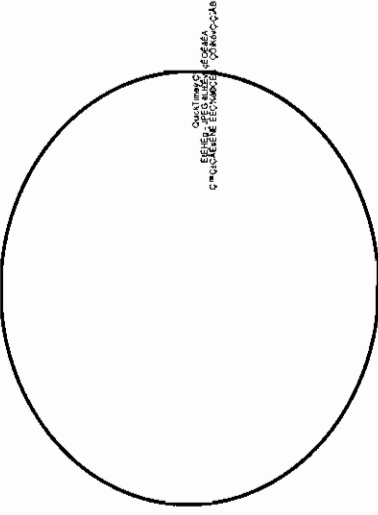


消炎鎮痛剤、特に非ステロイド性消炎剤は、アルツハイマー病脳皮質の炎症を抑制するのではないか？

NSAIDsの一部は、Notch切断に影響を及ぼさないで、Aβ42産生を選択的に抑制するらしい。さらにこの作用は、抗炎症作用とは関係がない。

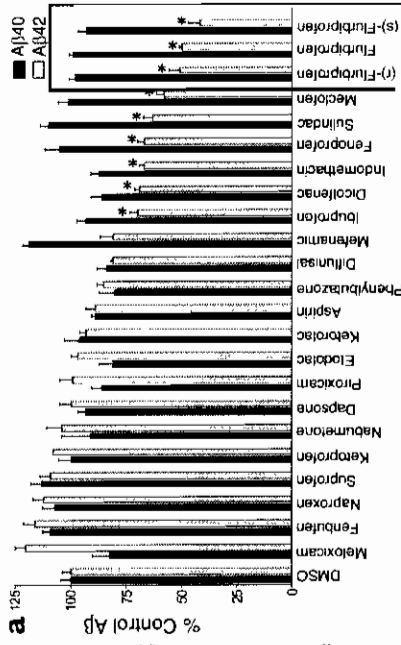
Weggen S, Eriksen JL, Das P, Sagi SA, Wang R, Pietrzik CU, Findlay KA, Smith TE, Murphy MP, Bultter T, Kang DE, Marquez-Sterling N, Golde TE, Koo EH: A subset of NSAIDs lower amyloidogenic Aβ42 independently of cyclooxygenase activity. Nature 414: 212-216, 2001

# イブプロフェン (NSAID) はアミロイド沈着を抑制する

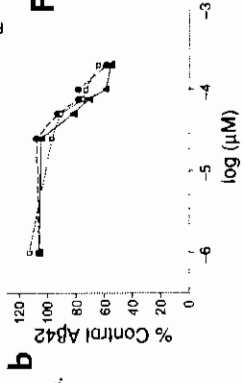


ELISA measurement of water-soluble and SDS-insoluble Aβ. These histograms illustrate Aβ levels plus or minus 95% confidence interval of formic acid-extracted (SDS-insoluble) Aβ (nanograms per total pellet) or soluble Aβ (picograms per microgram of protein) as measured by sandwich ELISA for dissected brain regions of the Tg2576 brain. A two-way ANOVA (treatment x region) showed significant treatment effects in insoluble Aβ levels (\*p < 0.05) and regional effects (p < 0.0001) with no treatment-region interaction. Decreases in soluble Aβ levels were consistent in all regions but did not quite reach statistical significance (p = 0.06).

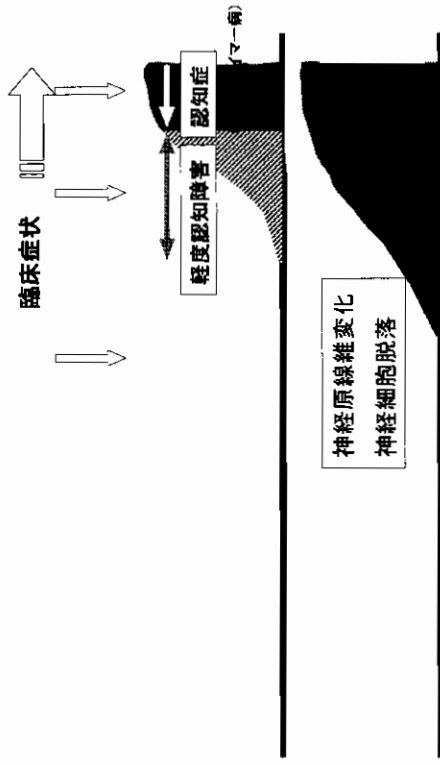
## 種々のNSAIDs



Effects of NSAIDs on Aβ42 production in human neurogloma line. (a) H4 cells were treated for 6 hours with 100 μM of the compounds dissolved in DMSO vehicle, and Aβ levels in the media were determined by Aβ ELISA. Results are the average of two experiments, each performed in duplicate. Compounds are ordered by effect on Aβ42. Experimental values are compared to six control samples. \*p < 0.05 by ANOVA with Dunnett's post hoc correction. Aβ40 production was not significantly affected by any of the compounds when tested at 100 μM. (b) Dose response of racemic, R- and S- flurbiprofen. H4 cells were treated with various concentrations of racemic flurbiprofen or its purified enantiomers. All three forms of flurbiprofen selectively lower Aβ42 to approximately identical extents. At concentrations above 300 μM, moderate reductions in Aβ40 were seen, but LDH assays indicated cells treated at these doses exhibited signs of toxicity. In these experiments, control values for secreted Aβ40 and Aβ42 were greater than 500 pM and 40 pM, respectively.



# アルツハイマー病の 発症を遅らせる

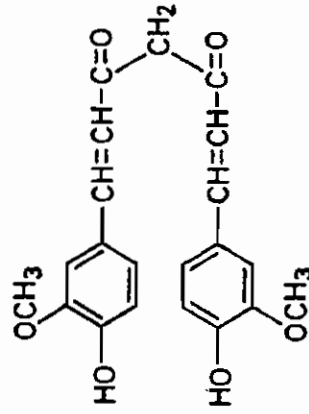


老人斑

## 食事と

トランスジェニックマウスを用いた検討

Curcumin  
(diferulomethane)



カレールイス  
アルツハイマー病の脳内では、カレールイスが蓄積し、神経細胞を死滅させる。

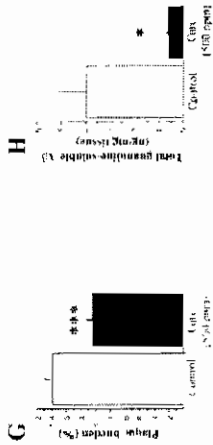
コントロールマウス

17ヶ月齢

22ヶ月齢

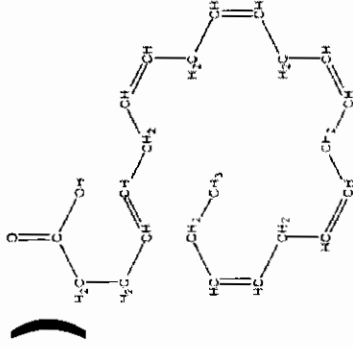


クルクミンマウス



Curcumin suppresses amyloid accumulation in aged APP transgenic mice. Tg2576 mice were placed on chow with (n = 4) or without 500 ppm curcumin (n = 6) at 17 months of age. At 22 months of age, brains were removed for histological and immunological measurement (ELISA) of amyloid A-β. Depict plaque burden analyzed from coronal sections through anterior and posterior hippocampus of control mice (A-C) and curcumin-treated mice (D-F). Representative photos of low magnification views show fewer amyloid deposits in curcumin mice (D) compared with control mice (A). Bar, 1 mm. This suppression can be easily seen with the higher magnification photos from anterior (B and E) and posterior hippocampal sections (C and F). Bar, 40 μm. Image analysis revealed a significant treatment effect, where plaque burden was reduced by 32.5% in curcumin-treated animals (p < 0.0001) (G). H, a bar graph of ELISA measurements of total guanidine-soluble Aβ showing an 85% reduction in Aβ levels with curcumin treatment. Samples of 5 M guanidine extracts were applied in triplicate, and data were square root-transformed to achieve quality of variance before submission to one-way ANOVA. p values of <0.05 were considered significant.

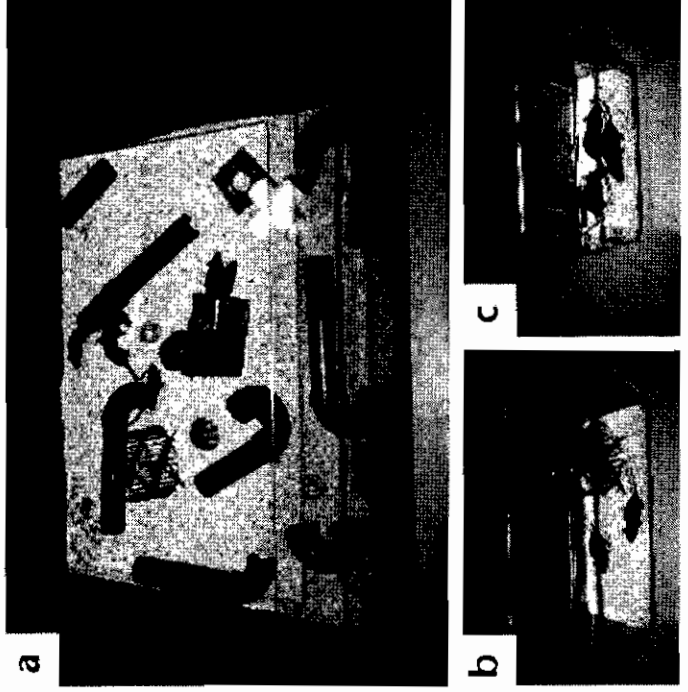
# Docosahexaenoic Acid (DHA)



トランスジェニックマウスを用いてクルクミンの効果を判定する

# 豊かな環境

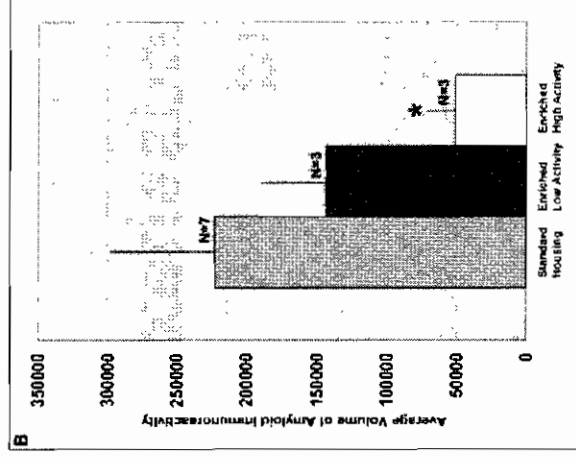
トランスジェニックマウスを用いた検討



Living conditions in the different experimental groups.  
 (a) Cage for an enriched environment (8676 cm). Enrichment consisted of social interaction (14 mice per cage), stimulation of exploratory behavior with objects such as toys and a rearrangeable set of tunnels and running wheels for exercise. (b) Cage containing running wheel for voluntary physical exercise (48, 26 cm). (c) Standard housing cage (30, 18 cm).

A

Enrichment	Enriched High activity	Enriched Low activity
% time running	44.3-62.4	<10.9
% time climbing	<0.5	<1
% time resting	<0.1	3.6-33.6



豊かな環境では、とくに運動をする場合には、老人斑は有意に抑制される。  
 このような環境下では脳内の遺伝子発現が大きく変化することが分かっている。

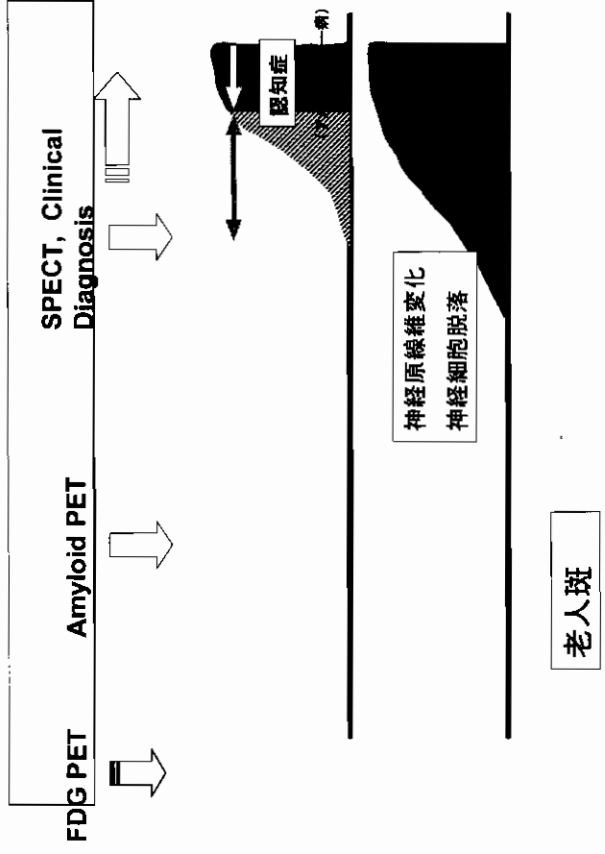
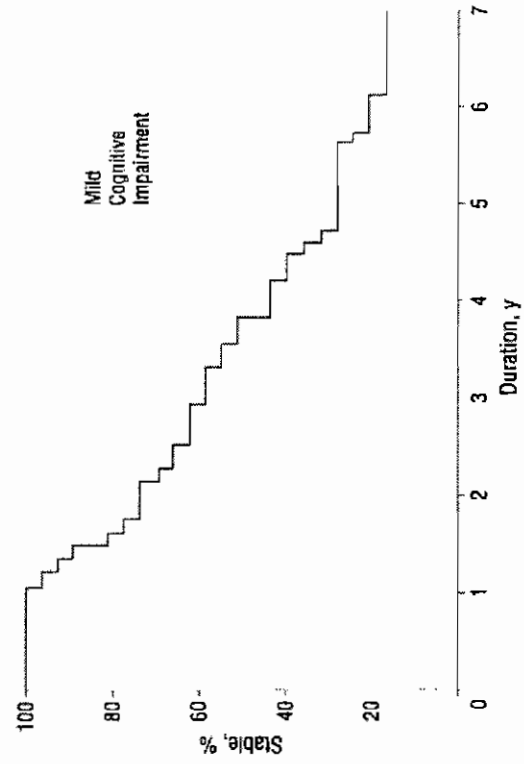
### まとめ

- ・受動ワクチン療法の治療法の効果判定はまだ数年先かもしれない。
- ・予防という観点からするといろいろ効果的な手段が見つかりつつある。
- ・しかし、これらの効果のあるものはトランスジェニックマウスで確かめられているが、ヒトではまだ確かめられていない。

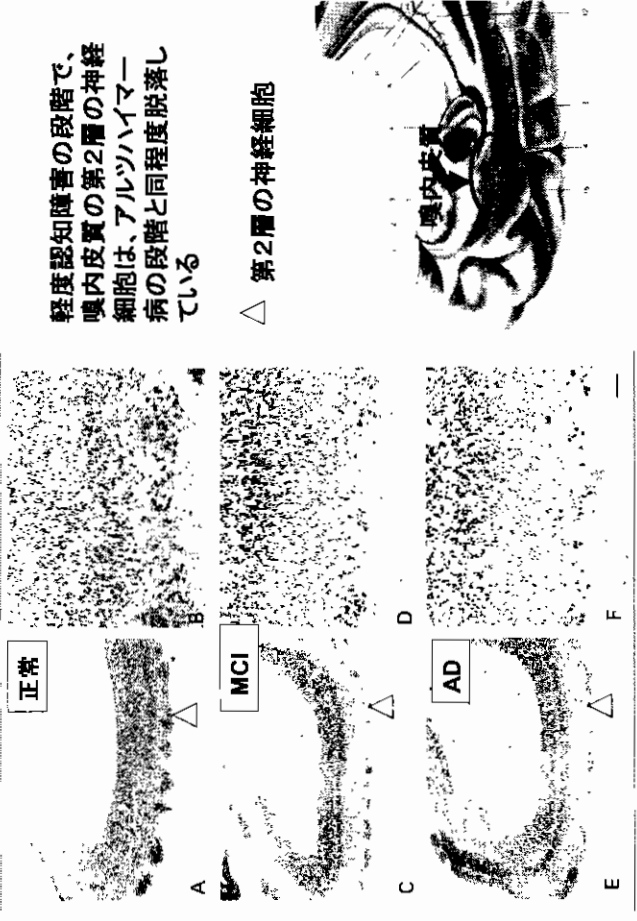
# アミロイド・イメージング

現在最も必要とされている技術

# 軽度認知障害は高率にアルツハイマー病に転化する

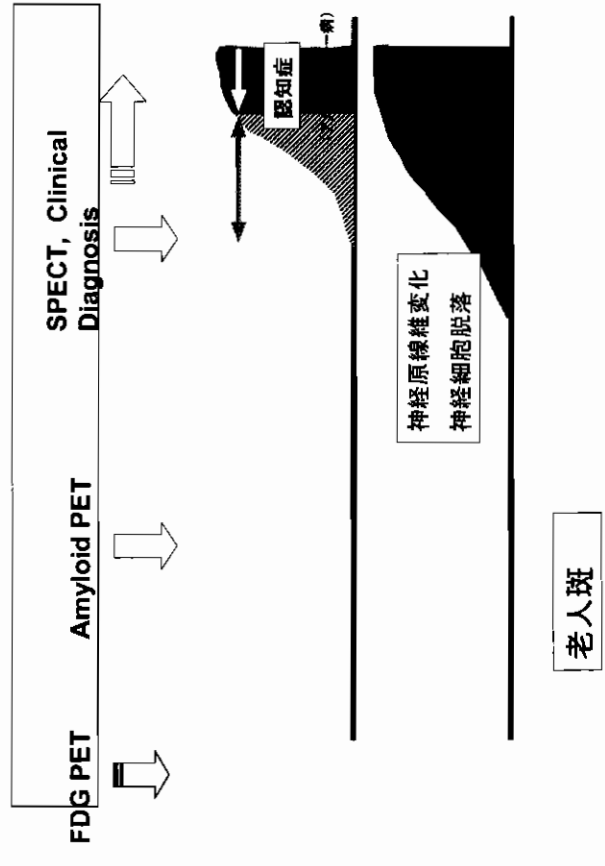


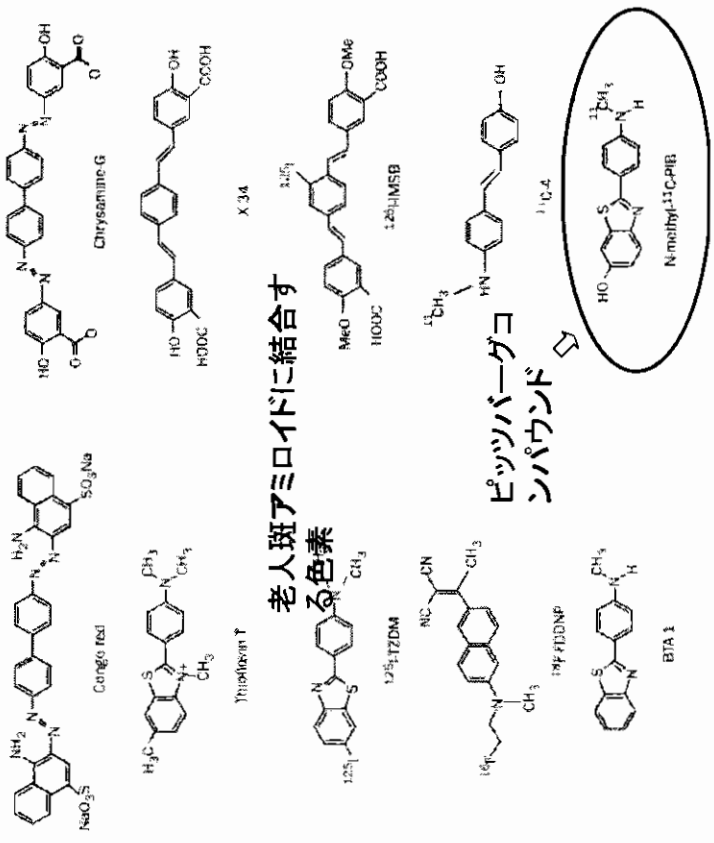
## 軽度認知障害の神経病理



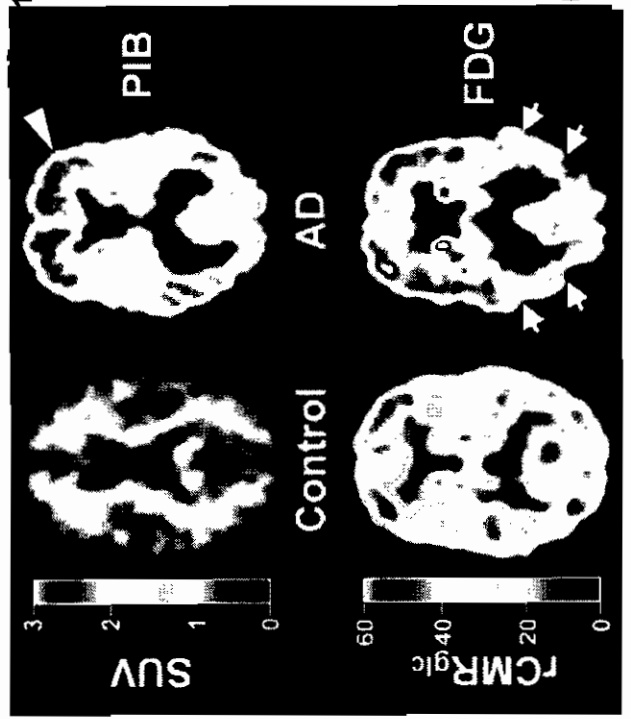
軽度認知障害の段階で、嗅内皮質の第2層の神経細胞は、アルツハイマー病の段階と同程度脱落している

△ 第2層の神経細胞





PIB PET and FDG PET



り込み低下

近未来のアルツハイマー病対策

