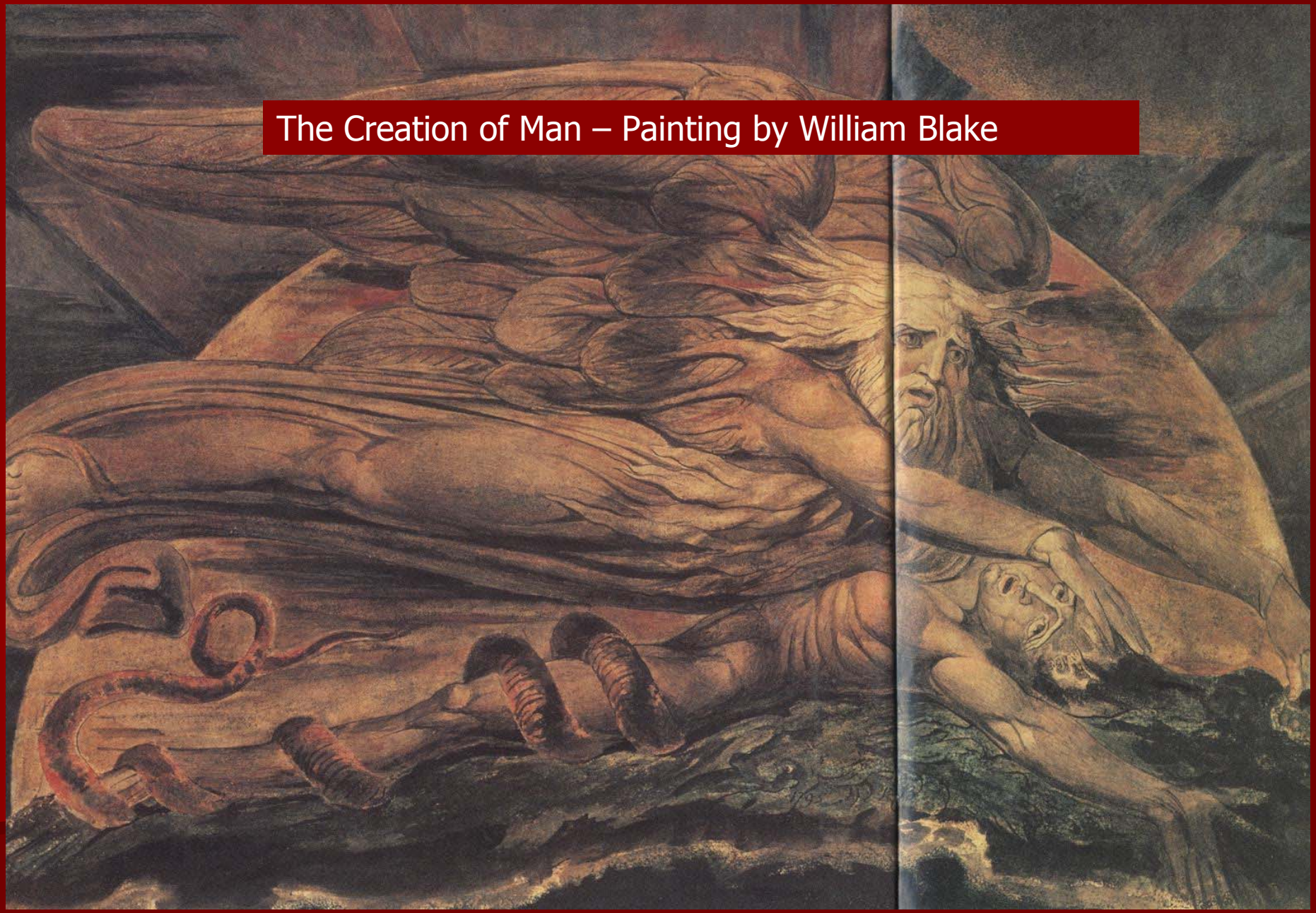
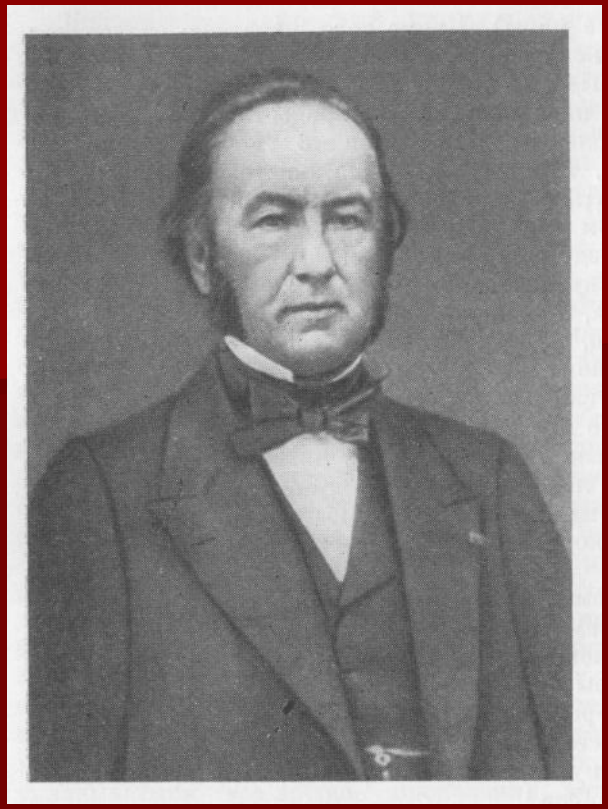
А.Л.Маркель

ГЕНЕТИ-ЧЕСКИЕ МОДЕЛИ ПАТОЛОГИИ ЧЕЛОВЕКА:

АРЕТРИАЛЬ-НАЯ ГИПЕР-ТОНИЯ И ДР.


The Creation of Man – Painting by William Blake



Клод Бернар (1813-1878)

Введение к изучению опытной медицины (1865)

«Единственной нашей целью всегда было и есть – содействовать тому, чтобы всем известные начала опытного метода проникли в медицинские науки»

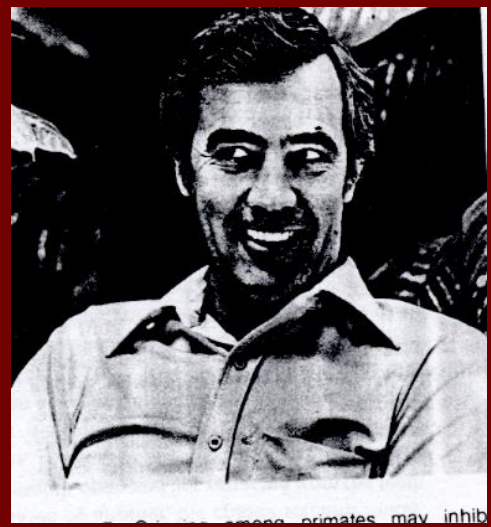
«Всепроника-ющее око экспери-мен-тальной биологии и медицины»

TIME, v148, N14

Displacement activity

«умывание»

«Песни любви»



"The Morbid Anatomy of the Human Genome" (MacKusick)

Cystic fibrosis (Mucoviscidosis)

Severe progressive disease of the bronchial system and gastro-intestinal tract

Disturbed function of a chloride ion channel by mutations of the *CFTR* gene

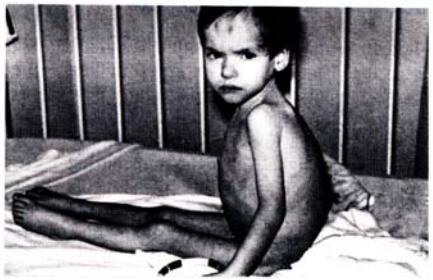
Autosomal recessive

Gene locus 7q31.3

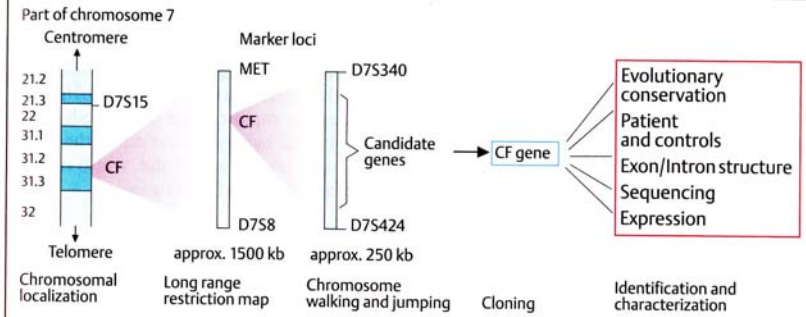
Disease incidence approx. 1:2500

Heterozygote frequency approx. 1:25

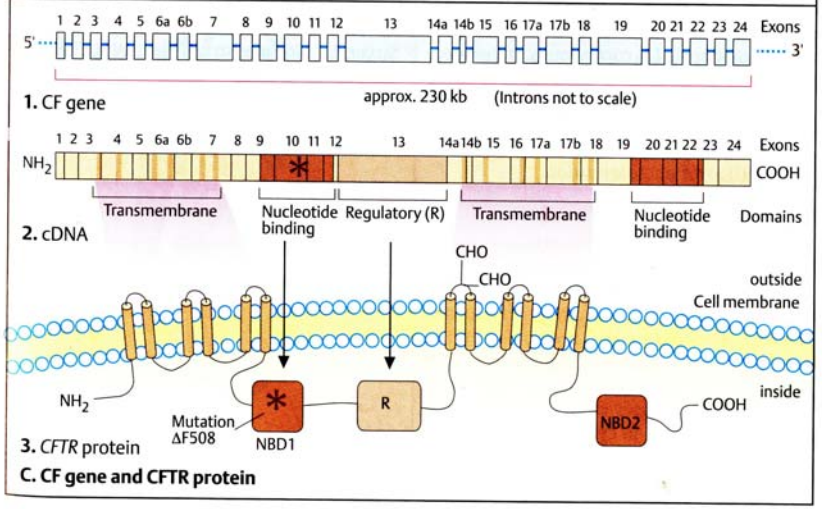
Mutation ΔF508 in approx. 70%



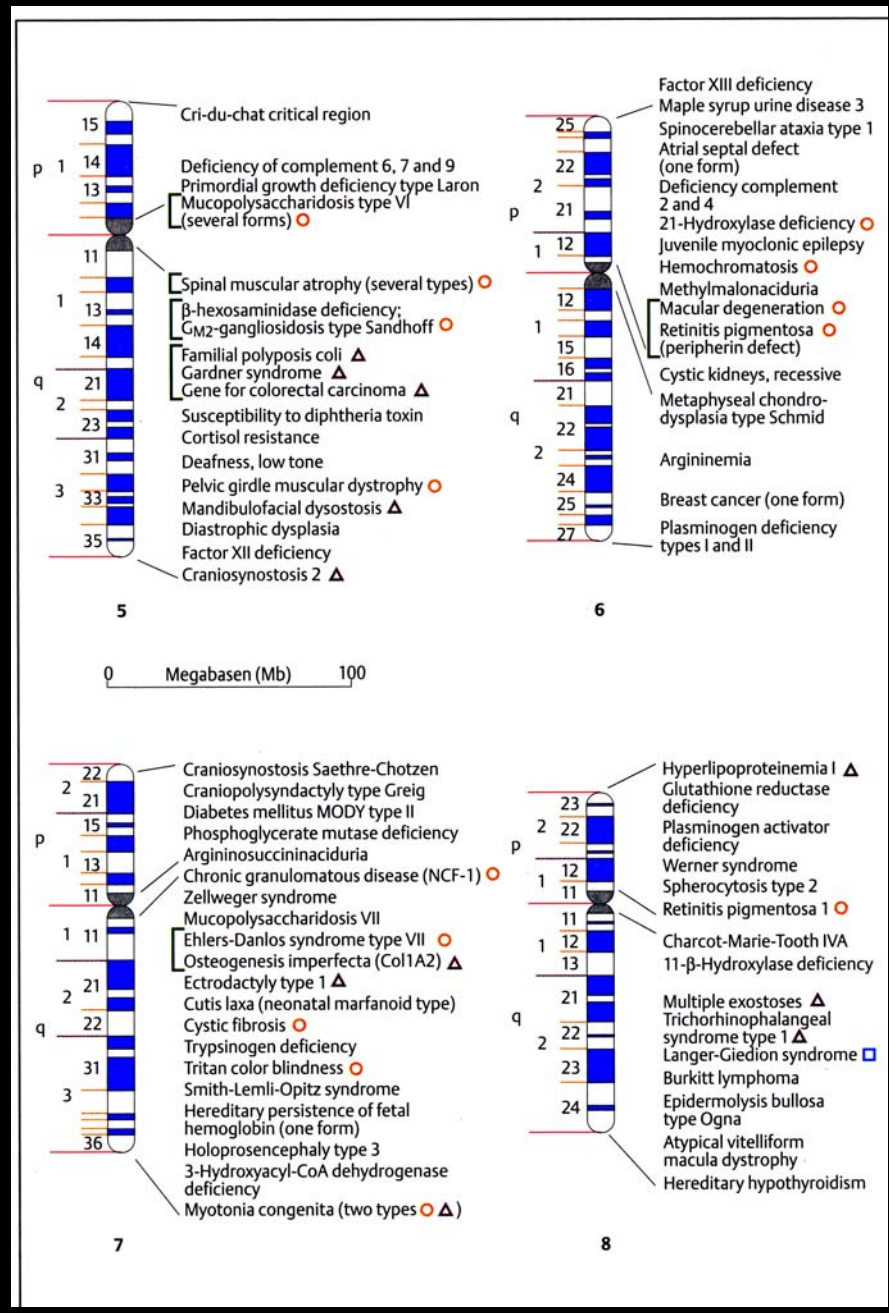
A. Cystic fibrosis, a very frequent recessive disease in Europe and North America

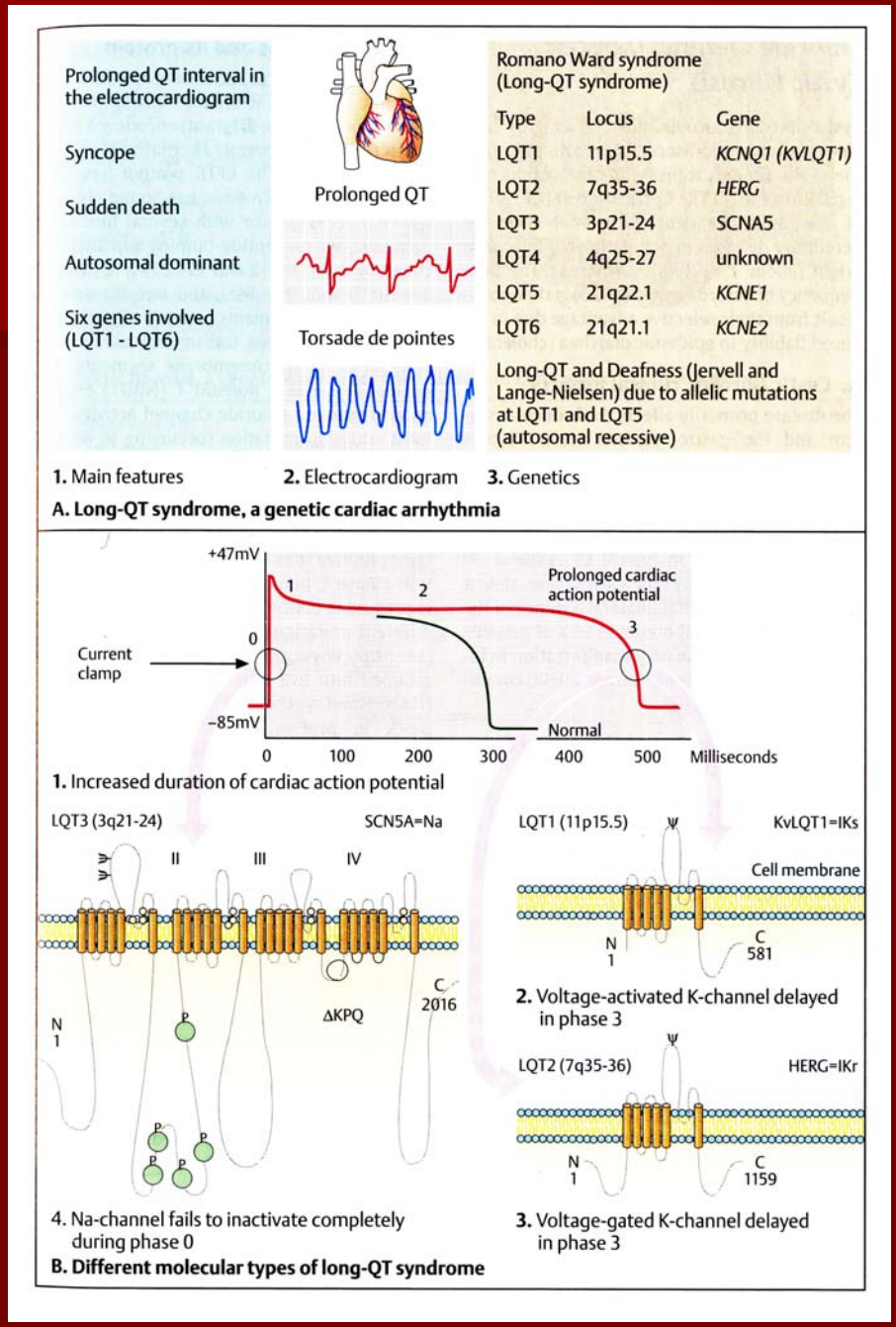


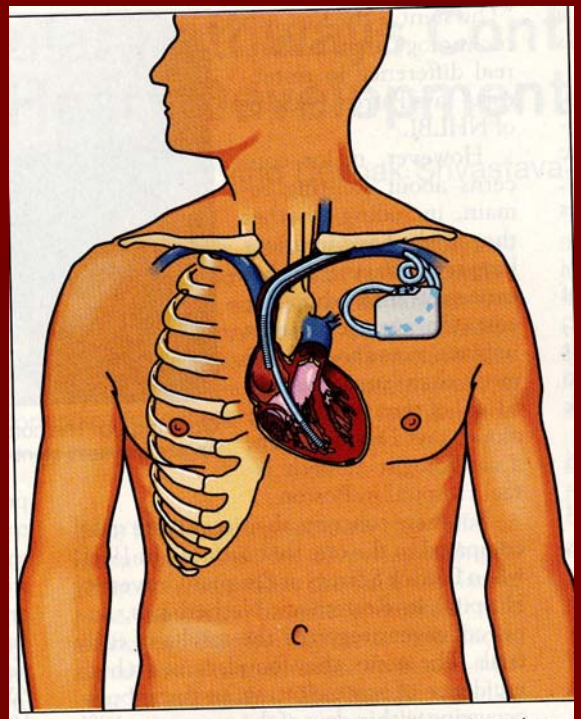
B. Positional cloning of the gene for cystic fibrosis (CF)



C. CF gene and CFTR protein



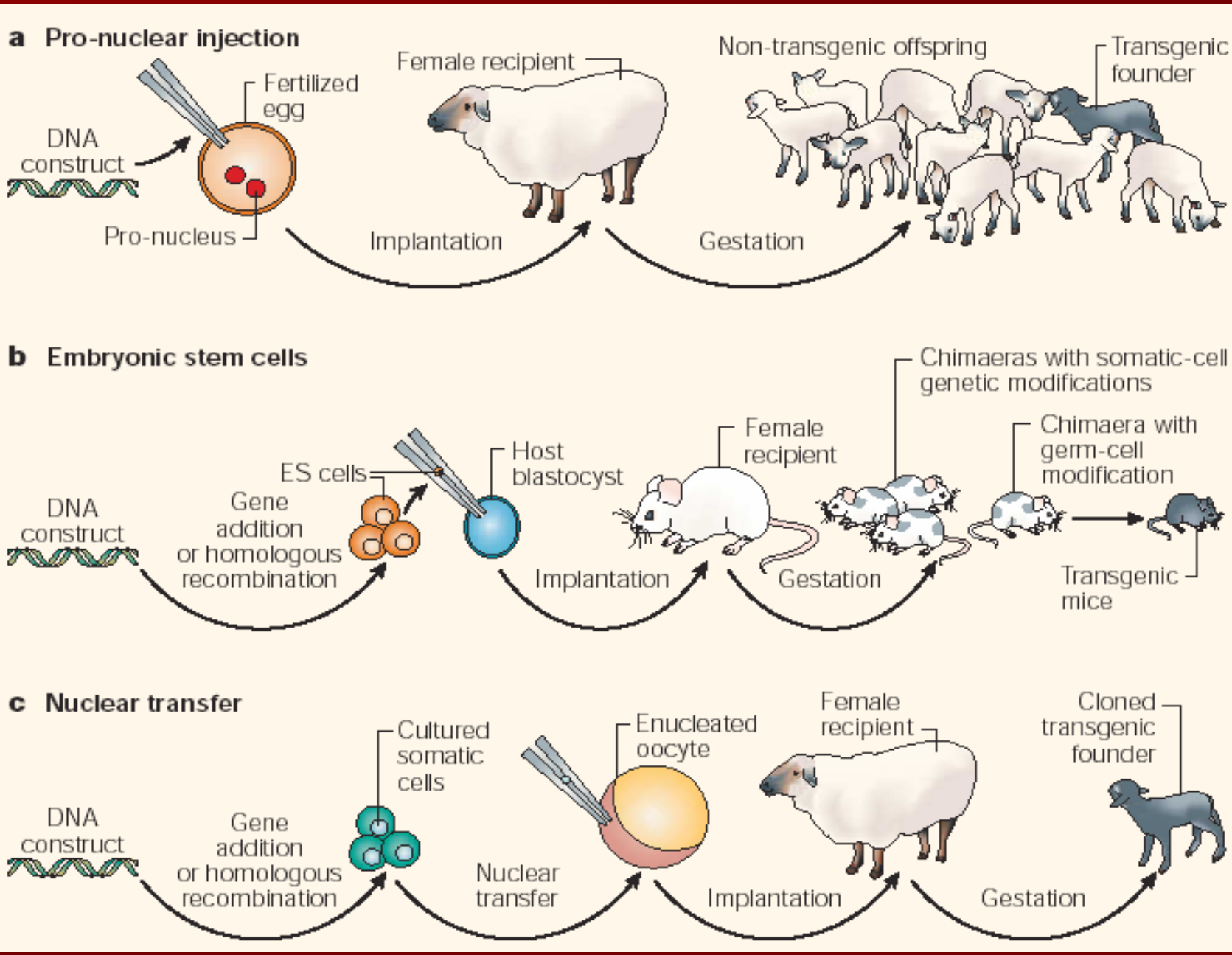




A shock in time. Implantable defibrillators, such as the one shown here, are already saving lives.

"My whole body jumped, and I was hollering pretty loud. But at least those shocks saved my life" –

remembered 71-year-old patient Salvatore Viviani, who received seven shocks soon after his defibrillator was implanted.



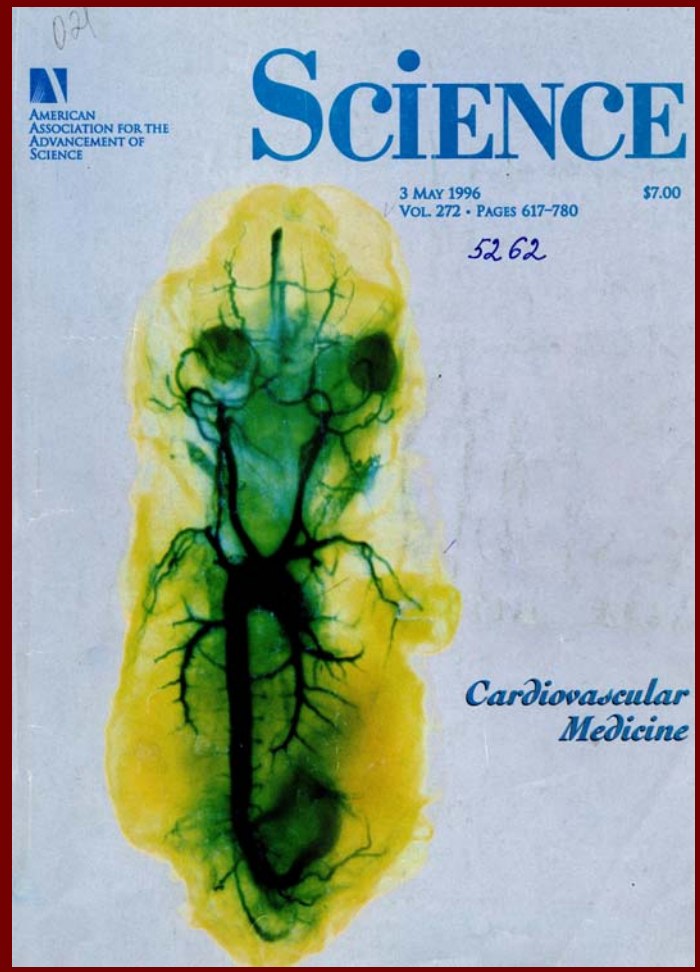
NATURE REVIEWS | GENETICS, 2003

Molecular Genetics of Human Blood Pressure Variation

Richard P. Lifton

ypertension is a common multifactorial vascular disorder of largely unknown cause

- «As the era of focus on research on monogenic diseases comes to a close, the focus of genetics research is turning to studies of complex, multifactorial disorders such as cardiovascular diseases».
- *Markus Perola*

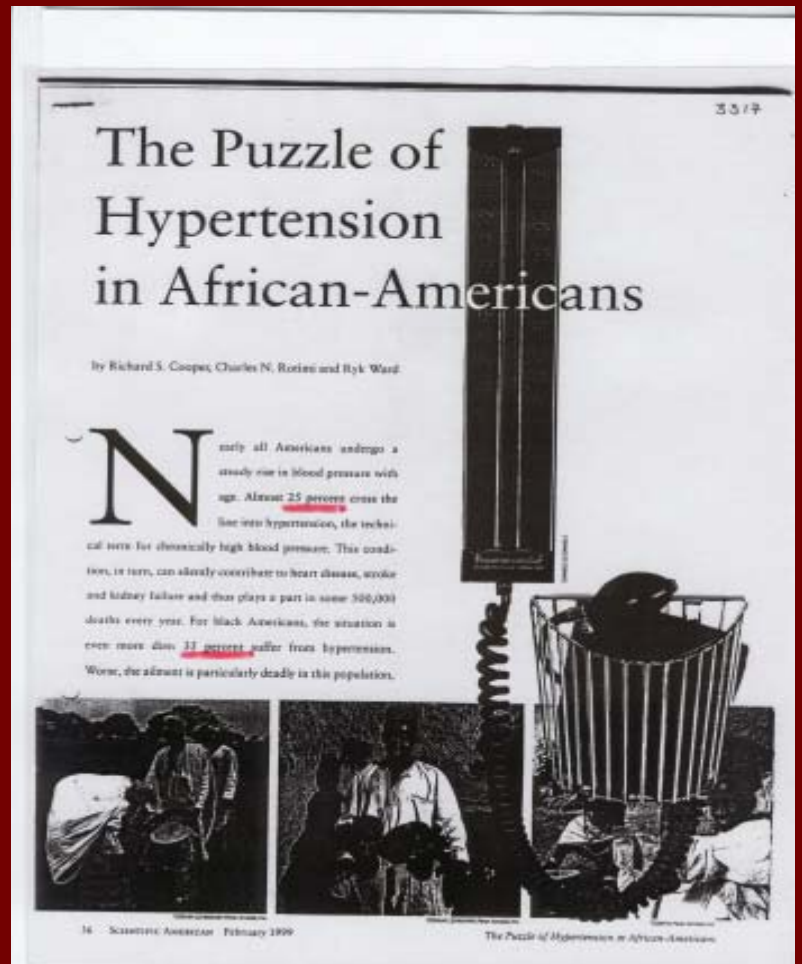


High Blood Pressure Rising, yet Often Ignored
60% of Americans Have or Are at Risk for High Blood Pressure

By Jennifer Warner
Reviewed By Brunjl
WebMD Medical News on Monday, October 25, 2004
http://my.vebmd.com/content/

60%
(2004 г.)

35%
(1995 г.)



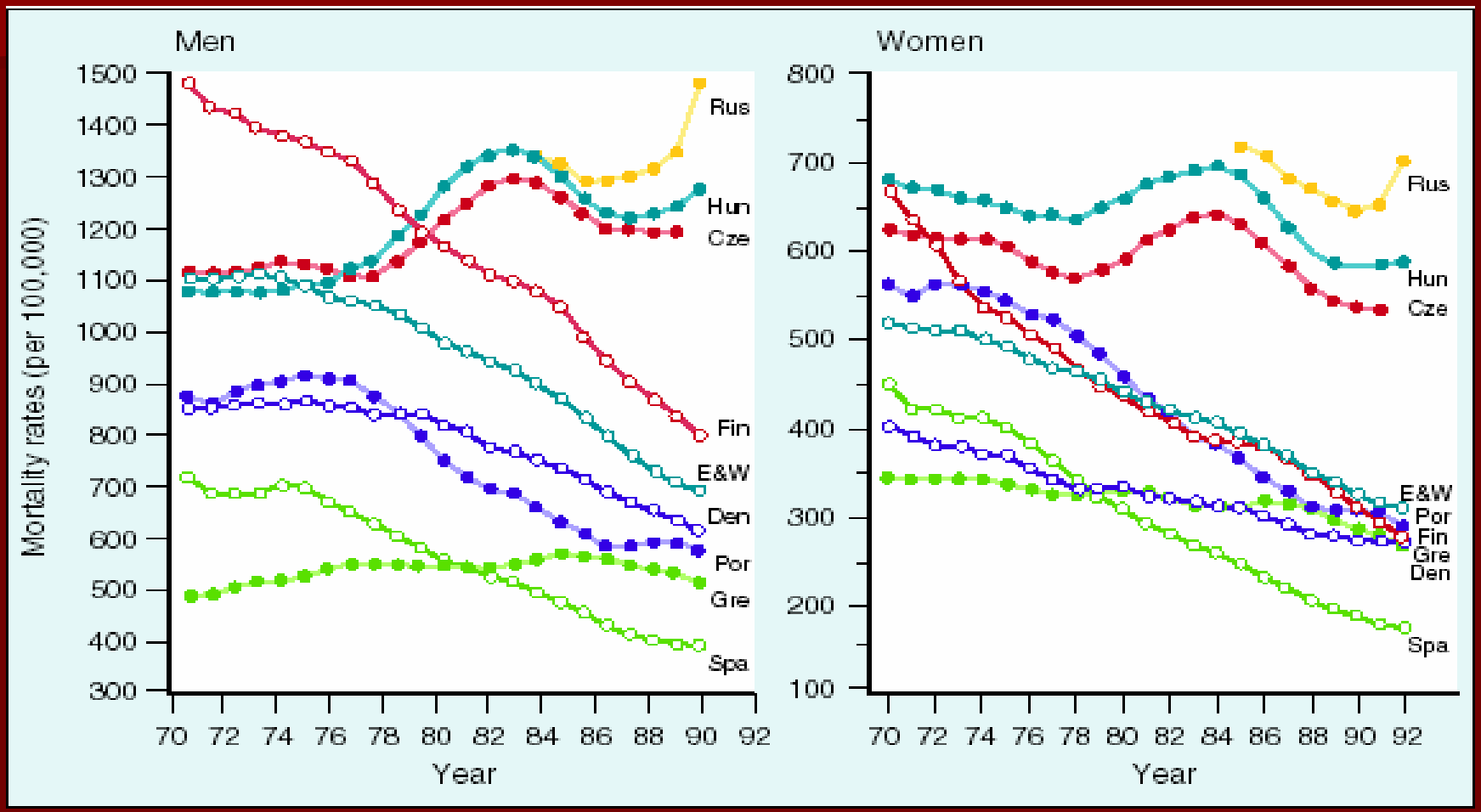
The Puzzle of Hypertension in African-Americans

by Richard S. Cooper, Charles N. Rotimi and Ryk Ward

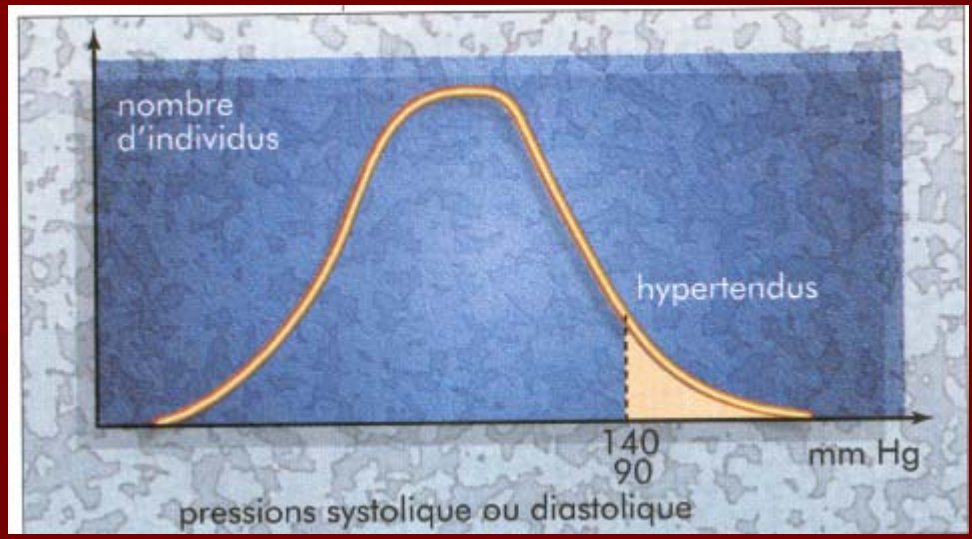
Nearly all Americans undergo a steady rise in blood pressure with age. Almost 25 percent cross the line into hypertension, the technical term for chronically high blood pressure. This condition, in turn, can already contribute to heart disease, stroke and kidney failure and thus plays a part in some 500,000 deaths every year. For black Americans, the situation is even more dire: 33 percent suffer from hypertension. Worse, the ailment is particularly deadly in this population.

Global Burden of Cardiovascular Disease

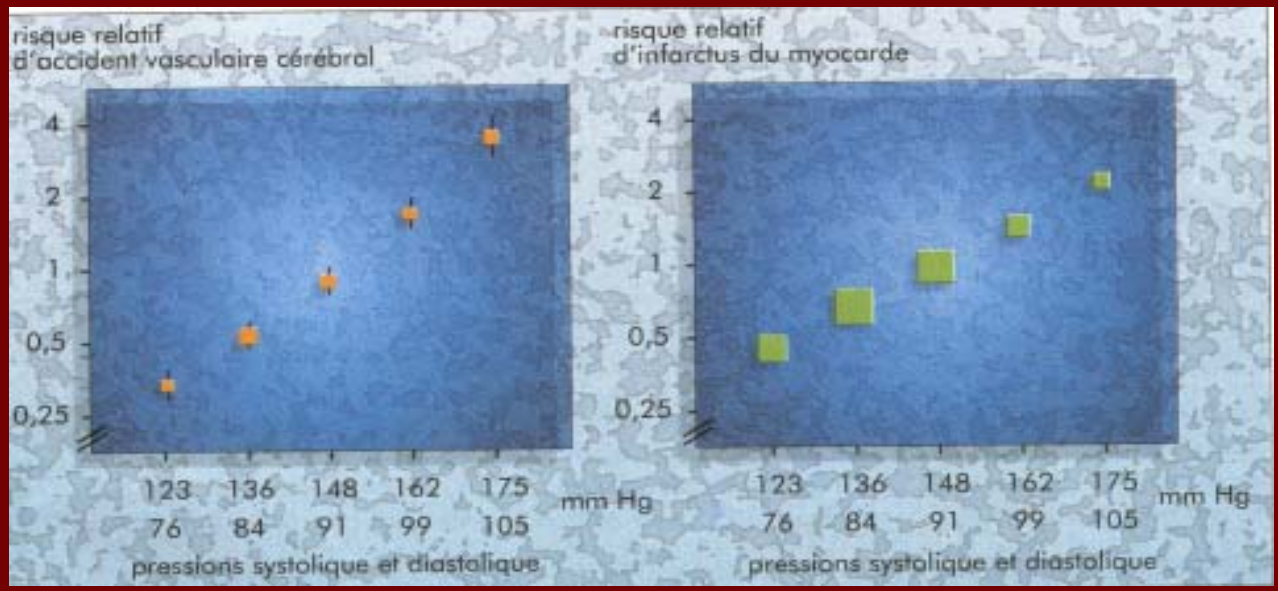
J. Michael Gaziano



140/90



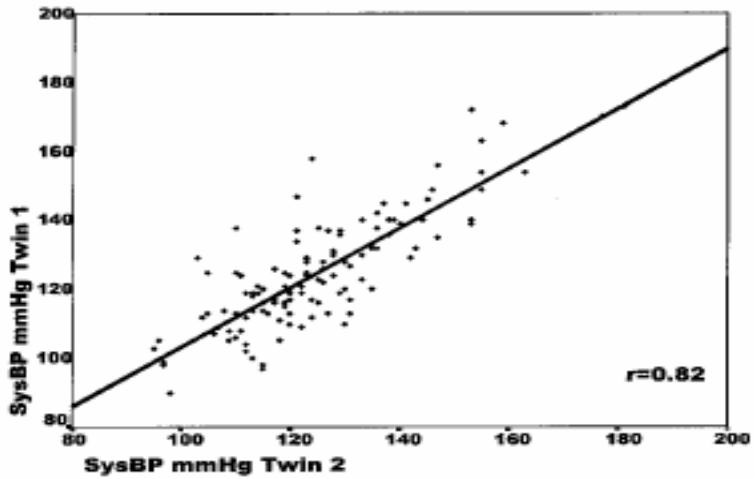
Какое давление можно считать нормальным и какое - повышенным?

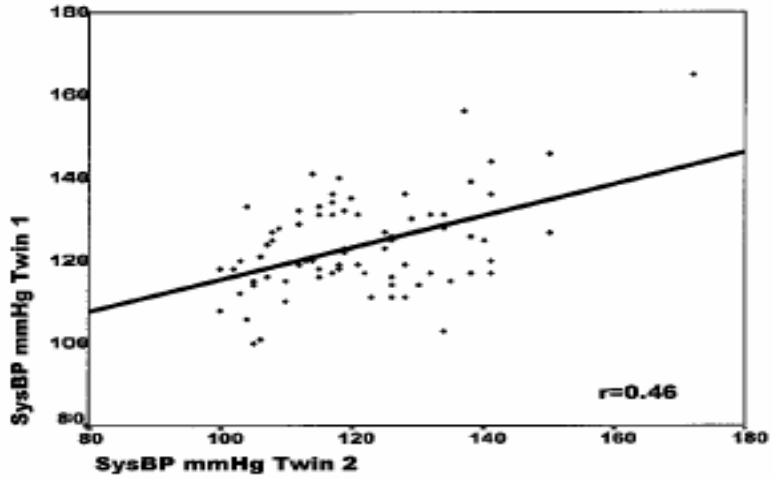


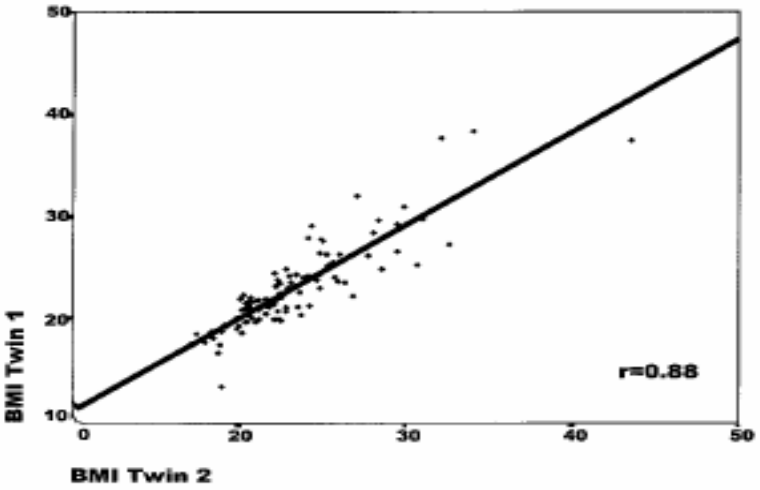
125/75

From: Twins in Cardiovascular Genetic Research

Friedrich C. Luft, 2001







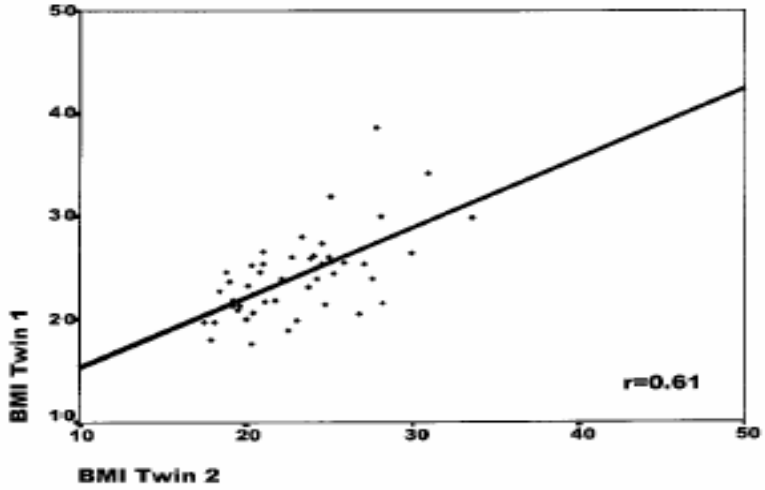
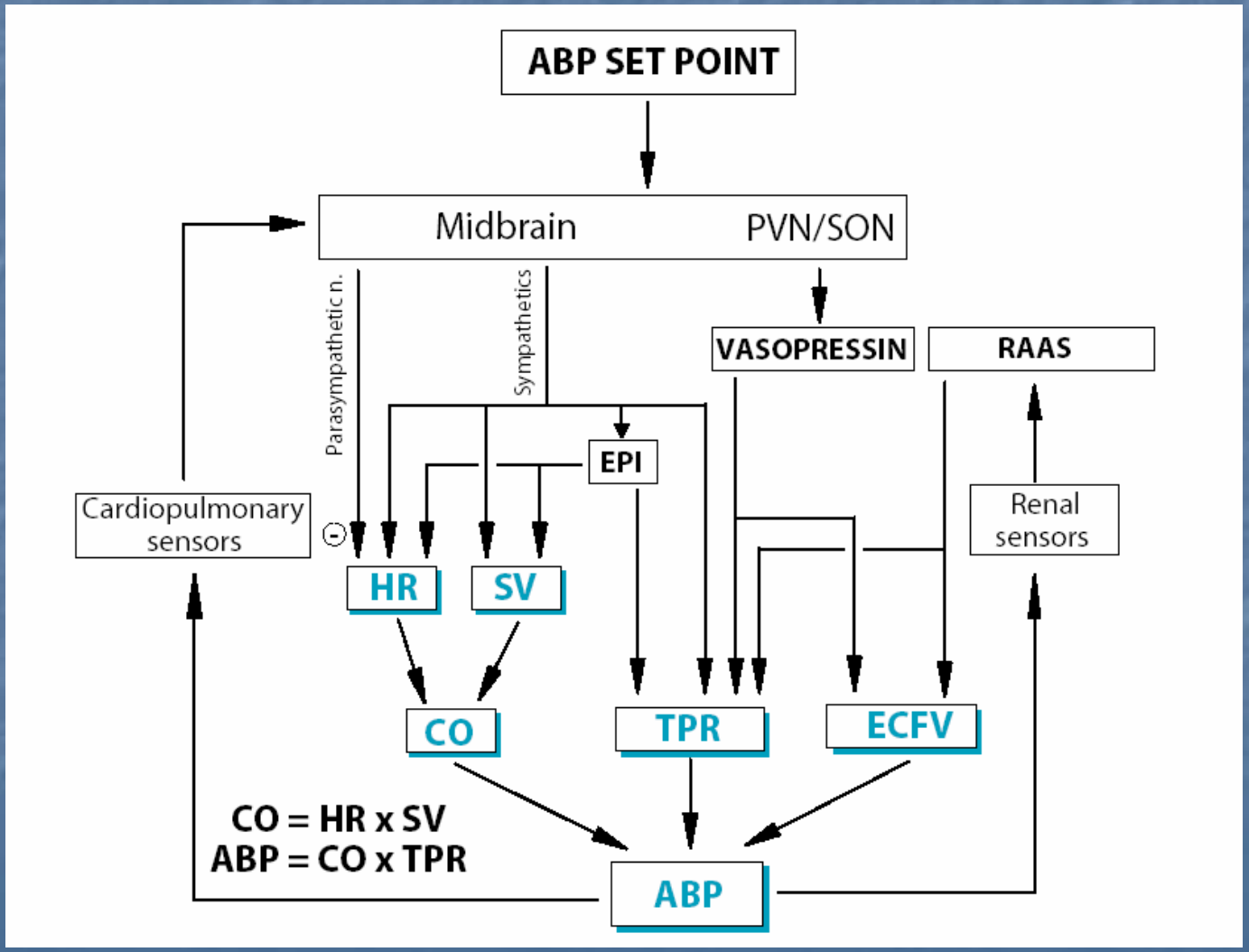


Figure 12. The annual number of publications on genetics or, more specifically, hypertension genetics, reported in MEDLINE© for the years 1967-1995.

From Marcus Perola, 1999

АД = ОПС x МОС

V = R x I



Tigersted and Bergman 1898 г. – экстракты из ткани почки («ренин») повышают АД

Ambard – 1904 – низкосолевая диета способствует снижению АД

Dole, Dahl, Cotzias – 1951 г. – снижение натрия в пище до уровня менее 230 мг/сутки приводит к понижению АД до 140/90 мм рт.ст. у 30-50% гипертоников

Skeggs – 1940 г. – идентификация ангиотензина II

Tait and Simpson – 1952-3 гг. – открытие альдостерона

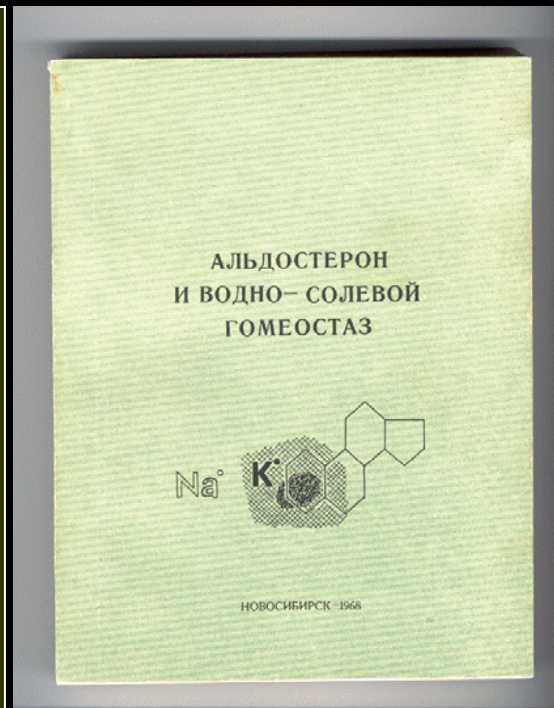
Genest, Laragh, Davis, Ganong, Mulrow, Колпаков – 1959-70 гг – развитие представлений о ренин-ангиотензин-альдостероновой системе – регуляторе водно-солевого гомеостаза и АД

1968 г.

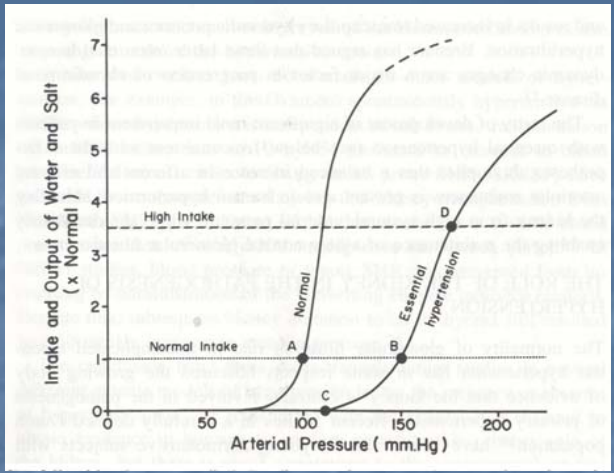
Новосибирск
Академгородок
Дом ученых

Симпозиум

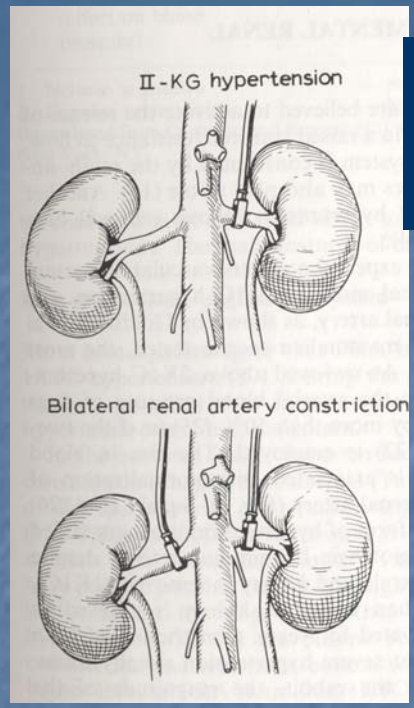
Альдостерон и водно-солевой гомеостаз



Почка и АД

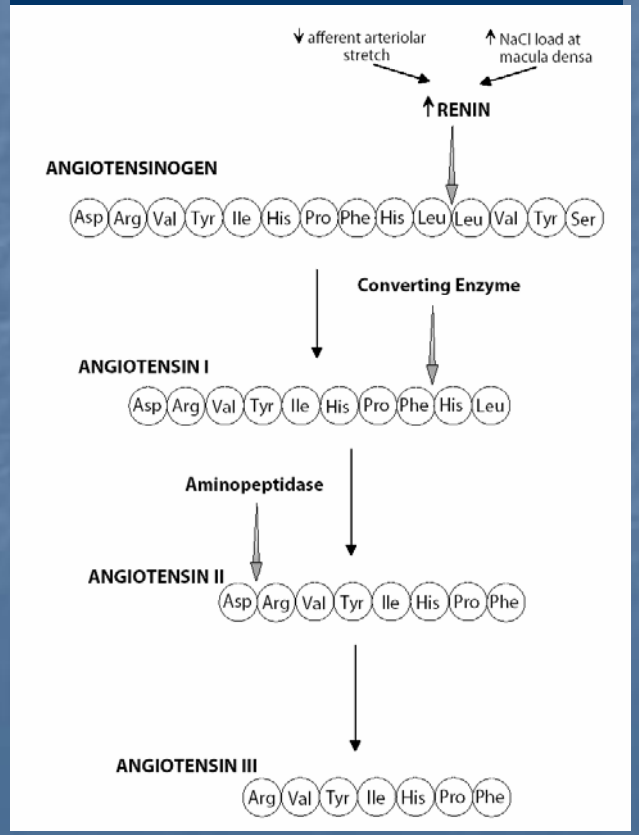


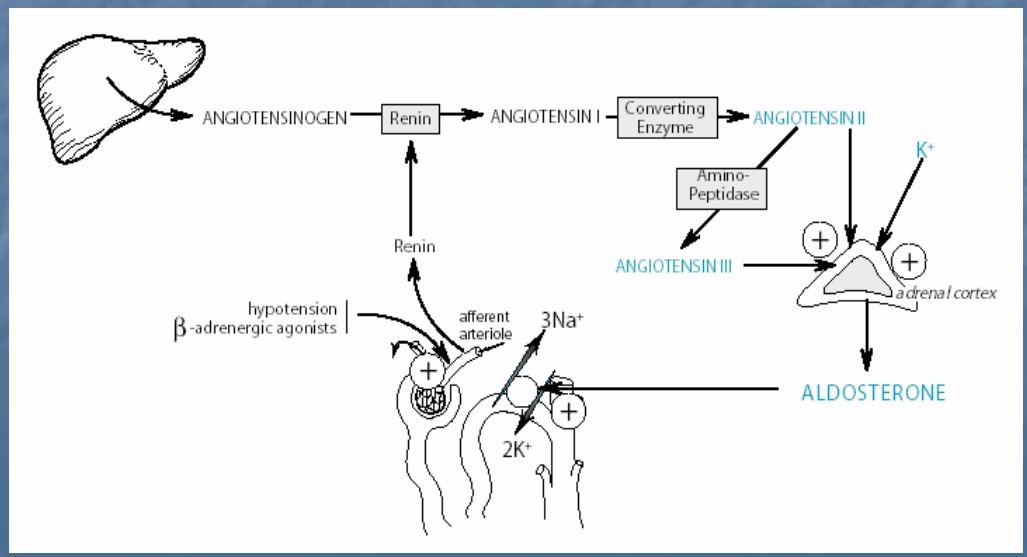
Переключение «установочной точки» (set point) при артериальной гипертонии



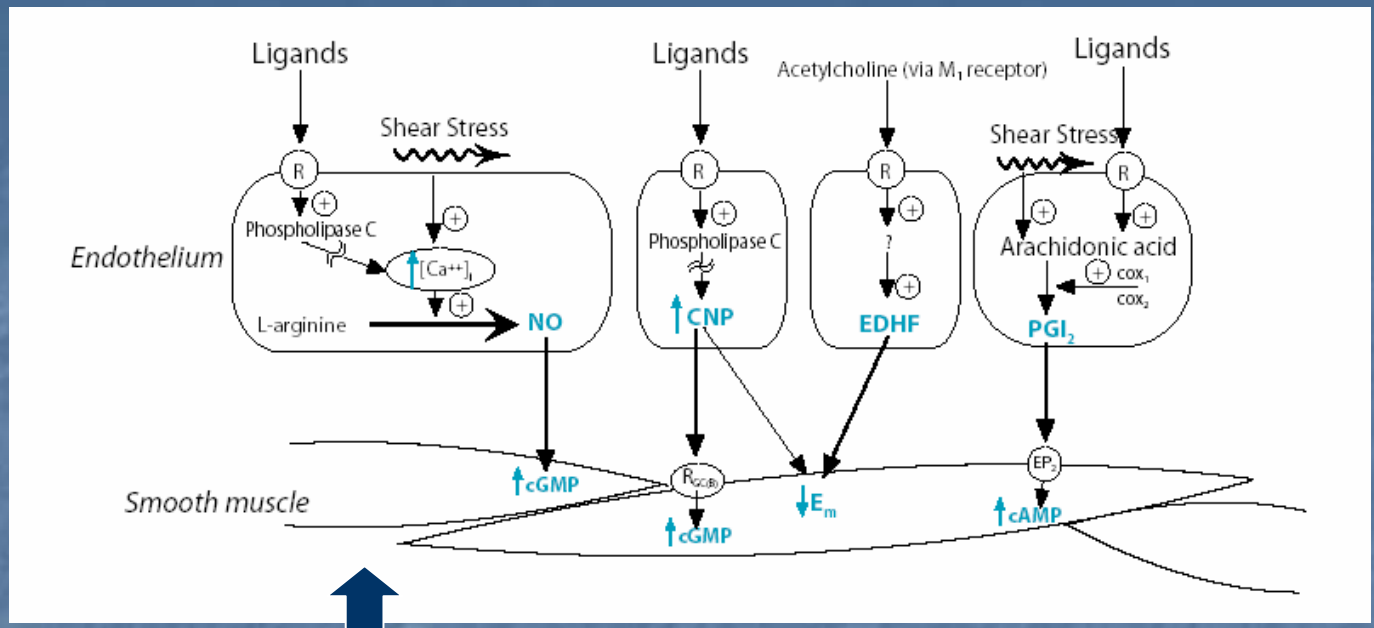
Сужение почечной артерии – модель гипертонии

Ренин-ангиотензиновая система

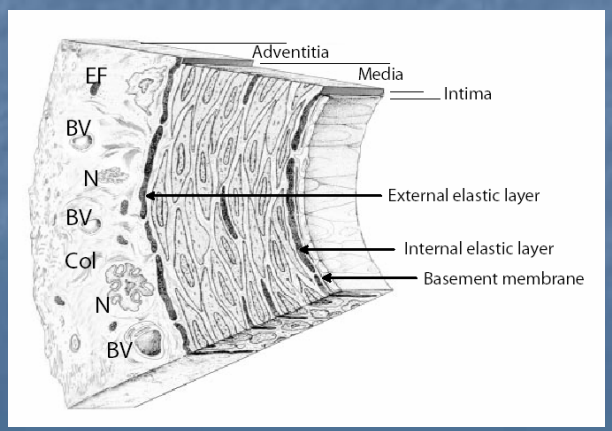




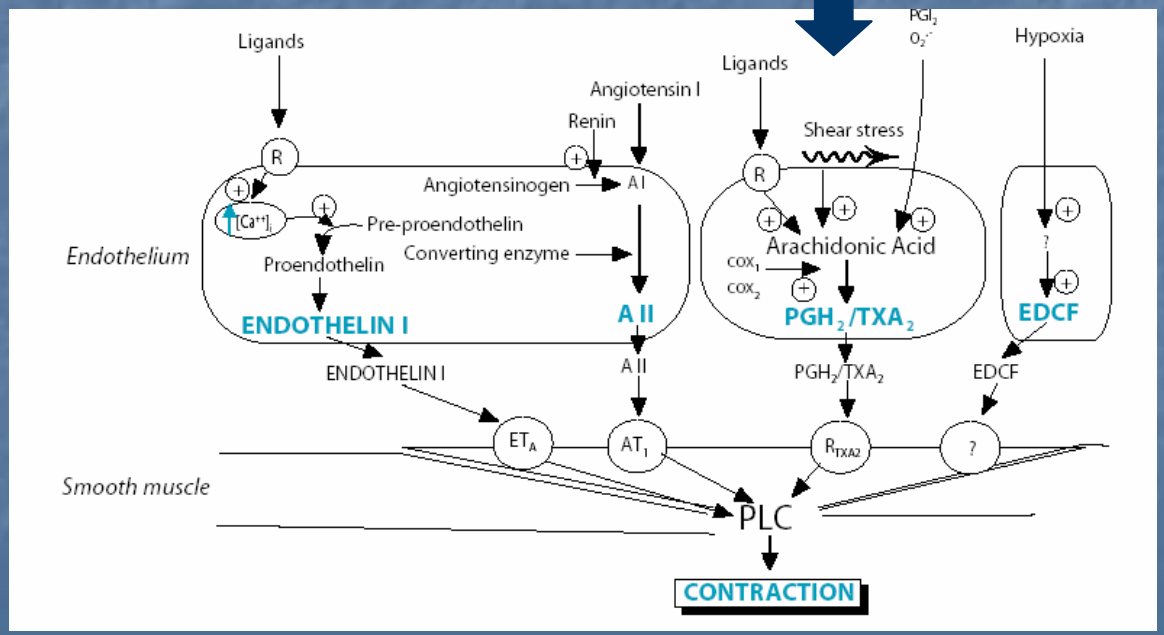
Региональные факторы регуляции АД

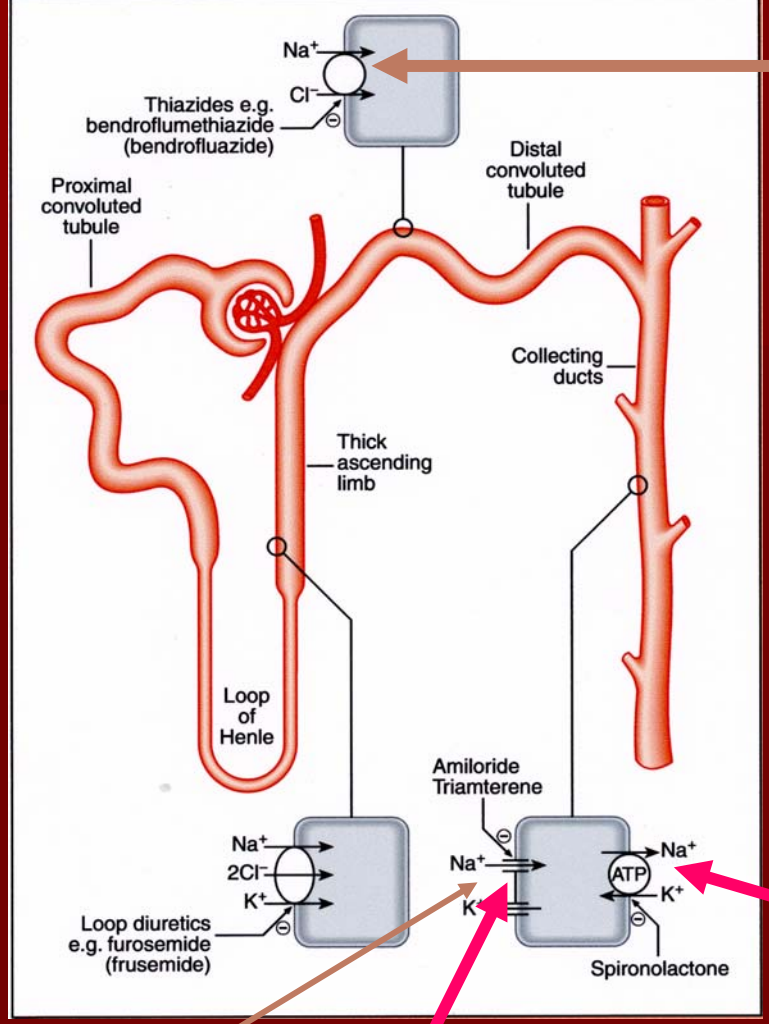


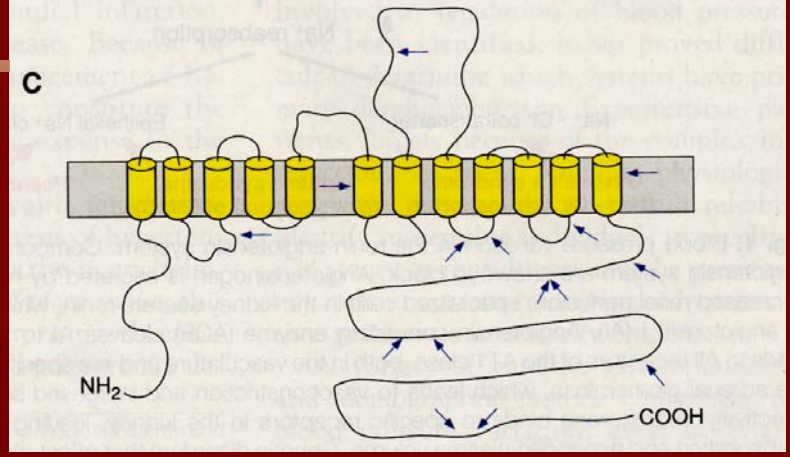
Вазодилятация



Вазоконстрикция



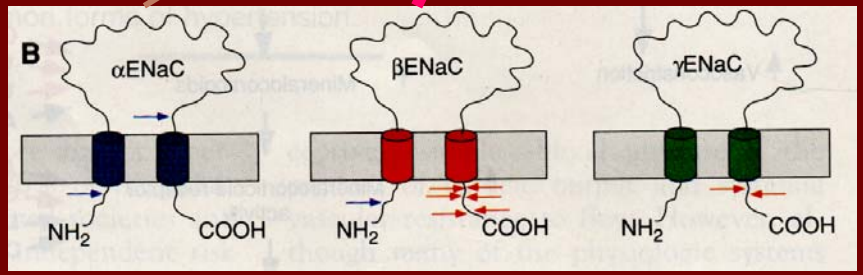


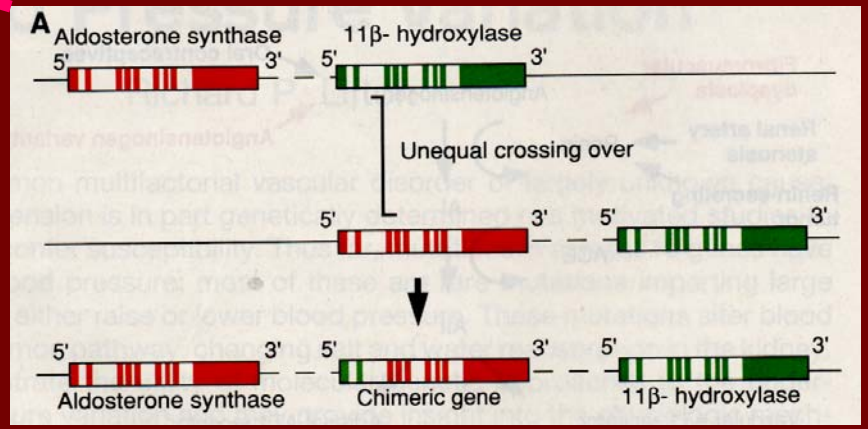


Мутации, приводящие к нарушениям функции натриевых каналов почки и к изменениям артериального давления

Повышение АД

Понижение АД





Hypertension Candidate Genes

CWRU Genomics

Welcome to the on-line resource for Hypertension Candidate Genes. Below is a list of 150 candidate genes. Each gene is clickable and will open to a new web page showing all available data collected. Available data includes map location and genetic interval, OMIM number, sequence data, and expression data for each gene. If you would like a tab-delimited text file of this information, click here.

List By Gene Names | List By Gene Symbols | GIST

Genes sorted by functional class

Apolipoproteins | Channels and Transporters | Cytoskeletal and Adhesion Molecules | Endothelins
Fat and Lipid Regulation | Glucose Regulation | Growth Factors and Hormones
Hypothalamus-Pituitary Axis | Intracellular Messengers | Kallikrein-Kinin pathway | Natriuretic Peptides
Renin-Angiotensin-Aldosterone pathway | Steroids | Sympathetic Nervous System
Thromboxanes and Prostaglandins | Miscellaneous

Apolipoproteins

Apolipoprotein A1 (APOA1)
Apolipoprotein A2 (APOA2)
Apolipoprotein C2 (APOC2)
Apolipoprotein C3 (APOC3)
Apolipoprotein C4 (APOC4)
Apolipoprotein E (APOE)
Apolipoprotein E Receptor 2 (APOER2/LRP8)

Channels / Transporters

Aquaporin 2 (AQP2)
ATP-Sensitive K Channel (KCNJ6)
Cardiac L type Calcium Channel, alpha-1 (CACNA1C/CACNL1A1)
Chloride Bicarb. Exchanger 1 (AE1/SLC4A1)
Chloride Bicarb. Exchanger 2 (AE2/SLC4A2)
Chloride Bicarb. Exchanger 3 (AE3/SLC4A3)
Chloride Channel, kidney, A (CLCNKA)
Chloride Channel, kidney, B (CLCNKB)
Glucose Transporter 1 (GLUT1/SLC2A1)
Glucose Transporter 2 (GLUT2/SLC2A2)
Glucose Transporter 3 (GLUT3/SLC2A3)
Glucose Transporter 4 (GLUT4/SLC2A4)
Potassium-chloride cotransporter (hKCC1)

Sodium Bicarbonate Cotransporter (NBC/HNBC1)
Sodium Calcium Exchanger 1 (NCX1/SLC8A1)
Sodium Calcium Exchanger 2 (NCX2/SLC8A2)
Sodium Channel (SCNN1A)
Sodium Channel (SCNN1B)
Sodium Channel (SCNN1D)
Sodium Channel (SCNN1G)
Sodium Channel - Heart (SCN5A)
Sodium Chloride Cotransporter (SLC12A3/HTSC)
Sodium Hydrogen Exchanger 1 (NHE1/SLC9A1)
Sodium Hydrogen Exchanger 2 (NHE2/SLC9A2)
Sodium Hydrogen Exchanger 5 (NHE5/SLC9A5)
Sodium Potassium ATPase alpha1 (ATP1A1)
Sodium-Glucose Cotransporter, renal (SGLT2/SLC5A2)
B-cell K/ATP Channel (BIR/KCNJ11)

Cytoskeletal / Adhesion Molecules

Adducin - alpha (ADD1)
Adducin - beta (ADD2)
Adducin - gamma (ADD3)
E-Selectin (ELAM/SELE)
Intercellular Adhesion Molecule 1 (ICAM1)
Intercellular Adhesion Molecule 2 (ICAM2)
Intercellular Adhesion Molecule 3 (ICAM3)

Endothelins

Endothelin 1 (EDN1/ET1)
Endothelin 2 (EDN2/ET2)
Endothelin 3 (EDN3/ET3)
Endothelin Convert. Enzyme1 (ECE1)
Endothelin Receptor Type A (EDNRA)
Endothelin Receptor Type B (EDNRB)

Fat and Lipid Regulation

Bombesin-like Receptor 3 (BRS3)
LDL Receptor (LDLR)
Leptin (LEP/OB)
Leptin Receptor (LEPR)
Lipoprotein Lipase (LPL)
Uncoupling Protein 3 (UCP3)

Glucose Regulation

Aldose Reductase (ALDR1)
Amylin (IAPP)
Gastric Inhibitory Polypeptide Receptor (GIPR)
Glucagon (GCG)
Glucagon Receptor (GCGR)
Glucagon-like Peptide 1 Receptor (GLP1R)

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Frustrating Search for Hypertension Genes Continues

By Edward R. Winstead

July 11, 2003

Despite years of searching, researchers have yet to discover a human gene that controls blood pressure or contributes to hypertension. The worldwide effort has generated a list of chromosome regions that may contain these genes but no specific genes or variants.

Now, a region of chromosome 6 has been added to the list. British researchers discovered the region by "scanning" the genomes of 2,000 pairs of siblings from families with severe hypertension for DNA they had in common. In addition to chromosome 6, several other areas were implicated, but the statistical evidence was modest.

The next step is to screen the regions for gene candidates, but the researchers acknowledge that whatever they find will not be the whole story on the genetics of hypertension.

Indeed, the story seems to be that many genes (or variants) contribute in small degrees to inherited differences in blood pressure, and that different genes may confer risk for hypertension in different populations.

'Where are all the blood-pressure genes?'

"We really don't know how many blood pressure genes there are," says Mark J. Caulfield of Queen Mary's School of Medicine, London, who led the new study. "We hope they number 5 or 10, but there could be 20 or more."

As with other complex diseases, like schizophrenia and heart disease, pinpointing genetic risk factors for hypertension will not be easy.

Consider a recent analysis of data from genome scans for hypertension genes published in the scientific literature. This "meta-analysis" found that no single chromosome region consistently had large effects on blood pressure or hypertension in all the study populations. It was published in the *American Journal of Hypertension* in February.

The original genome scans were done at medical centers in the United States as part of the National Heart, Lung, and Blood Institute Family Blood Pressure Program (FBPP). The subjects came from different ethnic groups and represented the racial diversity of the U.S. population.

The new research is part of the Medical Research Council's BRItish Genetics of HyperTension (BRIGHT) study. The findings appear in *The Lancet* along with a commentary entitled "Where are all the blood-pressure genes?"

Citing the challenges of finding genes underlying common diseases, the commentary's author, Stephen B. Harrap of the University of Melbourne, Australia, suggests that it simply may not be possible to discover gene variants for hypertension that would be valuable in the diagnosis of the disease.

Rather than search for every gene variant underlying hypertension, he argues, the field needs to "search for molecular clues to the common physiological mechanisms underlying disease."

The study in *The Lancet* may ultimately lead to new risk factors for severe hypertension. None of the chromosome regions in the study was associated with the disease in humans until now. But part of chromosome 2 corresponds to a region of the rat genome associated with elevated blood pressure.

"We are encouraged by this because it means we may have found a region that actually contains genes" for hypertension, says Caulfield. "We're making some progress, though perhaps not as much as we would like."

"If finding the genes were easy, we would not have undertaken such large studies."

...

Caulfield, M. *et al.* Genome-wide mapping of human loci for essential hypertension. *Lancet* **361**, 2118-2123 (June 21, 2003).

Harrap, S.B. Where are all the blood-pressure genes? *Lancet* **361**, 2149-2151 (June 21, 2003).

Province, M.A. *et al.* A meta-analysis of genome-wide linkage scans for hypertension: The National Heart, Lung and Blood Institute Family Blood Pressure Program. *American Journal of Hypertension* **16**, 144-147 (February 2003).

Indeed, the story seems to be that many genes (or variants) contribute in small degrees to inherited differences in blood pressure, and that different genes may confer risk for hypertension in different populations

«ПОИСК ГЕНОВ ОТВЕТСТВЕННЫХ ЗА ПАТОГЕНЕЗ МУЛЬТИФАКТОРИАЛЬНЫХ БОЛЕЗНЕЙ ИНОГДА ПОДОБЕН ПОИСКУ ИГОЛКИ В СТОГЕ СЕНА»

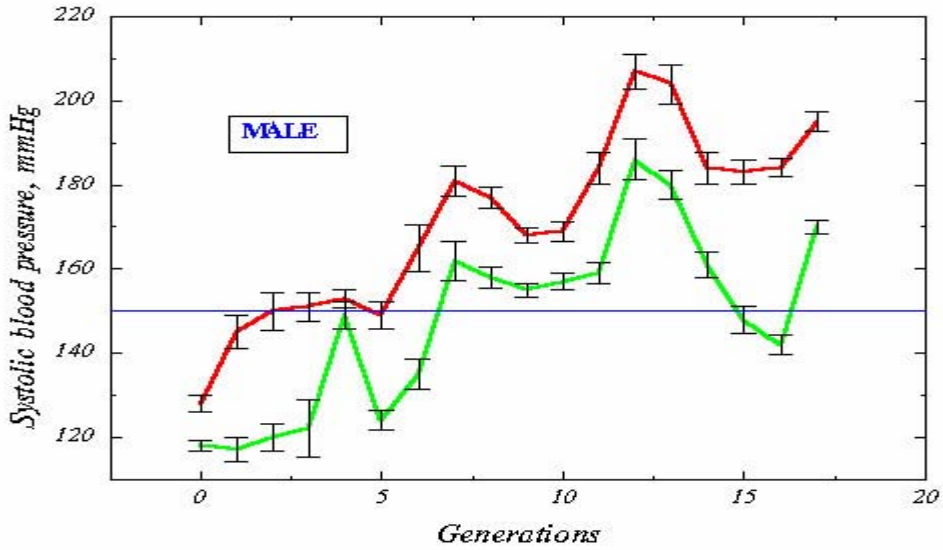
TABLE 1. *Rodent strains selectively bred for blood pressure*

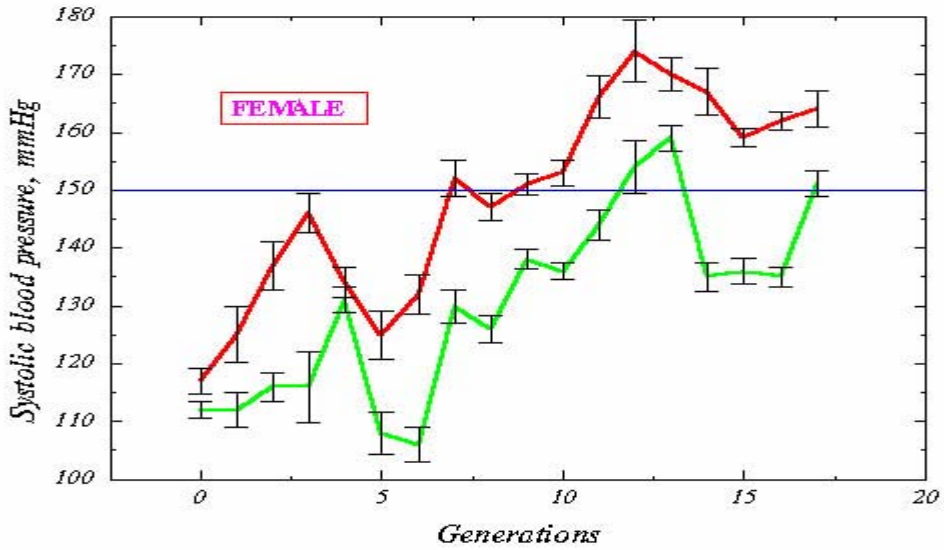
Strain	Lines	Original Stock	Year First Reported (Reference No.)
		Rat	
New Zealand (Dunedin): genetically hypertensive (GH) rats	H, C	Wistar derived	Smirk and Hall, 1958 (234)
USA (Brookhaven): Dahl salt-sensitive (S) and Dahl salt-resistant (R) rats	H, L	Sprague-Dawley	Dahl et al., 1962 (30, 31)
Japan (Kyoto): spontaneously hypertensive rats (SHR)	H	Wistar derived	Okamoto and Aoki, 1963 (175)
Japan (Kyoto): spontaneously hypertensive rats-stroke prone (SHRSP)	H	Wistar derived	Okamoto et al., 1974 (176)
Israel (Jerusalem): DOCA salt-sensitive (SBH) and resistant (SBN) rats	H, L	Unknown	Ben-Ishay et al., 1972 (7)
France: Lyon hypertensive (LH), Lyon normotensive (LN), and Lyon low blood pressure (LL) rats	H, C, L	Sprague-Dawley	Dupont et al., 1973 (53)
Italy: Milan hypertensive strain (MHS) and Milan normotensive (MNS) rats	H, C	Wistar	Bianchi et al., 1974 (8)
The Netherlands (Utrecht): fawn-hooded hypertensive (FHH) and fawn-hooded low blood pressure (FHL) rats	H, L	Greman brown × white Lashley	Kuijpers and Gruys, 1984 (124)
Russia (Novosibirsk): inherited stress-induced arterial hypertension (ISIAH) rats	H	Wistar derived	Markel, 1985 (158)
Czech Republic: Prague hypertensive rat (PHR), Prague normotensive rat (PNR)	H, L	Wistar derived	Heller et al., 1993 (80)
		Mouse	
USA (University of Kansas)	H, C, L	Eight-way cross of inbred strains	Schlager, 1974 (217)
		Hamster	
Canada (Halls Harbor)	H	Cardiomyopathic × gold Syrian hamsters	Thomas et al., 1997 (252)

Kinds of lines developed in each model were as follows: H, line selected for high blood pressure; C, control line, unselected, random bred; L, line selected for low blood pressure.

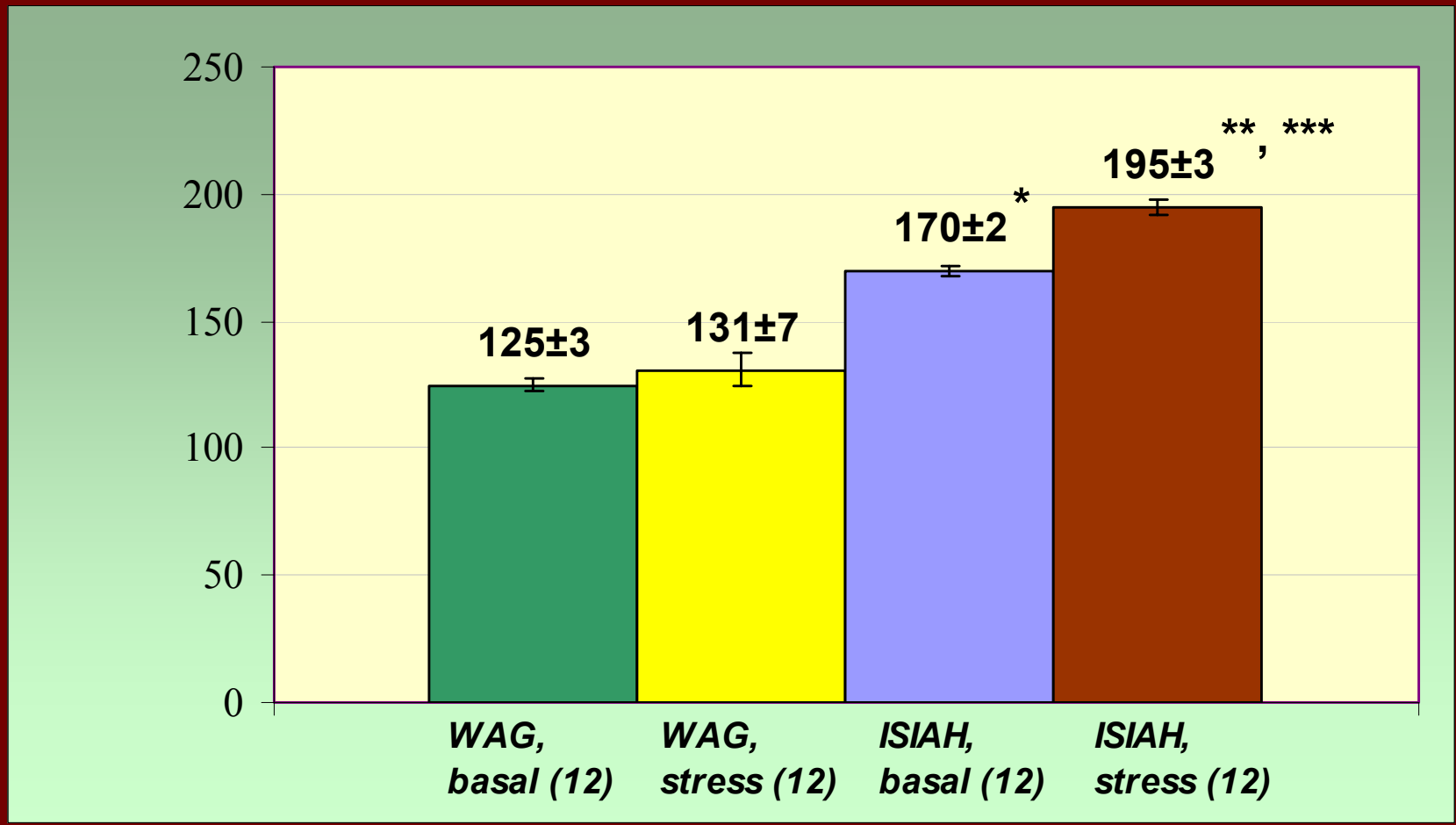
From: John P. Rapp, 2000

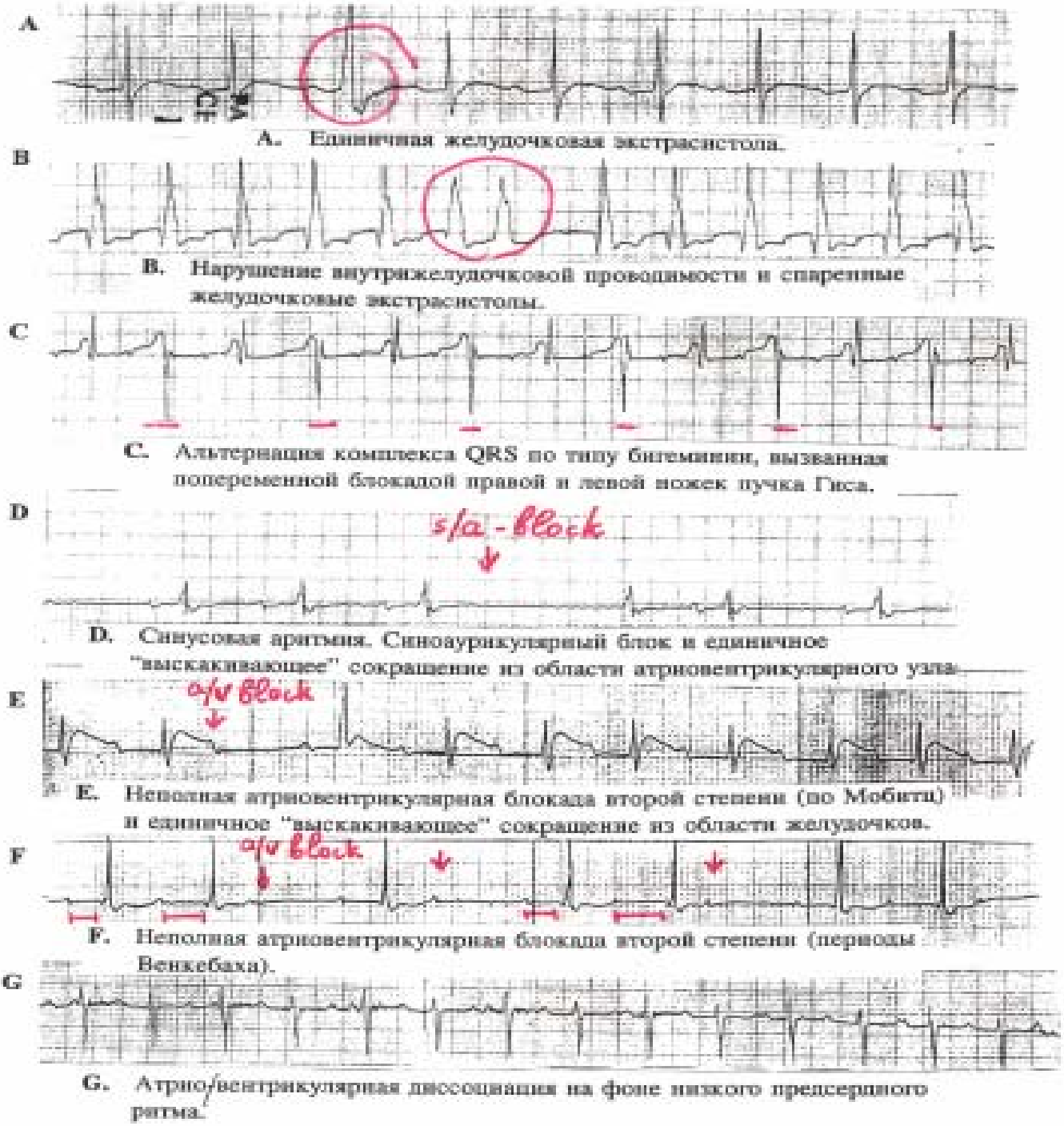
ISIAH rat strain: An experimental model of stress-sensitive arterial **hypertension**


MALE
Systolic blood pressure, mmHg
220
200
180
160
140
120
0
5
10
15
20
Generations


FEMALE
Systolic blood pressure, mmHg
180
170
160
150
140
130
120
110
100
0
5
10
15
20
Generations

Basal and stress-induced BP levels in WAG and ISIAH rat strains





A. Единичная желудочковая экстрасистола.

B. Нарушение внутрижелудочковой проводимости и спаренные желудочковые экстрасистолы.

C. Альтернация комплекса QRS по типу бигеминии, вызванная попеременной блокадой правой и левой ножек пучка Гиса.

D. Синусовая аритмия. Синоаурикулярный блок и единичное "выскакивающее" сокращение из области атриовентрикулярного узла.

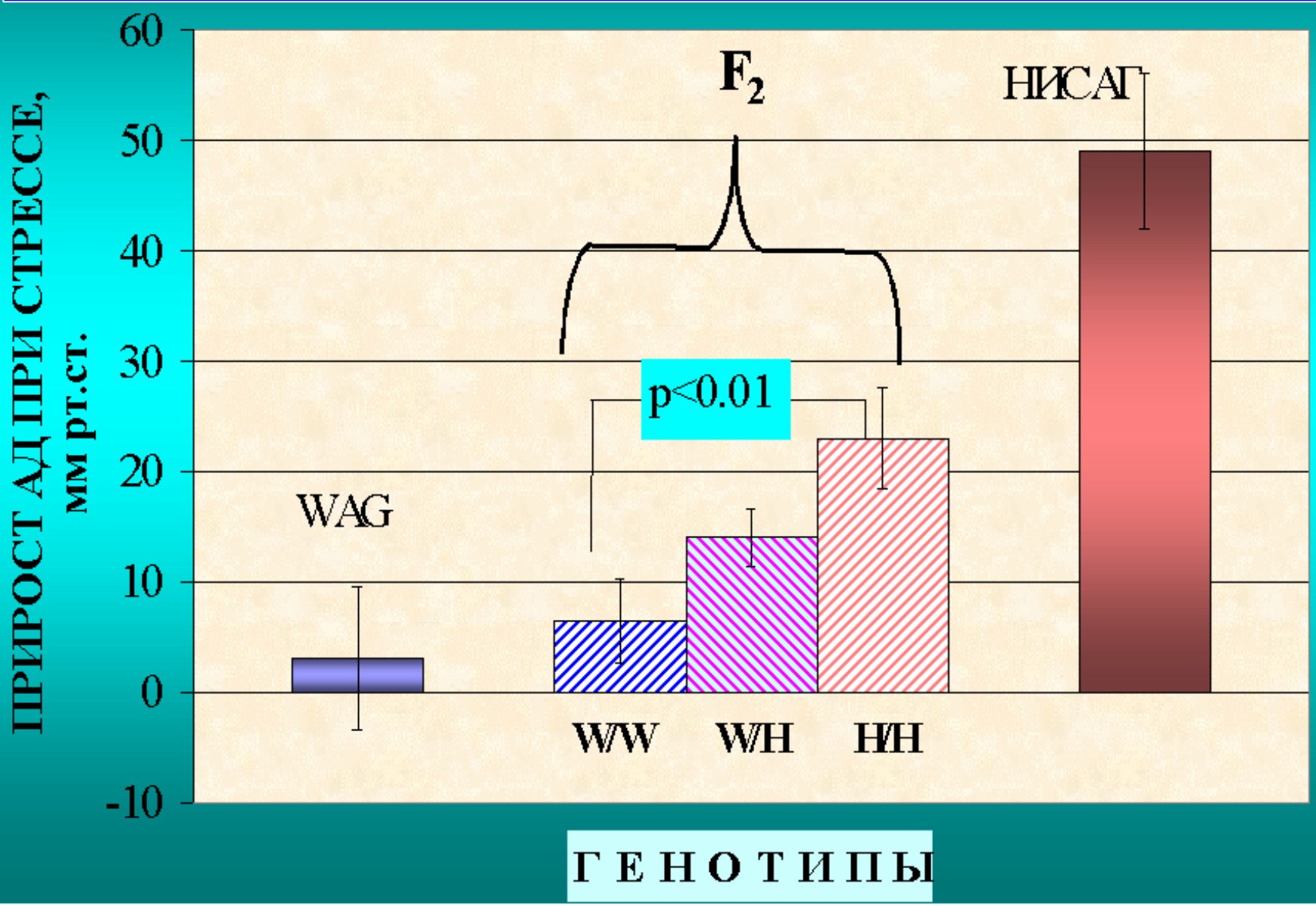
E. Неполная атриовентрикулярная блокада второй степени (по Мобитц) и единичное "выскакивающее" сокращение из области желудочков.

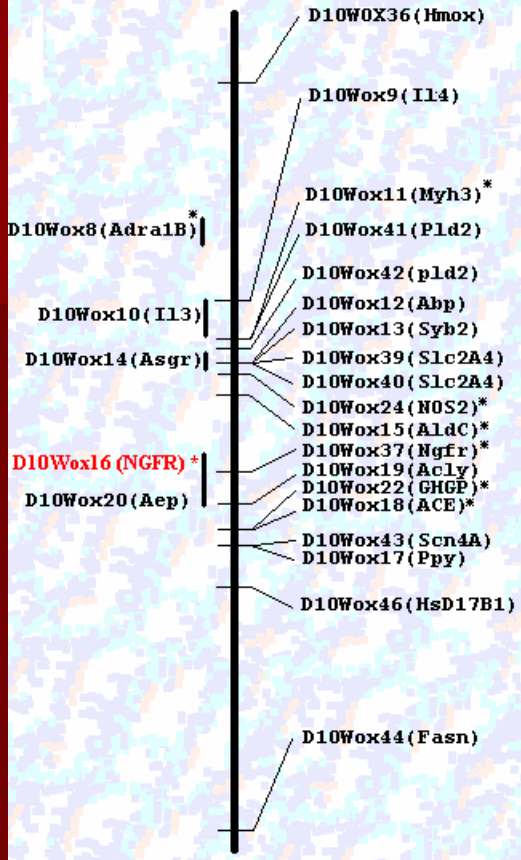
F. Неполная атриовентрикулярная блокада второй степени (периоды Венкебаха).

G. Атрио/вентрикулярная диссоциация на фоне низкого предсердного ритма.

Нарушения сердечного ритма у крыс линии НИСАГ по данным ЭКГ исследо-вания

Локус *NGFR* и величина прироста АД при стрессе



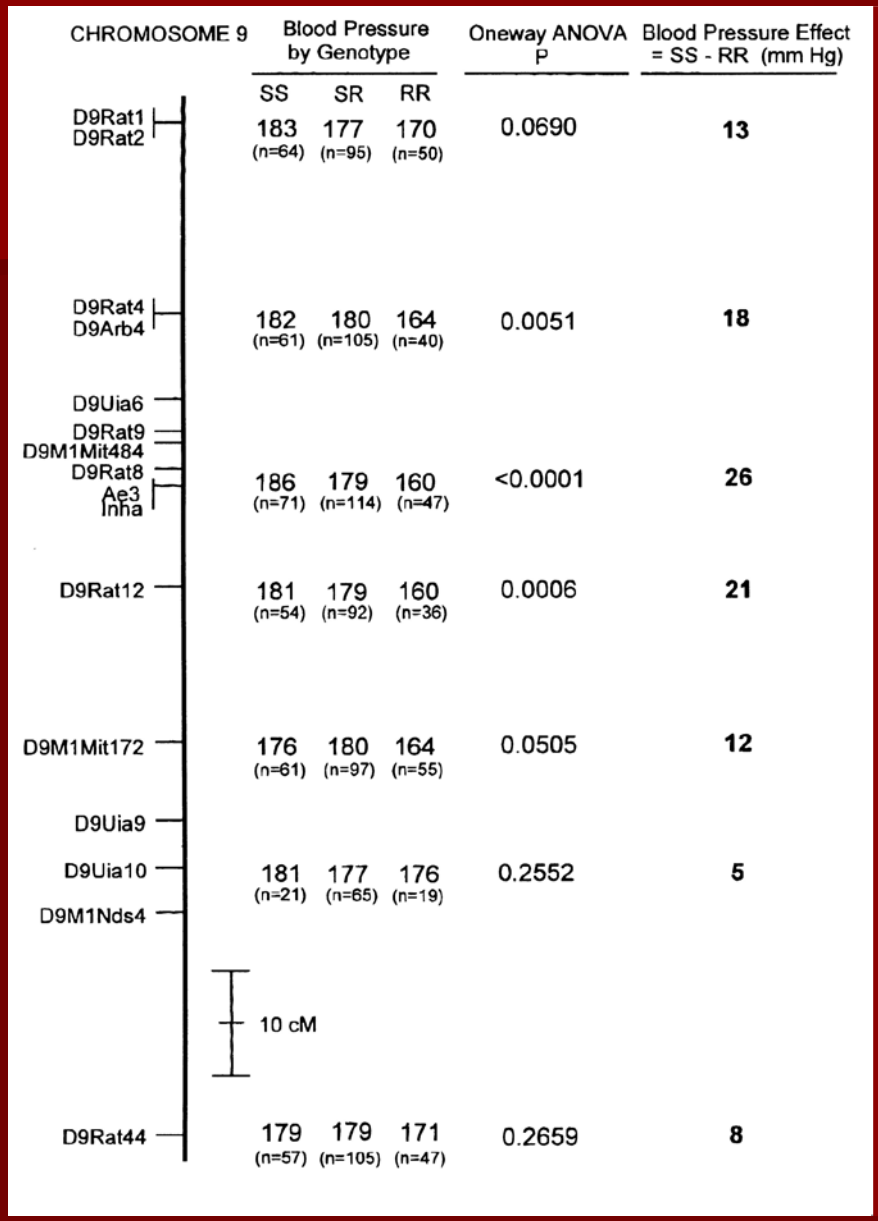


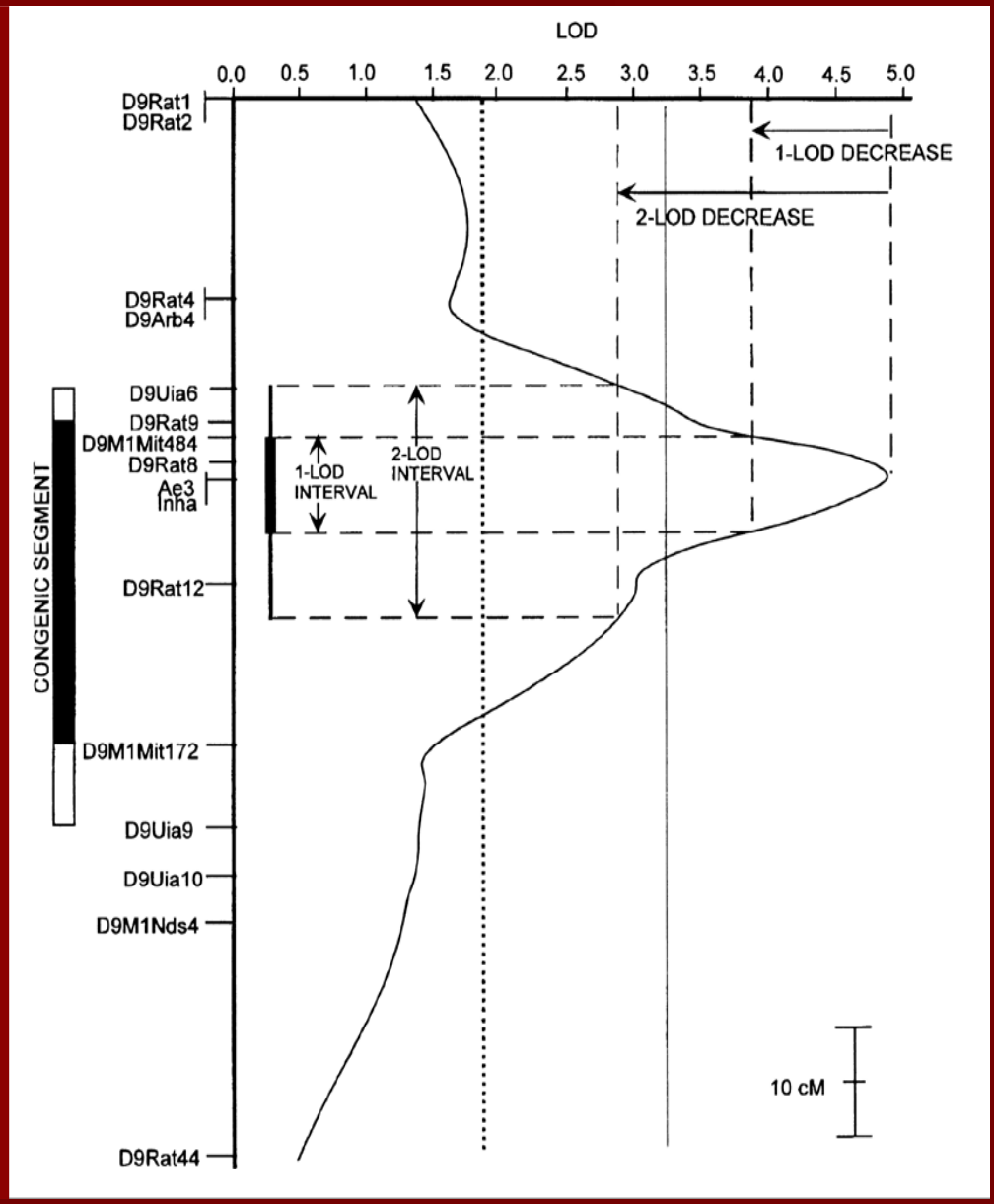
Hmox - гем оксигеназа 2
Il4 - интерлейкин 4
Myh3 - эмбриональный миозин, тяжелая цепь
Adra1B- альфа 1 В-адренергический рецептор
Pld2 - фосфолипаза D
Abp - андроген-связывающий белок
Il3 - интерлейкин 3
Syb2 - синаптобревин 2
Asgr - асиалогликопротеиновый рецептор
Slc2A4- переносчик глюкозы 4
NOS2 - индуцибельная NO-синтаза
AldC - альдолаза С
Ngfr - рецептор фактора роста нервов
Acly - АТФ-цитрат лиаза
Aep - анион-обменный канал
GHGP - гормон роста
ACE - ангиотензин превращающий фермент
Scn4A - альфа субъединица потенциал-зависимого натриевого канала
Ppy - панкреатический пептид
Hsd17B1- гидроксистероид дегидрогеназа 17 бета
Fasn - синтаза жирных кислот

Звездочкой (*)обозначены локусы генов-кандидатов, для который была найдена ассоциация с гипертонией у человека или на какой-либо из моделей экспериментальных животных

Карта сцепления 10-й хромосомы крысы

From: John P. Rapp, 2000





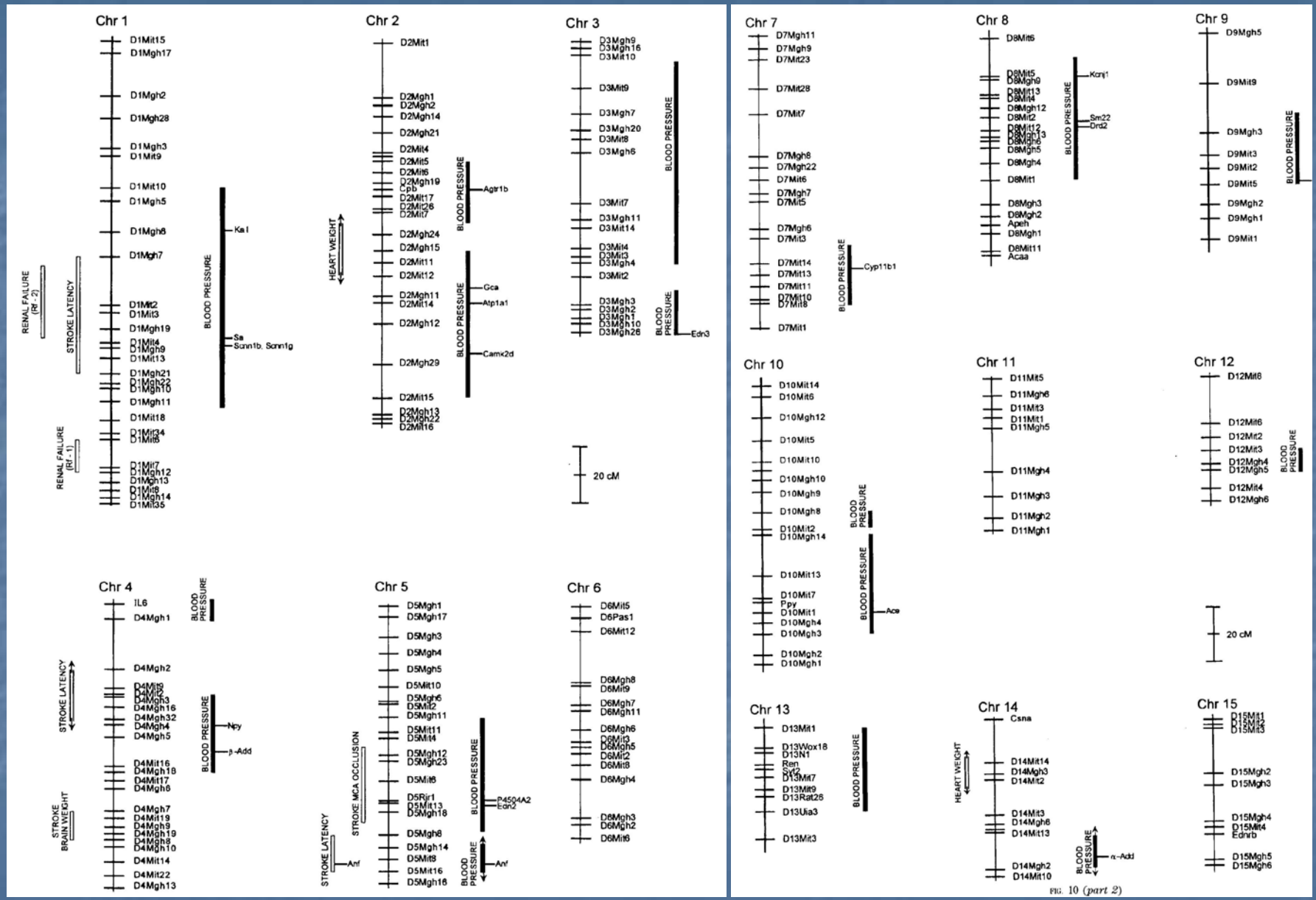
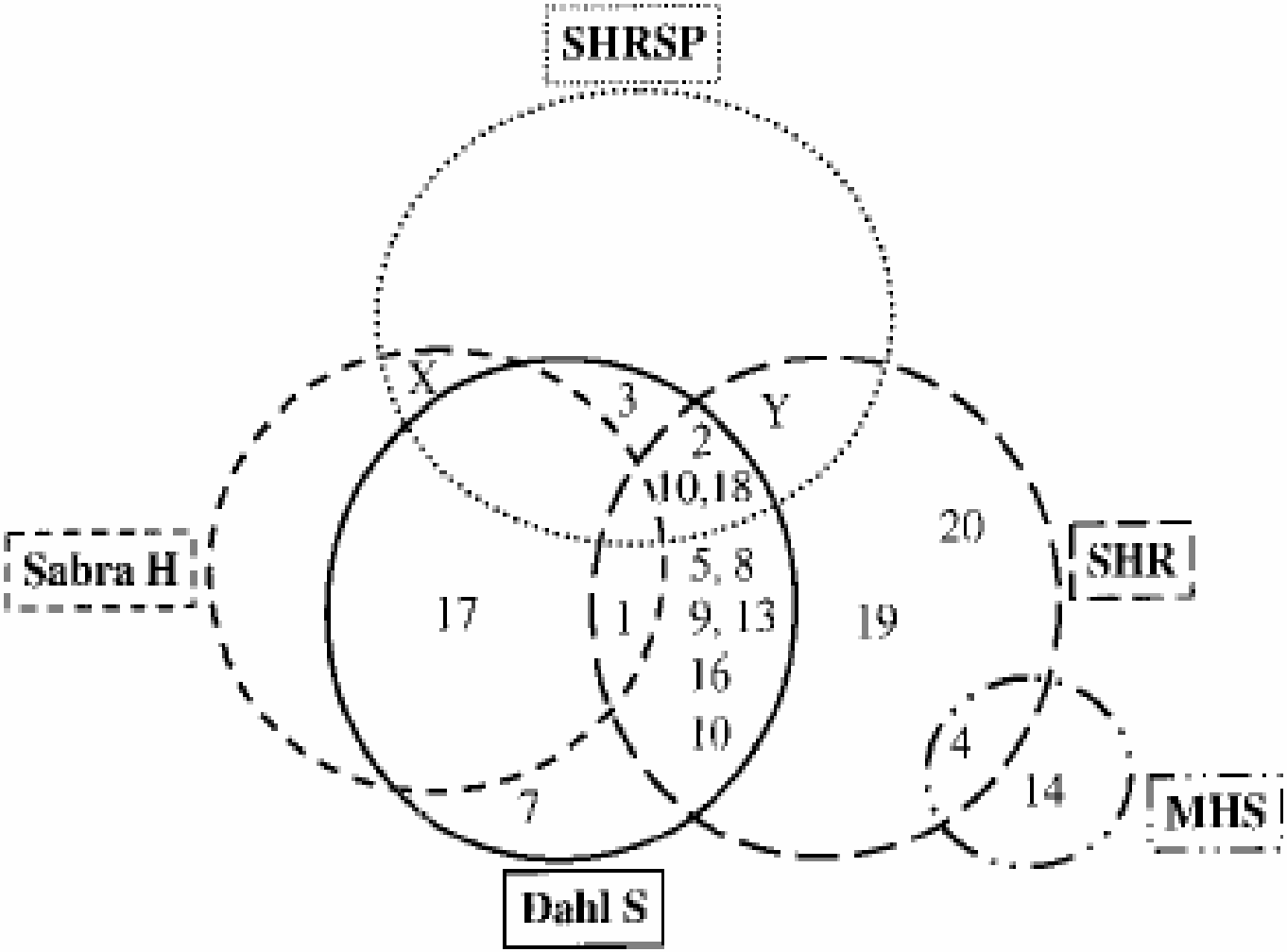

Chr 1
D1Mit15
D1Mgh17
D1Mgh2
D1Mgh28
D1Mgh3
D1Mit9
D1Mit10
D1Mgh5
D1Mgh8
D1Mgh7
D1Mit2
D1Mit3
D1Mgh19
D1Mit4
D1Mgh9
D1Mit13
D1Mgh21
D1Mgh22
D1Mgh10
D1Mgh11
D1Mit18
D1Mit34
D1Mit5
D1Mit7
D1Mgh12
D1Mgh13
D1Mit8
D1Mgh14
D1Mit35
RENAL FAILURE (Rf - 2)
STROKE LATENCY
RENAL FAILURE (Rf - 1)
BLOOD PRESSURE
Kal
Sa
Scnn1b, Scnn1g
Chr 2
D2Mit1
D2Mgh1
D2Mgh2
D2Mgh14
D2Mgh21
D2Mit4
D2Mit5
D2Mit6
D2Mgh19
Cpb
D2Mit17
D2Mit26
D2Mit7
D2Mgh24
D2Mgh15
D2Mit11
D2Mit12
D2Mgh11
D2Mit14
D2Mgh12
D2Mgh29
D2Mit15
D2Mgh13
D2Mgh22
D2Mit16
HEART WEIGHT
BLOOD PRESSURE
Agtr1b
Gca
Atp1a1
Camk2d
Chr 3
D3Mgh9
D3Mgh16
D3Mit10
D3Mit9
D3Mgh7
D3Mgh20
D3Mit8
D3Mgh6
D3Mit7
D3Mgh11
D3Mit14
D3Mit4
D3Mit3
D3Mgh4
D3Mit2
D3Mgh3
D3Mgh2
D3Mgh1
D3Mgh10
D3Mgh26
BLOOD PRESSURE
BLOOD PRESSURE
Edn3
20 cM
Chr 4
IL6
D4Mgh1
D4Mgh2
D4Mit3
D4Mit23
D4Mgh3
D4Mgh16
D4Mgh32
D4Mgh4
D4Mgh5
D4Mit16
D4Mgh18
D4Mit17
D4Mgh6
D4Mgh7
D4Mit19
D4Mgh9
D4Mgh19
D4Mgh8
D4Mgh10
D4Mit14
D4Mit22
D4Mgh13
STROKE LATENCY
STROKE BRAIN WEIGHT
BLOOD PRESSURE
BLOOD PRESSURE
Npy
β-Add
Chr 5
D5Mgh1
D5Mgh17
D5Mgh3
D5Mgh4
D5Mgh5
D5Mit10
D5Mgh6
D5Mit2
D5Mgh11
D5Mit11
D5Mit4
D5Mgh12
D5Mgh23
D5Mit6
D5Rjr1
D5Mit13
D5Mgh18
D5Mgh8
D5Mgh14
D5Mit8
D5Mit16
D5Mgh16
STROKE LATENCY
STROKE MCA OCCLUSION
Anf
BLOOD PRESSURE
P4504A2
Edn2
BLOOD PRESSURE
Anf
Chr 6
D6Mit5
D6Pas1
D6Mit12
D6Mgh8
D6Mit9
D6Mgh7
D6Mgh11
D6Mgh6
D6Mit3
D6Mgh5
D6Mit2
D6Mit8
D6Mgh4
D6Mgh3
D6Mgh2
D6Mit6
Chr 7
D7Mgh11
D7Mgh9
D7Mit23
D7Mit28
D7Mit7
D7Mgh8
D7Mgh22
D7Mit6
D7Mgh7
D7Mit5
D7Mgh6
D7Mit3
D7Mit14
D7Mit13
D7Mit11
D7Mit10
D7Mit8
D7Mit1
BLOOD PRESSURE
Cyp11b1
Chr 8
D8Mit6
D8Mit5
D8Mgh9
D8Mit13
D8Mit4
D8Mgh12
D8Mit2
D8Mit12
D8Mgh13
D8Mgh6
D8Mgh5
D8Mgh4
D8Mit1
D8Mgh3
D8Mgh2
Apeh
D8Mgh1
D8Mit11
Acaa
BLOOD PRESSURE
Kcnj1
Sm22
Drd2
Chr 9
D9Mgh5
D9Mit9
D9Mgh3
D9Mit3
D9Mit2
D9Mit5
D9Mgh2
D9Mgh1
D9Mit1
BLOOD PRESSURE
Chr 10
D10Mit14
D10Mit6
D10Mgh12
D10Mit5
D10Mit10
D10Mgh10
D10Mgh9
D10Mgh8
D10Mit2
D10Mgh14
D10Mit13
D10Mit7
Ppy
D10Mit1
D10Mgh4
D10Mgh3
D10Mgh2
D10Mgh1
BLOOD PRESSURE
BLOOD PRESSURE
Ace
Chr 11
D11Mit5
D11Mgh6
D11Mit3
D11Mit1
D11Mgh5
D11Mgh4
D11Mgh3
D11Mgh2
D11Mgh1
Chr 12
D12Mit8
D12Mit6
D12Mit2
D12Mit3
D12Mgh4
D12Mgh5
D12Mit4
D12Mgh6
BLOOD PRESSURE
20 cM
Chr 13
D13Mit1
D13Wox18
D13N1
Ren
Sv2
D13Mit7
D13Mit9
D13Rat26
D13Uia3
D13Mit3
BLOOD PRESSURE
Chr 14
Csna
D14Mit14
D14Mgh3
D14Mit2
D14Mit3
D14Mgh6
D14Mit13
D14Mgh2
D14Mit10
HEART WEIGHT
BLOOD PRESSURE
α-Add
Chr 15
D15Mit1
D15Mit2
D15Mit3
D15Mgh2
D15Mgh3
D15Mgh4
D15Mit4
Ednrb
D15Mgh5
D15Mgh6

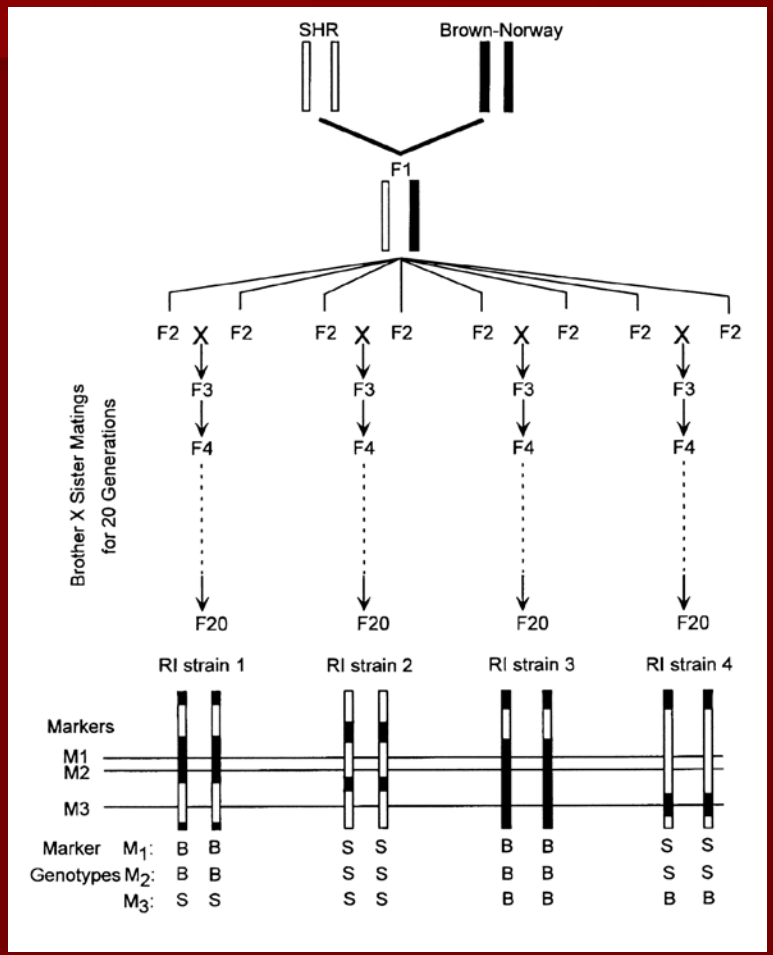
FIG. 10 (*part 2*)

Common or reproducible blood pressure QTL identified in several independent experiments

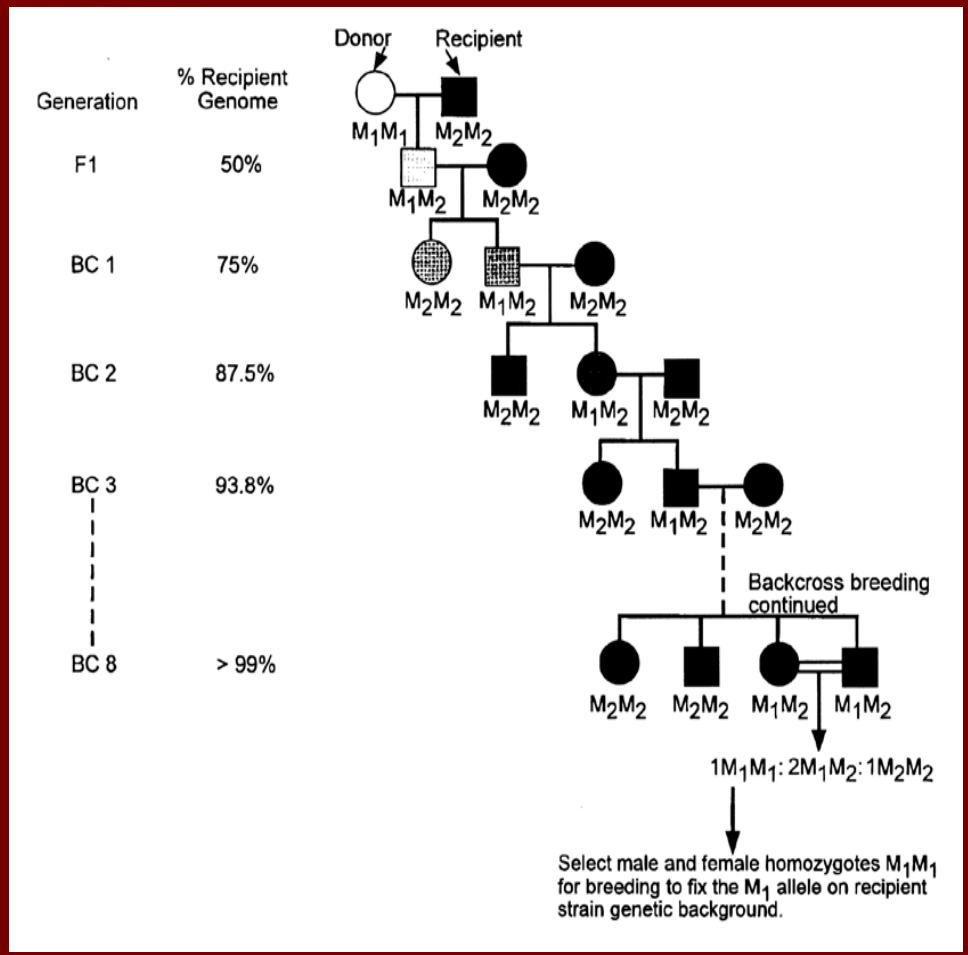


From: John P. Rapp, 2000

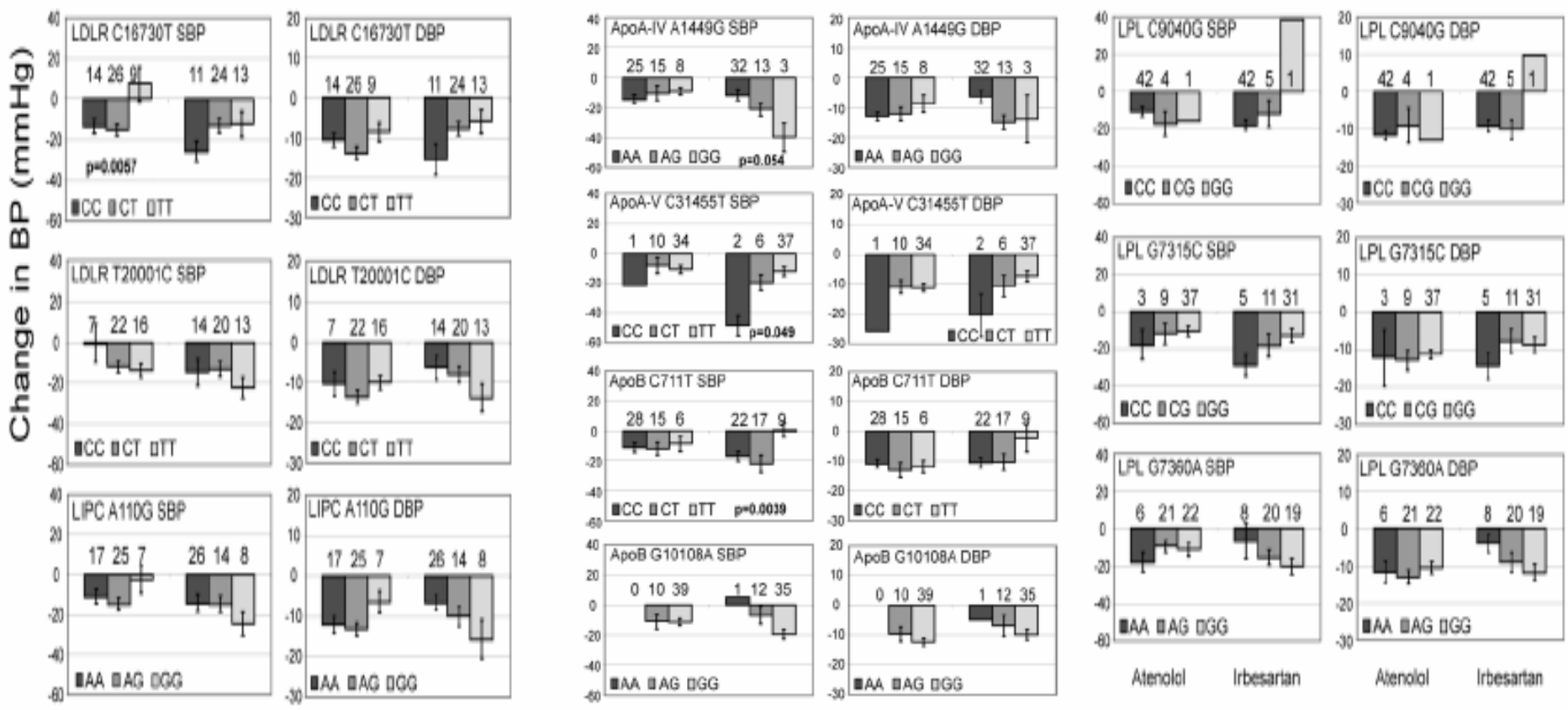
Рекомбинантные линии



Конгенные линии

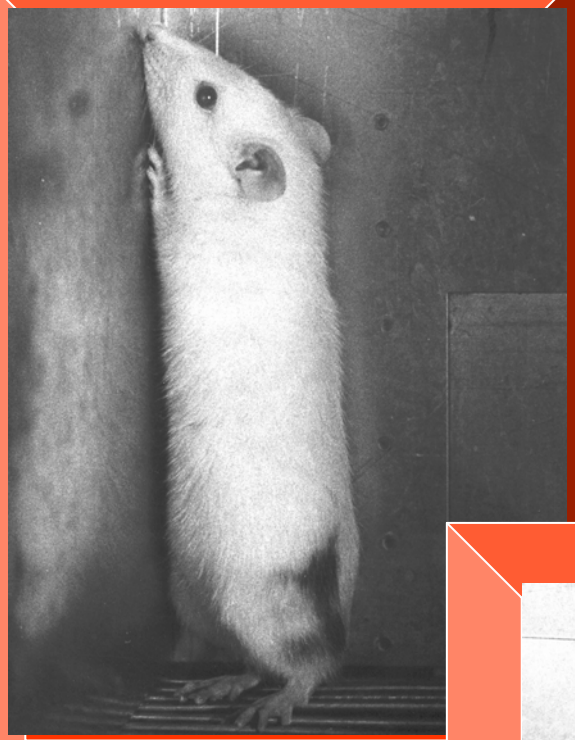


Effect of SNP genotype on the change in blood pressure after 12 weeks of treatment for the ten SNPs.



From: BMC Cardiovascular Disorders, 2004

Крысы линии ГК (генетическая каталепсия)

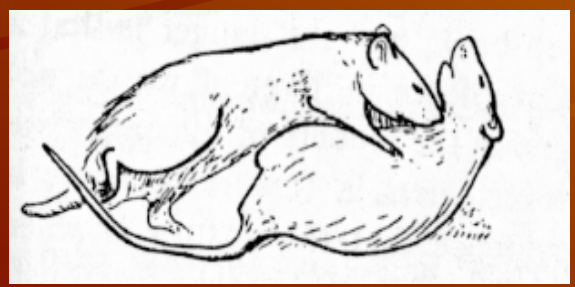


Автор линии –

В.Г.КОЛПАКОВ

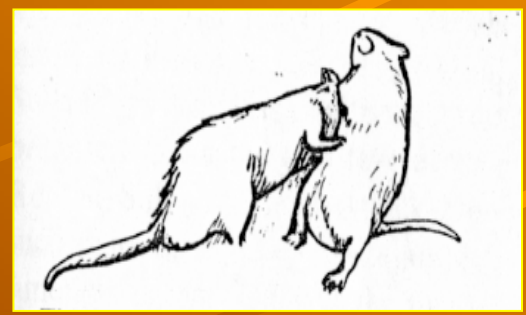
ИЦиГ СО РАН

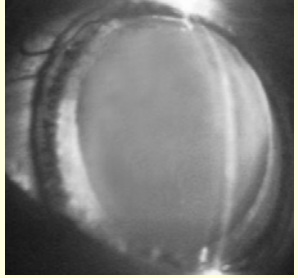
ДЕПРЕССИЯ



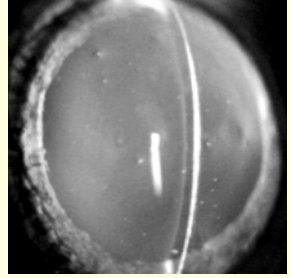
Создание и изучение экспериментальной модели депрессии

Д.б.н. Н.Н.Кудрявцева

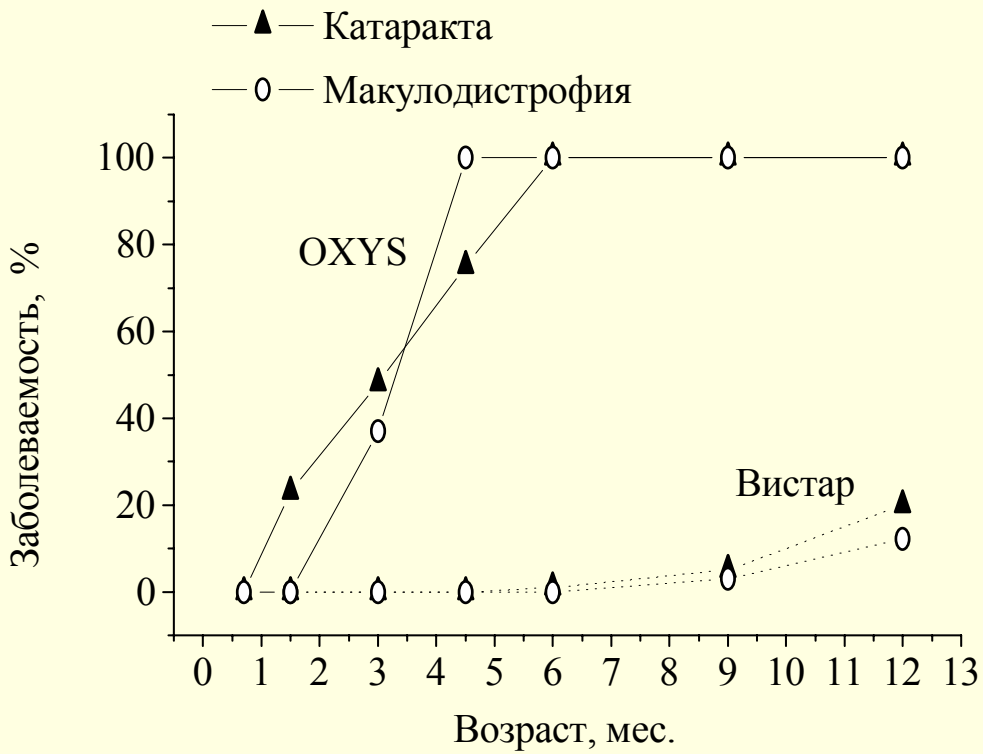




Здоровый хрусталик у крыс Wistar



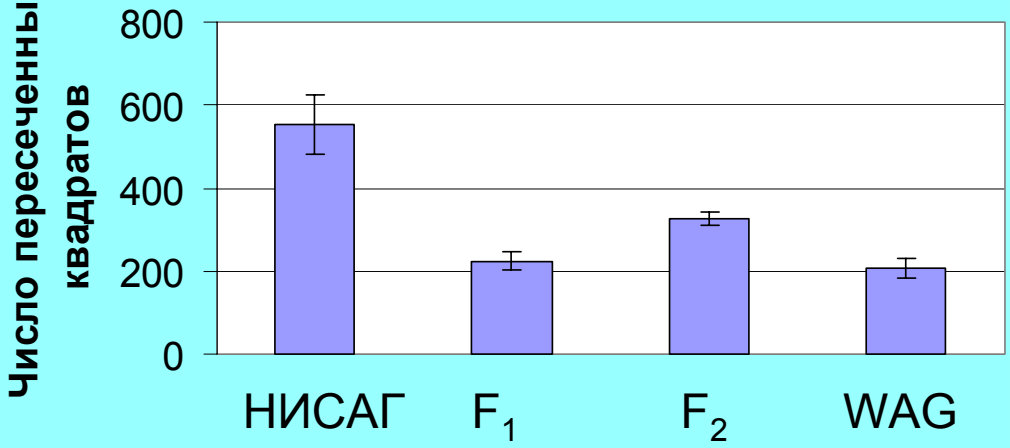
Точечная катаракта хрусталика у крыс OXYS

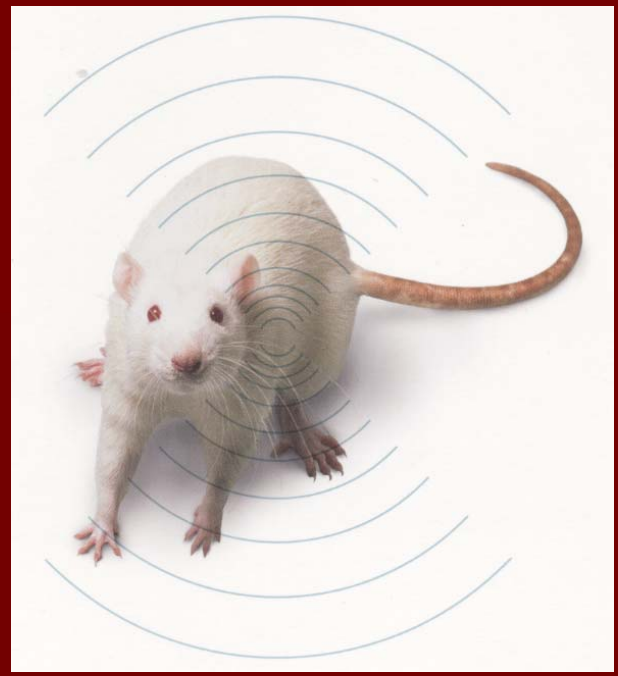


Содержание продуктов перекисного окисления липидов (ПОЛ) в плазме крови крыс OXYS повышено и связано с выраженностью патологических изменений. Проявления раннего старения органа зрения у крыс OXYS обусловлено окислительным стрессом, что подтверждается высокой эффективностью антиоксидантов в их профилактике.

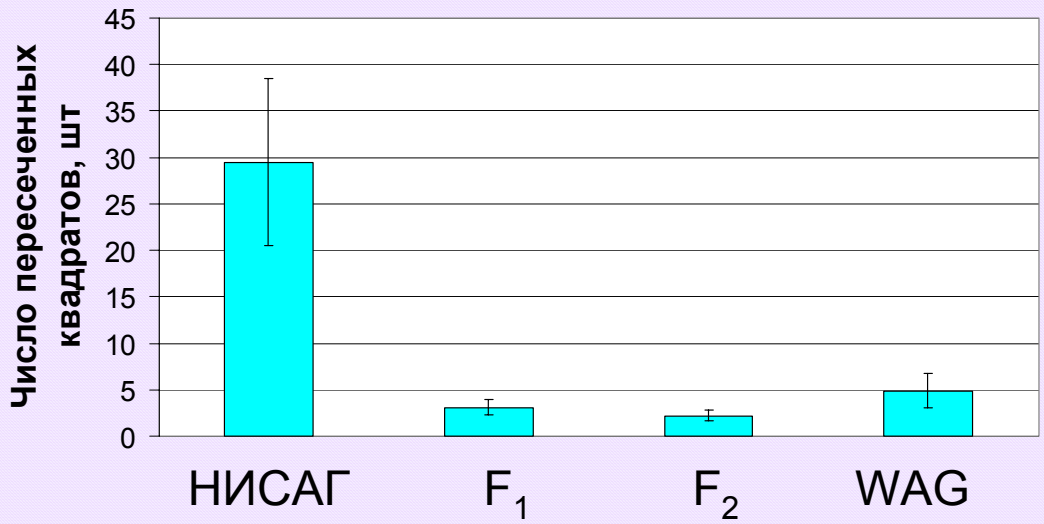
2.1.1. Блок 3 (Н.Г. Колосова)

Двигательная активность на периферии площадки "открытого поля" (сумма за 4 теста)



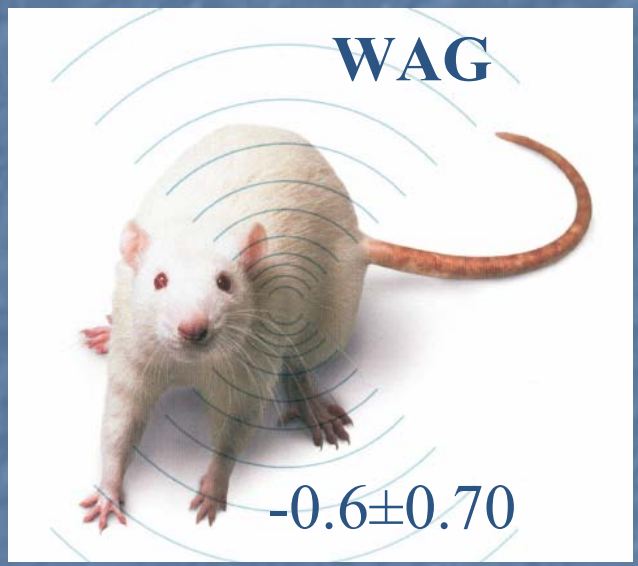


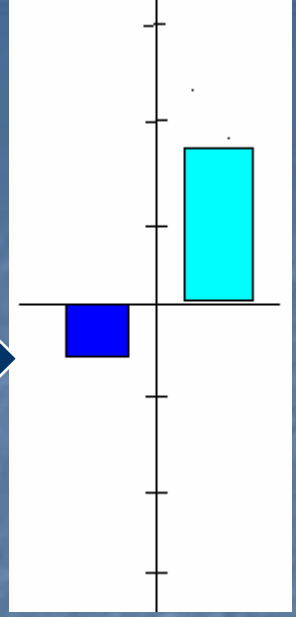
Двигательная активность в центре площадки "открытого поля" (сумма за четыре теста)



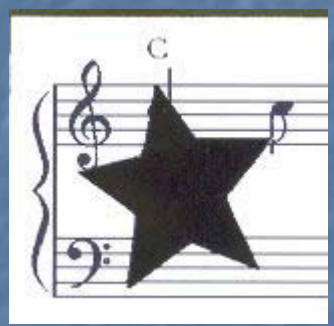
Негативная реакция

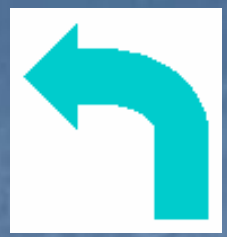
(страх)





$P < 0.05$





Позитивная реакция

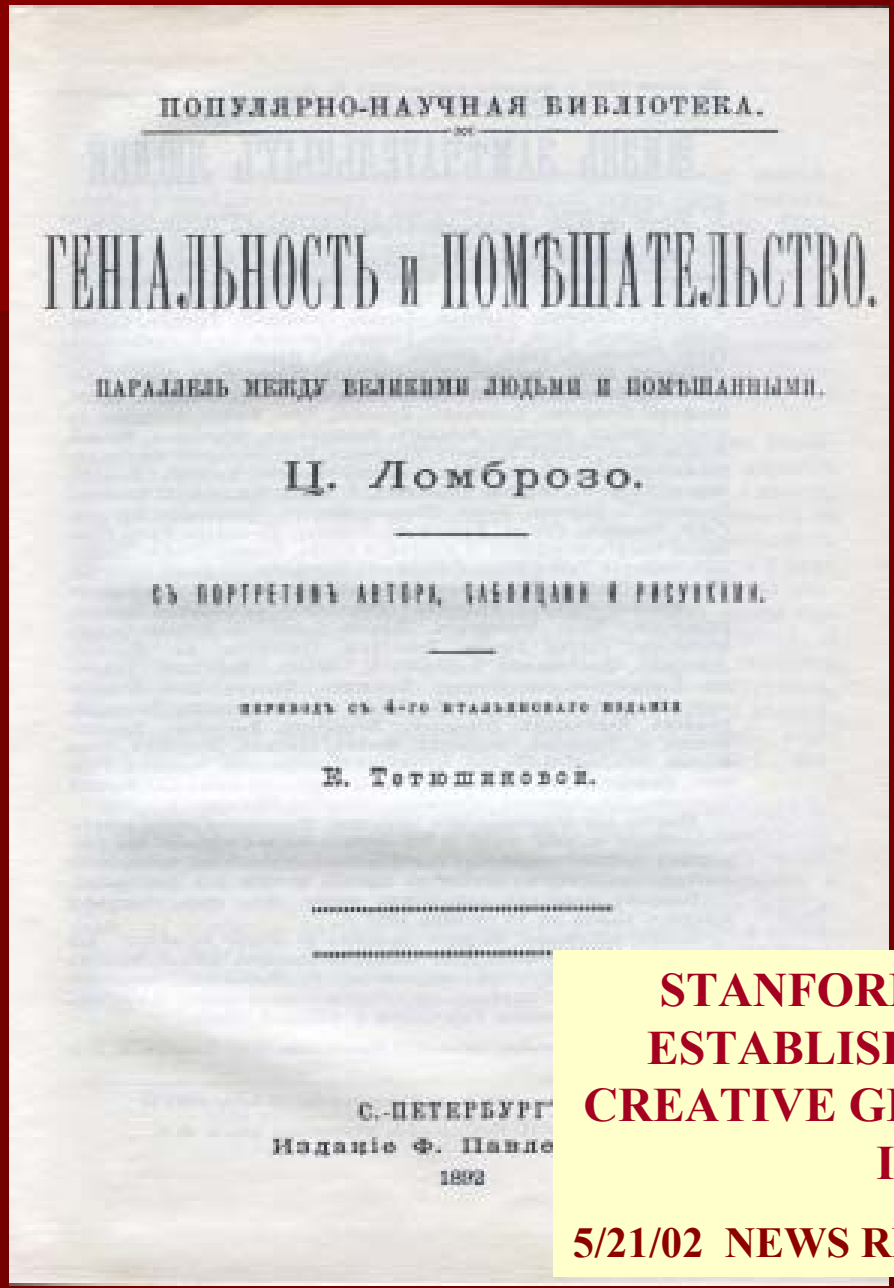
(исследование)

Внезапное появление звукового или зрительного стимула

«Не бывает гения без примеси помешатель-ства»

Сенека

3 до н.э. – 65 н.э.



ПОПУЛЯРНО-НАУЧНАЯ БИБЛІОТЕКА.

ГЕНІАЛЬНОСТЬ и ПОМѢШАТЕЛЬСТВО.

ПАРАЛЛЕЛЬ МЕЖДУ ВЕЛИКИМИ ЛЮДЬМИ И ПОМѢШАННЫМИ.

Ц. Ломброзо.

СЪ ПОРТРЕТОМЪ АВТОРА, ТАБЛИЦАМИ И РИСУНКАМИ.

ПЕРЕВОДЪ СЪ 4-го ИТАЛЬЯНСКАГО ИЗДАНІЯ

Ж. Тютюнниковой.

С.-ПЕТЕРБУРГ
Изданіе Ф. Павле
1892

“You don’t have to be mad to be a genius… but it helps”

Dr. Kenneth Lyen

2002 г.

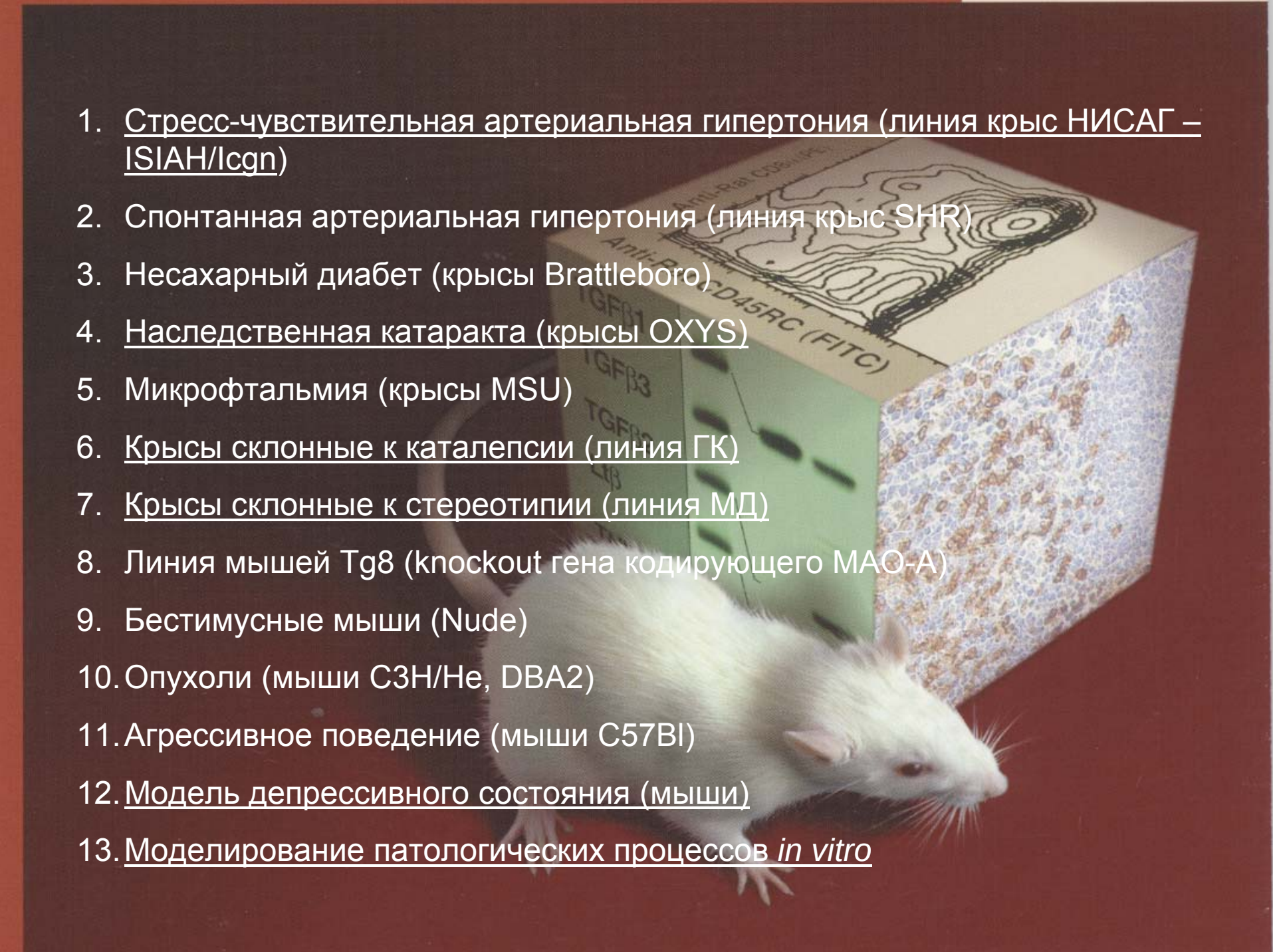
From an Essay

Is there a link between genius and madness?

STANFORD RESEARCHERS ESTABLISH LINK BETWEEN CREATIVE GENIUS AND MENTAL ILLNESS

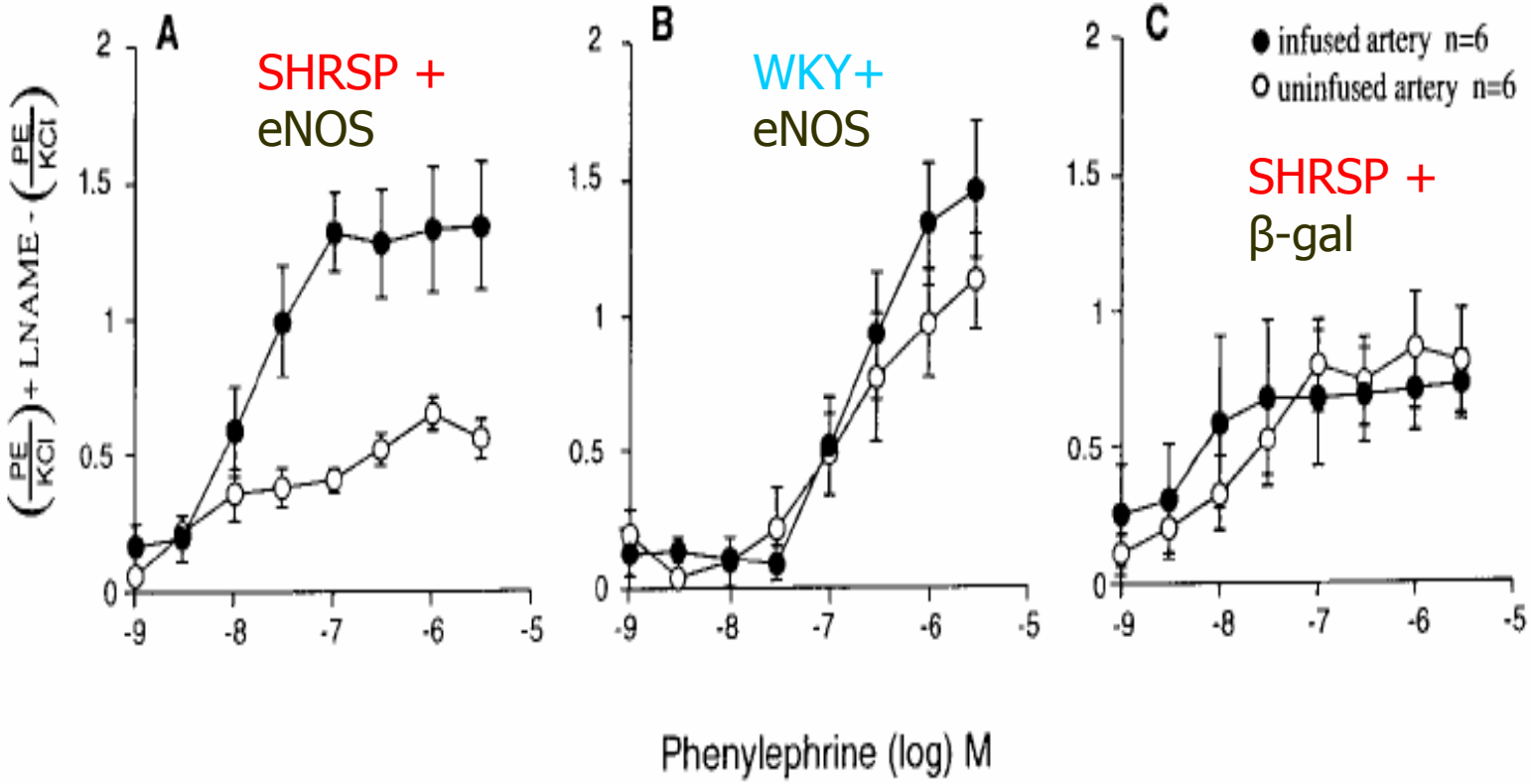
5/21/02 NEWS RELEASE

1. Стресс-чувствительная артериальная гипертония (линия крыс НИСАГ – ISIAH/Icgn)
2. Спонтанная артериальная гипертония (линия крыс SHR)
3. Несахарный диабет (крысы Brattleboro)
4. Наследственная катаракта (крысы OXYS)
5. Микрофтальмия (крысы MSU)
6. Крысы склонные к каталепсии (линия ГК)
7. Крысы склонные к стереотипии (линия МД)
8. Линия мышей Tg8 (knockout гена кодирующего МАО-А)
9. Бестимусные мыши (Nude)
10. Опухоли (мыши C3H/He, DBA2)
11. Агрессивное поведение (мыши C57Bl)
12. Модель депрессивного состояния (мыши)
13. Моделирование патологических процессов *in vitro*



Basal NO availability after infusion of the adenovirus encoding endogenous eNOS cDNA driven by cytomegalovirus promoter

(From Anna F. Dominiczak et al., 2000)



Editorial

Gene Therapy for Common Acquired Diseases of the Heart

The Sirens' Song

Eduardo Marbán, MD, PhD

Then the queenly Circe spoke in words and addresse
come first of all to the Sirens, who are enchanters of a
whoever comes their way: and that man who un
proaches them, and listens to the Sirens singing, has
coming home. You must drive straight on past. . .
Homer

faced with the Sirens. The song we hear is all the more seductive because it originates deep within ourselves. Nevertheless, our roles as physicians and as guardians of the public trust dictate that we do all we can to resist the temptation to jump into human studies until we have gathered overwhelming evidence for both safety and efficacy. For the

The prospect of using genes as therap presents myriad opportunities. No physic to appreciate the power of this approa abandon the shackles of the limited pharmac device repertoire and focus instead on reeng culprit tissue by somatic gene transfer? The genomic information leaves us with an emba riches in terms of potential therapeutic agents. V line at nature's own genes expressed in their u Genes can readily be tailored to exhibit special found in nature, altering the function of their protein products for specific ends. Alternatively, wild-type genes can be expressed in tissues where they are normally silent.

See p 1578

In this issue, Weig et al[1] describe a clever application of the latter approach: V2 vasopressin receptor genes, usually expressed only in kidney, were delivered to myocardium packaged in recombinant adenoviruses. Expression of these adenyl cyclase–activating receptors in the myocardium converted the basal negative inotropic response to infused vasopressin into a positive one. Because vasopressin levels are elevated in heart failure, a situation in which β-receptors are uncoupled from cyclase,[2] ectopic expression of V2 receptors would logically be predicted to recruit cAMP-mediated contractility in failing myocardium while bypassing the desensitized β-adrenergic pathway. The work has conceptual beauty. It also presents 2 important methodological innovations: first, the use of in situ viral transduction followed by myocyte isolation to enable careful phenotypic characterization of genetically altered cells; second, the adaptation for in vivo use of previously described strategies for optimizing transcor-

long-term studies with the sam
not suffice and may potentia
myocardial diseases such as h
fundamental properties of exc
fer so greatly between mice a
humans) that conclusions so
Nevertheless, mice can help
candidate genes, and larger
platform for pushing the enve

No matter how smart we th
our animal studies may be, we
when it comes to real therapeu
with well-reasoned but ultimat
misadventures, notably with a
patients[9] and with phosphoc
failure.[5] In such cases, at
terminated as soon as adverse
therapy has the potential dange
dosing difficulties. Such conc
to the application of gene the
such as hemophilia; the culprit
of a secreted protein, even
expression, may suffice to cor
the use of gene transfer to a
differs fundamentally in its philosophy. Here the goal is not to correct a well-defined genetic disorder; instead, genes are used to manipulate the very workings of the diseased organ,

Sirens

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.
From the Institute of Molecular Cardiobiology, Johns Hopkins University School of Medicine, Baltimore, Md.

WHL · NEWSLETTER

News from the World Hypertension League (WHL).
A division of the International Society of Hypertension, and in official relations with the World Health Organization.

No. 99, February 2005

Editorial

Korotkov sounds – what do we know about this 100 year old discovery?

Nikolai Sergeievich Korotkov (1874–1920)

This year, 2005, is the 100th anniversary of one of the most famous discoveries in the field of hypertension: the auscultative method of blood pressure measurement. The method, named after the Russian physician and scientist Nikolai Sergeievich Korotkov (1874–1920), has now been widely used for one century. Unfortunately, while the method itself and the name of its inventor are world famous, much less is known about the history of this outstanding discovery and the real role of Korotkov in the interpretation of the discovered sounds and the implementation of the new method into clinical practice.

Korotkov was only 31 years of age when he made a short presentation at the Scientific Meeting of the Military Hospital of the Imperial Military Academy about an easy, non-invasive method of blood pressure measurement. This was on November 5, 1905. The brief title of his presentation was "Concerning the problem of the methods for investigating blood pressure". He described the following sequence of sounds: first sound, ten murmurs, loud sounds, decreasing sounds and complete disappearance. These observations are now classified as different phases of the Korotkov sounds. Later, Russian scientists and investigators all over the world continued to find an explanation for the auscultative phenomenon. Although our modern understanding of the nature of the sounds has changed, the method remains the standard for hypertension diagnosis and management. Even today, 100 years later, devices are being devel-

continued on page 2

WHL News

Report from the 6th International Symposium on Hypertension and Related Diseases from October 15–18, 2004 in Beijing, China

On the occasion of this Symposium, the World Hypertension League (WHL) held a Regional Meeting on the Prevention of Hypertension. It was chaired by Prof. Liu Lisheng, Vice President of the WHL, Prof. Zhou Beifan, and Dr. Claude Lenfant, President of the WHL. There were 8 presentations describing research and public health activities in the respective countries.

Dr. Lenfant summarized 4 studies from the United States which exemplify the significance and effectiveness of programs to reduce excess weight, to encourage physical exercise, and to reduce salt and alcohol consumption to maintain, or reduce blood pressure (BP) to a normal level (i.e. <140/85 mmHg). He noted that to control hypertension we have the choice between pharmacological and preventive interventions: he concluded that preventive interventions are effective and far less costly than pharmacological regimens.

continued on page 2

Contents

WORLD HYPERTENSION DAY May 14, 2005

Initiated by the World Hypertension League

Saturday, May 14, 2005

The objectives of the **World Hypertension League** are to promote the detection, control and prevention of arterial hypertension in populations. Bringing together and stimulating organizations committed to the control of hypertension is the goal and the raison d'être of the WHL.

HYPERTENSION - THE SILENT KILLER

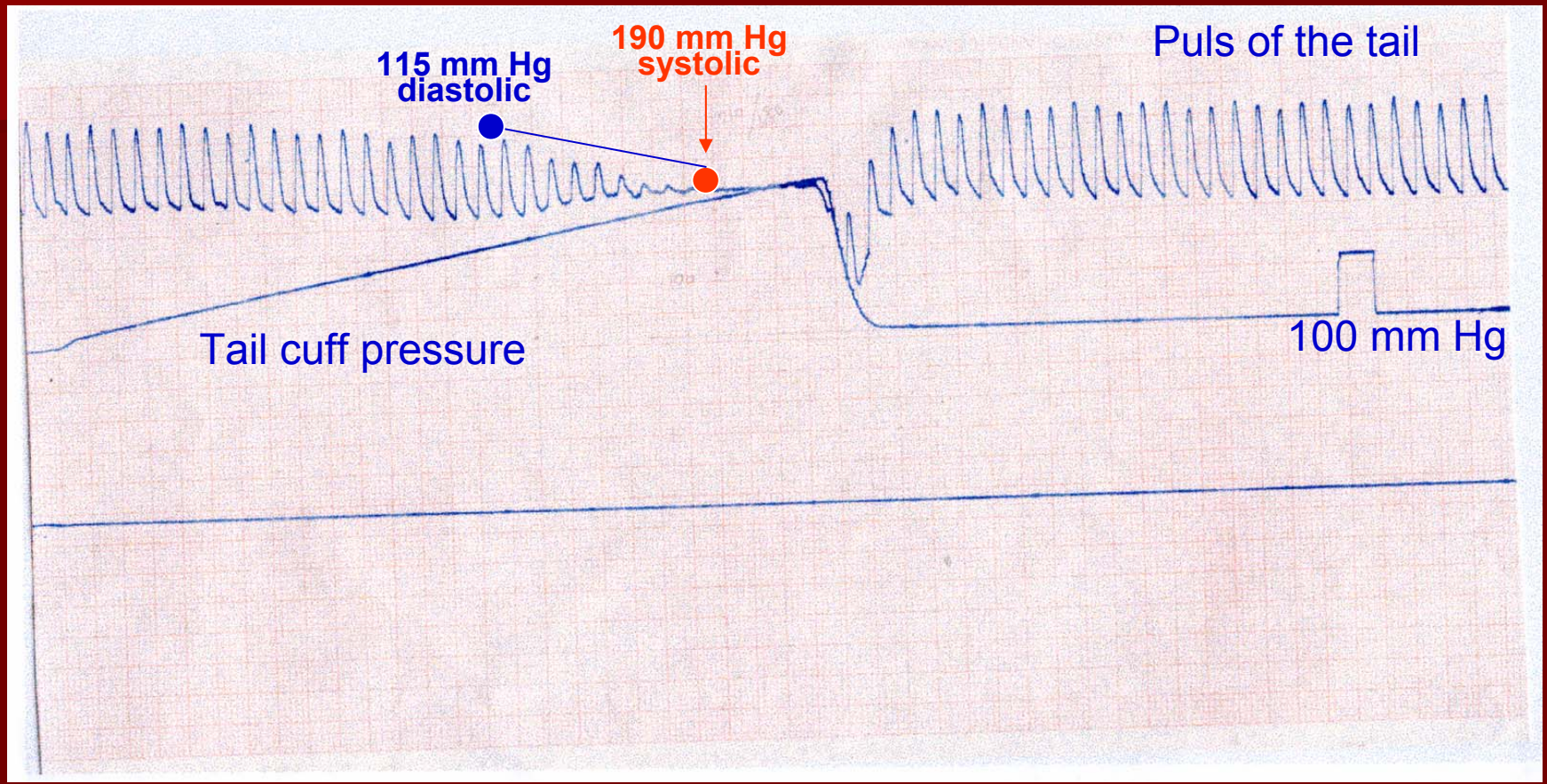
KNOW YOUR BLOOD PRESSURE

GENERAL RULES FOR BLOOD PRESSURE MEASUREMENT

- Rest for 5 minutes before measurement
- Refrain from smoking or ingesting caffeine for 30 minutes prior to measurement
- Be seated with feet flat on the floor, back and arm supported, and arm at heart level
- Use appropriate sized cuff
- Use recently validated device
- An average of two or more readings should be taken, at least two minutes apart

Under special circumstances measuring blood pressure in standing and supine positions may be indicated.

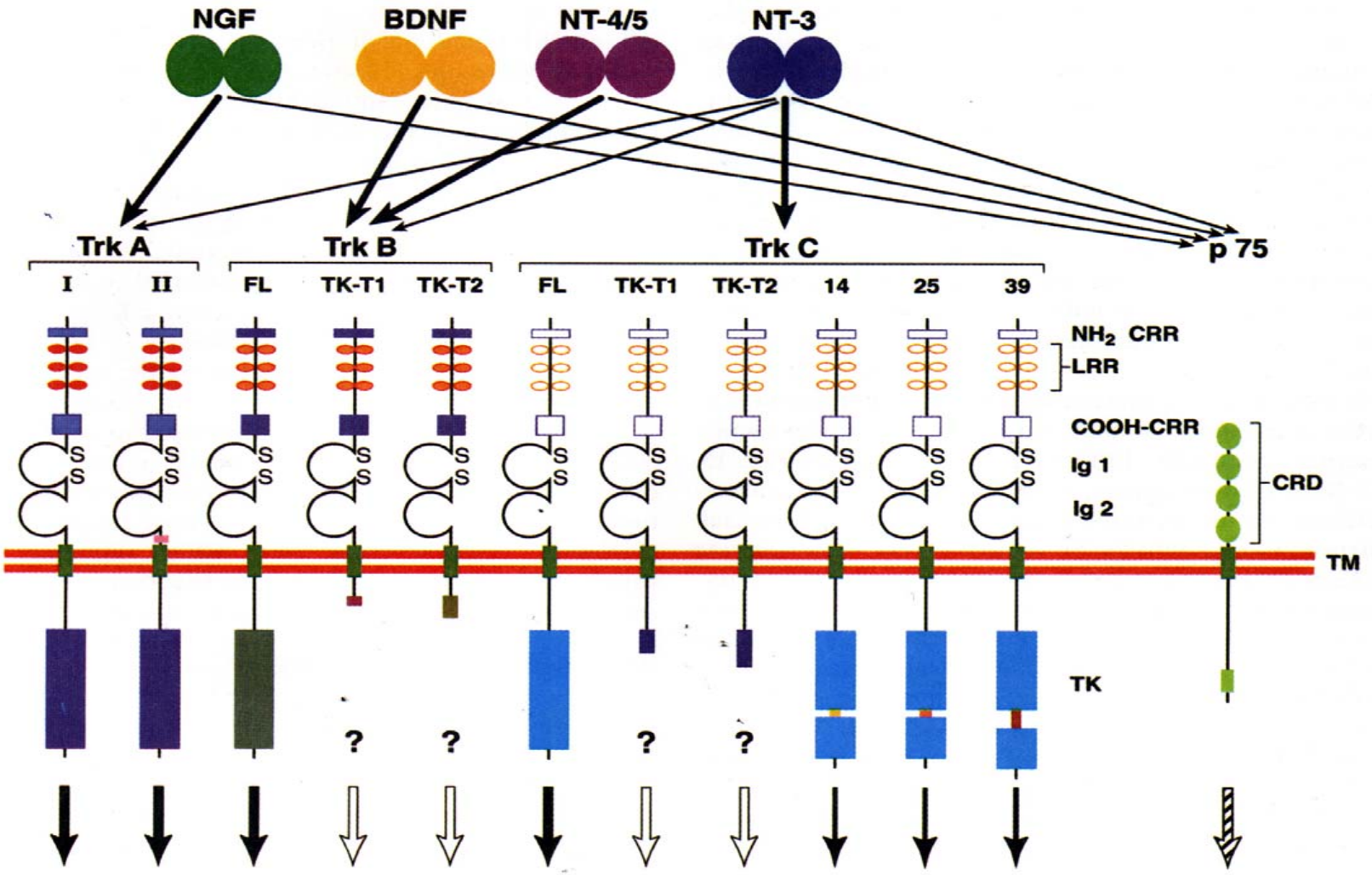
For further information see the WHL website at www.worldhypertensionleague.org



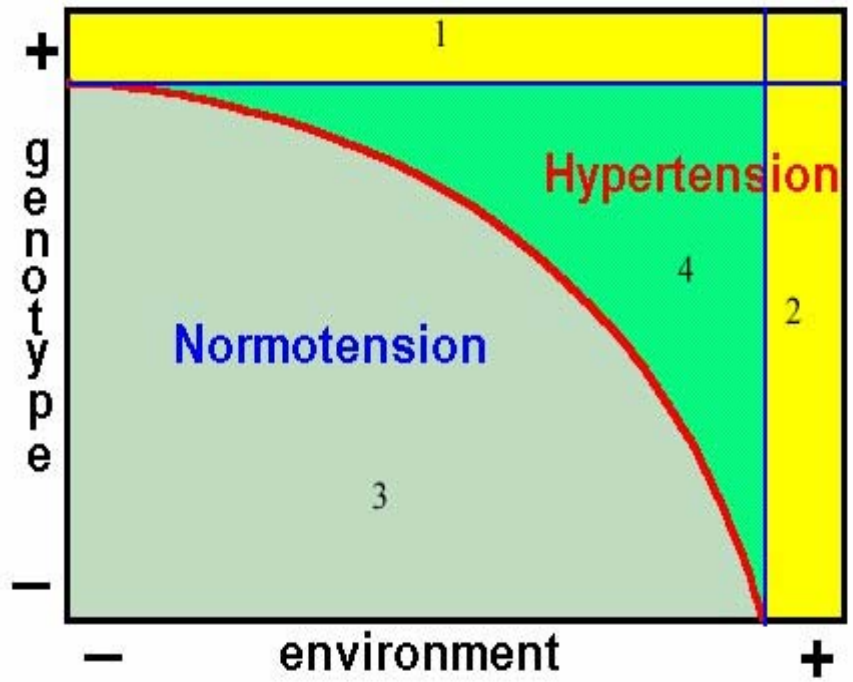
Tail-cuff blood pressure measurement


Благодарю за
внимание!

Nervous growth factor receptors family



GENOTYPE-ENVIRONMENT INTERACTION IN HYPERTENSION DEVELOPMENT



1 - Genotype-dependent hypertension

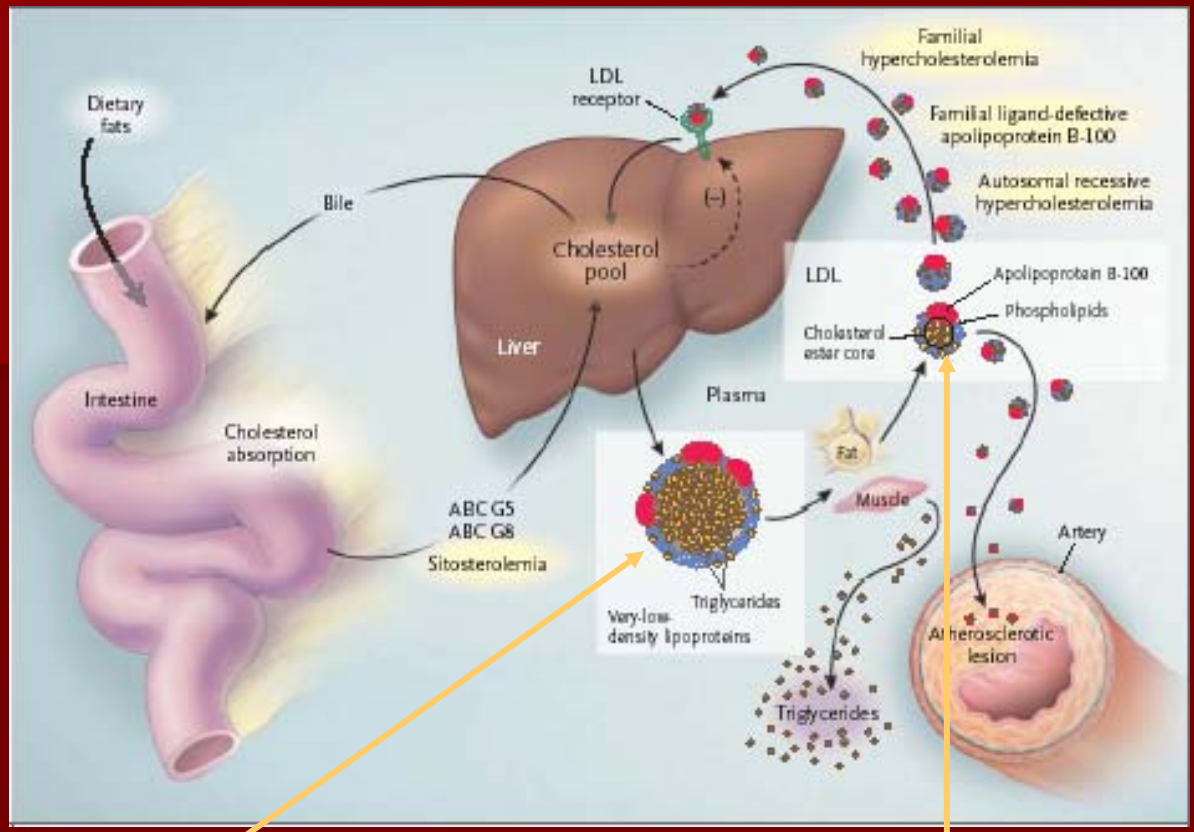
2 - Environment-dependent hypertension

3 - Normotension

4 - Hypertension dependent on genotype-environment interaction

+ -"Hypertensive" genes or environments

- - "Normotensive" genes or environments



Печень секретирует липопротеины очень низкой плотности, включающие эфиры холестерина и триглицериды в оболочке из фосфолипидов и аполипопротеина B-100

Липопротеин низкой плотности (LDL) – главный носитель холестерина в плазме крови и один из главных факторов сердечно-сосудистой патологии

НОСИТЕЛИ ХОЛЕСТЕРИНА

Мутации снижающие клиренс холестерина плазмы крови

Семейная гиперхолестеринемия: мутации (>600 вариантов) гена, кодирующего LDLR (гетерозиготы – 1:500, гомозиготы – 1:1 000 000)

Нарушения связывания LDLR с лигандом – APOB-100: нарушен клиренс холестерина плазмы крови вследствие мутаций гена *APOB-100* (гетерозиготы – 1:1000)

Ситостеролемия – нарушение транспорта и абсорбции холестерина в просвет кишечника: мутации генов *ABC G5* и *ABC G8* (встречаются редко) – накопление холестерина в печени и подавление синтеза LDLR

Гиперхолестеринемия: редкая аутосомальная мутация (1:10000000) гена *ARH* приводит к нарушению функции рецептора LDLR

Два пути создания генетических моделей

С последующим изучением эффектов на уровне фенотипа

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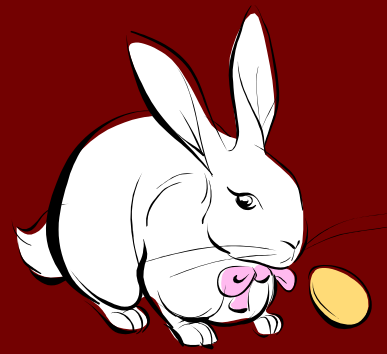
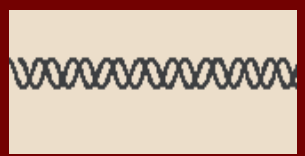


Изменение ДНК

Селекция ДНК

Селекция по фенотипу



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С последующим анализом генома