

DIALYSIS THERAPY IN THE 21ST CENTURY

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Transplantation Trends

▣ United States Transplant Data

Year	Transplants	Waiting List	Deaths while waiting
1998	12,318	53,315	2528
2007	16,119 (up 31%)	94,741 (up 78%)	4452 (up 76%)

- ▣ Kidney allograft failure is now the third most common cause of incident ESRD
- ▣ 5 year nonrenal organ transplantation leading to ESRD is running 7% to 21% depending on the organ

Transplantation trends in the 21st century, Samaniego M., Nephrology News and Issues, March 2008, pp. 57-58

Transplant – Good News

- ▣ Urine protein test predicts early failure
 - Offers opportunity to eliminate biopsies
 - Protein profiles identified for
 - ▣ Interstitial fibrosis and tubular atrophy
 - ▣ Chronic antibody-mediated rejection w/ kidney dysfunction
 - 100% of patients correctly identified from group of 50 which included healthy individuals and stable kidney transplants
- ▣ ImmuKnow Blood Test (Cylex, Inc)
 - Predicts potential early acute transplant rejection in patients in the first 90 days following transplantation
 - Measures vitality of the patients immune systems

New test can predict transplant rejection, Nephrology News and Issues, April 2008 , p. 26

Urine protein test detects kidney dysfunction in transplant patients, N N & I, Jan 2009, p. 26

Xenotransplantation

- ▣ Need based on lack of human donors
- ▣ Practical Challenges
 - Rejection
 - Correct functioning across species barriers
 - Minimize new infection agents into humans
 - Primates ruled out in countries allowing transplants
- ▣ Rejection
 - Hyper acute Rejection – Human antibodies and complement
 - Acute Vascular rejection
 - T cell response
 - Chronic Xenograft rejection

http://www.vatican.va/roman_curia/pontifical_academies/acdlife/documents/rc_pa_acdlife_doc_20010926_xenotrapianti_en.html

Diabetes Statistics

- ▣ NIH data: *Diabetes Care* – February, 2009
 - 13% Of all adults 20 years and older have diabetes
 - 40% of those have not been diagnosed
 - For those over 65 years of age nearly one third have diabetes and another 30% are pre-diabetes
 - Study base: Oral Glucose Tolerance Test (OGTT) which is better than a Fasting Blood Glucose Test (FBG) especially with older people

- ▣ 25 year projection: *Diabetes Care* – December, 2009
 - USA Population: 2009 = 23.7 million, 2034 = 44.1 million
 - Cost: 2009 - \$113 billion, 2034 - \$336 billion
 - Medicare population: 2009 – 6.5 million, 2034 – 14.1 million
 - Medicare costs: 2009 - \$45 billion, 2034 - \$171 billion

Diabetes – 21st Century drugs

- ▣ New Class: DPP-4 Inhibitors (Oral hypoglycemics)
- ▣ DPP-4 = Dipeptidyl peptidase – 4
- ▣ Decreasing DPP-4 prolongs the activity of incretins which regulate insulin secretion and blood glucose levels.

Drug	Generic Name	Company	Status
Januvia	sitagliptin	Merck	FDA approved 10/2006
Onglyza	saxagliptin	Bristol – Myers Squibb	FDA approved 6/2009
Galvus	vildagliptin	Novartis	EU approved 2008
----	alogliptin	Takeda Pharmaceutical	FDA suspended 6/2009
Ondero	linagliptin	Boehringer Ingelheim	Phase III clinical trials

Alzheimer's Disease – Type 3 diabetes?

- ❑ Alzheimer's patient's brains are resistant to insulin the same way as diabetes type 2 patients
- ❑ Toxic proteins ADDLs ("amyloid beta-derived diffusible ligands") attach to brain synapse's insulin receptors disabling communication resulting in memory loss.
- ❑ Damage to neurons by ADDLs is blocked by insulin
- ❑ Anti-diabetic drugs shield synapses against ADDLs
- ❑ Implication is that weight loss and exercise which reduces the chance of developing diabetes may also work for Alzheimer's Disease

Alzheimer's disease might become type 3 diabetes, Galvan A., NN&I, January 2008, p 24.
<http://www.northwestern.edu/newscenter/stories/2009/02/synapses.html>

Survival vs. Treatment Time

- ▣ Study: 451 patients
 - Patients started: Jan 1, 1996 – Dec 31, 2001
 - Study ended November 30, 2008
- ▣ Survival at 10 years ($p < 0.0001$)
 - Tx Time > 4.0 hours = 39.7 %
 - Tx Time (3.75 – 4.0 hours) = 18.9%
 - Tx Time < 3.75 hours = 15.4 %
- ▣ Time and Adequacy vs. Survival
 - $Kt/V > 1.6 + t > 4.0$ hours = 54.3%
 - $Kt/V > 1.6 + t < 4.0$ hours = 38.9%
($p < 0.04$)
 - $Kt/V < 1.6 + t > 4.0$ hours = 17.9%
 - $Kt/V < 1.6 + t < 4.0$ hours = 3.1%
($p < 0.0001$)

Long Term Patient Survival on Hemodialysis: Association with Time, Singh S, Ashby D, et. Al., Poster at ASN. West London Renal and Transplant Centre, London, United Kingdom

Home Hemodialysis

- ▣ Top 10 Providers (about 80% of US ESRD population)
 - 1,736 HHD patients (2008), 2,836 HHD patients (2009)
 - Increase in number = 63.3%
 - Still less than 1% of the total ESRD population
- ▣ Benefits due to daily HHD
 - Regression of Left Ventricular Hypertrophy
 - Reduced Hypertension
 - Improved fluid overload status
 - Improved anemia status/reduced drugs
 - Treatment tolerance and quality of life

Home HD equipment needs

- ▣ Most present machines were designed for in center use on multiple patients
- ▣ Home machines need to be smaller, more automated, and user friendly.
 - ▣ DaVita has an exclusive relationship with NxStage Medical and their SystemOne HHD machine
 - ▣ Fresenius has purchased Renal Solutions and their Allient sorbent HD machine
 - ▣ Baxter Healthcare has invested in an HHD machine being developed by DEKA who acquired the assets of Aksys Ltd and their PhD machine.

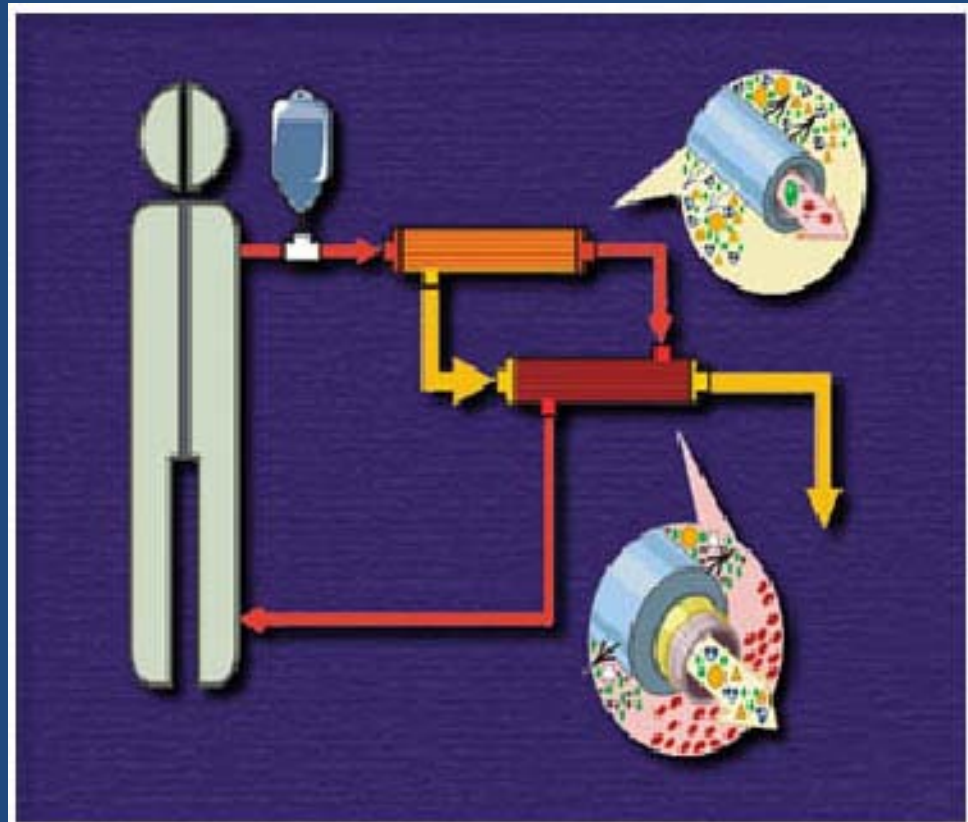
The Bioartificial Kidney

- ▣ David Humes MD – University of Michigan
- ▣ William Fissell MD – Cleveland Clinic

Stage 1 filter lined with blood vessel cells.

Stage 2 reabsorbing unit lined with tubule cells

Next stage
Add oxygen sensing cells to produce EPO



A Look at Potential ESRD Treatment Alternatives for the Future, NN&I, July 1997, pp. 14-15

Protein indicator for Kidney Failure

- ▣ Research at Columbia Univ. Medical Center
- ▣ Urine test used to detect small protein, NGAL (neutrophil gelatinase associated lipocalin)
- ▣ Test done for those with sudden kidney failure
- ▣ May detect kidney failure 1 -2 days sooner than standard creatinine test
- ▣ May also distinguish between acute and chronic failure
- ▣ Results for patients with positive NGAL tests:
 - 65% need care of a nephrologist
 - 32% would need dialysis
 - 29% would require care in the ICU

Stem Cell Research

- ▣ Northwestern Univ. Feinberg School of Medicine
 - Type 1 diabetics avoid insulin injections through infusion of their own stem cells
 - Done for early stage type 1 patients (within 1st 6 months of detection)
 - 20 of 23 cases were insulin free for at least a few months
 - 12 patients averaged 31 months without insulin need
 - Next step: Compare stem cell success to intensive insulin injection therapy.

Stem cells may help type 1 diabetics avoid insulin shots, NN&I, May 2009, p.22
<http://www.cnn.com/2009/HEALTH/04/15/stem.cells.diabetes/index.html>

Stem Cell Research

- ▣ Intermountain Medical Center and AlloCure
 - Modified stem cells used on patients with acute renal failure
 - Cells administered following surgery.
 - Injured organ sends chemical signals that attract cells
 - Cells work to boost kidney repair and are then flushed from the patient's system after about 72 hours
 - Kidney improvements include:
 - Decreased apoptosis (cell death)
 - Increased mitogenesis (cell generation)
 - Decreased expression of pro-inflammatory cytokines
 - Increased expression of anti-inflammatory cytokines
 - Clinical trial phase I ends in the spring of 2009 and phase II begins.

Bioimpedance Analysis

- ▣ Bioelectrical Impedance Analysis (BIA) or Bioimpedance Spectroscopy (BIS)
- ▣ Body ICF and ECF ratios to total body fluid and body electrical impedance are related to voltage frequency
- ▣ Used to measure electrical impedance of body tissues to provide estimate of total body water (TBW)
- ▣ Fat-free mass (FFM), Fat mass (FM) and Body mass index (BMI) can be determined from BIA results using various algorithms.
- ▣ Typical current frequency range is 5 - 1000 kHz
- ▣ More frequencies used – better results
 - XiTRON Hydra 4200 = 50 frequencies
 - ImpediMed SFB7 = 256 frequencies

Bioimpedance

▣ Advantages

- Identifies volume of fluid space (total body water), thus:

Quantifies actual state of hydration

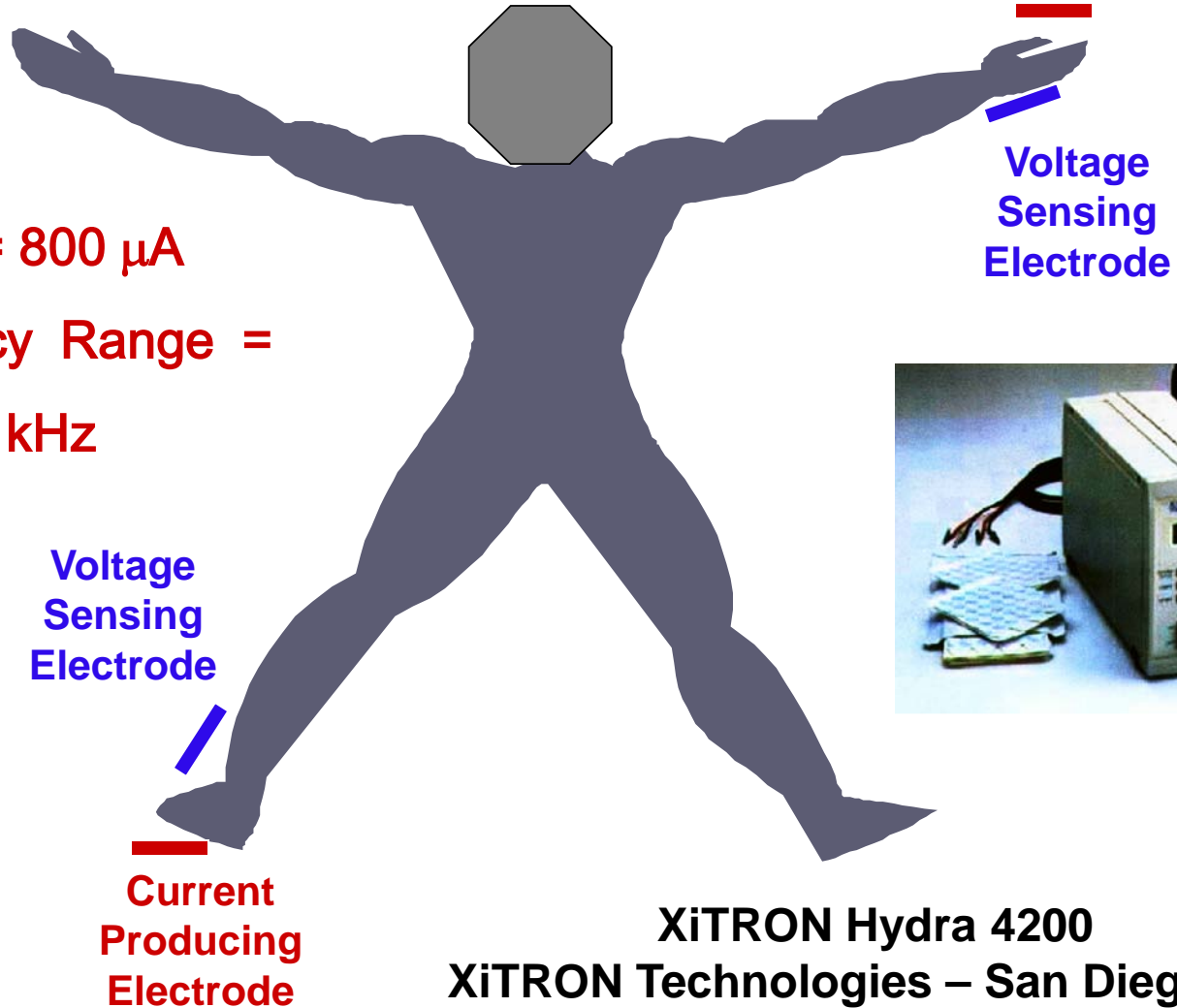
- Non-invasive test
- 3 minutes/test

▣ Disadvantages

- Cost
 - ▣ Machine
 - ▣ Electrode/sensor pads
- Dubious accuracy in dialysis patients
 - ▣ Unable to accurately measure trunk volume
 - ▣ Currently acceptable only for measuring acute Δ in ECW¹

1. Cox-Reijven P, et al: Role of bioimpedance spectroscopy in assessment of body water compartments in HD patients. *Am J Kidney Dis*, 2001, 38(4):832-838.

Current = 800 μ A
Frequency Range =
5 - 1000 kHz



Current
Producing
Electrode

Voltage
Sensing
Electrode

Voltage
Sensing
Electrode

Current
Producing
Electrode



XiTRON Hydra 4200
XiTRON Technologies – San Diego CA

Electronics Evolution

- Moore's Law (1975) –
 - Complexity of circuits doubles every 2 years
 - Today –
 - Transistor is 32 nanometers wide
 - Lithography limit is 22 nanometers
 - AMD Phenom X4 processor has 758 million transistors on a surface area of less than 0.5 square inch
 - Hewlett Packard –
 - Developing crossbar design of nanowires
 - Wire intersections create “memristors” = 10 to 15 transistors
 - The Challenge –
 - The more compact, the higher the operating temperature
 - Transistors breakdown at high temperatures
- “The next twenty years of Microchips”, Scientific American, January 2010, pp 82-89

Dealing with the Heat

- MacBook Air Notebook – Case acts as a heat sink made of thermally conductive Aluminum
- Apple Power Mac G5 – Uses microchannels on the underside of the processor to run liquid coolant.
- Intel – Builds a thin-film superlattice of bismuth telluride a thermoelectric material into the chip case. It converts a temperature gradient into electricity and acts as a refrigerant.
- Purdue University - makes a solid state fan using the Corona wind effect. Live wires generate a microplasma of ions that are driven to a plate. This is the same effect used in silent home air purifiers.

“The next twenty years of Microchips”, Scientific American, January 2010, pp 82-89

The Next Generation

- Optical Computing – connecting processors using light instead of wires – Hewlett-Packard, UC – Santa Barbara
- Molecular Computing - Molecules replace transistors. Referred to as “moelectronics”. – Yale and Rice Universities
- Biological Computing - replacing transistors with DNA and RNA molecules. – An area occupied by a billion transistors could hold a trillion DNA strands. - Weizmann Institute of Science – Israel
- Quantum Computing – Transistor made from individual atoms, electrons, or photons. Can have “on”, “off” and “quasi” states. $2^8 = 256$, $3^8 = 6561$ – Univ. of Maryland, National Institute of Standards and Technology

“The next twenty years of Microchips”, Scientific American, January 2010, pp 82-89

Need for Improvement

- ▣ Present Environment
 - Mortality exceeds 20% annually
 - Costs are running \$34 billion
 - Patient Rehabilitation is less than 20%
 - Hospital costs are greater than \$20K per patient per year
- ▣ Leading cause of death
 - Infection who's main source is catheters
 - Cardiovascular disease due to left ventricular hypertrophy (LVH)
- ▣ What to do
 - Longer treatments, more frequent treatments (DHHD, SNHD)
 - Better initial care for new patients
 - Get rid of catheters

Knowledge Growth (Linear vs. Exponential)

- ▣ 20th century – linear, 21st century – exponential
- ▣ Assume linear growth of knowledge increase at 5% of known information in 2000 for each year successive year
 - By 2010 the knowledge base would be 50% greater
 - By 2020 it would double
 - By 2100 it would have increased by 500%
- ▣ Assume exponential growth of knowledge at 5% of known information compounding each year
 - By 2010 the knowledge base would be 63% greater
 - By 2020 it would be 165%
 - By 2100 it would be 13,050% !!
- ▣ Put yourself in “Education Mode” if you want to keep up.

“Health care jobs defying recession”

St. Petersburg Times – January 11, 2010

Occupation	New Jobs by 2018	Median Wage (2008)	Education
Registered Nurse	581,500	\$62,450	Associate's degree
Home Health Aid	460,900	\$20,460	Short term - OJT
Personal and Home Care Aids	375,800	\$19,180	Short term - OJT
Medical Assistants	163,900	\$28,300	Moderate - OJT
Physician Assistant	29,200	\$81,230	Master's degree