Experimental Design

HEALTH

FROM TIME MAGAZINE, JUNE 8TH, 1992

Ultra Think Fast

Smart drugs and think drinks promise to brighten your personality, boost your brain and jump-start your sex drive, but truly smart consumers will be wary

By ANDREW PURVIS

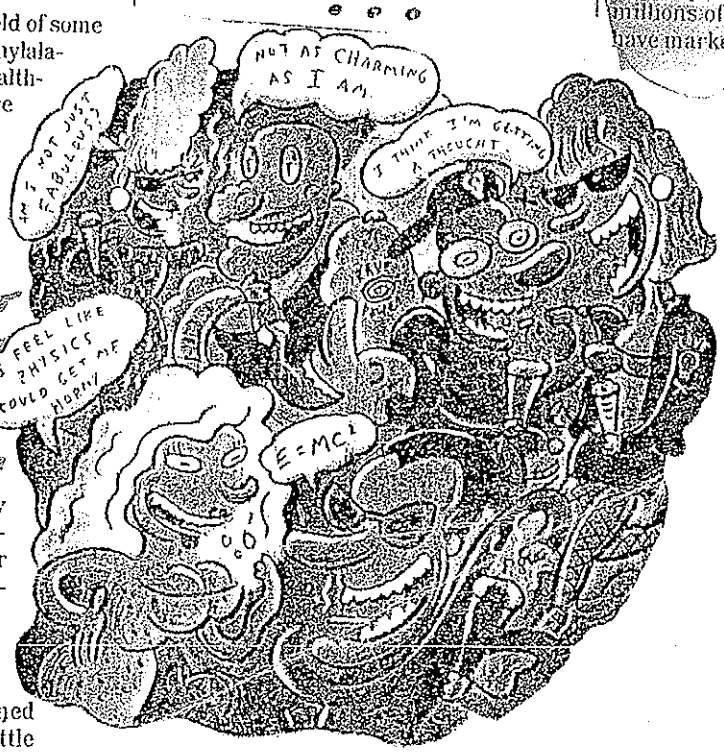
AS A SALESMAN OF HIGH-TECH COMmunications equipment, Bill Willoughby needs to be mentally sharp at all times. Unfortunately, his 15-hour shuttles to Europe or Asia often leave him feeling more like he left his brain in San Francisco. "In this business," he says, "no matter how tired you are, if you start talking and sound dumb, it's no deal."

A few months ago, he got hold of some mysterious pills called L-phenylalanine and melatonin, sold in health-food stores, that he claims have changed his life. "It's amazing. It's like tuning up your car, only it's your mind. You take the drugs, and you're firing on all eight cylinders again. Sometimes you're firing on nine."

Welcome to the wide-eyed world of "smart drugs." Over the past two years a growing number of IQ-hungry Americans—from high school students to octogenarians—have taken to chemical means of cognitive enhancement, downing a variety of food supplements and prescription drugs to prepare for tests, prime themselves for business meetings or just burn a little brighter at parties.

• • •

The smart-pill movement blossomed in 1990 with the publication of a little book called *Smart Drugs and Nutrients: How to Improve Your Memory and Increase Your Intelligence Using the Latest Discoveries in Neuroscience*, by gerontologist Ward Dean and science writer John Morgenthaler. It lists three dozen steroids for the brain, or, to the cognoscenti, "nootropics" (from the greek *noos*, for mind). The authors claim that these substances resuscitate memory, jump-start the intellect, fuel sex drive and even reverse the mental aging process.

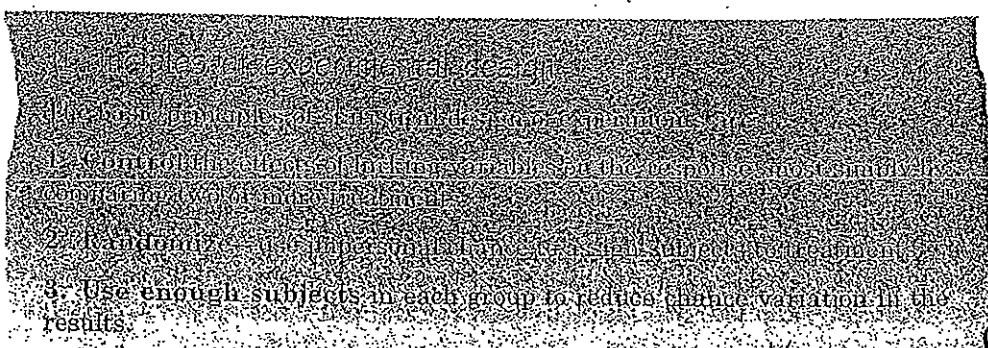


Salesmen of smartness have embraced an impressive vocabulary to explain how the drugs work: one amino acid, said a pumped-up advocate, "inhibits an enzyme that breaks down the endorphins and enkephalins localized in the brain." Another "causes an increase in a particular neurotransmitter involved in mental alertness. Your arousal index is much higher."

Despite such techno talk, none of these drugs has been proved effective in properly designed, double-blind trials. "I think they are silly," says the University of California's McGaugh, who dismisses the elaborate explanations of how the drugs work as "scientific mumbo jumbo." If such substances were indeed effective—and safe—he points out, drug companies, which stand to gain hundreds of millions of dollars from their sale, would have marketed them years ago.

It should not surprise you to learn that medical researchers adopted randomized comparative experiments only slowly—many doctors think they can tell "just by watching" whether a new therapy helps their patients. Not so. There are many examples of medical treatments that (like gastric freezing) became popular on the basis of one-track experiments and were shown to be worth no more than a placebo when some skeptic tried a randomized comparative experiment. One search of the medical literature looked for therapies studied both by proper comparative trials and by trials with "historical controls." A study with historical controls compares the results of a new treatment, not with a control group, but with how well similar patients had done in the past. Of the 56 therapies studied, 44 came out winners with historical controls. Only 10 passed the placebo test in proper randomized comparative experiments. Expert judgment is too optimistic even when aided by comparison with past patients. At present, the law requires that new drugs be shown to be both safe and effective by randomized comparative trials. There is no such requirement for other medical treatments, such as surgery. You can expect new drugs to beat a placebo. New surgical ideas, like gastric freezing in the past, may not.

There is one important caution about randomized experiments. Like random samples, they are subject to the laws of chance. Just as an SRS of voters might by bad luck choose nearly all Republicans, a random assignment of subjects might by bad luck put nearly all the smokers in one group. We know that if we choose *large* random samples, it is very likely that the sample will match the population well. In the same way, if we use *many* experimental subjects, it is very likely that random assignment will produce groups that match closely. More subjects means that there is less chance variation among the treatment groups and less chance variation in the outcomes of the experiment. "Use enough subjects" joins "compare two or more treatments" and "randomize" as a basic principle of statistical design of experiments.



Major principles of experimental design:
1. Control the effects of lurking variables on the response by comparing 2 or more appropriately (e.g. new drug vs. pl
2. Randomize using impersonal chance to assign subjects to "treatments".
3. Use enough subjects for each "..." to reduce chance variation in the average result

One common design that combines matching with randomization is the **matched pairs design.** A matched pairs design compares just two treatments. Choose pairs of subjects that are as closely matched as possible. Assign one of the treatments to each subject in a pair by tossing a coin or reading odd and even digits from Table A. Sometimes each "pair" in a matched pairs design consists of just one subject, who gets both treatments one after the other. Each subject serves as his or her own control. The *order* of the treatments can influence the subject's response, so we randomize the order for each subject, again by a coin toss.

Example 9. Coke versus Pepsi

Pepsi wanted to demonstrate that Coke drinkers prefer Pepsi when they taste both colas blind. The subjects, all people who said they were Coke drinkers, tasted both colas from glasses without brand markings and said which they liked better. This is a matched pairs design in which each subject compares the two colas. Because responses may depend on which cola is tasted first, the order of tasting should be chosen at random for each subject.

When more than half the Coke drinkers chose Pepsi, Coke claimed that the experiment was biased. The Pepsi glasses were marked *M* and Coke glasses were marked *Q*. Aha, said Coke, the results could just mean that people like the letter *M* better than the letter *Q*. The matched pairs design is OK, but a more careful experiment would avoid any distinction other than Coke vs. Pepsi.

Matched pairs designs use the principles of comparison of treatments and randomization. However, the randomization is not complete—we do not randomly assign all the subjects at once to the two treatments. Instead, we only randomize within each matched pair. This allows matching to reduce the effect of variation among the subjects. Matched pairs are an example of *block designs.*

Block design: A block is a group of subjects that are known to be very similar before treatment. Randomization is carried out separately within each block.

A block design combines the idea of creating equivalent treatment groups by matching with the principle of forming treatment groups at random. Blocks are another form of *control.* They control the effects of some outside variables by bringing those variables into the experiment to form the blocks. ~~Here are some typical examples of block designs.~~

Homework Problems for Chapter 1 (Experimental Design)

1. A study to see whether or not birds remember color was done by putting bird seed on a piece of cloth and letting the birds eat it. Later, empty pieces of cloth of varying colors (red, purple, white, and blue) were displayed. The birds headed for the red cloth. The researcher concluded that the birds remembered the color.
   a. Give an alternative explanation for the birds' behavior.
   b. Suppose there were 20 birds available and they could each be tested separately. Suggest a better method for the study than the one used.

2. An experiment that was publicized as showing that a mediation technique lowered the anxiety level of subjects was conducted as follows: The experimenter interviewed the subjects and assessed their levels of anxiety. The subjects then learned how to meditate and did so regularly for a month. The experimenter reinterviewed them at the end of the month and assessed whether their anxiety levels had decreased or not.
   a. This experiment is fatally flawed. Why? What extraneous variable(s) may be confounded with the effect of meditation?
   b. The experimenter who diagnosed the effect of the treatment knew that the subjects had been mediation. Explain how this knowledge could bias the experimental conclusions.
   c. Briefly discuss a proper experimental design, with controls and blind diagnoses, to assess the effect of mediation on anxiety level.

3. Taste test ask subjects to compare the taste of two food products such as Pepsi and Coke and say which they prefer. There is no separate control group; each subject serves as his or her own control by tasting both products.
   a. Randomization remains important in a taste test. How should randomization be used?
   b. How does the idea of blindness apply in a taste test?
   c. Now, briefly describe the design of a (matched-pairs) experiment to investigate if "consumers" prefer the taste of Pepsi or Coke.

4. There is good evidence that physical stress – even someone stroking the leaves of a plant for a minute a day – inhibits plant growth. Some claim (without good evidence) that speaking kindly to plants encourages growth. We are going to investigate the effects of physical contact, talking to plants, or both, on growth. Our experimental units are tomota seedlings that have just developed their first pairs of true leaves. Discuss the design of such an experiment. You must carefully describe the treatments and other aspects of the protocol as well as the statistical design.

most basic, cross-species flying maneuvers: turning.

$2.5 billion and Still No Cur

6/11/0

Government research on alternative medicine has found that most of the remedies do not work

THE ASSOCIATED PRESS

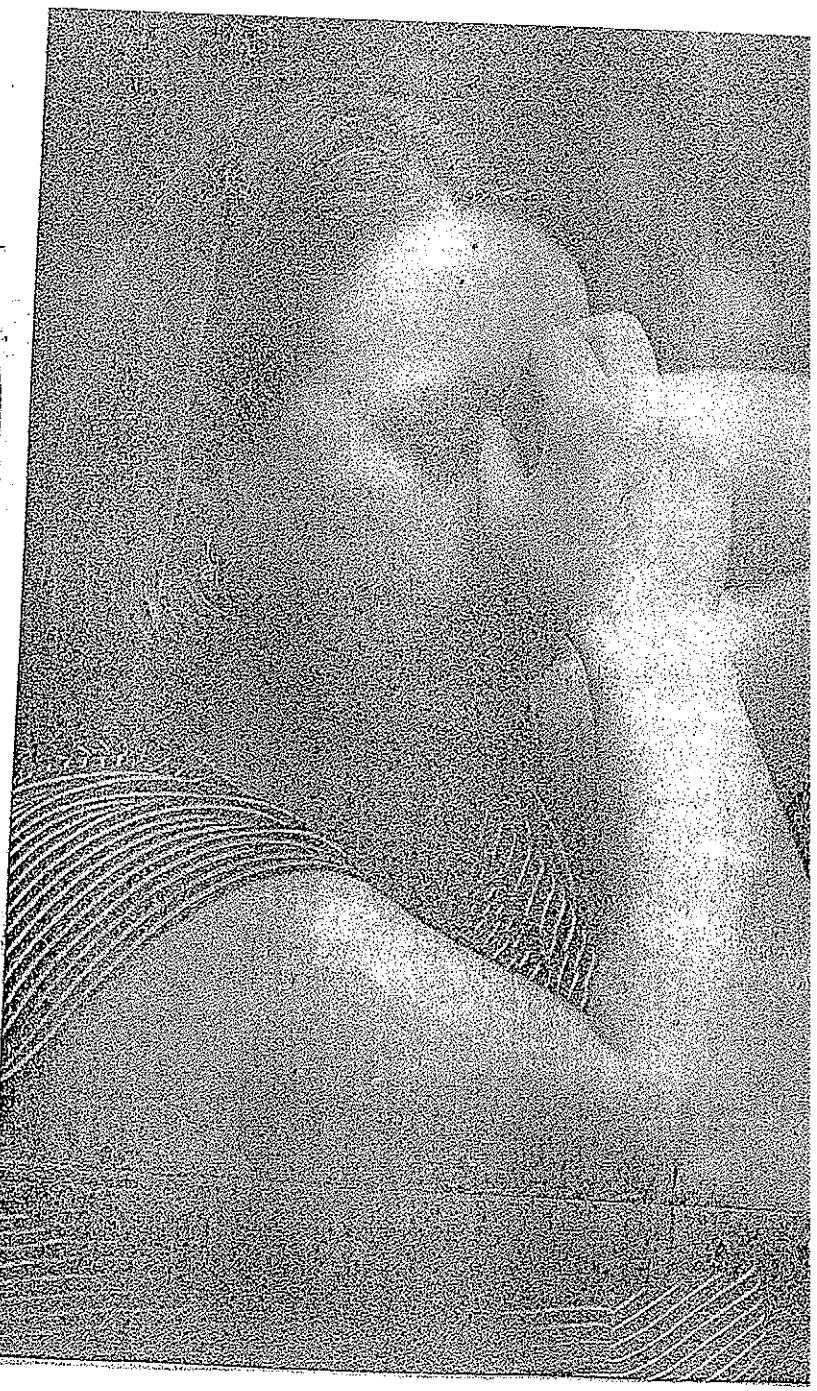
BETHESDA, Md. — Ten years ago the government set out to test herbal and other alternative health remedies to find the ones that work. After spending $2.5 billion, the disappointing answer seems to be that almost none of them do.

Echinacea for colds. Ginkgo biloba for memory. Glucosamine and chondroitin for arthritis. Black cohosh for menopausal hot flashes. Saw palmetto for prostate problems. Shark cartilage for cancer. All proved no better than dummy pills in big studies financed by the National Center for Complementary and Alternative Medicine. The lone exception: ginger capsules may help chemotherapy nausea.

As for therapies, acupuncture has been shown to help certain conditions, and yoga, massage, meditation and other relaxation methods may relieve symptoms like pain, anxiety and fatigue.

However, the government also is paying for studies of purported energy fields, distance healing and other approaches that have little if any biological plausibility or scientific evidence.

Taxpayers are bankrolling studies of whether pressing various spots on your head can help with weight loss, whether



February 19, 2009

Outsourcing of Drug Trials Is Faulted

By NATASHA SINGER

As many American companies in the last decade have sent tasks like customer service and computer support to other countries, drug makers have followed suit by outsourcing clinical trials — the human studies that determine the safety and efficacy of medicines.

Now, an article about the globalization of clinical trials, published Thursday in The New England Journal of Medicine raises questions about the ethics and the science of increasingly conducting studies outside the United States — when the studies are meant to gather evidence for new drugs to gain approval in this country.

The article, by several Duke University researchers, suggests an ethical quagmire when drugs intended for wealthy nations are tested on people in developing countries. The authors suggest that human volunteers in foreign countries may be unduly influenced with the promise of financial compensation or free medical care to participate in clinical trials.

The report, "Ethical and Scientific Implications of the Globalization of Clinical Research," also asks whether drug research conducted in developing countries is relevant to the treatment of American patients.

"We don't want to imagine that lower-income countries are the clinical trial mill for higher-income countries," Dr. Kevin A. Schulman, the lead author of the article, said in a phone interview last week. Dr. Schulman is a professor of medicine at the Fuqua School of Business at Duke, in Durham, N.C.

But some critics say the authors used overly simplistic data mining to raise an alarm, without presenting hard evidence of widespread ethical or scientific problems.

"More places outside the United States are participating in research — is that a bad thing?" said Dr. Ezekiel J. Emanuel, the chairman of bioethics at the Clinical Center of the National

PROCEDURE FOR DRUG APPROVAL

(1) Preliminary "library study" to determine promising drugs

(2) Computer simulation with compounds and cell culturing (when possible) to further examine potential.

(3) If still promising, then apply for begin of study on animals.

(4) Submit results of animal expts to FDA for approval to run study on humans

(5) If approved, run a small study (~) on healthy individuals - purpose to see if drug presents a large danger

(6) Then do ~~not~~ small studies on individuals - mainly looking for danger & potential for solving problem. (perhaps have Apply for to FDA to continue study) meta-analysis to combine studies

(7) If looks good & FDA approves, then do small, ~~on infected individuals~~ studies to help determine correct dosage (like Piedmont Res. Assoc. company) to ~~test the drug~~

(8) Then do ~~less~~ many studies to look at ~~dosage~~ potential for drugs

Experimental Design

Application: Does Aspirin Help Prevent Heart Attacks? The Physician's Health Study*

During the 1980s, approximately 22,000 physicians over the age of 40 agreed to participate in a long-term health study for which one important question was to determine whether or not aspiring helps to lower the rate of heart attacks (myocardial infarctions). The treatment for this part of the study was aspirin, and the control was a placebo. Physicians were randomly assigned to one treatment or the other as they entered the study so as to minimize bias caused by uncontrolled factors. The method of assignment was equivalent to tossing a coin and sending the physician to the aspirin arm of the study if a head appeared on the coin? After the assignment, neither the participating physicians nor the medical personnel who treated them knew who was taking aspirin and who was taking placebo. This is called a double-blind experiment. (Why is the double blinding important in a study such as this?) The method of measurement was to observe the physicians carefully for an extended period of time and record all heart attacks, as well as other problems, that might occur.

Other than aspirin, there are many variables that could have an effect on the rate of heart attacks for the two groups of physicians. For example, the amount of exercise they get and whether or not they smoke are two prime examples of variables that should be controlled in the study so that the true effect of aspirin can be measured. The tables below show how the subjects eventually divided according to exercise and to cigarette smoking. (See the complete tables at the end of this section for more details.) Do you think the randomization scheme did a good job in controlling these variables? Would you be concerned about the results for aspirin being unduly influenced by the fact that most of the aspirin takers were also nonsmokers? Would you be concerned about the placebo group possibly having too many who do not exercise?

*Source: "The final report on the aspirin component of the ongoing physicians' health study," *The New England Journal of Medicine*, 231(3) 1989, pp. 129–135.

	Aspirin	Placebo
Exercise Vigorously		
yes	7,910	7,861
no	2,997	3,060
Cigarette smoking		
never	5,431	5,488
past	4,373	4,301
current	1,213	1,225

The data analysis for this study reports that 139 heart attacks developed among the aspirin users and 239 heart attacks developed in the placebo group. This was said to be a significant result in favor of aspirin as a possible preventative for heart attacks. To see why this was so, work through the following steps.

1. Given that there were approximately 11,000 participants in each arm of the study, calculate the proportion of heart attacks among those taking aspirin. Calculate the proportion of heart attacks among those taking placebo.

2. Calculate the standard deviations for each of these proportions and use them to form confidence intervals for the true proportions of heart attacks to be expected among aspirin users and among nonaspirin users in the population from which these sampling units were selected.

3. Looking at the two confidence intervals, can you see why the researchers in this study declared that aspirin had a significant effect in reducing heart attacks? Explain.

However, heart attacks aren't the only cause for concern. Another is that too much aspirin can cause an increase in strokes. Among the aspirin users on the study, 119 had strokes during the observation period. Within the placebo group, only 98 had strokes. Although the number of strokes is higher than the researchers would have liked, the difference between the two numbers was no cause for alarm. That is, there did not appear to be a significant increase in the number of strokes for the aspirin group. Follow the three steps listed above for constructing and observing confidence intervals to see why the researchers were not overly concerned about the difference in numbers of strokes between the two arms of the study.

Much more data relating to this study are provided in the tables here. This should lead to other questions of interest regarding the relationships among aspirin use, heart

attacks, and other factors. (For example, does age play a role in the effectiveness of aspirin? How about cholesterol level?)

Table 1 CONFIRMED CARDIOVASCULAR END POINTS IN THE ASPIRIN COMPONENT OF THE PHYSICIANS' HEALTH STUDY, ACCORDING TO TREATMENT GROUP*

End Point	Aspirin Group	Placebo Group	Relative Risk	95% Confidence Interval	P Value
Myocardial infarction					
Fatal	10	26	0.34	0.15–0.75	0.007
Nonfatal	129	213	0.59	0.47–0.74	<0.00001
Total	139	239	0.56	0.45–0.70	<0.00001
Person-years of observation	54,560.0	54,355.7	—	—	—
Stroke					
Fatal	9	6	1.51	0.54–4.28	0.43
Nonfatal	110	92	1.20	0.91–1.59	0.20
Total	119	98	1.22	0.93–1.60	0.15

ARE YOU A DIABETIC WITH A SORE THAT WILL NOT HEAL?

We are conducting a study of an investigational medication used on the skin to promote wound healing. You may be eligible if:

- You have one or two non-healing ulcers on your feet or legs that have existed more than 8 weeks.
- You are at least 19 years of age.
- If you are a female of childbearing potential, you must be using either an IUD, oral contraceptives for birth control or be surgically sterile.

HIGH BLOOD PRESSURE

If you have high blood pressure you may be eligible to participate in a research study to evaluate the relationship between dietary sodium and currently marketed blood pressure medications. If you qualify you will receive:

Free physical exam and diagnostic testing, free dietary counseling, free study medication and up to $400 compensation for participation.

VAGINITIS STUDY

Currently seeking females age 18 or older to participate in a study to compare two medications for the treatment of vaginitis (yeast infection). If you are currently experiencing any of the following symptoms, please call for more information.

1. Vaginal Burning
2. Vaginal Itching
3. Vaginal Irritation

The medication, laboratory tests and physical examination by the doctor will be provided free of charge, providing you meet eligibility requirements.

BIRTH CONTROL PILL STUDY

Healthy, sexually active women, between the ages of 18-50, are needed to participate in a birth control pill research study for a 6 month period. Participants must be available for 5 clinic visits. If qualified, participants receive free experimental birth control pills, physical and gynecological exams and financial compensation up to **$100** for those who qualify.

PAST ULCER?

If you have had a stomach ulcer diagnosed by a doctor in the past, you may qualify for a research study. A Board-Certified gastroenterologist will oversee your participating in this 6 week study.

Laboratory testing and physical exams at no charge. Financial compensation provided to qualified participants.

PRA

Piedmont Research Associates

If you are interested in participating, call

768-8062

If after working hours, please leave a message.

WSJ 3/8/01

Stem-cell treatment for Parkinson's is no cure and of little help, study says

THE ASSOCIATED PRESS

An experimental treatment for Parkinson's in which holes are drilled in the skull and cells from aborted fetuses are implanted in the brain does not cure the disease, according to a controversial new study.

The study had raised ethical questions because some participants, for the sake of comparison, underwent sham surgery in which mere indentations were drilled in their heads.

The implanted stem cells — cells that can develop into many types of tissue — survived and grew into the right kind of brain cells. But they did not help patients older than 60.

Younger patients — who make up about 40 percent of the 60,000 people found to have Parkinson's each year in the United States — improved a bit, but only for a year.

After that, the cells apparently did their job too well in some patients, causing excess movements because they produced more of the needed nerve transmitter dopamine than the body could use.

"There was tremendous hope that stem-cell therapy could be a cure. This study really points out the problems we have to solve before that can happen," said Dr. J. William Langston, a neurologist and the founder of the Parkinson's Institute in Sunnyvale, Calif.

The study was conducted by doctors at Columbia University and the University of Colorado and is published in today's *New England Journal of Medicine*.

Dr. Curt R. Freed, who led the study as the director of the University Of Colorado Neurotransplantation Center for Parkinson's Disease, has begun work to see if he gets better results by dripping the cells into other parts of the brain. Langston said that the results indicate that stem-cell research for Parkinson's should go back to the animal laboratory.

Parkinson's disease, whose sufferers include former Attorney General Janet Reno and actor Michael J. Fox, is a progressive brain disease marked by tremors, stiffness, slowness and loss of balance.

FDA approves two new drugs for glaucoma

Treatment with Travatan seems to work particularly well for blacks, study finds

THE ASSOCIATED PRESS

WASHINGTON — Glaucoma patients are about to get two new medicines to help fend off blindness — including one that seems to work particularly well for black patients, who are at special risk.

Travatan and Lumigan work by draining fluid buildup that is the hallmark of glaucoma.

The Food and Drug Administration approved them yesterday, saying that both work equally well and thus offer an alternative to standard therapies.

But Travatan comes with an added attraction: A study found that it worked best in black glaucoma sufferers, making it the first treatment to target a group especially hard-hit by the disease.

Glaucoma is the nation's second-leading cause of blindness, afflicting about 3 million Americans and blinding about 80,000 of them a year.

Black Americans are four times more likely than whites to suffer glaucoma, it typically strikes them at younger ages, and they go blind faster. Glaucoma patients suffer a painless but dangerous buildup of pressure within the eyeball that eventually damages the delicate optic nerve until they begin losing sight.

The most common form usually occurs after age 40.

Treatment, including medication and surgery, can stall the disease's progression but any vision loss is permanent.

Standard first-line therapy is timolol, an eyedrop that makes the eye produce less fluid, thus reducing pressure.

But it has numerous side effects and people with heart or respiratory problems cannot use it.

A second therapy, the drug latanoprost or Xalatan, is based on the natural chemical prostaglandin, which helps the eye drain off fluid.

The two new drugs work the same way, the first competitors for Xalatan.

All three prostaglandin-based eyedrops effectively drop patients' eye pressure, said FDA ophthalmology chief Dr. Wiley Chambers.

They also have similar side effects, including sometimes turning blue or green eyes brown.

Nobody knows whether that's just a cosmetic side effect, or if the changing color signals additional eye damage, he cautioned. But eye-color difference may play yet another role: Some drugs bind to eye pigment differently than others, Chambers said, and doctors have long known that timolol works better in light-colored eyes than dark ones.

Travatan's maker studied 600 patients who took either Travatan, Xalatan or timolol, including about 50 black patients in each drug group.

After a year of treatment, 65 percent of blacks had significantly lower eye pressure vs. 51 percent of non-blacks, said manufacturer Alcon Universal Ltd.

There was no racial difference for Xalatan, which helped between 44 and 47 percent of patients, Alcon said.

Timolol helped 30 percent of blacks and 37 percent of non-blacks.

Neither Lumigan nor Xalatan have been adequately studied for racial differences, Chambers said.

Meanwhile, the FDA is letting Alcon advertise Travatan's benefit to black patients.

Both prescription-only drugs should be in pharmacies within a few weeks. Travatan, known chemically as travoprost, will cost about $38 wholesale for a month's supply, said Alcon, based in Fort Worth, Texas.

Allergan Inc., of Irvine, Calif., declined to disclose the price for its Lumigan, known chemically as bimatoprost.

MTH 109 Test 1
Chapters 1-6
Spring 1996

1. What would you additionally like to know about Emini's HIV studies (shown below) before you weighed their merits.

WS Journal 1/30/96 WS Journal 1/30/96

Drugs able to thwart HIV

New treatment, used with standard drugs, is getting promising results

LOS ANGELES TIMES

WASHINGTON

In some of the strongest evidence thus far that a new generation of AIDS drugs can inhibit the human immunodeficiency virus, scientists reported yesterday that HIV became virtually undetectable in most patients six months after starting treatment with one of the new drugs in combination with two standard ones.

"For the first time, we may be close to achieving almost total suppression of the AIDS virus in most patients," said Dr. Emilio Emini, the executive director of the antiviral research division of Merck & Co., which makes indinavir — also known as Crixivan — one of the drugs of a new generation.

Speaking at the Third Conference on Retroviruses and Opportunistic Infections here, Emini said that the virus could not be found in the blood of 85 percent of the patients who took the triple combination, which also included the drugs AZT and 3TC.

EXPERTS BELIEVE that AIDS cannot be cured, so the longtime approach has been to slow or eliminate disease progression through drug therapy, thus prolonging survival — ultimately, it is hoped, to a normal lifespan.

The new findings bolster those hopes that powerful drug combinations can delay the virus' reproduction. As long as the virus has the ability to replicate, it can produce mutant strains, making drug resistance inevitable and rendering drug thera-

See HIV DRUGS, Page A4

The New York Times
nytimes.com

Controlled

July 25, 2006

Research Finds Little Proof on Menopause Treatments

By NICHOLAS BAKALAR

Almost half of American women seek alternative or complementary treatments for the unpleasant symptoms of menopause. But a systematic review of the evidence has found little proof that any of them work.

Researchers reviewed 70 randomized controlled trials of alternative treatments and found insufficient scientific evidence to support the effectiveness of any of the commonly used remedies: herbs, mind-body techniques, energy therapies using magnets or electrical nerve stimulation, homeopathy, naturopathy or culturally based non-Western medical treatments. The review was published yesterday in The Archives of Internal Medicine.

Most of the studies were of poor quality, but even those judged by the researchers to be "fair" or "good" on a three-point scale most often demonstrated little difference between alternative treatments and placebo. For example, a study that compared 56 patients given a soy drink with 55 who drank a medically inactive liquid found no difference between the groups, although both groups got some symptom relief.

Three of four trials of the herb black cohosh, a common alternative treatment for menopausal symptoms, showed no improvement, but the studies suffered from poor methodology. The fourth, judged "fair" by the researchers, enrolled 304 women, half of whom took black cohosh and the other half a placebo for 12 weeks. Compared with placebo, there was greater improvement in the treatment group as measured by the participants' own reports. Dr. Anne Nedrow, the lead author of the review, said the study "did show some benefits, but we had to balance it with studies that showed none."

The scientists examined nine studies of mind-body therapies, treatments that focus on the ways in which emotional, mental, social, spiritual and behavioral factors can affect health. While they varied considerably in quality, none found a significant improvement compared with placebo treatment using stress-management techniques, meditation, relaxation exercises, audiotape relaxation or supportive counseling.

Therapies involving reflexology, bone manipulation and magnetic devices were found to be almost completely useless. In one small study of magnets, the placebo group showed more improvement than the group that received the magnet treatment.

Acupuncture was also ineffective. The reviewers examined four trials; three demonstrated no difference between real and sham procedures. The fourth, judged by the reviewers to be of fair quality, compared standard estrogen therapy, sham acupuncture and electroacupuncture, a variation on the practice in which continuous electrical pulses are delivered through the needles. Only the estrogen group improved.

None of six trials of traditional Chinese medicinal herbs, three using a combination of medicines, showed a significant benefit over controls for menopausal symptoms.

The New York Times
nytimes.com

September 5, 2006

Research Shows That Plants Like a Path to Biodiversity

By CORNELIA DEAN

For years, ecologists have theorized that establishing landscape corridors to connect otherwise isolated plant and animal habitats would encourage biological diversity. Now researchers working in South Carolina have demonstrated it, at least with plants.

The researchers, who report their findings in the current issue of the journal Science, surveyed dozens of test plots in forested areas of the Savannah River Site, a 310-square-mile swath of southeastern South Carolina originally set aside to produce nuclear weapons for the military. (The plots are now managed by the federal Forest Service for pine production.)

The researchers surveyed their sites regularly starting in 2000 and found that, over time, there was more plant diversity in patches connected by corridors than in other patches, even if they had the same total area or the same amount of "edge" space between cleared and wooded areas.

Patches connected by landscape corridors "had 20 percent more species of plants than unconnected patches," said Ellen Damschen, the lead author of the report and a postdoctoral fellow at the University of California, Santa Barbara.

The finding is important, ecologists say, because the fragmentation of wild land by human activities is one of the most important threats to biodiversity. More and more, landscape managers are incorporating corridors into their plans, but there is relatively little data on effectiveness.

"People have done corridor experiments with fruit flies in bottles, but that's hardly the sort of thing that is going to be very compelling to a wildlife manager," said Stuart L. Pimm, a professor of conservation ecology at Duke University, who is familiar with the new study.

"Were the results surprising? No," he said. "But it's the kind of example that's going to go into a textbook because this shows that corridors work instead of us just thinking that they work."

Wildlife corridors have been established in areas like the Rocky Mountains, but researchers there are still studying whether the ones linking protected areas from the Yukon to Yellowstone actually improve wildlife diversity.

"It is surprising that we would see such a dramatic change over a short time scale," Dr. Damschen said. But the research, also carried out by scientists from several other universities, shows that "plants can change relatively quickly through their interactions with the landscape and the animals that interact with them," like birds and rodents that disperse seeds or insects that act as pollinators.

In part because the corridor-connected patches have more varieties of birds, insects and animals like mice, she said, "the number of seeds that reach a patch that's connected by a corridor is higher."

Ethics Time 6/7/94

ETHICS

Madness in the Print

Using mentally ill subjects for psychiatric experiments too often means extracting and relying on their ill-informed consent

By JAMES WILLWERTH LOS ANGELES

HARRY CUMMINGS REMEMBERS hearing voices and seeing images the very day he was discharged from the Army: "Voices told me all kinds of stuff about the government. It scared me." Cummings, 38, had done two Army tours, including time in South Korea, and had worked his way up to sergeant. After his discharge, he began wandering, hitchhiking from Seattle to Miami, living on the streets, getting by on odd jobs, before stumbling into Los Angeles in the summer of 1982. "A black guy gave me a ride from the California border and dropped me downtown. He gave me a few bucks and encouraged me to get help. I had only the clothes on my back, and I slept outside that night." The next day he talked to a cop and eventually was driven to the Veterans Affairs treatment center in West Los Angeles.

At the center, he told the doctor about the voices, the images. "I was mixed up, dirty, wired up and spacy," Cummings relates. "He said he wanted me to sign this paper for experimental research. He told me I didn't have an obligation to be in it. He said I could quit if I wanted, but he wouldn't advise that. He said the drugs they would be giving were completely harmless. He said the hospital would kick me out on the streets if I didn't participate. That was the word he used: kick."

Cummings signed, was formally diagnosed as paranoid schizophrenic, and says he spent the next five years in an experiment with a powerful antipsychotic drug. He suffered bad side effects: partial blindness, impotence, constant migraines. He says the researchers at the VA never allowed him to see an eye doctor and wouldn't let him change drugs. Only in 1987, after complaining for years, did Cummings finally manage to get out of the experiment and see other doctors. "My vision came back but not as good as I expected," he says. The VA last week said a "cursory glance" did not turn up Cummings' records.

Most of the country's 2.3 million VA patients are poor or mentally ill. And over the decades, many have signed up for experiments after doctors suggested that it was the only way they could receive meaningful help. Now, however, those methods of obtaining recruits for psychiatric experiments are undergoing a radical change, one that may transform the way schizophrenia is studied in years to come. This summer the National Institutes of Health rebuked the University of California, Los Angeles for serious "deficiencies" in setting up schizophrenia experiments that UCLA runs at the Veterans Affairs Medical Center in West Los Angeles. A UCLA experiment reported in TIME last year—in which one patient suffered a severe psychotic breakdown and another committed suicide—was formally sanctioned and is now said to be undergoing an ethics review by the American Psychological Association.

Other psychiatric studies around the country are coming under increasing scrutiny, raising fresh examples in the ongoing

The New York Times
nytimes.com

August 23, 2006

EDITORIAL

Safe Drug Testing in Prisons

Prisoners' rights advocates are understandably worried about an advisory panel's recommendation that the government overhaul the rules for testing drugs on prison inmates. The advocates fear a return to the medieval situation of just 30 years ago, when inmates were often subjected to dangerous and unethical experimental procedures. Some were infamously exposed to radioactive, carcinogenic and hallucinogenic chemicals at the Holmesburg prison in Philadelphia.

This shameful history makes it imperative that any change in testing policies be accompanied by oversight regulations far stronger than those now in existence. That said, a new report from the Institute of Medicine offers a possible outline for moving toward a system of testing that could benefit both the population as a whole and prison inmates, who tend to be among the sickest, most disease-prone people in society.

The report calls for greatly expanding the protections given to subjects of medical research who are imprisoned or under other forms of correctional supervision. It also calls on the government to strengthen federal oversight of these kinds of studies and to rewrite a set a vague regulations that don't actually protect the rights of medical research subjects within the corrections system.

The new arrangement would minimize inmate risk by limiting drug trials to the final, therapeutic stage, after researchers have already determined that drugs look safe and potentially effective. Instead of loading up studies with captive subjects, as was commonly done in the past, prison inmates would not be permitted to make up more than half of the subjects of a test.

No research can ever be seen as legitimate without informed consent of the participating subjects. Critics of the new report argue that there can be no such thing as informed consent in the coercive environment of a prison. While acknowledging the seriousness of the problem, the report's authors believe that it can be overcome — at least in some institutions and in some settings — by having careful independent boards oversee the process. If voluntary informed consent is not obtainable, the report said, the research should not be allowed to proceed.

The dismal state of medical care in many prisons also raises the possibility that inmates would rush to sign up for drug trials simply to get treatment for chronic problems. The report's authors appear to have argued vigorously among themselves about whether drug testing should be permitted at institutions where health care is particularly poor. The answer should be no, in all but the rarest cases. Making sure inmates have decent medical care should be the first order of business.

The country should move slowly on this issue. The savage and dishonorable legacy of drug testing in prison makes it imperative that any change be carried out carefully, with maximum transparency and concern for inmate safety. That will require far more federal oversight than current law provides.

RESEARCH ETHICS

JOURNAL PHOTOS BY ALLEN AYCOCK

Bowman Gray keeps 1,500 monkeys, mostly for research on hardening of the arteries, at its farm in Davidson County.

Bowman Gray Staff Defends Animal Use

By Rachel Stiffler
JOURNAL REPORTER

Monkeys eat high-fat, high-cholesterol diets so that they will develop fatty deposits in the arteries of their hearts. Rats give themselves cocaine. Researchers do heart surgery on dogs.

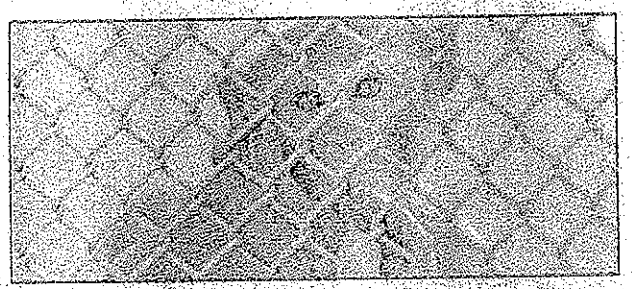
Animal-rights activists say that these experiments, conducted at Bowman Gray School of Medicine, are cruel to animals. Doctors describe them as necessary to find new medical treatments for humans.

FIRST OF TWO PARTS

The controversy is one reason that Bowman Gray is hold- research. The last lecture in the series, on the ethics of using animals in research and teaching, will be Wednesday at Bowman Gray.
will be held Wednesday at Bowman Gray.

Bowman Gray said it purposely invited speakers perceived as holding the "middle ground" — those who believe that animal research is ethical if researchers treat the animals humanely.

But to Maria Sommer, who opposes all animal research, the speakers do not represent the middle ground. Mrs. Sommer, who has a doctorate in

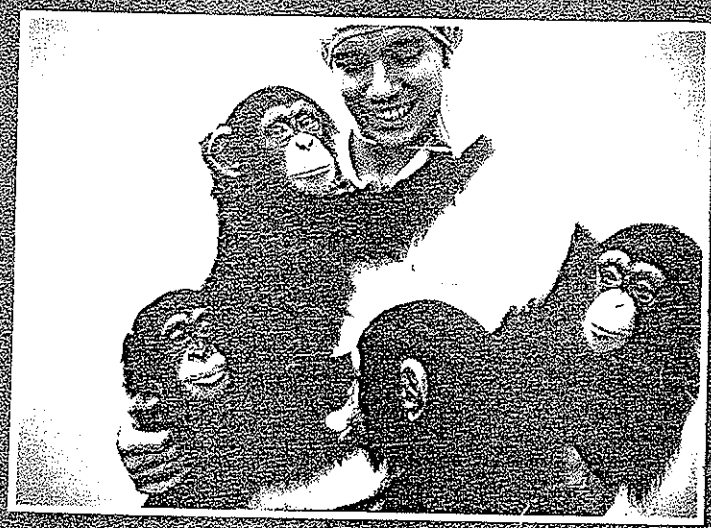


Bowman Gray's Animal Studies

These are some of the animals and the areas in which they help researchers at the Bowman Gray School of Medicine.

- **Monkeys/** Atherosclerosis, heart disease
- **Pigs/** Wound healing
- **Sheep/** The use of pain medicine in obstetrics, hormones, fetal heart
- **Ferrets/** Vision
- **Dogs/** Simulated heart attacks, coronary bypass surgery, cerebral blood flow and hemorrhaging, laser surgery, lung injuries
- **Pigeons/** Atherosclerosis
- **Rabbits/** Immunology, infectious diseases
- **Cats/** Human mental retardation, the brainstem, hydrocephalus, the esophagus

Animals in Medical Science



Commonly Asked Questions and Answers

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service

National Institute of Mental Health

Exptl Design

Groups debate ethics of paying for human eggs in re

Scientists use the eggs in creation of stem cells

THE ASSOCIATED PRESS

NEW YORK

Say you're a woman who wants to have fertility treatment but can't afford the $5,000 to $6,000 cost.

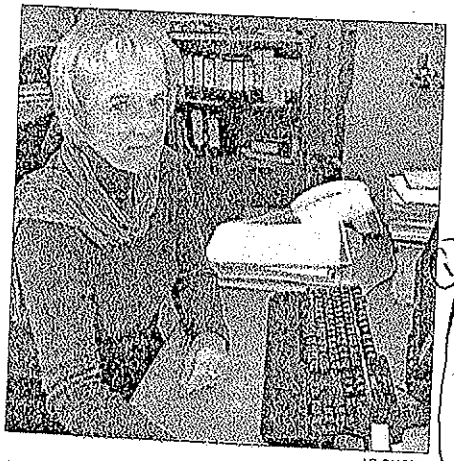
What if you could get it for half-price, by agreeing to donate half the eggs you produce for stem-cell research?

Interested?

British women may get a crack at that deal in a few months, under a plan pursued by Dr. Alison Murdoch of Newcastle University.

This concept, which resembles a strategy sometimes used to get eggs for fertility treatments, is just one of several new efforts to increase the supply of human eggs needed for research. The shortage has triggered an ethical debate on both sides of the Atlantic: Should women be paid for supplying eggs?

Scientists need eggs for a process called therapeutic cloning, which creates stem cells genetically matched to an individual. It may be used someday to create tissue to treat such illnesses as diabetes and Parkinson's disease, providing transplant material that's genetically matched to the patient so that it won't be rejected. Therapeutic cloning may also help scientists develop better drug treatments.



AP PHOTO

Alison Murdoch, an English researcher, has a plan to increase the supply of eggs.

The process involves transferring DNA into human eggs and growing them into 5-day-old embryos, from which stem cells are harvested.

It's not clear just how many eggs scientists need for this research. But it is clear that, for a woman, donating eggs is a significant undertaking. By various estimates, a woman can spend 40 to 56 hours in medical offices, being interviewed, counseled and subjected to a surgical procedure, under sedation, that retrieves eggs from her body. Before that procedure, she takes hormone injections daily for more than a week to stimulate egg development.

Women donate thousands of eggs in the United States every year to help other women have babies. They are paid. The American Society of Reproductive Medicine doesn't recommend a figure but says that $5,000 or more requires some justification and that $10,000 is too much. (In fact, some ads for eggs offer far more).

The medical group also says that it's fine to pay women for producing eggs for stem-cell research. But other guidelines and laws on that topic favor just reimbursing women for expenses. That's the word from the law books of California and Massachusetts and a committee of the National Research Council, a congressionally chartered nonprofit organization that advises the federal government.

In fact, the compensation question has split American feminists and advocates for reproductive health and rights, said Marcy Darnovsky, the associate executive director of the Center for Genetics and Society.

One side says that offering money beyond reimbursement risks exploiting disadvantaged women by offering undue inducement to participate, while the other side calls that stance paternalistic, she said.

Darnovsky said that her center has no position on paying women to provide eggs for fertility clinics but holds that if women give eggs for stem-cell research, they should be reimbursed only for expenses, including lost wages.

Why the difference? It's a matter of a woman's gauging the risks and benefits of donating her eggs, Darnovsky said.

On the risk side, there's been too little follow-up of women to know for sure how safe the egg-retrieval process is, she said.

On the benefit side, while donating eggs to a fertility clinic often produces a baby, the potential payoff in stem-cell research is promising but only speculative at the moment, Darnovsky said. But women, like society, have so bought into the expectation of "miracle cures" from stem cells that they overestimate the benefit from donating eggs, she said.

The result? If stem-cell researchers offer the kind of money that fertility clinics do, "I th
trying to pay th
the table, and p
lot of money to
tempted to disc
value the benefi

Similarly, eth
Northwestern U
paying compen
some women. W
fertility clinics
money, she said,
don't ... want th
used for the need

"You do not se
or CEOs selling
house-cleaners,"

Zoloth, who
strongly support
that would use t
lieves that wome
such research sh
only for expenses
donating organs,
tic act, she said.

But others b
should be paid.

Participants in
medical research
their time, inconve
participating, says
director of the Gen
icy Center at Johns

The New York Times nytimes.com

Dept Design

June 7, 2007

Biologists Make Skin Cells Work Like Stem Cells

By NICHOLAS WADE

In a surprising advance that could sidestep the ethical debates surrounding stem cell biology, researchers have come much closer to a major goal of regenerative medicine, the conversion of a patient's cells into specialized tissues that might replace those lost to disease.

The advance is an easy-to-use technique for reprogramming a skin cell of a mouse back to the embryonic state. Embryonic cells can be induced in the laboratory to develop into many of the body's major tissues.

If the technique can be adapted to human cells, researchers could use a patient's skin cells to generate new heart, liver or kidney cells that might be transplantable and would not be rejected by the patient's immune system. But scientists say they cannot predict when they can overcome the considerable problems in adapting the method to human cells.

Previously, the only way to convert adult cells to embryonic form has been by nuclear transfer, the insertion of an adult cell's nucleus into an egg whose own nucleus has been removed. The egg somehow reprograms the nucleus back to an embryonic state. That procedure is known as therapeutic cloning when applied to people, but no one has yet succeeded in doing it.

The new technique, developed by Shinya Yamanaka of Kyoto University, depends on inserting just four genes into a skin cell. These accomplish the same reprogramming task as the egg does, or at least one that seems very similar.

The technique, if adaptable to human cells, is much easier to apply than nuclear transfer, would not involve the expensive and controversial use of human eggs, and should avoid all or almost all of the ethical criticism directed at the use of embryonic stem cells.

"From the point of view of moving biomedicine and regenerative medicine faster, this is about as big a deal as you could imagine," said Irving Weissman, a leading stem cell biologist at Stanford University, who was not involved in the new research.

David Scadden, a stem cell biologist at the Harvard Medical School, said the finding that cells could be reprogrammed with simple biochemical techniques "is truly extraordinary and frankly something most assumed would take a decade to work out."

The technique seems likely to be welcomed by many who have opposed human embryonic stem cell research. It "raises no serious moral

Exact Design

kers

ooney and
l family
confer-
e in Venice,
, yesterday
noting
r new
n broth-
film, *Burn*
r Reading,
ied to the
n of Pitt's
is with
tner **Ange-**
Jolie, and
ever settle
on a look
"I am so
question.
st time I
Clooney
has grown
birth of
ed to share
ey. The
l yesterday
is a
hap-

Cell transformation called a 'spectacular first'

Study of mice sidesteps stem-cell debate; it may lead way to human cures

THE WASHINGTON POST

WASHINGTON

Scientists have transformed one type of fully developed adult cell directly into another inside a living animal, a startling advance that could lead to cures for a plethora of illnesses and sidestep the political and ethical problems that have plagued embryonic stem-cell research.

Through a series of painstaking experiments involving mice, the Harvard biologists pinpointed three crucial molecular switches that, when flipped, completely convert a common cell in the pancreas into the more precious insulin-producing ones that diabetics need to survive.

The feat, published online yesterday by the journal *Nature*, raises the prospect that patients suffering from not only diabetes but also heart disease, strokes and many other ailments could eventually have some of their cells reprogrammed to cure their afflictions without the need for drugs, transplants or other therapies.

"It's kind of an extreme makeover of a cell," said Douglas Melton, a co-director of the Harvard Stem Cell Institute, who led the research. "The goal is to create cells that are missing or defective in people. It's very exciting." The findings left other researchers reaching for new superlatives to describe the implications.

"I'm stunned," said Robert Lanza, the chief scientific officer of Advanced Cell Technology in Worcester, Mass., a developer of stem-cell therapies. "It introduces a whole new paradigm for treating disease."

"I think it's hugely significant," said George Daley, a stem-cell researcher at Children's Hospital in Boston. "This is a very spectacular first."

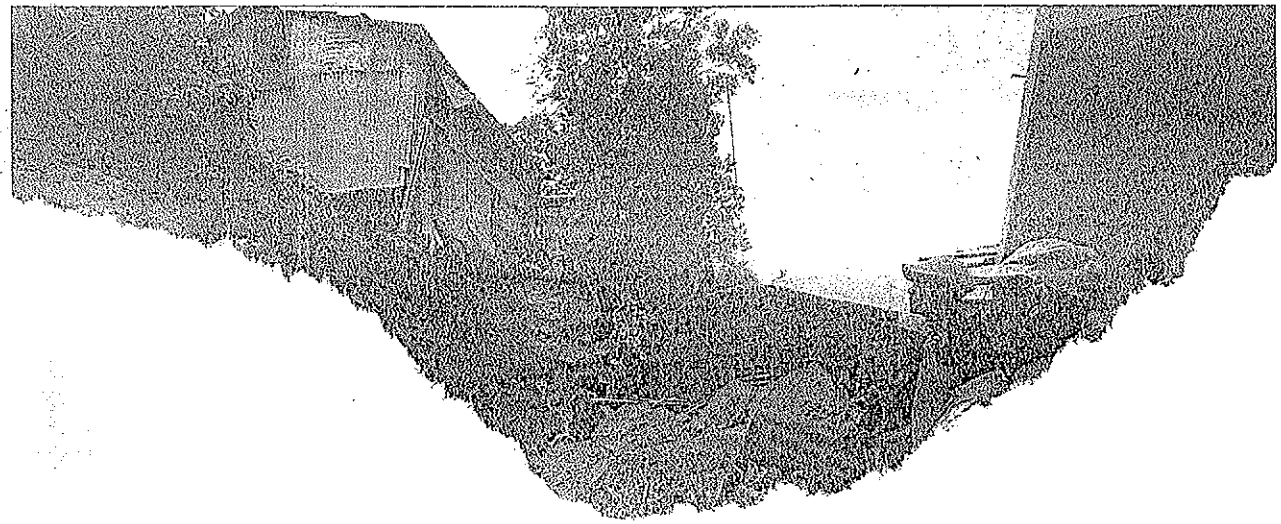
Even the strongest critics of embryonic stem-cell research hailed the development as a major, welcome development. "I see no moral problem in this basic technique," said Richard Doerflinger of the U.S. Conference of Catholic Bishops.

Melton and other researchers cautioned that years of research lie ahead to prove whether the development would translate into cures.

"It's an important proof of concept," said Lawrence Goldstein, a stem-cell researcher at the University of California, San Diego. "But these things always look easier on the blackboard than when you have do them in actual patients."

Researchers were optimistic that the approach would work in people. "You never know for sure — mice aren't humans," Daley said. "But the biology of pancreatic development is very closely related in mice and humans."

WATCHING GUSTAV: U.S. GULF COAST IS LIKELY TARGET



Arctic ice data adds

FDA stops the sale of two popular diet dr

Redux, Pondimin may result in damage to heart valves

THE ASSOCIATED PRESS

WASHINGTON — Two of the nation's most popular diet drugs were pulled off the market yesterday after the government uncovered disturbing new evidence that they could seriously damage patients' hearts.

The Food and Drug Administration urged millions of dieters to immediately stop taking Redux, also known as dexfenfluramine, and Pondimin, also known as fenfluramine.

Pondimin is one-half of the wildly popular fen-phen diet combination; the other half, phentermine, appears safe when used by itself, the FDA said.

But doctors said that phentermine, the sole remaining prescription diet drug, has only mixed results.

"We are anticipating lots of very desperate patients that need help," said Dr. John Foreyt, an obesity expert at Baylor College of Medicine.

"Obesity does kill," said Dr. Richard Atkinson of the American Obesity Association, who said that many Redux and Pondimin users will regain their weight.

The FDA asked Wyeth-Ayerst Laboratories, which sells Redux here and whose parent com-

See DIET DRUGS, Page A6

Dyan Eccker, a patient of Dr. Richard in Nashville, Tenn., has been takin

August 2001

Recall of Baycol stirs fears about other drugs

THE ASSOCIATED PRESS

BOSTON

When the cholesterol-lowering drug Baycol was pulled off the market three weeks ago, Joan Gedies' doctor prescribed another similar medication. But Gedies hasn't filled her prescription.

Like many other patients, Gedies is nervous about taking any of the popular medications in the family of drugs called statins, even though they have been shown to dramatically lower cholesterol and reduce the risk of heart attack.

Doctors say they have been swamped with calls from patients since Bayer Pharmaceutical recalled Baycol, which has been linked to deadly muscle destruction.

"I've had patients call me who I haven't seen in three years who have been on a statin. A lot of these people wonder whether they should continue taking the drug in view of this red flag," said Dr. Richard Nesto, the chairman of cardiovascular medicine at the Lahey Clinic in Burlington.

Bayer recalled the drug Aug. 8 after it was linked to 31 U.S. deaths and at least nine more abroad. About 700,000 Americans were taking the drug.

Baycol was tied to rhabdomyolysis, a life-threatening condition in which muscle cells are destroyed and released into the bloodstream. The condition, which can cause extreme muscle pain, is occasionally so severe that patients develop potentially fatal kidney failure.

Doctors across the country have been busy reassuring their patients that the other popular statins — Lipitor, Zocor, Meva-

WS Journal
Wed Sept 17 '97
New FDA
Chpt 1

THE NATION

Group urges independent center to monitor the safety of drugs

Diet pills revealed dangers that may be repeated, doctors say

THE ASSOCIATED PRESS

WASHINGTON

The diet-drug fiasco has consumer groups and doctors issuing their own warning: It could happen again.

The Food and Drug Administration is under intense pressure to approve new drugs faster — even now that Congress is trying to further speed the process. Yet the country has no foolproof way to catch such surprise side effects as the heart damage that forced two diet drugs off the market this week after millions of Americans had taken them.

"This is a tragedy and a disaster," said Dr. Raymond Woosley of Georgetown University. And he warned: "As we get drugs approved more rapidly, it will happen more often."

Woosley joined a group of drug-safety experts who urged the government yesterday to establish an independent Center for Drug Surveillance to monitor the nation's 3,200 prescription drugs for unexpected safety problems, much as the National Transportation Safety Board investigates plane crashes.

For $100 million — or a half-cent for every prescription written — such a center could provide a better early warning system, Woosley said.

The FDA acknowledges that its own drug monitoring needs improvement. Today, the FDA relies mostly on doctors voluntarily reporting side effects to an agency program called MedWatch, and then on the FDA's handful of MedWatch employees spotting a dangerous trend.

"I've been real unhappy about our internal system," said Dr. Janet Woodcock, the FDA's director of drug evaluation who told The Associated Press that the MedWatch program will be updated and computerized this fall to better detect potential problems.

Today, the MedWatch office has four employees and a $140,000 budget.

Stopping sales of already approved drugs is fairly rare. Counting the diet drugs Redux and Pondimin, withdrawn Monday, only 13 drugs have been pulled off the market since 1980.

The discovery that the diet drugs could seriously damage patients' heart valves came somewhat by chance.

A North Dakota laboratory technician spotted the first two possible cases three years ago when she questioned two women whose heart tests showed very unusual valve damage. Both took Pondimin together with another diet drug. Her curiosity prompted a Mayo Clinic study of the possible side effect. But Woodcock said that the FDA didn't learn about the potential problem until April, three months before Mayo finished its study and issued the first public warnings.

The diet drugs were unusual. Pondimin has been sold since 1973 but wasn't used widely until the early 1990s, when it was combined with another drug as the popular "fen-phen" combination. The FDA never approved the drug mix, but doctors can prescribe medicines as they see fit.

The FDA agonized over approving Pondimin's chemical cousin, Redux. It can increase the risk of a rare but potentially fatal condition called pulmonary hypertension, and high doses in animals killed brain cells, something never studied in people.

The New York Times
nytimes.com

Dept Design

June 6, 2007

Diabetes Drug Still Has Heart Risks, Doctors Warn

By STEPHANIE SAUL and GARDINER HARRIS

A medical study intended to demonstrate the heart safety of a well-known diabetes treatment seems, instead, to have added to the controversy over the drug.

Its manufacturer, GlaxoSmithKline, says preliminary results of the clinical trial provide reassurance that the drug, Avandia, an oral medication for Type 2 diabetes that has been used by an estimated seven million people worldwide, does not raise the risk of a heart attack or death from cardiovascular disease.

Influential doctors said that the data published online yesterday in a major medical journal did nothing to ease their concerns about the heart risks. The doctors raised their concerns in three editorials accompanying the Avandia study in The New England Journal of Medicine.

Questions about the safety of Avandia and how regulators have dealt with its risks are to be the subject of a Congressional hearing today. The data could intensify criticism, expected at the hearing, that the Food and Drug Administration should have warned about the potential heart risks years ago.

A supervisor in the drug safety office at the agency said in an interview yesterday that she was rebuked last year after calling for a stronger warning label on Avandia and a competing drug, Actos.

The supervisor, Dr. Rosemary Johann-Liang, said that in March 2006 she approved a recommendation from a safety reviewer at the agency that the drugs be required to carry the strongest warning, a so-called black box warning, because they posed a risk of unusual swelling that could lead to heart failure.

But after officials at the agency who dealt more closely with Glaxo complained, Dr. Johann-Liang said she was ordered to retract her approval of the warning, lost her power to approve such assessments and no longer supervised reviews of the safety of Avandia and Actos.

"This was a very careful review that came to an inescapable conclusion," Dr. Johann-Liang said in the interview. "They decided to act like the review never happened and punish me for approving it."

The New York Times
nytimes.com

July 31, 2006

A Small Charity Takes Lead in Fighting a Disease

By STEPHANIE STROM

PATNA, India — The drug that could have cured Munia Devi through a series of cheap injections was identified decades ago but then died in the research pipeline because there was no profit in it.

So Mrs. Devi lay limp in a hospital bed here recently, her spleen and liver bulging from under her rib cage as a bilious yellow liquid dripped into her thin arm. The treatment she was receiving can be toxic, and it costs $500. But it was her best hope to cure black fever, a disease known locally as kala azar, which kills an estimated half-million people worldwide each year, almost all of them poor like Mrs. Devi.

Soon, however, all that may change. A small charity based in San Francisco has conducted the medical trials needed to prove that the drug is safe and effective. Now it is on the verge of getting final approval from the Indian government. A course of treatment with the drug is expected to cost just $10, and experts say it could virtually eliminate the disease.

If approval is granted as expected this fall, it will be the first time a charity has succeeded in ushering a drug to market.

This novel way of helping people whose needs have not been met by for-profit pharmaceutical companies is gaining traction. Several partnerships are working to develop drugs to fight neglected diseases, underwritten by the Bill and Melinda Gates Foundation, Doctors Without Borders and other groups. Another nonprofit agency, the Aeras Global TB Vaccine Foundation, is searching for a means to prevent tuberculosis.

For its first project, the San Francisco charity, the Institute for OneWorld Health, focused on reclaiming the all but abandoned drug, paromomycin, which research found promising in the 1960's.

That was the easy part. Its hurdles lay elsewhere. The Internal Revenue Service at first denied the charity nonprofit status, concerned that it looked too much like a for-profit enterprise. The World Health Organization, which controlled the drug, was reluctant to hand over the data needed for further development. And OneWorld Health had to set up clinical trials matching United States and European standards in one of the poorest parts of the world.

Nor was it obvious where the money would come from. The idea of a nonprofit drug company struck many as folly when Dr. Victoria Hale, a former Genentech executive and Food and Drug Administration official, founded OneWorld Health in 2001. So Dr. Hale and her husband started the project using their own money, though they have since won support from the Gates foundation, among others.

"My colleagues and mentors in the pharmaceuticals industry told me it was a wild idea, that it would never work out, that I was jeopardizing my reputation," Dr. Hale said. "I started this

The New York Times
nytimes.com

July 6, 2006

New AIDS Pill to Treat People in Poor Countries

By DONALD G. McNEIL Jr.

The Food and Drug Administration has approved the first 3-in-1 antiretroviral pill for use by the American-sponsored plan for AIDS treatment, something that the White House's acting global AIDS coordinator said yesterday should greatly improve treatment for AIDS patients in poor countries.

Although it is not yet clear how much money it will save, having patients take only one pill twice a day "should facilitate better therapies and better adherence," said the coordinator, Dr. Mark R. Dybul.

The agency posted the approval of the drug on its Web site on Friday evening. It approved the 3-in-1 pill, made by an Indian generic drug company, for patients in countries helped by the President's Emergency Plan for AIDS Relief.

Under that plan, the United States is now the largest provider of antiretroviral drugs in the world, paying for treatment for 561,000 patients in Africa, Asia and the Caribbean.

The Global Fund for AIDS, Malaria and Tuberculosis, the second-largest provider, pays for about 541,000 patients, Dr. Dybul said, although there is some overlap in countries where both agencies work. (The United States also pays one-third of the Global Fund's budget.)

The new pill, made by Aurobindo Pharma of Hyderabad, India, combines three common first-line drugs, AZT, 3TC and NVP, which are also known as zidovudine, lamivudine and nevirapine and sold in the United States as Retrovir, Epivir and Viramune.

Dr. Dybul said he was also pleased that the new pill did not contain D4T, also known as stavudine and Zerit, which is another common first-line drug, but somewhat more toxic than the others.

In poor countries, where it is harder to do frequent blood and liver tests, toxicity can be harder to control.

The plan Dr. Dybul runs, known as Pepfar, was created after President Bush's announcement in his 2003 State of the Union address that he would spend $15 billion over five years to fight AIDS.

At the time, many Bush administration critics feared the money would be reserved for expensive American and European brand-name drugs. But, defying those expectations, the program in May 2004 began buying generics and now pays for 24 generic formulations, including liquid solutions for infants. Also, the major Western companies dropped their prices for poor countries, sometimes as low as the prices of generics.

However, rather than subscribing to the World Health Organization's drug-approval process,

The New York Times
nytimes.com

June 19, 2007

BEHAVIOR

On the Horizon, Personalized Depression Drugs

By RICHARD A. FRIEDMAN, M.D.

Imagine that you are depressed and see a psychiatrist who explains that you have clinical depression and would benefit from an antidepressant. So far, so good. But then the doctor tells you there is a 60 percent chance that you'll feel better with this antidepressant and that it could take as long as four to six weeks to find out, during which time you'll probably have some side effects from the drug.

I have just described the state-of-the-art pharmacologic treatment of major depression in 2007. Don't get me wrong; we have very effective and safe treatments for a broad array of psychiatric disorders. But in everyday clinical practice, we have little ability to predict which specific treatment will work best for you.

Laura is a case in point. A successful management consultant in her late 30s, she sought help for lifelong depression. Her treatment began with four weeks of the antidepressant Lexapro, a selective serotonin reuptake inhibitor, or S.S.R.I., without any effect. Next, I switched her to Zoloft, another S.S.R.I., since the chance of response to another member of the same drug family is about 60 percent. Again, no response. Then we moved on to Wellbutrin, an entirely different type of antidepressant, but this didn't work either. Laura was now ready to call it quits, and who could blame her?

After nearly three months, I had still not found an effective treatment for her. Then she came in one day and said her father had recently revealed that he had been depressed and had done well on Prozac, another S.S.R.I., and she wondered if she could try it. Within three weeks, she felt markedly better, and the symptoms of her depression began to melt away.

Instead of the hit-or-miss approach I had to use with Laura, it will soon be possible for a psychiatrist to biologically personalize treatments. With a simple blood test, the doctor will be able to characterize a patient's unique genetic profile, determining what biological type of depression the patient has and which antidepressant is likely to work best.

Scientists have identified genetic variations that affect specific neurotransmitter functions, which could explain why some patients respond to some drugs but not to others. For example, some depressed patients who have abnormally low levels of serotonin respond to S.S.R.I.'s, which

Expl Des

May 21, 2011

Drugs Stop AIDS. Take Your Medicine.

By DONALD G. McNEIL Jr.

THERE is now, for the first time, hard clinical evidence of an effect that AIDS doctors have suspected for years: If you are H.I.V.-positive, being on antiretroviral drugs will probably save not only your life, but also the lives of your sexual partners.

This month, a randomized clinical trial — the gold standard in medical research — showed that the drugs lowered the chances of infecting a partner by 96 percent.

This is good news for the infected and their lovers. But it is a moral dilemma for doctors whose infected patients do not want to start taking drugs immediately, usually because they do not yet feel sick and have heard exaggerated rumors about side effects.

What does a responsible doctor do with a patient who is sexually active and teeming with a fatal and incurable virus? Advise him to use condoms and trust him to act decently? Beg?

Behind each doctor — whose primary duty is to one patient — there is a government public health bureaucracy, whose duty is to protect the whole country. The epidemic has been killing Americans for 30 years now.

Whose rights should be paramount? Those of the patient? Or those of his healthy spouse — or boyfriend, or date, or hookup, or client, or rape victim, or incest target?

This debate has been going on since AIDS began, and has always been inextricably mixed with the circumstances of its birth: it was a sexually transmitted disease that emerged among gay men in the middle of the sexual revolution and the new gay rights movement. AIDS still carries a huge stigma and provokes hatred wildly out of proportion with the fact that it is simply a new virus. (Neither SARS nor H1N1 were called "God's wrath.")

But the fact that there is a new form of prophylaxis reopens old questions.

Several AIDS clinicians interviewed for this article said the idea of forcing treatment onto a patient was repulsive to them.

"It was unthinkable when we had this debate in the early 1980s, and it's unthinkable in

2011," said Dr. Myron S. Cohen of the University of North Carolina, who led the study that found the 96 percent protection rate. During a long discussion, he called the idea "medieval" and "a violation of civil rights."

Recalcitrant patients "ultimately do come around," argued Dr. Wafaa El-Sadr, who has treated AIDS patients in Harlem and Africa for decades. "You talk to them, you talk to them, you talk to them. Forcing them would make them run away."

Ronald Bayer, who teaches ethics at Columbia University's Mailman School of Public Health, agreed, even as he reflected that he is "rarely in the position where I'm the one urging restraint — they used to call me 'Dr. Coercion' because I'm often on the side of public health trumping individual rights."

Hypothetically, he said, if there were a single pill that could render a patient noninfectious for a year, forced treatment might be imaginable.

But there is not, and the practical barriers to forcing someone onto daily pills for life are enormous. Dr. Bayer compared it to Jeremy Bentham's notion of a Panopticon — a late 18th century jail where every prisoner knows he can be watched at all times.

Furthermore, several doctors said, it would be unethical to expend effort on forcing a tiny minority of selfish and self-destructive patients into treatment when so many others lack it, when 8,000 Americans are on waiting lists for the drugs, and millions of others, mostly in Africa, have little hope of getting them.

And yet in many legal circumstances, people can be forced into treatment to protect others. In New York's outbreak of drug-resistant tuberculosis in the 1990s, uncooperative patients were locked into Bellevue Hospital. Mental patients can be involuntarily medicated if a judge or medical panel rules them dangerous; "Kendra's Law" permitting just that in New York State was named for a young woman killed by one.

Women with hepatitis B can be forced to immunize their babies within 12 hours of birth. Children must have shots before they enter school not just for their own sake but also to protect their classmates who are allergic to vaccines or have compromised immune systems.

And most of the quarantine laws written a century ago, when cholera, typhus and plague were around, are still on the books. "Typhoid Mary" was not imprisoned for 25 years for treatment. She was never sick, didn't believe in germs although she carried them, and attacked a public health official with a fork when he demanded a stool sample. She was imprisoned because she kept taking jobs as a cook, sometimes under false names, infecting 51 people.

Dr. Thomas R. Frieden has been on both sides of the dilemma. As head of the Centers for Disease Control and Prevention, he is a leader in the national response to AIDS. As health commissioner of New York City during the tuberculosis outbreak, he had to imprison some patients.

"I see a bright line between tuberculosis, which can be passed standing next to someone in an elevator, and H.I.V., which usually requires consensual sexual activity," he said in an interview.

But, it was argued to him, even consensual sex isn't truly consensual when someone is lied to, or drunk, or in a dozen other situations that would negate the ideal of "informed consent" if, say, a contract were being signed.

"I know," he said, describing interviews he had done with infected men early in the epidemic. "The stories were heartbreaking — young men, moving to New York to finally come out as gay, and they'd say, 'I know who did it. I just can't believe they'd have lied to me about something like this.' "

Nonetheless, he said, he still would never force a patient into treatment.

"It's a small subset of people who pass on the virus by lying," he said, "and people have a right to refuse treatment."

Dr. Howard Markel, a medical historian at the University of Michigan, said that, even after 30 years, there is still a sense of what he called "AIDS exceptionalism" — the belief that this illness is like no other, despite historical precedents. (The obvious one is syphilis, which until antibiotics became widespread in the 1940s was the exemplar of a slow-progressing fatal disease. To stop it, mandatory testing was adopted; many states would not issue a marriage license without a negative result. AIDS tests are not only not mandatory, but also it is often legally difficult to add them to routine blood work.)

"Is it time for AIDS exceptionalism to become a historical relic?" Dr. Markel asked. "That's an interesting question. It may be time for it to just blend in with the others. But that might not happen until some other attention-getting disease comes along."