Published in final edited form as:
Neurotoxicology. 2009 September ; 30(5): 832–850. doi:10.1016/j.neuro.2009.01.008.

The first 83 and the next 83: perspectives on neurotoxicology

Bernard Weiss
Department of Environmental Medicine, Environmental Health Sciences Center, and Center for Reproductive Epidemiology, University of Rochester School of Medicine and Dentistry, Rochester, NY, USA

INTRODUCTION

From my perch (Figure 1), viewing the past and speculating about the future, the 20th century witnessed some of the most degrading and horrifying characteristics of our species. It suffered through two world wars and eruptions of violence unparalleled in human history. One imaginative novelist foresaw the form these catastrophes would take.

The Shape of Things to Come is the title of a novel wrtten by HG Wells in 1933. The author is known more widely for another science fiction novel, *War of the Worlds*, about an invasion from Mars that, as a radio drama by Orson Welles in 1938, terrified much of the nation. *The Shape of Things to Come* depicted his speculations about the events that would overtake the world from 1933 until 2106. Wells envisaged a world that, after a devastating plague, is then ruled by a benevolent dictatorship until it itself is overthrown and the state withers away. It was loosely translated into a film (Figure 2), *Things to Come*, in 1936.

The film offers a vision of the transformation of the world between 1936 and 2036. It accurately depicted the savagery of WWII and the role of strategic bombing. After a war lasting for decades, during which civilization on both sides is destroyed, the world is ruled by an autocratic dictatorship from which humanity is rescued by a group of scientists based in Basra, Iraq, of all places.

Air power plays a leading role in the film, both as a source of destruction and as the means by which the dictatorship is vanquished. Wells was quite aware of the role that air power had played in the first world war.

Air power during my own lifetime has represented adventure and progress as well as Wells's dystopic vision. I was born in 1925, two years before Lindbergh's flight over the Atlantic while he was squeezed into his seat with hardly any food for nourishment, just like today's air passengers (Figure 3) But the only flying I did, growing up in Brooklyn (Figure 4), was in my imagination. Depression era Brooklyn was not a setting where you could imagine flying to exotic destinations. Still, that magazine, *Flying Aces*, seduced me, while in high school, and without telling my mother, to sign up for the Air Force after Pearl Harbor. Like most 16-year old males, I suffered from a deficit of imagination of the more serious consequences accompanying flying in combat. That is how I came to be part of a bomber crew in WWII in the Pacific theatre (Figure 5). After the Japanese surrender, my squadron moved from Okinawa

Corresponding author: Bernard Weiss, Department of Environmental Medicine, University of Rochester Medical Center, Rochester, New York 14642, Tel: 585-275-1736, Fax: 585-256-2591, e-mail: bernard_weiss@urmc.rochester.edu.

to the air base at Fukuoka, on the southernmost Japanese island of Kyushu (Figure 6). In one of those adventitious ironic connections that dot our lives, Fukuoka is a three-hour trip to Minamata, the fishing village that taught us the horrors of methylmercury neurotoxicity and that has played such a large role at Rochester and in neurotoxicology.

Is this portrait of aviation, both adventure and devastation, a description of the world our successors, and my grandchildren and great-grandchildren, will be facing during the next 80 years? Think of what futurists foresaw during the last eighty years: the end of civilization, and a society suffering constant clashes between warring tribes; elimination of life on earth by atomic weapons, foreseen by HG Wells; or, a technological utopia where we zipped around in personal aircraft freed from the fictions of airline schedules (Figure 7) and lived to 160 years of age (Figure 8).

BACK TO BROOKLYN AND A PROFESSION

I returned to civilian life in 1946 to attend college under the G.I. Bill. My experiences during the war had changed my view of the world. Before those experiences, the most exotic features of my boyhood in Brooklyn (Figure 9) consisted of Ebbets Field, the home of the Brooklyn Dodgers and baseball's most committed fans, and the Brooklyn Public Library, where I could find many other worlds. In high school, my imagination had been excited by electronics. I became president of the Radio Club, where one of my duties, as I now remember it, was to serve as a reviewer of a textbook on radio being written by the faculty advisor, Mr. Marcus. He would give me the chapters as they were delivered by the typist, and I wrote out my comments. It prepared me, I suppose, for all the reviews I've written since then.

Now, coming home from my adventures, my imagination glowed with a more expansive view of the world. I felt the urge to write about them. I attended three different colleges**]** as an undergraduate (Figure 10) and majored in English literature during my first two college years. During this period, I had become entranced by the writings of James Joyce (Figure 11), who captured my literary imagination, I took the middle name "Ulysses" when the registrar at Brooklyn College insisted that I adopt one.

It would have been quite natural, given my assigned title, "The Next Eighty-Three Years," to follow the model of H.G. Wells and embark on a science fiction fantasy. Actually, by the end of my sophomore year, my literary ambitions had begun to erode when I became aware of how ineffectively novelistic imagination is translated into social action and a steady income. I then moved into psychology when my friend, Marty (see Figure 10), asked me what I planned to do after graduation. I shrugged. I had no plans. Marty convnced me that psychology offered opportunities. I became a Psychology major and went on to graduate school where, recapitulating my high school career, I resumed building electronic and mechanical devices (Figure 12) like the ones I used for my doctoral dissertation on the psychophysics of movement (Weiss, 1954). I translated some of that experience into instrumentation to be used for our studies in the Seychelles (Davidson et al, 2006).

The next step on my journey, following graduate school, took me to the U.S. Air Force School of Aviation Medicine in 1954 (Figure 13). I was unaware then of what was germinating in the treatment of behavioral disorders such as schizophrenia with the introduction of neuroleptic drugs, and the birth of a new discipline, behavioral pharmacology. I began my own program there in San Antonio with studies of how opiates and opiate antagonists affected schedule-controlled operant behavior (Weiss, 1956). It was among the earliest papers in the new discipline of behavioral pharmacology. I also became intrigued by behavioral thermoregulation and how it could be altered by nutrients and drugs (Figure 14). It was an attempt to use behavior as an index of physiological processes (Weiss, 1957a, b; Yeh and Weiss, 1963; Weiss and Laties, 1963b; Stern et al, 1979).

Developments in psychopharmacology moved me in 1956 to Johns Hopkins, where Victor Laties, my roomate from graduate school, had established a beachead in the Division of Clinical Pharmacology, the fiefdom of Louis Lasagna, one of the pioneers of clinical pharmacology. There, we embarked on studies of analgesics, because of Lasagna's interests, and developed operant behavioral methods for assaying analgesia in animals (e.g., Weiss and Laties, 1958, 1961, 1963a, 1964a). Previous methods relied on reflexes such as withdrawal from heat, but we argued that clinical pain is a more complex process whose translation into behavior is far from a simple reflex, so our system allowed the subjects to set the level of electrical stimulation they were willing to tolerate. We also studied the behavioral effects of amphetamine-barbiturate combinations (Weiss and Laties, 1964b) after learning that such combinations were used by Baltimore teenagers to generate a super-high experience (Figure 15). We also undertook our first foray into endocrinology with studies of thyroid function and behavioral thermoregulation (Laties and Weiss, 1959).

TECHNOLOGY PURSUITS

By 1962, I had become frustrated by the inabiity of the behavioral instrumentation available at the time to allow me to control and analyze behavior at what would correspond to the molecular level in biochemistry. Because Johns Hopkins had purchased two IBM computers for administrative use, it occurred to me that I might connect them to our laboratory equipment and conduct the kind of on-line control and subsequent microanalyses I had been contemplating. Except for one of their more sympathetic engineers, IBM diagnosed me as delusional. My project went into suspended animation although, in 1962, I had written a paper for an electrical engineering journal on how computer technology could be used to control and analyze behavioral experiments (Weiss, 1962).

Victor then found a notice in Science magazine asking for applictions from life scientists interested in applying computer technology to biomedical research. The notice came from NIH, which then had the foresight supplied by staff such as Bruce Waxman to underwrite what became the Linc Computer Evaluation Project. **[http://history.nih.gov/exhibits/linc/docs/page_06.html].** The Linc computer, developed by Wesley Clark and his collaborators at MIT's Lincoln Laboratories, was the first mini-computer. Clark viewed it as a laboratory instrument that, much like other instruments such as centrifuges, was used by scientists to conduct their experiments. It was not a machine secured in some fortress that could be accessed only by professionals. The researchers did their own programming and interfaced the Linc to their own equipment.

Because of my enthusiasm for the project, and my 1962 paper, I was one of 12 researchers accepted into the program and spent the summer of 1963 in Cambridge, MA, where I assembled my very own Linc and learned to program and service it. I brought it back to the lab at Johns Hopkins, interfaced it, and began to use it to run and analyze experiments (Figure 16). Although it had only 1,024 words of 12-bit memory, it was such a briliant design that these limitations (by today's bloated standards) hardly mattered. It led to several papers exploring the microanalysis of behavior (e.g., Weiss and Laties, 1965; Weiss, 1970) and a book (Weiss, 1973).

TOXICOLOGY AND TECHNOLOGY

In 1963, the Department of Radiation Biology at the University of Rochester School of Medicine and Dentistry approached me about an appointment. The new joint chairs, Aser Rothstein and William Neuman, had decided that they needed a behavioral toxicology component for the new doctoral training program in toxicology that the medical school had been granted permission by New York State to offer. It was the first such program in the U.S. They had been led to include behavioral toxicology at the instigation of Harold Hodge, chair

of Pharmacology and the first president of the Society of Toxicology. In 1961, they had dispatched a technician to the laboratory of Peter Dews, in the Department of Pharmacology at Harvard, to learn the techniques of operant behavior. When he returned, the technician, Robert Armstrong, set up a behavior lab. Their first experiment exposed trained pigeons, the favored species at Harvard, to mercury vapor. The behavior soon deteriorated, but without any discernible pathology (Armstrong et al, 1963). They were convinced.

I told Rochester that I could not move in 1963 because I had just undertaken the Linc project, so they agreed to wait until 1965, when the building my laboratory still occupies was scheduled to be finished. Rochester also offered an appointment to Vic, and in 1965 we moved our behavioral test chambers, the Linc, 12 monkeys, and a regiment of Baltimore cockroaches to the medical school.

At Rochester, we set up a lab, attracted students who were also enthusiastic abut computer technology, and began to expand our computer resources (Figure 17). As a graduate student, I had always been too busy and focused to take advantage of the beauties of New York State. I was prompted to write a poem (Figure 18) about them after a visit to the Adirondacks, which covers one-quarter of the state.

EVERGREEN

Only the pines
Endure the northern winter's
Elongated suffering.
Braced behind a hierarchy
of boughs
They aim green quills
at the intruder.
Better
to be deciduous
Unfolding buds
at spring's moist urging
Blanketing heedless branches
with fresh growth
Rustling to the breeze
with a genital quiver.

By the late 1960s, behavioral measures of toxicity—behavioral toxicology—had aroused enough interest for Annual Reviews to ask us to write a chapter for the 1969 Annual Review of Pharmacology that include behavioral toxicology as well as behavioral pharmacology (Weiss and Laties, 1969). It had also aroused enough interest for me to contemplate one of our Rochester Conferences on Environmental Toxicity devoted to the topic. It was held in 1972, and resulted in a book (Weiss and Laties, 1975). Two of those chapters, one by Joan Cranmer on the remote consequences of methylmercury exposure during gestation (Spyker, 1975) and one by me and William Simon on how the course of aging might be altered by exposure to neurotoxicants (Weiss and Simon, 1975) are still being cited (Figure 19).

It was in 1973 that mercury became a featured theme in our research. A group of women employed in an upstate New York factory had developed signs of mercury vapor poisoning in the course of using equipment designed for pipette calibration. Because the cardinal sign of mercury vapor toxicity is tremor, Dr. David Goldblatt, a neurologist and the lead clinician on the case, asked for our help in measuring tremor. The Linc was the perfect technology for doing so, and our method (Figure 20) was the first published use of computer technology to measure and analyze tremor (Wood et al, 1973). We measured tremor by having the patient rest a finger on a transducer while she tried to keep the force within limits denoted by two lights. Here we found that, as the body burden of mercury fell with no further exposure, tremor amplitude also diminished, and other aspects of the tremor, such as its variance, decreased as well. Our approach here illustrates the laboratory's approach to measurement: precision quantification; without it, we are swamped in uncertainty. It exemplifies our approach to other toxicant and endpoints as well.

The Minamata catastrophe, a mass methylmercury poisoning, had emerged in the 1960s as an emblem of heedless industrialization (Weiss, 1996, 2007a), but was considered a problem not relevant to us because it arose from industrial discharge in a limited area. But in 1970, substantial levels of methylmercury had been discovered in Great Lakes fish, and then, in the winter of 1971–72, another episode of mass poisoning swept through Iraq, this time from contaminated grain treated with a methylmercury fungicide, that was documented by Dr. Thomas Clarkson and other Rochester colleagues (Bakir et al, 1973; Clarkson et al, 1976). Although we knew methylmercury to be a potent neurotoxicant, we lacked reliable quantitative information on its functional effects, particularly how they progressed with exposure. All we knew then were the ultimate toxic endpoints.

We selected the monkey visual system as our guide. Neuropathology in human victims told us that, in victims with visual impairment, severe damage was apparent in the medial portions of visual cortex, which map to the peripheral visual fields as represented in the retina. While the central portion of the retina is dominated by cones, which are responsive to colors and high luminance, peripheral areas are dominated by rods, which are sensitive to low luminance targets. As shown in Figure 21, Hugh Evans, then a postdoctoral fellow in the lab, trained monkeys to press one of three buttons, on which a geometric figure was projected, to obtain a squirt of apple juice (Evans et al, 1977). The correct figure was always, say, a triangle. Even after prolonged weekly dosing with methylmercury, photopic (high luminance) discriminations remained relatively intact, while scotopic (low luminance) discriminations vanished, even after dosing stopped. The brains of these monkeys showed extensive damage to the relevant brain areas. These data told us that one of the earliest signs of methylmercury damage is impaired ability to see objects under low light conditions. They showed, again, the importance of precise behavioral measures in tracing the progression of neurotoxicity. Later, William Merigan developed a method for conducting perimetry in monkeys that showed similar results (Merigan et al, 1983).

Manganese neurotoxicity captured our interest because of proposals by industry to use a manganese fuel additive as a replacement for lead, which had been eliminated from gasoline. Gasoline combustion would then release high levels of manganese into the environment, an outcome that concerned many scientists because it was a venerable neurotoxicant, producing a syndrome resembling Parkinson's disease in workers such as manganese miners. Here, we also used monkeys as the model species, exposing them chronically to manganese (Newland et al, 1992) and measuring motor function. The monkey's task was designed to induce fatigue, one of the symptoms that intoxicated humans complain of. But Newland had another brilliant idea. An experimental MRI machine had been installed in the department and, because manganese is paramagnetic, its localization in the brain could be visualized with the proper imaging parameters. Figure 22 shows how successfully we were able to localize manganese

deposition in the brain (high levels in globus pallidus). We also showed a progressive decline in the rate at which the exposed monkeys performed.

Jacques Maurissen came to Rochester to pursue a degree in toxicology, by way of his training in behavior at the University of Liege. Acrylamide is a chemical with many uses, mostly in the polymer form, but the monomer was identified as neurotoxic from observations of exposed workers, who exhibited both motor and sensory impairment. It damages peripheral nerves, and causes exposed workers to complain of sensations of numbness and pins and needles. No one had precisely quantified its sensory effects up to the time that Jacques conducted his thesis research. He trained monkeys to detect vibratory stimuli applied by an computer-controlled rod to the monkey's fingertip (Figure 23), which enabled him to trace the onset and progression of sensory loss with repeated dosing (Maurissen et al, 1983). He used the same system to follow the course of impairment produced by the radiation sensitizer, misonidazole, which had been observed to produce such effects in cancer patients (Maurissen et al, 1981). Figure 23 also shows Jacques posing for an equivalent system he devised for testing humans; instead of reinforcing correct responses with apple juice, which we used with the monkeys, the figure shows Jacques' reward to be a sip of wine. Bill Merigan, who had been a postdoctoral fellow in the lab, in associated studies with acrylamide, showed subtle effects on the monkey visual system (Merigan et al, 1985) some of which apparently were permanent.

The kind of precise quantification exemplified by the previous figures can also be applied, with the assistance of computer technology, to what superficially seem to be rather straightforward measures such as activity in a running wheel. Laboratory investigators, making use of the same kinds of running wheels you see in pet stores, have investigated patterns of activity by this methods for decades. Rats and mice, for example, because they are nocturnal animals, run mostly during the night, and females run more during estrus. We thought it might be more interesting and sensitive, as well, to ask another question: how much effort would an animal expend so as to have access to a running wheel? We knew that gaining such access is reinforcing, so we constructed systems in which running wheels were operative only when an electronically-controlled brake was released. Figure 24 shows a system in which the rat has to press a lever on the wall a prescribed number of times (a Fixed Ratio) to release the brake for a specified number of seconds. We used such a system to show that quite low doses of the dioxin TCDD reduced the willingness of female rats to work for access and also reduced the amount they ran (Markowski et al, 2002). In earlier work (Tepper and Weiss, 1986), we showed, with a comparable system, that low concentrations of the air pollutant, ozone, reduced the inclination of rats to gain access to an operative wheel, presumably because of the irritant properties of ozone. We have also used running as an operant response; in this guise, the animal has to earn food pellets by rotating the wheel a specified number of times (e.g., Tepper and Weiss, 1986; Youssef et al, 1993).

Much of our work, and much of the work undertaken in behavioral pharmacology and behavioral toxicology has relied on schedule-controlled operant behavior. It is a technology superbly equipped to ask questions about complex behavior such as cognitive function and memory. It affords a degree of experimental flexibiliity not available with other approaches, and was my original motivation for my investment in computer technology. Figure 25 shows not only a standard operant chamber for rats, but also how human behavior is captured by schedules of reinforcement and their reliance on intermittent reinforcement.

Operant behavior, however, requires three kinds of commitment on the part of the experimenter. First, a commitment to control and analyze behavior at what I call the molecular level, and that I have written about throughout my career; for example, a chapter written in 1970 (Weiss, 1970). Second, a willingness to study the principles of behavior and to frame experimental questions in those terms. And third, a willingness to grapple with the computer

technology and associated instrumentation required to conduct contemporary behavioral research. Many researchers, unfortunately, in my view, have adopted procedures that seem superficially simpler, easier, and cheaper, but at the cost of depth of understanding. Figure 26 is one example. Inset A shows a version of the Morris maze, which requires the rat or mouse to learn the location of a hidden platform beneath the water surface. The subject relies on visual cues in the environment to orient itself, so that one laboratory's environment differs from that of another; there is no uniform environment. The same manufacturer whose catalog lists the Morris maze also lists the Forced Swim test (inset B), designed to produce the "learned helplessness" response used widely to screen for antidepressant drugs. Because plunging rats and mice into water also evokes neuroendocrine stress responses (Engelmann et al, 2006), the Morris maze is not useful if the experimenter wishes, for example, to trace performance at different lifetime stages after prenatal exposures, a great advantage of operant technology.

The other two panels in Figure 26 are from Joan Cranmer's work in the early 1970s (Spyker, 1972). They show, with underwater photography, the peculiar swimming postures adopted by mice exposed prenatally to methylmercury. These photographs should be a warning to researchers who blithely adopt the Morris maze as a measure without simultaneously measuring swimming performance and posture.

Figure 27 summarizes what I see as a regrettable development in neuroscience, including neurotoxicology; namely, the tendency to spurn detailed analyses of behavior and behavioral principles in favor of quick, easy behavioral tests or, even more disheartening, the tendency to ignore behavior altogether in favor of abstract speculations about mechanisms, which is why I inserted the panel with the Invisible Man. We cannot escape the fundamental premise of neuroscience: The predominant goal of neuroscience is to understand the relationship between the brain and behavior. It is a goal that cannot be achieved without dedication to measuring and understanding behavior.

NEUROTOXICOLOGY FORERUNNERS

Investigators relatively new to neurotoxicology may not be familiar with its roots. Figure 28 is a compressed history of sorts. I've already alluded to the common themes of behavioral pharmacology and behavioral toxicology. Psychopharmacology first bloomed in the 1950s with the discovery of drugs that, for the first time, offered the possibility of treatment for severe behavioral disorders such as schizophrenia. But then we needed a technology for testing new compounds with therapeutic promise and for expanding our knowledge of the behavioral mechanisms by which these agents act. Behavioral pharmacology grew from this need. Workplace exposure standards also contributed to the development of neurotoxicology. Standards such as those set for volatile organic solvents largely rested on their potential to impair worker behaviors such as judgment in the avoidance of accidents. The courtroom's contribution came in the form of litigation such as suits based on harm to worker health due to neurotoxicant exposure. Then, especially with the crack epidemic, and discussions about "crack babies," the public became concerned about exposure during gestation, And finally, the influence of the Soviet Union, whose exposure standards fell far below those set in the West, presumably because of its reliance on nervous system function rather than pathology as measures of adverse effects.

Intrigued by these differences, an American delegation visited the USSR in the early 1960s, and wrote a report (Figure 29) about how the Soviets determined exposure standards in the workplace. Magnuson et al (1964), after visiting many laboratories and holding discussions with Soviet scientists, offered the observation shown in the figure about the role of behavior (conditioned reflexes) in assessing neurotoxicity. The prestige of I.P. Pavlov, shown in the upper panel, in fostering this viewpoint is undeniable. He was the giant among Soviet scientists.

I had an opportunity to visit several Soviet laboratories during my time as part of the US-USSR Environmental Health Exchange Agreement, signed by Nixon and Brezhnev in 1972. The lower panel shows me sitting at Pavlov's desk in Koltushi, outside of Leningrad (now renamed again as St. Petersburg).

Figure 30 depicts some of what we found in Soviet laboratories. The four photos illustrate some of those at the Institute for General and Communal Hygiene in Moscow in 1973. At top left, a laboratory that studies the effects of heat and light on performance. At bottom left, a rabbit with electrodes implanted in the brain to measure electrical activity produced by exposure to gases and vapors via the system shown. At top right, Joan Cranmer, a member of my first delegation, modeling how human subjects are exposed to gases and vapors. At bottom right, how an actual experiment is conducted, with EEG and EKG electrodes attached to the subject, who is also performing a behavioral task.

There are other aspects to neurotoxicology's forerunners and roots that deserve contemplation. Harvey Wiley was the first FDA commissioner, and a fierce advocate of consumer protection. He was also an advocate for testing. In 1902, as Chief of the Bureau of Chemistry, four years before the FDA came into being, Wiley assembled a group of volunteers, young men who consumed meals containing some of the adulterants used by the food industry at the time, largely to mask undesirable properties. They became known as the Poison Squad, because it was their responses that Wiley used to test for toxicity. They took their tainted meals at the Hygienic Table, as depicted in the upper left panel of Figure 31. Testing became part of the FDA's mandate when it was signed into law in 1906.

Developmental toxicity became embedded into regulation with the thalidomide disaster, which erupted into public consciousness in 1962. Only the stubborness of Dr. Francis Kelsey at the FDA prevented thalidomide from reaching the U.S. market. The top right panel of Figure 31 shows two thalidomide victims with missing limbs. At a meeting at Rochester, David Rall, the Director of NIEHS at the time, asked his disturbing question accompanying his photograph in the lower left panel. That question now exemplifies much of neurotoxicology because of our awareness of the exquisite sensitivity of the developing brain to chemical challenges and how it might be manifested in the form of subtle functional degradation. The lower right panel, adapted from an article I wrote twenty years ago (Weiss, 1988) shows how even a minor shift in the mean of the IQ distribution exercises profound effects on the tails of the distribution if we examine population rather than individual effects.

In a manner not intended by them, the authors of *The Bell Curve*, a book that elicited vehement debate, demonstrated how neurotoxic chemicals could produce widespread societal damage (Herrnstein and Murray, 1994). The book argued that our status in society, and our success in it, depended on IQ. Their analysis of the available data showed how even a small, 3% decline in IQ can lead to marked social pathology; again, an argument from the tails of the IQ distribution. I inverted their argument (Figure 32) to show the effects of a 3% rise, which could be achieved, say, by reducing lead exposure in disadvantaged communities.

THE LOOMING CHALLENGE OF AGING

One aspect of neurotoxicology that is assuming more and more importance is how environmental chemicals might be contributing to neurodegenerative disorders such as Alzheimer's disease whose prevalence is rising with our aging population. I've written several papers on aging, most recently on neurogenesis and endocrine disruption (Weiss, 2007b). I thought I'd introduce the topic with the lines in Figure 33 from the famous poem by T.S. Eliot.

Literary interpretations of the poem abound. It has been analyzed down to the level of individual syllables. Prufrock's musings, connected in a stream of consciousness dialogue, are suffused

with regret, and passively accept the waning of energy and ambition that allegedly accompany aging. A crisper philosophical viewpoint of aging came from Satchel Paige, the noted baseball pitcher who was confined for most of his professional life to the Negro Leagues. Paige warned, “Don’t look back; something may be gaining on you.” For neurotoxicology, that something is neurodegenerative disease, but we are learning that it is not inevitable, etched in our genes, but also an outcome influenced by our exposure to environmental chemicals. Figure 34 is a list of factors suspected as risk factors for Parkinson’s disease, the best established of which is pesticide exposure, probably because exposure tends to occurr over a working lifetime. Let me remind you that the underlying lesion, so to speak, is the loss of dopamine-producing cells in the structure known as the substantia nigra (SN), as shown in Figure 35. Dopamine deficits and accompanying pathology have been shown in animal models to result from exposure to certain pesticides (e.g., Cory-Slechta et al, 2005).

The connection with aging is plotted in Figure 36 (Weiss, 2006). The uppermost curve was fitted to points based on McGeer et al (1988) who, based on autopsy data, showed progressive declines in SN cell populations with age, a finding consistent with the increased prevalence of Parkinson’s disease with aging. The middle curve is derived from a model in which the “natural” rate of decline is accelerated by 0.1% annually, and the lowermost curve by 0.3% annually. “Natural” aging produces a reduction of cell number in SN of 40% at about age 72. An acceleration of as little as 0.1% annually incurs such a loss at about 64 years of age. The consequences are plotted in Figure 37. The rightmost curve plots age versus prevalence for a reference population. At age 60, the prevalence is about 300 per 100,000. The middle curve plots an age versus prevalence curve based on a displacement of the function to earlier ages of five years. Here, the prevalence is about 700 per 100,000. A minute acceleration of cell loss of less than 0.1% annually, according to this model, more than doubles the prevalence.

The progessive decline in cell number plotted in Figure 36 is not characteristic of all parts of the brain. In fact, new cells, in some brain areas, are produced throughout the lifetime. Such findings contradict what was the established dogma until about 15 years ago, and which is shown in Figure 38. Ramon y Cajal won the Nobel prize in 1906 for work in which he showed the basic structure of the nervous system. His writings, supported by most neuroscientists, reflected the doctrine that we peak in our nerve cell population early in life and then continue to lose them over time. We now know that new cells and connections continue to proliferate over the lifetime, although diminishing with age. Figure 39 describes the process, beginning with new stem cells then choosing path to a specific cell type that then is integrated into a neural system, as it were. The brain structure most relevant to cognitive function is the hippocampus, as depicted in Figure 39, although new cells have been found in the cerebral cortex in adult rats and monkeys (Gould and Gross, 2002). This process should be of immense interest for neurotoxicology. Isn’t It reasonable to assume that some neurotoxicants, especially those shown to interfere with cell proliferation and migration early in cevelopment, will produce similar effects in the adult or senescent brain (Alverez-Buylla and Liim, 2004)? It seems to be the case with lead (White et al 2007).

One of the contributions to the overthrow of the belief that neurogenesis did not occur in the adult brain came from studies of ovarian steroids, which increase the proliferation of granule cell precursors in the dentate gyrus region (Tanapat et al, 2005). A considerable body of evidence, in fact, shows the critical role of hormones in neurogenesis (Weiss, 2007b). The conjunction of environmental chemical exposures and endocrine function was largely unappreciated until the publication of a seminal volume on the topic (Colborn et al, 1996), which popularized the term, “endocrine disruptor.” Its cover is shown in Figure 40, along with three charts that plot trends in male reproductive health: rising rates of testicular cancer and hypospadias and falling sperm counts. The author P.D. James (James, 1992) translated these trends into a novel in which males had lost their ability to reproduce (Figure 41). I note there

the possible role of environmental estrogens, which many observers hold responsible for much of these reproductive trends, although the testicular dysgenesis syndrome, which includes lowered sperm counts and testicular cancer, can be induced by anti-androgens.

A staggering number of environmental chemicals exhibit estrogenic activity, and a few seem to act as anti-estrogens. The list in Figure 42 is no more than a partial sample, and can be seen to include a number of chemical classes. Figure 43 lists recognized anti-androgenic chemicals, which also include a number of chemical classes. Both figure 42 and figure 43 testify to the abundance of environmental endocrine disruptors, defined as chemicals that interfere in a multitude of ways with the natural actions of our hormones.

That portion of the endocrine disruptor literature dealing with neurobehavioral assessment is overwhelmingly devoted to effects on early development. Emphasis on that phase of the life cycle is warranted because, for example, gonadal hormones during gestation determine sexual differentiation of the brain (Weiss, 1997, 2002). Aging is another vulnerable period of life, however. Gonadal hormone levels wane in both sexes, leading not only to reproductive system changes, but to changes in neurobehavioral function that might be exacerbated by exposure to endocrine disruptors (Weiss, 2007b). One source of data on this issue comes from animal studies. Rapp et al (2003) undertook a study with elderly female monkeys to evaluate their ability to perfom a complex behavioral task after ovariectomy. One form of the delayed response task is described in Figure 44. Ovariectomized animals performed at a level far below that of controls, while ovariectomized subjects given periodic injections of estrogen virtually matched controls. Although the human data on ovariectomized women are consistent with these results (Phillips and Sherwin, 1992), the Women's Health study found that hormone replacement therapy exerted negative effects. One flaw of those results, however, lies in their choice both of the drug and timing; the mean age of participants was 73, long after menopause. The long latency to treatment onset may account for these results Sherwin (2006).

The story with men is more direct. Yaffe et al (2002) studied the relationship between free testosterone levels and neuropsychological test performance in elderly men (Figure 45). They divided testosterone values into tertiles, and, as shown by the figure, lower testosterone values were associated with worse test performance. Such results are consistent with those indicating that treatment with antiandrogens for prostate cancer also degrades performance (Janowsky, 2006) and with a plethora of animal laboratory evidence.

Only a handful of papers have addressed the question of how endocrine disruptors might act on adult neurobehavioral function. The plasticizer Bisphenol A, a pivot of controversy because of its widespread distribution, is an acknowledged endocrine disruptor, presumed to act as an estrogen mimic. It is a more complex story, however. In ovariectomized nonhuman primates, it diminishes synaptogenesis evoked by estradiol in the hippocampus and prefrontal cortex (Leranth et al, 2008). It also inhibits synaptogenesis in the brains of both gonadally-intact adult males and in castrated males treated with testosterone. Such data question superficial extrapolations to neurobehavioral function on the basis of classifications of environmental endocrine disruptors as estrogenic, anti-estrogenic, or anti-androgenic.

Advancing age also brings with it an increasing risk of stroke. Statins have been shown in rodent models of acute ischemic stroke to reduce neuronal injury and infarct size in a dose-dependent fashion. In clinical trials, statins can apparently reduce the risk of stroke occurrence in high risk patients and seem also to reduce stroke recurrence. Furthermore, there is some evidence that statins are able to reduce the formation of beta-amyloid peptide, which plays a key-role in the pathogenesis of Alzheimer disease. Neurotoxicologists should be paying attention to data such as these and those in Figure 46, which shows both behavioral and morphological indications of how statin treatment can counteract the effects of traumatic brain

injury in mice (Wang et al, 2007). Figure 47 displays the results of an experiment in rats in which the injury arose from inducing a stroke, and its amelioration by treatment with tadalafil, a phosphodiesterase-5 inhibitor orignally marketed for erectile dysfunction (Zhang et al, 2006).

Because of our emphasis on environmental chemicals, we neurotoxicologists deal typically with exposure levels that produce subtle effects and damage. Accordingly, only rarely have we considered the application of countermeasures based on the treatment of grave injuries such as stroke or, as I've recently written, those produced by cancer chemotherapy (Weiss, 2008). These are neglected opportunities; they may show us how to check adverse effects arising from both acute and chronic envronmental exposures, and they may offer, as well, additional clues to underlying mechanisms.

Figure 48 is presented as an amusing comment, but it has a serious core. With aging comes elevated risks of heart attacks, and it is now established that quick treatment after the appearance of symptoms with aspirin helps by inhibiting platelet formation. Stroke risk also rises with aging, and viagra (sildenafil) is a phosphodiesterase-5 inhibitor, which, like tadalafil, improves function after experimental stroke. Perhaps patients at risk for stroke, who probably are at risk as well for cardiovascular events, should consume a PDE-5 inhibitor at the first signs of a possible stroke.

GENES AND DESTINY

"*The most valuable of all capital is that invested in human beings; and of that capital the most precious part is the result of the care and influence of the mother*." Alfred Marshall. *Principles of Economics*. (1890).

The astonishing and unprecedented advances in molecular genetics during the recent past seem to have imprinted on the public the conviction that our destiny is inscribed in our genome. But it is not just the hazards posed by environmental chemicals that contradict that doctrine. We have always been aware of the weight of the social environment, but we never knew how it acted. From the perspective of behavior, although we could identify social factors statistically, we could not confer on them biological plausibility. Data from experiments on enriched environments (e.g., Diamond, 2001) and stress (e.g., Cory-Slechta et al, 2004) provided some biological foundations for certain environmental influences. We are now beginning to understand how they might act at the level of the genome. In a kind of Lamarckian renaissance, the new science of epigenetics is begnning to inform us about how environmental influences might embed themselves, as it were, in the genome without altering DNA. Figure 49 (Champagne et al, 2008) sketches how maternal behavior patterns can be nongenomically transmitted to succeeding generations. Extending research originated by Michael Meaney and his collaborators, the authors showed how the maternal behaviors of licking and grooming, whose frequency varies from dam to dam, modify gene expression by mechanisms such as selective methylation of particular gene promotor regions. These methylation patterns appear in the offspring, who then transmit them to their offspring. Procedures to alter licking and grooming, such as stressing the dam, alter transmitted methylation patterns. Such findings suggest studies of neurotoxicant-lead interactions on maternal behavior in offspring.

In their review of how endocrine disruptors may induce transgenerational disease such as prostate hyperplasia via epigenetic programming of the germ line, Anway and Skinner (2008) chose the antiandrogenic fungicide vinclozolin as an example. Exposure of dams of the F0 generation exposed to vinclozolin during gestation led to F1 to F4 males with a deformed ventral prostate phenotype. Behavioral consequences can also flow from associated toxicities. Crews et al (2007) examined how female mate preferences can be used to identify epigenetic modifications of the male germ cell line. Figure 50 is a diagram of a device to measure mate

preference. The female is placed in the central compartment. A control male is placed in one of the side compartments, and an F3 vinclozolin male in the other. Crews et al (2007) found that female rats spent more time near the control male than near the vinclozolin male, presumably because of preferences based on pheromones. Male preferences did not distinguish between control and F3 females. This is a rather subtle behavioral indication of an adverse consequence traceable to an exposure three generations earlier.

B.F. Skinner, the leading psychologist of the last century, would have been intrigued by epigenetics. His novel. Walden Two (Skinner, 1945) describes a utopian community organized around the principles of behavior, especially the principle that behavior should be shaped by positive reinforcement rather than by punishment (Figure 51). In such a setting, if epigenetic mechanisms prevailed as they have in Figure 47, inhabitants of Walden Two would be transmitting these behaviors to successive generations. My own view was formed by my experiences during the 20th century, as my visit to a former concentration camp erected by the Germans near Riga, Latvia, when I was traveling in the USSR as part of the Environmental Health Exchange Agreement (Figure 52). Imagining the horrors that occurred there offers little encouragement to the hope that benign governments will transmit their behaviors to succeeding generations.

Reflecting on the 20th century without cynicism about human behavior is an elusive undertaking. Properly wrought cynicism, though, is a hopeful sign because it signifies that at least some among us are not deceived; in fact, these icons of cynicism can also produce great art. I think of the German playwright Berthold Brecht (1898–1956), who, with the composer Kurt Weill, gave us The Threepenny Opera (1928) and the opera Rise and Fall of the Town of Mahoganny (1930). (The Weill archives are held by the Eastman School of Music of the University of Rochester.) In the early 1980s, I attended a performance of “Brecht on Brecht” in, I think, Minneapolis. It is a theatre piece that weaves together some of his plays, poems, lyrics, and parts of his testimony before the notorious House Unamerican Activities Committee, a Congressional committee created to search out “disloyalty” and “subversive” activities. It remained in existence from 1938–1975. Brecht was their target in 1947 because he was a committed Marxist. His interchange with the chairman had the committee shaking their heads in befuddlement:

> “You are certain you have never been to Communist Party meetings?” Brecht is asked, at one point.
>
> “I think I am certain,” he replies.
>
> “You think you are certain!”
>
> “Yes. I have not attended such meetings, in my opinion.”

While sitting in the hotel lobby, I saw a parade of high schoolers, dressed in gowns and tuxedos for, I inferred, their senior prom. The contrast with the performance I had just attended prompted me to write the poem in Figure 53. Brecht left the United States soon afterward; his existence here had become intolerable.

BRECHT ON STAGE

I’m sure Brecht had dirt

under his fingernails.

A public declaration of fallibility.

He had heard the Pope

fart in Saint Peter’s.

Elegance did not become him.

No soft litany of comfort.

No cozy plot

sucking up to a happy ending.

No.

He spit words to shock the skin.

A cold needle spray

of contempt.

Then laughed.

It's easier

When the gall

slides down your throat

To grin.

TOXIC LEADERSHIP

Because my own history covers three-quarters of the 20th century, my perspectives on the future are inevitably shaped by its most salient events, as I observed in the Introduction. War subsumed progress, but it was not inevitable. It reflected failures in leadership, and I wonder if these failures themselves may be attributed as much to brain damage as the traditional interpretations of international politics. We are always at risk from blunders of leadership, as we have seen even at the beginning of the current century. The 25th amendment to the U.S. Constitution (Figure 54) is a partial response to a situation in which the president is incapable of carrying out the duties of the office. A coma, for example, like that of Ariel Sharon? But suppose the impairment is considerably more subtle?

I tried to challenge my colleagues, in the mid 1980s, during the tenure of Ronald Reagan, about how they would propose dealing with a president exhibiting the early signs of Alzheimer's disease. I wrote a novella about such a situation and had an artist at our medical center prepare illustrations I could use as slides for presentations at meetings and seminars. It is accessible at the URL shown in Figure 55, which shows one of the illustrations. It depicts my protagonist, a young neurologist, appearing, with his attorney, before a congressional committee.

A cognitively-impaired president is not a fantasy. It was a situation, at the end of World War One, that, as noted in Figure 56, may have planted the seeds for World War Two. Woodrow Wilson held the office of president from 1913–1921. He suffered from chronic neurological problems, and a catastrophic stroke in 1919 that his wife and staff hid from the public. His attempts to construct a lasting peace in Europe after World War One and to enlist the United States in such a venture ended in failure, probably because he lacked the vigor and stamina to fight for them. His failure is often seen as the source of World War Two.

More recent examples of impaired leadership are provided by World War Two. The Yalta agreement, undertaken early in 1945 before the end of the war, divided postwar Europe in a manner that fostered the Cold War. It was signed by three leaders all of whom by then had suffered strokes (Figure 57). Would a different postwar world have been designed by intact leaders? The election of 2008 offered us two candidates whose conventional medical status was at least partially known. Did we know anything then, or do we know anything now, about

what risks are posed by their potential to suffer brain dysfunction? Doesn"t the public need such information as much as it needs information about their susceptibility to heart attacks?

The Next 83 Years: Stealth Questions for Neurotoxicology

Ludwig Wittgenstein is often considered to be the most eminent philosopher of the 20th century. In many ways he was a keen analyst of how we use language, and trod close to experimental psychology. But not close enough for me. As a graduate student in psychology, I found myself in endless debates with philosophy graduate students because I argued that much of analytical philosophy can be translated into experiments, which I thought the more fruitful pursuit. Figure 59 is an example of Wittgenstein's ability to tease us with language that has the consistency of freshly-poured concrete. It is also an example of why it is essential to adopt the science of behavior as the realm in which we clarify the use of language, not the realm of philosophical discourse.

Language is a behavioral function, which is why I included Wittgenstein. His analyses should remind us that the ultimate aim of neuroscience is to achieve an understanding of human behavior. Whatever biological level the scientist chooses to study, whether molecular, cellular, laboratory animal, or epidemiological, we almost invariably try to connect it with our own species. It is no less true of neurotoxicology. Or, perhaps it should be even more true.

At the beginning of this article, I told about futurist predictions made about the time I was born: the construction of Titan Cities (Figure 7) or the extension of life well beyond a century (Figure 8). I took them as a warning not to be excessively glib about the future of neurotoxicology.

Still, I expect that this discipline will continue to evolve, from its original focus on individual chemicals in a circumscribed landscape, to questions evoked by multiple chemicals in complex environmental settings embodying multiple risks. Some of these risks may lie dormant in individuals for decades, as we know from our experience with lead. Or, they may start to claim our attention only when we begin to discern shifts in population variables, as was the case with endocrine disruptors and declining numbers of certain species of wildlife and, more recently, declines in human male fertility.

I can be confident about one feature. Neurotoxicology or its successor discipline won't be asked simple questions. It will be asked what I call "stealth" questions. These are questions that are camouflaged to resemble another, usually simpler, query. We already have had experience with questions such as, what is a safe level of lead exposure? We now know some of the complexities: the non-classical shape of the dose-response function, the influence of socioeconomic status, the contribution of stress. A single question will expand into a universe of questions, including those that flow into social policy. Think about how little we know of the influence that environmental chemicals on children's temperament, which is shaped by biology and by experience.

Some observers believe that we can discover the toxic potential of chemicals by studying molecular and cellular mechanisms *in vitro* or *in silico*, eventually eliminating the need for assessing how they mold the whole organism. Such a development would deprive our science of its wealth of possibilities, of its challenges, and eventually of its relevance for human welfare.

I wrote the poem in Figure 59 after reading about Gertrude Stein's final words. They immediately evoked the image of Picasso's famous portrait (1906), which hangs in New York's Metropolitan Museum of Art. Figure 60 describes the enduring challenge of science: every answer evokes another question. I can't imagine that the next 83 years will alter the ceaseless search that drives those of us who practice science.

SKEPTICS

Gertrude Stein's dying words: "What is the answer?" she asked, and when no answer came she laughed and said, "Then what is the question?"

Picasso

would hardly have recognized the face

its power drained

into weary folds.

Only the eyes

were familiar.

An ebony gaze

flicking light

Into shadowed corners.

What answers lay there

that only the final

rasping breath

Could still that ceaseless search?

Acknowledgments

Almost all of the author's work described in this article was funded by NIH. Its preparation was supported in part by current NIEHS grants ES013247 and ES015509 and Center grant ES01247.

References

Alvarez-Buylla A, Lim DA. For the long run: Maintaining germinal niches in the adult brain. Neuron 2004;41:683–686. [PubMed: 15003168]

Anway MD, Skinner MK. Epigenetic programming of the germ line: Effects of endocrine disruptors on the development of transgenerational disease. Reprod Biomed Online 2008;16:23–25. [PubMed: 18252044]

Armstrong RD, Leach LJ, Belluscio PR, Maynard EA, Hodge HC, Scott JK. Behavorial changes In the pigeon following inhalation of mercury vapor. Am Ind Hyg Assoc J 1963;24:366–375. [PubMed: 14042496]

Bakir F, Damluji SF, Amin-Zaki L, Murtadha M, Khalidi A, al-Rawi NY, Tikriti S, Dahahir HI, Clarkson TW, Smith JC, Doherty RA. Methylmercury poisoning in iraq. Science 1973;181:230–241. [PubMed: 4719063]

Champagne FA. Epigenetic mechanisms and the transgenerational effects of maternal care. Front Neuroendocrinol 2008;29:386–397. [PubMed: 18462782]

Clarkson TW, Amin-Zaki L, Al-Tikriti SK. An outbreak of methylmercury poisoning due to consumption of contaminated grain. Fed Proc 1976;35:2395–2399. [PubMed: 964390]

Colborn, T.; Dumanoski, D.; Myers, JM. Our Stolen Future. New York: Dutton; 1996.

Cory-Slechta DA, Virgolini MB, Thiruchelvam M, Weston DD, Bauter MR. Maternal stress modulates the effects of developmental lead exposure. Environ Health Perspect 2004;112:717–730. [PubMed: 15121516]

Cory-Slechta DA, Thiruchelvam M, Richfield EK, Barlow BK, Brooks AI. Developmental pesticide exposures and the parkinson's disease phenotype. Birth Defects Res A Clin Mol Teratol 2005;73:136–139. [PubMed: 15751039]

Crews D, Gore AC, Hsu TS, Dangleben NL, Spinetta M, Schallert T, Anway MD, Skinner MK. Transgenerational epigenetic imprints on mate preference. Proc Natl Acad Sci U S A 2007;104:5942–5946. [PubMed: 17389367]

Davidson PW, Weiss B, Beck C, Cory-Slechta DA, Orlando M, Loiselle D, Young EC, Sloane-Reeves J, Myers GJ. Development and validation of a test battery to assess subtle neurodevelopmental differences in children. Neurotoxicology 2006;27:951–969. [PubMed: 16716399]

Diamond MC. Response of the brain to enrichment. An Acad Bras Cienc 2001;73:211–220. [PubMed: 11404783]

Engelmann M, Ebner K, Landgraf R, Wotjak CT. Effects of morris water maze testing on the neuroendocrine stress response and intrahypothalamic release of vasopressin and oxytocin in the rat. Horm Behav 2006;50:496–501. [PubMed: 16875693]

Evans HL, Garman RH, Weiss B. Methylmercury: Exposure duration and regional distribution as determinants of neurotoxicity in nonhuman primates. Toxicol Appl Pharmacol 1977;41:15–33. [PubMed: 408941]

Gould E, Gross CG. Neurogenesis in adult mammals: Some progress and problems. J Neurosci 2002;22:619–623. [PubMed: 11826089]

Herrrnstein, RJ.; Murray, C. The Bell Curve. New York: Free Press; 1994.

James, PD. The Children of Men. New York: Knopf; 1992.

Janowsky JS. The role of androgens in cognition and brain aging in men. Neuroscience 2006;138:1015–1020. [PubMed: 16310318]

Laties VG, Weiss B. Thyroid state and working for heat in the cold. Am J Physiol 1959;197:1028–1034. [PubMed: 14414443]

Leranth C, Hajszan T, Szigeti-Buck K, Bober J, MacLusky NJ. Bisphenol A prevents the synaptogenic response to estradiol in hippocampus and prefrontal cortex of ovariectomized nonhuman primates. Proc Natl Acad Sci U S A 2008;105:14187–14191. [PubMed: 18768812]

Magnuson HJ, Fassett DW, Gerarde HW, Rowe VK, Smyth HF Jr, Stokinger HE. Industrial toxicology in the Soviet Union--theoretical and applied. Am Ind Hyg Assoc J 1964;25:185–197. [PubMed: 14125871]

Markowski VP, Zareba G, Stern S, Cox C, Weiss B. Altered operant responding for motor reinforcement and the determination of benchmark doses following perinatal exposure to low-level 2,3,7,8-tetrachlorodibenzo-p-dioxin. Environ Health Perspect 2001;109:621–627. [PubMed: 11445517]

Maurissen JP, Conroy PJ, Passalacqua W, Von Burg R, Weiss B, Sutherland RM. Somatosensory deficits in monkeys treated with misonidazole. Toxicol Appl Pharmacol 1981;57:119–126. [PubMed: 7209982]

Maurissen JP, Weiss B, Davis HT. Somatosensory thresholds in monkeys exposed to acrylamide. Toxicol Appl Pharmacol 1983;71:266–279. [PubMed: 6636191]

McGeer PL, Itagaki S, Akiyama H, McGeer EG. Rate of cell death in parkinsonism indicates active neuropathological process. Ann Neurol 1988;24:574–576. [PubMed: 3239957]

Merigan WH, Maurissen JP, Weiss B, Eskin T, Lapham LW. Neurotoxic actions of methylmercury on the primate visual system. Neurobehav Toxicol Teratol 1983;5:649–658. [PubMed: 6669183]

Merigan WH, Barkdoll E, Maurissen JP, Eskin TA, Lapham LW. Acrylamide effects on the macaque visual system. I. Psychophysics and electrophysiology. Invest Ophthalmol Vis Sci 1985;26:309–316. [PubMed: 3972511]

Newland MC, Weiss B. Persistent effects of manganese on effortful responding and their relationship to manganese accumulation in the primate globus pallidus. Toxicol Appl Pharmacol 1992;113:87–97. [PubMed: 1553759]

Phillips SM, Sherwin BB. Effects of estrogen on memory function in surgically menopausal women. Psychoneuroendocrinology 1992;17:485–495. [PubMed: 1484915]

Rapp PR, Morrison JH, Roberts JA. Cyclic estrogen replacement improves cognitive function in aged ovariectomized rhesus monkeys. J Neurosci 2003;23:5708–5714. [PubMed: 12843274]

Sherwin BB. Estrogen and cognitive aging in women. Neuroscience 2006;138:1021–1026. [PubMed: 16310965]

Skinner, BF. Walden Two. New York: Macmillan; 1945.

Spyker, J. Behavioral teratology and toxicology. In: Weiss, B.; Laties, VG., editors. Behavioral Toxicology. New York: Plenum; 1975. p. 311-349.

Spyker JM, Sparber SB, Goldberg AM. Subtle consequences of methylmercury exposure: Behavioral deviations in offspring of treated mothers. Science 1972;177:621–623. [PubMed: 5049306]

Stern S, Margolin L, Weiss B, Lu ST, Michaelson SM. Microwaves: Effect on thermoregulatory behavior in rats. Science 1979;206:1198–1201. [PubMed: 505008]

Tanapat P, Hastings NB, Gould E. Ovarian steroids influence cell proliferation in the dentate gyrus of the adult female rat in a dose- and time-dependent manner. J Comp Neurol 2005;481:252–265. [PubMed: 15593136]

Tepper JS, Weiss B. Determinants of behavioral response with ozone exposure. J Appl Physiol 1986;60:198–875. [PubMed: 3511022]

Wang H, Lynch JR, Song P, Yang HJ, Yates RB, Mace B, Warner DS, Guyton JR, Laskowitz DT. Simvastatin and atorvastatin improve behavioral outcome, reduce hippocampal degeneration, and improve cerebral blood flow after experimental traumatic brain injury. Exp Neurol 2007;206:59–69. [PubMed: 17521631]

Weiss B. The role of proprioceptive feedback in positioning responses. J Exp Psychol 1954;47:215–224. [PubMed: 13152298]

Weiss B. The effects of various morphine-N-allyl-normorphine ratios on behavior. Arch Int Pharmacodyn Ther 1956;105:381–388. [PubMed: 13314744]

Weiss B. Thermal behavior of the sub-nourished and pantothenic-acid-deprived rat. J Comp Physiol Psychol 1957a;50:481–485. [PubMed: 13481187]

Weiss B. Pantothenic acid deprivation and thermal behavior of the rat. Am J Clin Nutr 1957b;5:125–128. [PubMed: 13410812]

Weiss B. Engineering perspectives in the analysis of behavior. Convention Record, Institute of Radio Engineers 1962;9:103–110.

Weiss, B. The fine structure of operant behavior during transition states. In: Schoenfeld, WN.; Farmer, J., editors. Theory of Reinforcement Schedules. New York: Appleton-Century-Crofts; 1970. p. 270-311.

Weiss, B., editor. Digital Computers in the Behavioral Laboratory. New York: Appleton-Century-Crofts; 1973.

Weiss B. Neurobehavioral toxicity as a basis for risk assessment. Trends Pharmacol Sci 1988;9:59–62. [PubMed: 3072731]

Weiss B. Long ago and far away: A retrospective on the implications of Minamata. Neurotoxicology 1996;17:257–263. [PubMed: 8784837]

Weiss B. Endocrine disruptors and sexually dimorphic behaviors: A question of heads and tails. Neurotoxicology 1997;18:581–586. [PubMed: 9291506]

Weiss B. Sexually dimorphic nonreproductive behaviors as indicators of endocrine disruption. Environ Health Perspect 2002;110 (Suppl 3):387–391. [PubMed: 12060833]

Weiss B. Economic implications of manganese neurotoxicity. Neurotoxicology 2006;27:362–368. [PubMed: 15936082]

Weiss B. Why methylmercury remains a conundrum 50 years after minamata. Toxicol Sci 2007a;97:223–225.

Weiss B. Can endocrine disruptors influence neuroplasticity in the aging brain? Neurotoxicology 2007b; 28:938–950. [PubMed: 17350099]

Weiss B. Chemobrain: A translational challenge for neurotoxicology. Neurotoxicology 2008;29:891–898. [PubMed: 18479752]

Weiss B, Laties VG. Fractional escape and avoidance on a titration schedule. Science 1958;128:1575–1576. [PubMed: 13615312]

Weiss B, Laties VG. Changes in pain tolerance and other behavior produced by salicylates. J Pharmacol Exp Ther 1961;131:120–129. [PubMed: 13784050]

Weiss B, Laties VG. Characteristics of aversive thresholds measured by a titration schedule. J Exp Anal Behav 1963a;6:563–572. [PubMed: 14055954]

Weiss B, Laties VG. Effects of amphetamine, chlorpromazine and pentobarbital on behavioral theromoregulation. J Pharmacol Exp Ther 1963b;140:1–7. [PubMed: 13999709]

Weiss B, Laties VG. Analgesic effects in monkeys of morphine, nalorphine, and a benzomorphan narcotic antagonist. J Pharmacol Exp Ther 1964a;143:169–173. [PubMed: 14163989]

Weiss B, Laties VG. Effects of amphetamine, chlorpromazine, pentobarbital, and ethanol on operant response duration. J Pharmacol Exp Ther 1964b;144:17–23. [PubMed: 14191461]

Weiss B, Laties VG. Reinforcement schedule generated by an on-line digital computer. Science 1965;148:658–661. [PubMed: 14268734]

Weiss B, Laties VG. Behavioral pharmacology and toxicology. Annu Rev Pharmacol 1969;9:297–326. [PubMed: 4892430]

Weiss, B.; Laties, VG., editors. Behavioral Toxicology. New York: Plenum; 1975.

Weiss, B.; Simon, W. Quantitative perspectives on the long-term toxicity of methylmercury and similar poisons. In: Weiss, B.; Laties, VG., editors. Behavioral Toxicology. New York: Plenum; 1975. p. 429-435.

White LD, Cory-Slechta DA, Gilbert ME, Tiffany-Castiglioni E, Zawia NH, Virgolini M, Rossi-George A, Lasley SM, Qian YC, Basha MR. New and evolving concepts in the neurotoxicology of lead. Toxicol Appl Pharmacol 2007;225:1–27. [PubMed: 17904601]

Wood RW, Weiss AB, Weiss B. Hand tremor induced by industrial exposure to inorganic mercury. Arch Environ Health 1973;26:249–252. [PubMed: 4696382]

Yaffe K, Lui LY, Zmuda J, Cauley J. Sex hormones and cognitive function in older men. J Am Geriatr Soc 2002;50:707–712. [PubMed: 11982672]

Yeh SD, Weiss B. Behavioral thermoregulation during vitamin B6 deficiency. Am J Physiol 1963;205:857–862. [PubMed: 5877413]

Youssef AF, Weiss B, Cox C. Neurobehavioral toxicity of methanol reflected by operant running. Neurotoxicol Teratol 1993;15:223–227. [PubMed: 8413075]

Zhang L, Zhang Z, Zhang RL, Cui Y, LaPointe MC, Silver B, Chopp M. Tadalafil, a long-acting type 5 phosphodiesterase isoenzyme inhibitor, improves neurological functional recovery in a rat model of embolic stroke. Brain Res 2006;1118:192–198. [PubMed: 16959227]

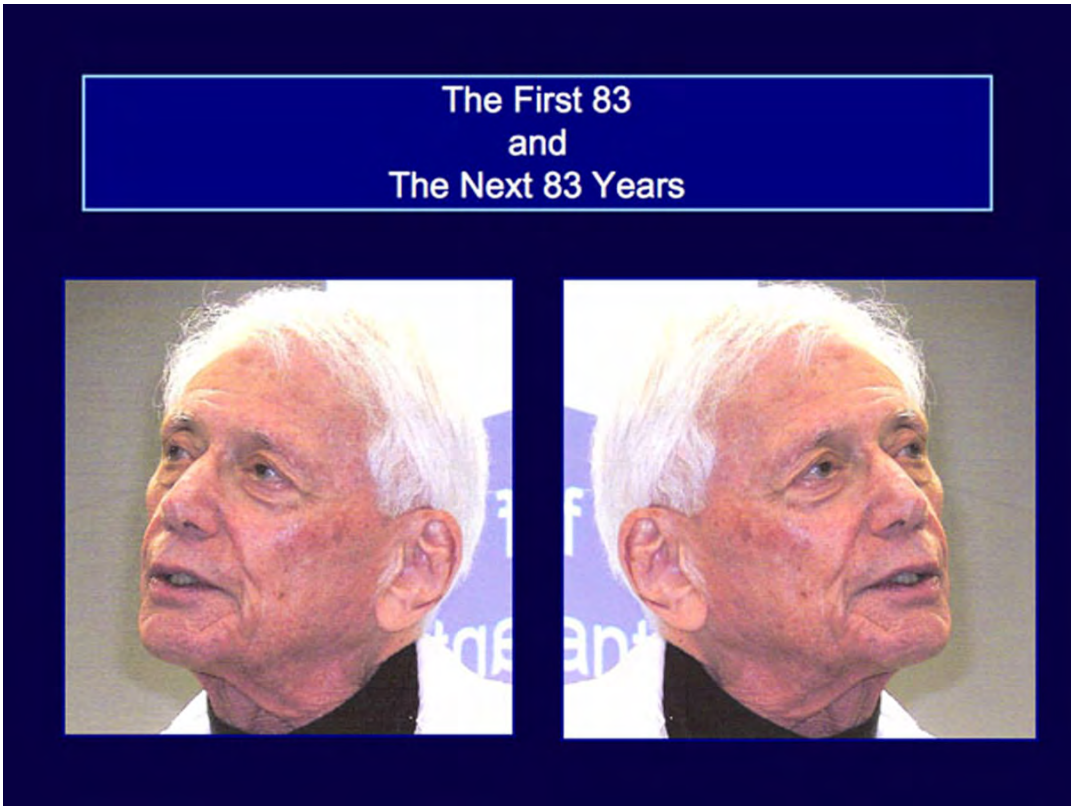

Figure 1.
a backward and forward view.

Figure 2.
HG Wells, the author, and a poster advertising the motion picture based on his novel.

Figure 3.
The Spirit of St. Louis, the plane with which Charles Lindbergh made the first transatlantic crossing by air.

Figure 4.
Covers of the pulp magazine *Flying Aces*, which fed the author's fascination with aviation.

Figure 5.
Lower left: photo of the author's B-24 crew, deployed in the Pacific during World War II. Upper right: B-24 bombers in formation. Lower right: the author with a fellow radio operator-gunner from another crew in his squadron.

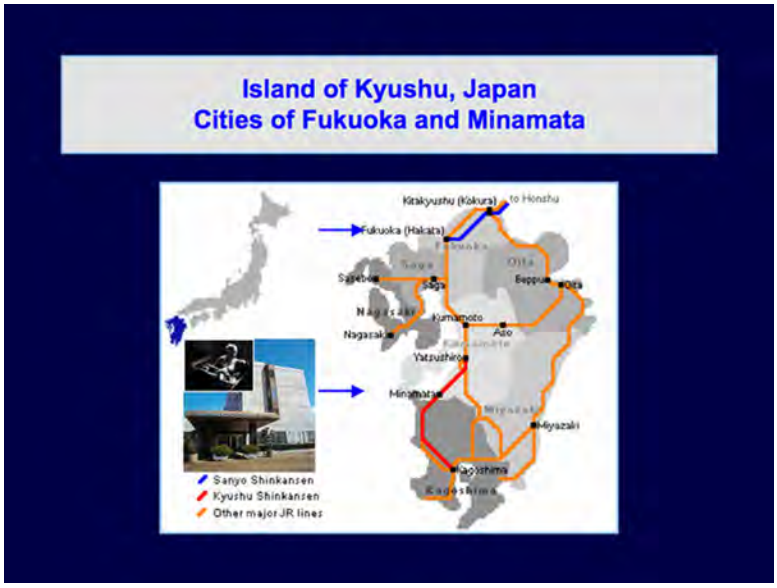

Figure 6.

Railway map of the southernmost Japanese island of Kyushu. Following the end of hostilities in 1945, the author's squadron moved to the air base at Fukuoka, located about two hours from Minamata. Inset: the Minamata Research Institute, and the famed photograph by Eugene Smith of a victim of the methylmercury poisoning tragedy at Minamata.

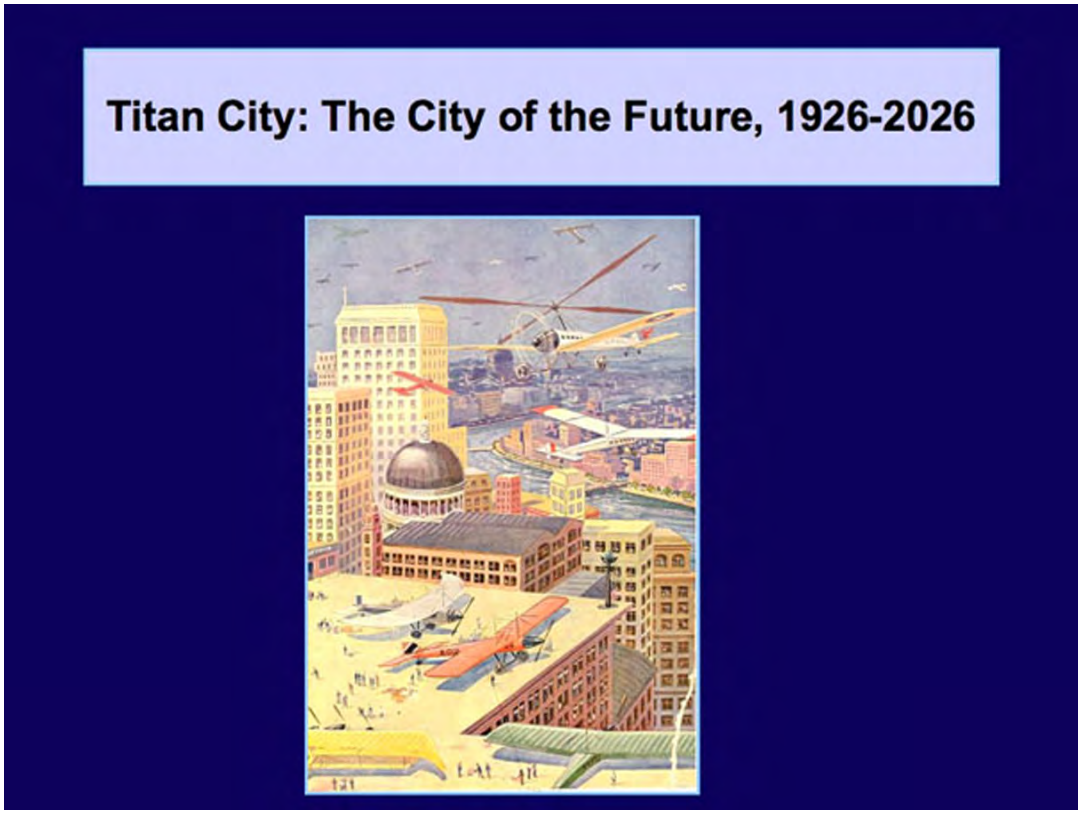

Figure 7.
A futurist's view from 1925, the year of the author's birth, of the modern city.

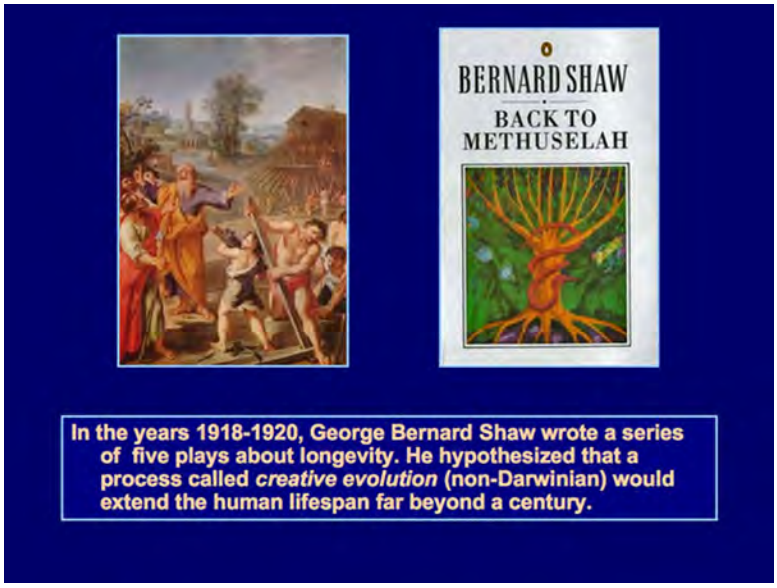

Figure 8.
Depicting the prediction of George Bernard Shaw about advances in longevity brought about by a form of evolution that today might be called epigenetics. The painting shows Methusaleh and his household.

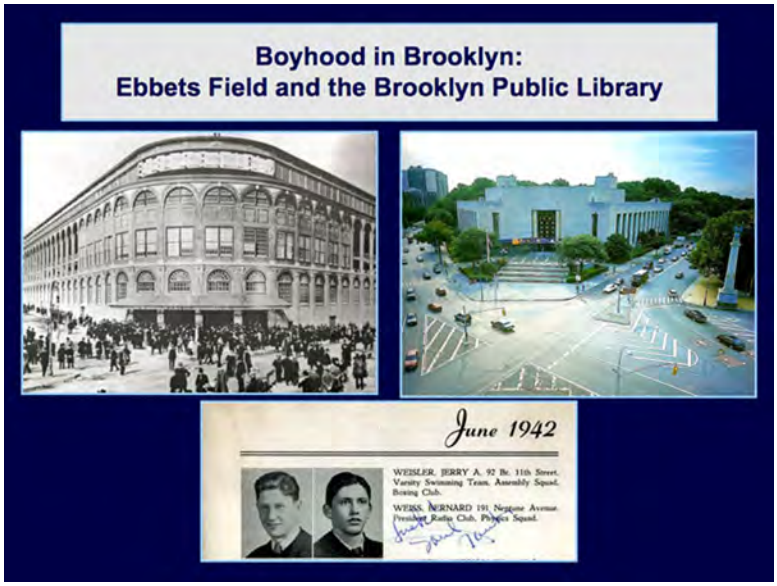

Figure 9.

Left: Ebbets Field was the baseball stadium that was home to the Brooklyn Dodgers, the team that broke the racial barrier when they took on Jackie Robinson. Right: The Brooklyn Public Library's main building, where the author found a world of books. Below: the author's entry in the 1942 yearbook of Abraham Lincoln High School.

Figure 10.
Upper right: the Bronx campus of Hunter College, opened to returning veterans in 1946. It had been converted to a training site for female navy personnel during the war. Upper left: the campus of Brooklyn College, attended by the author 1947–1948. Lower left: Washington Square in New York's Greenwich Village and New York University, attended by the author 1948–1949. Lower right: the author and friends from Brooklyn in 1948.

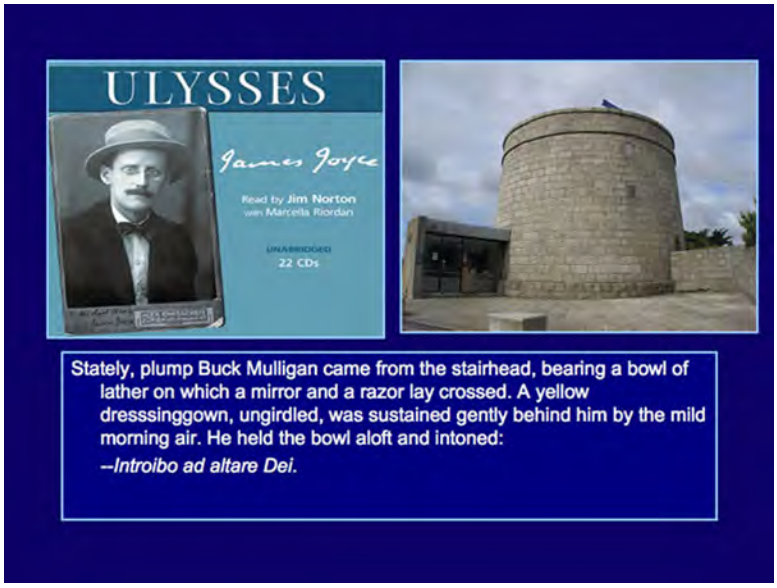

Figure 11.
Left: Photograph of James Joyce on an album cover of readings from the writer's novel *Ulysses*. Right: the Joyce museum in Sandymount, outside of Dublin. Bottom: the first sentence of *Ulysses*.

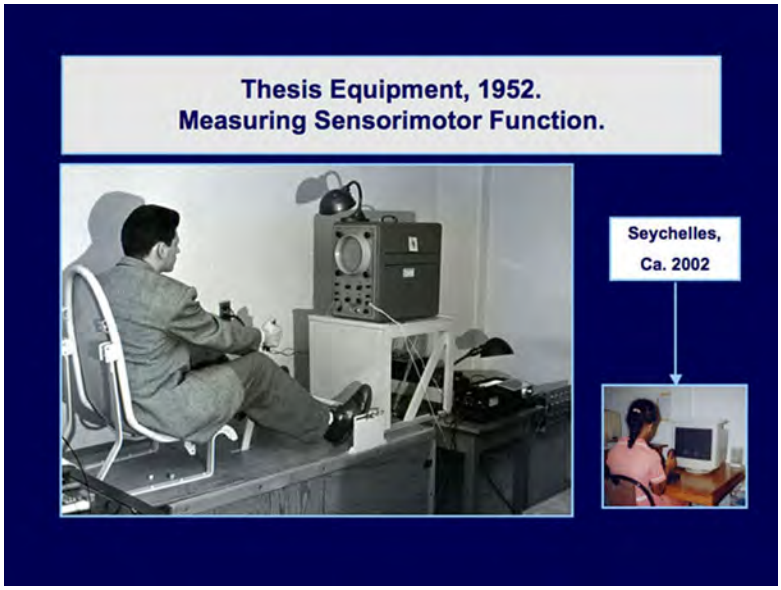

Figure 12.

The author majored in Psychology during his last college year, and went on to graduate school at Rochester (1949–1953). His doctoral thesis underook a study of variables involved in the precision of sensorimotor function using the system shown here that he designed and constructed for the purpose (Weiss, 1954). Inset: apparatus designed by the author for the Seychelles Child Development Study.

Figure 13.
The School of Aviation Medicine of the US Air Force at Randolph Field, Texas, where the author worked 1954–1956.

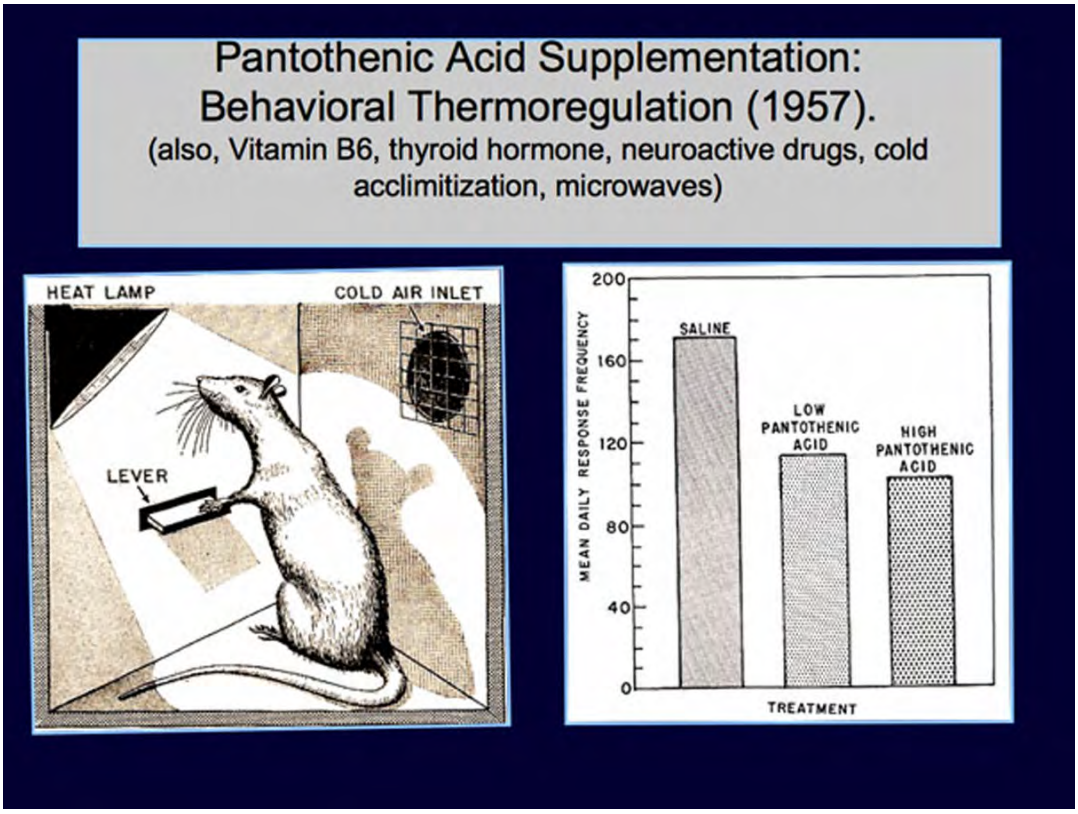

Figure 14.

One of the reseach projects undertaken by the author at the School of Aviation Medicine. Shaved rats in a cold environment (2° C) learn to press a lever to activate a heat lamp. Rats whose diets lack the vitamin pantothenic acid press at higher rates than rats supplemented with it, presumably because they cannot produce as much heat metabolically (Weiss, 1957). We later found behavioral thermoregulation to be sensitive to thyroid function, vitamin B6, microwave fields, and neuroactive drugs.

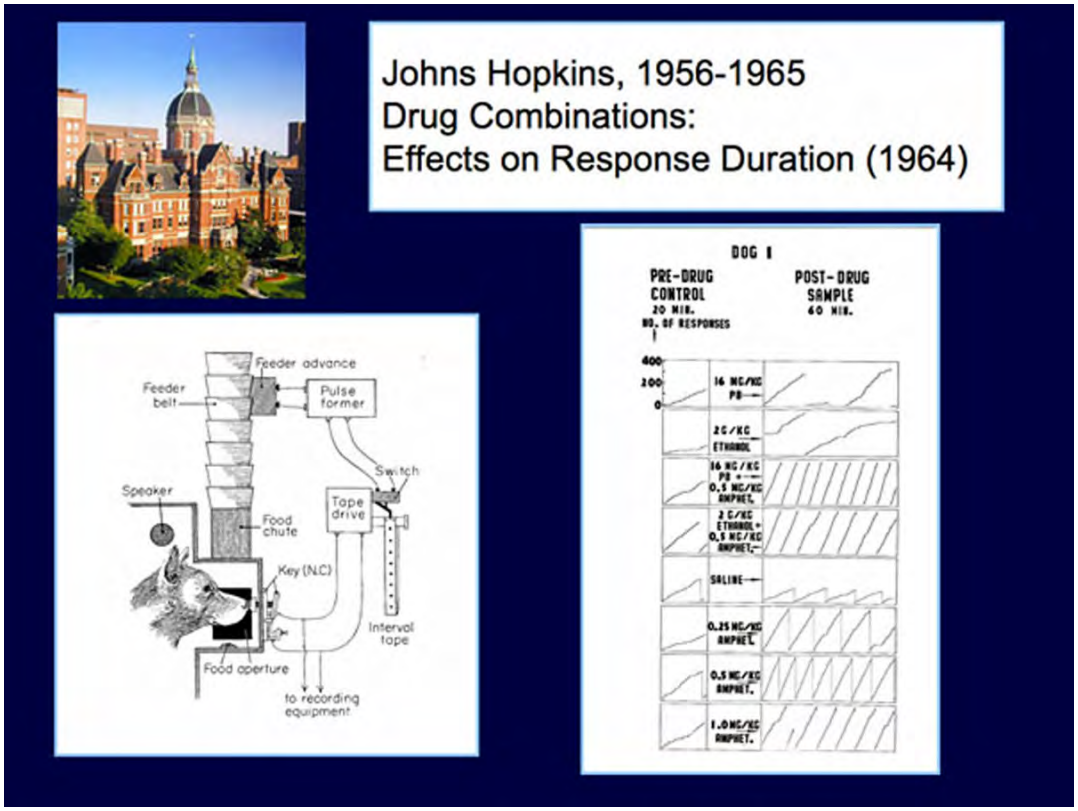

Figure 15.
At the Johns Hopkins School of Medicine (1956–1964), the author studied thermoregulation, analgesics, and central nervous system drugs. The insets show an experiment with dogs in which the subjects received food reinforcements each time they accumulated one minute of panel pressing. When administered combinations of amphetamine or alcohol with pentobarbital, they pressed at very high rates, with very short durations.

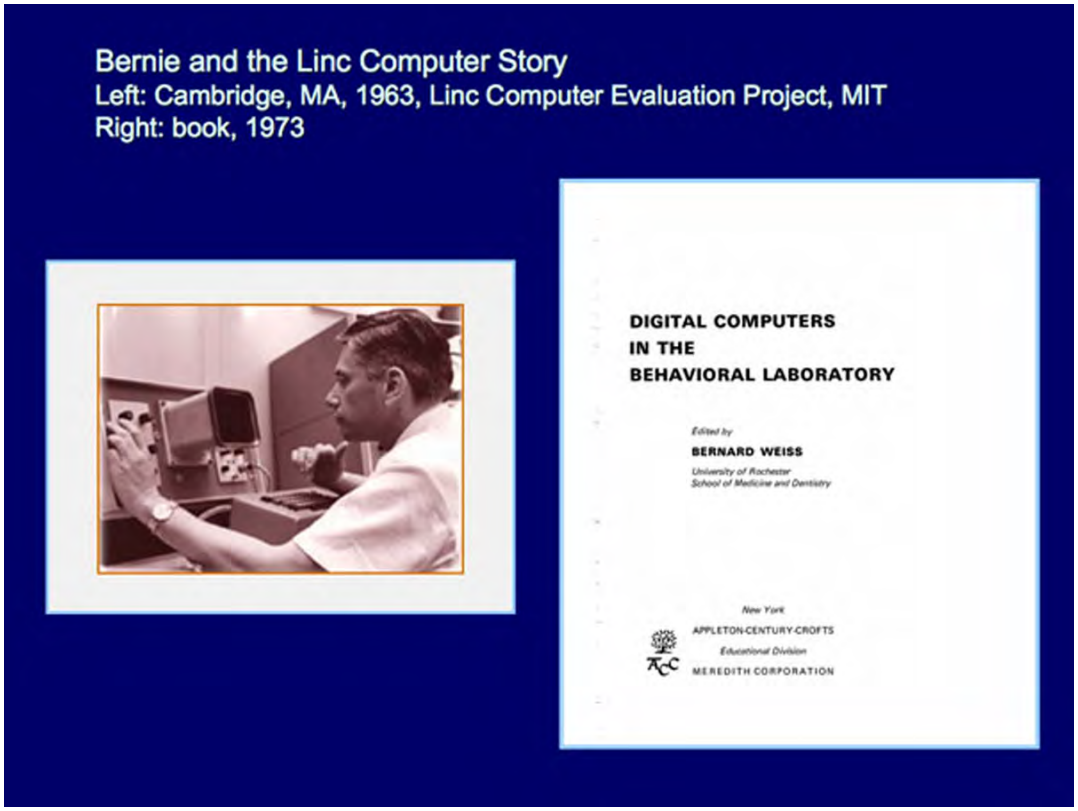

Figure 16.
Left: Author at the Linc, Cambridge MA, where he spent a month in the summer of 1963 assembling and testing his own computer and learning to program it. Right: the book (1973) edited by the author to demonstrate how digital computer techology could be used in the study of behavior and neuroscience.

Figure 17.
Top left: the Linc in the Rochester lab, 1966. Lower left: the author at a PDP-12, a successor to the Linc, in the 1970s. Lower right: other equipment in the lab plus computers, in the 1970s.

Figure 18.
A poem written by the author after a visit to the Adirondacks in the 1960s.

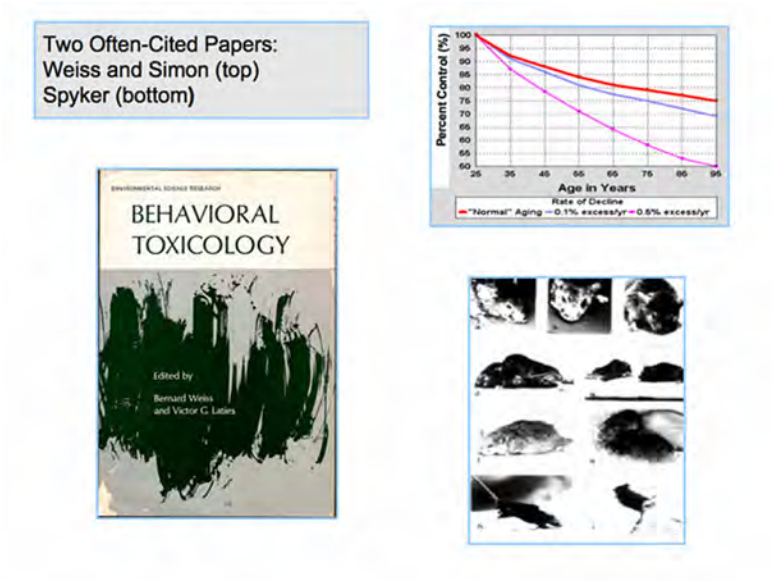

Figure 19.

Left: cover of the book, published in 1975, containing the proceedings of the first conference devoted to the new discipline of Behavioral Toxicology. Upper right: chart from Weiss and Simon (1975) showing how an environmental neurotoxicant such as methylmercury, by accelerating nerve cell loss, could lead to premature aging of the brain. Lower right: figures from chapter by Spyker (1975) illustrating how mice exposed prenatally to methylmercury develop adverse physical signs and behaviors at various postnatal stages.

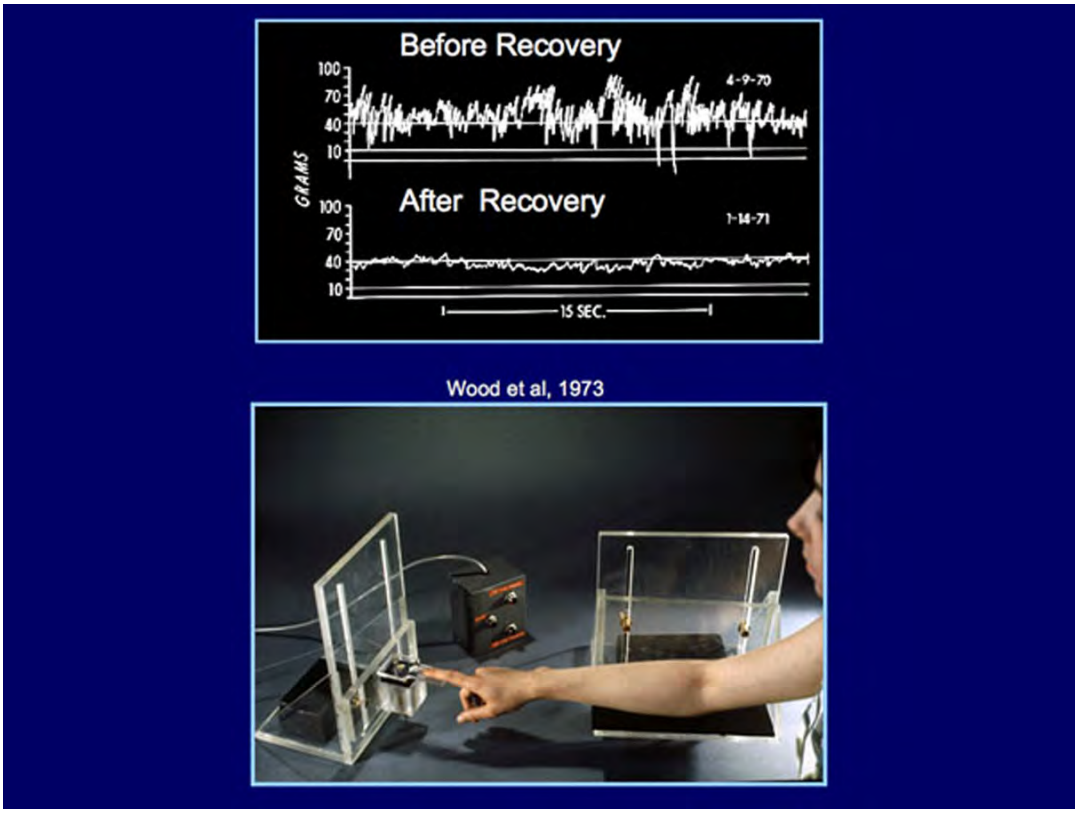

Figure 20.
A system for measuring tremor used in a study of workers exposed to mercury vapor in the course of calibrating pipettes (Wood et al, 1973). The workers were under the care of a neurologist who requested the author's assistance in quantifying the tremor. After nine months without further workplace or residential exposure, tremor amplitude returned to normal levels.

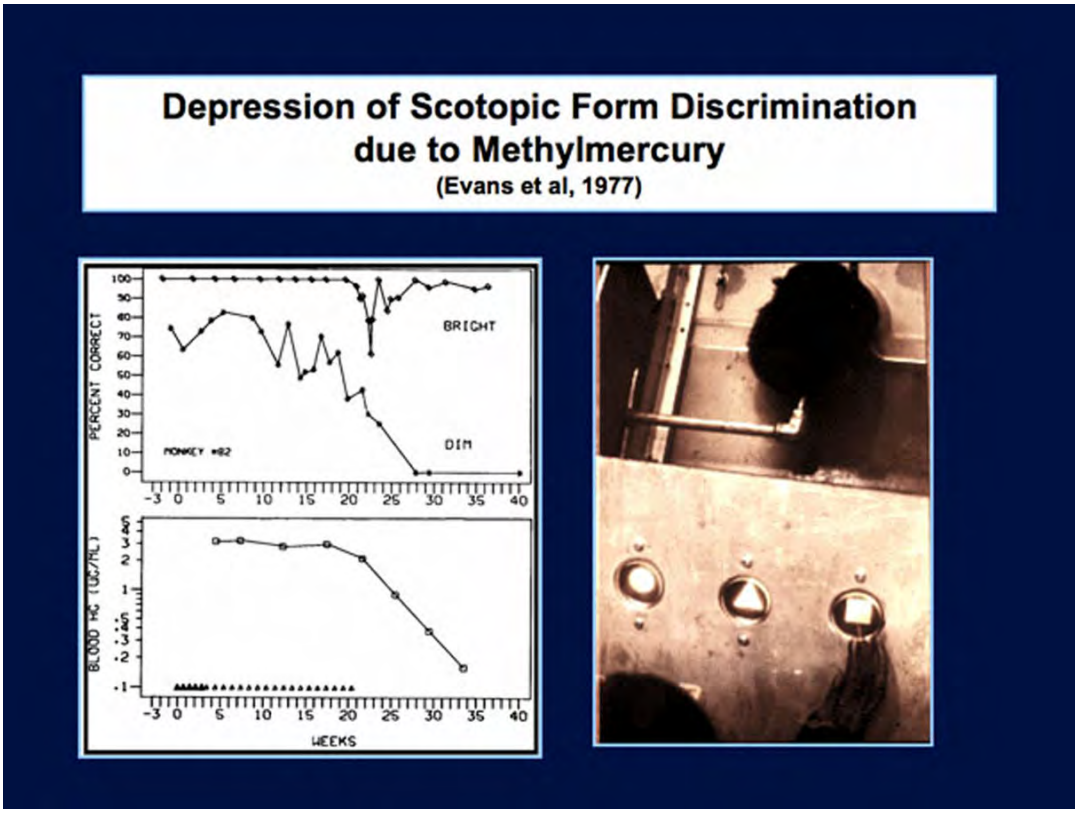

Figure 21.

The system devised in the author's lab for studying the effects of methylmercury on the primate visual system (Evans et al, 1977). The monkey subjects received juice rewards for selecting the appropriate geometric shape. The ability to discriminate dim stimuli (scotopic vision) was lost but the ability to discriminate bright stimuli recovered to preexposure levels.

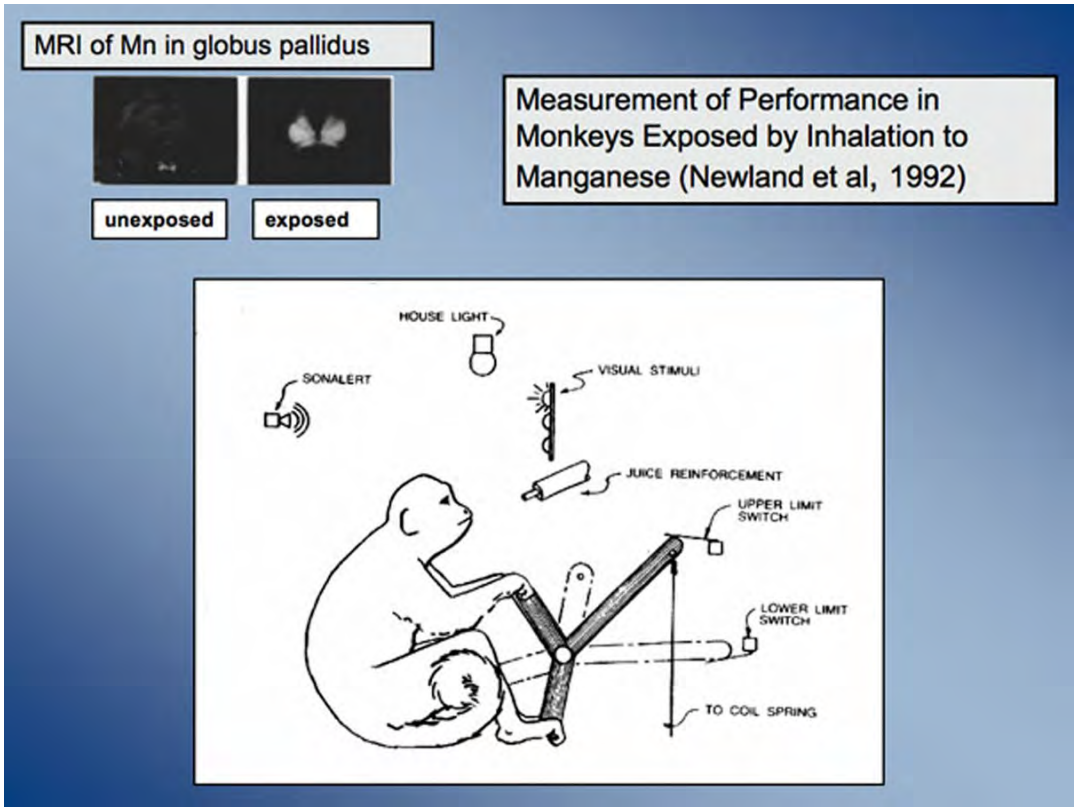

Figure 22.
System in the author's lab for measuring motor performance and fatigue in monkeys exposed to manganese (Newland et al, 1992). As shown by the MRI inset, manganese tends to concentrate in the globus pallidus. Chronic exposure led to deterioration of motor performance.

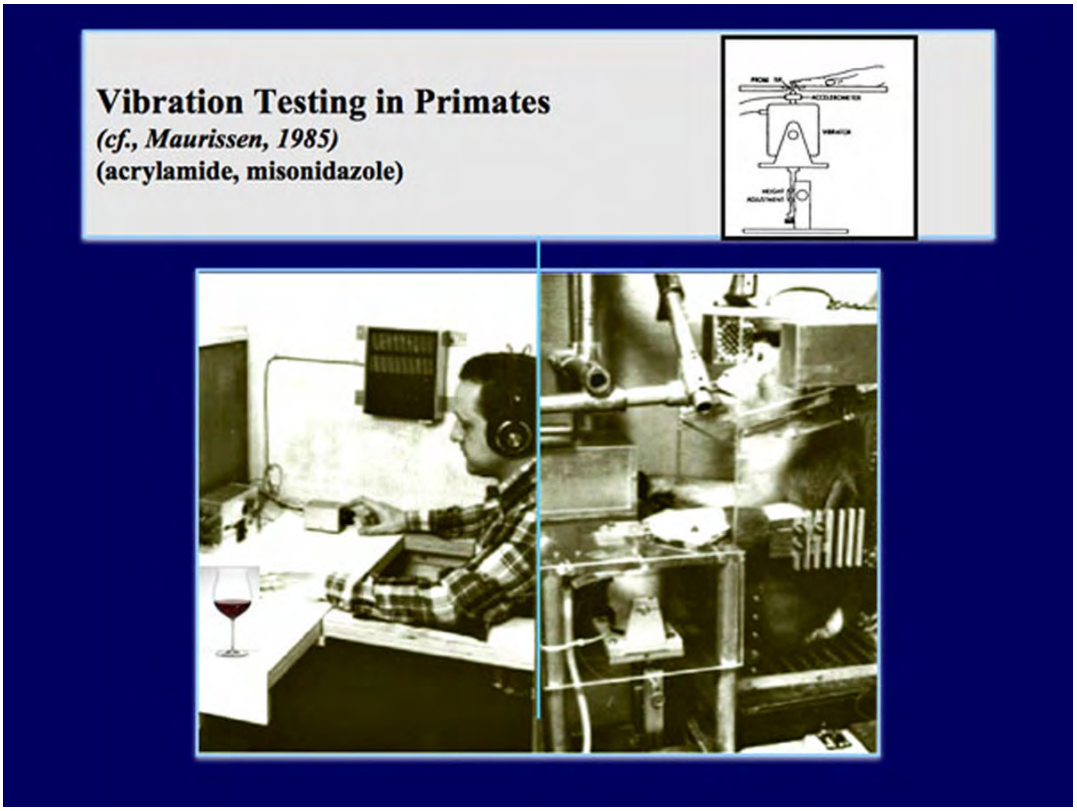

Figure 23.
Precise psychophysical measures of somatosensory function had not been undertaken when we began the work illustrated in figure 23. The inset shows the system for applying computer-controlled vibratory stimuli to a fingertip.

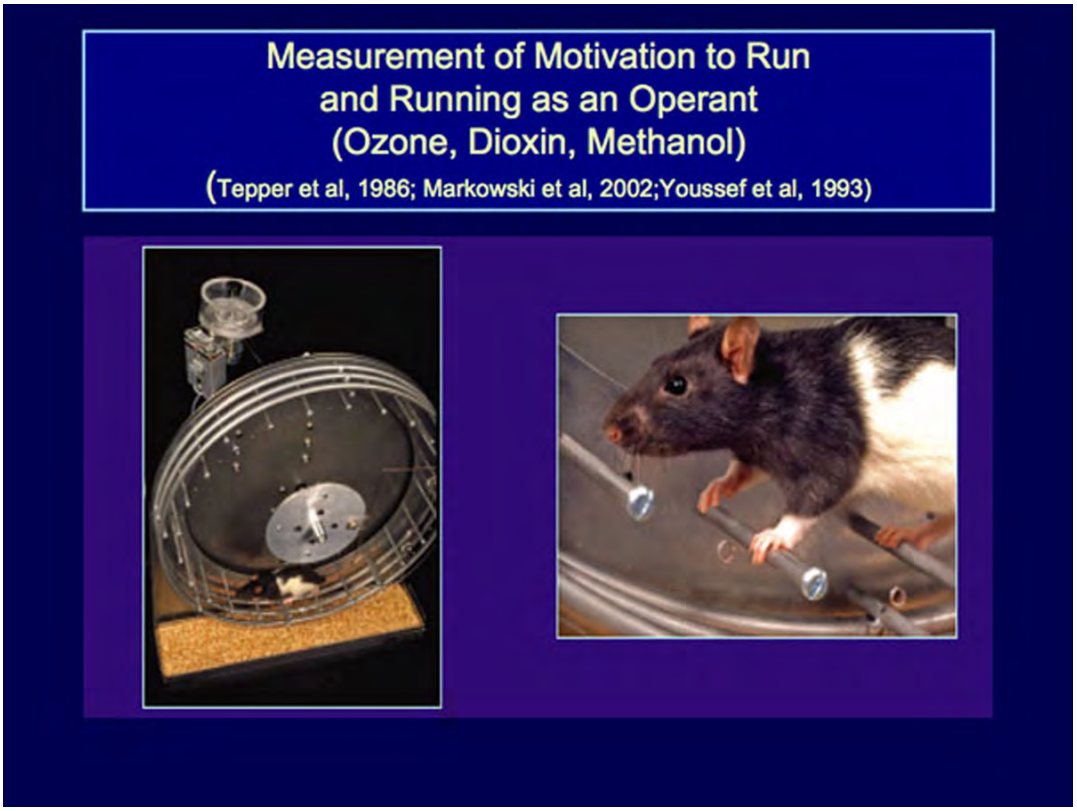

Figure 24.
Modified running wheel equipped with a computer-controlled brake, lever, and food pellet delivery chute.

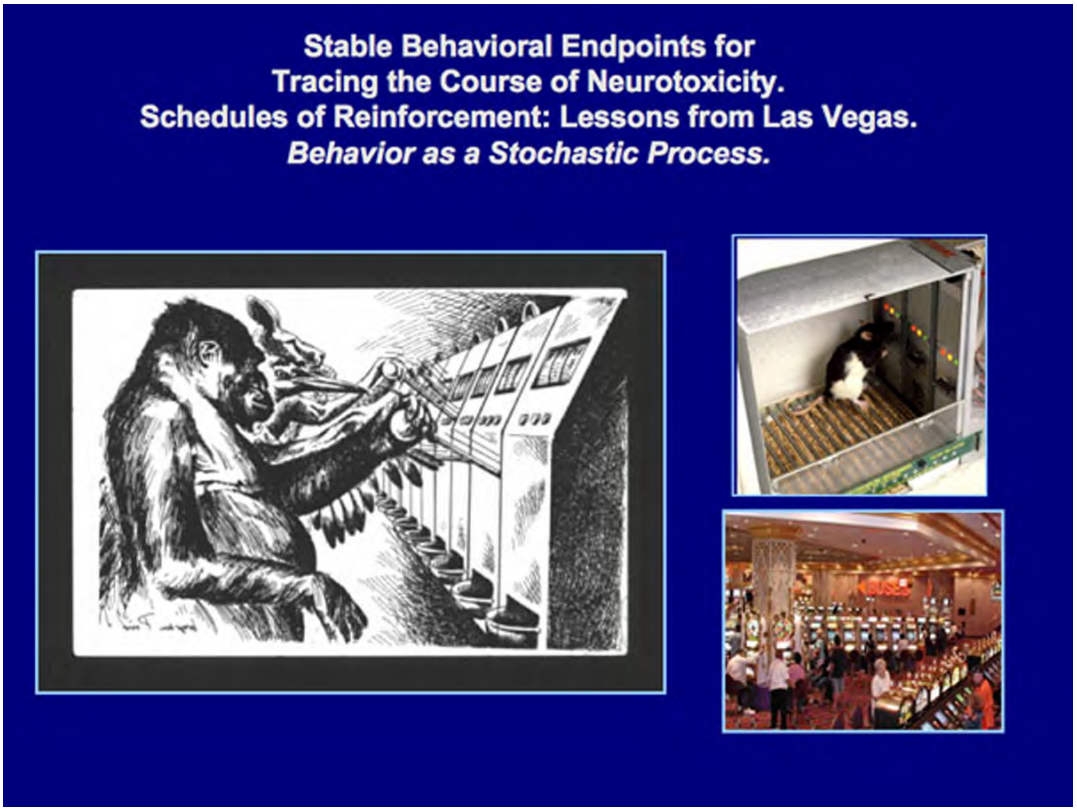

Figure 25.
Varieties of schedule-controlled operant behavior.

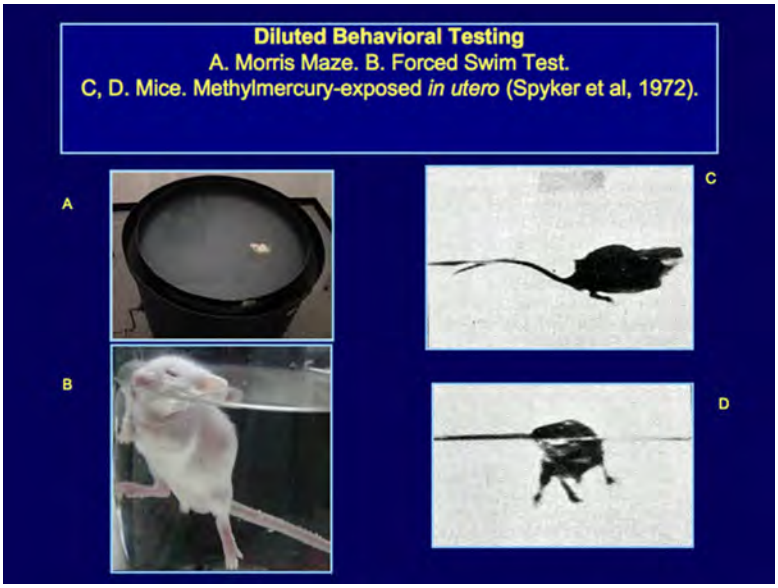

Figure 26.
The Morris maze (A). Inset B shows how a mouse or rat is placed in a container of water ("forced swim test") to measure what is called "learned hslplessness." Panels C and D show aberrant swimming postures in mice exposed prenatally to metthylmercury (Spyker, 1972).

Figure 27.
Statement of behavioral principles.

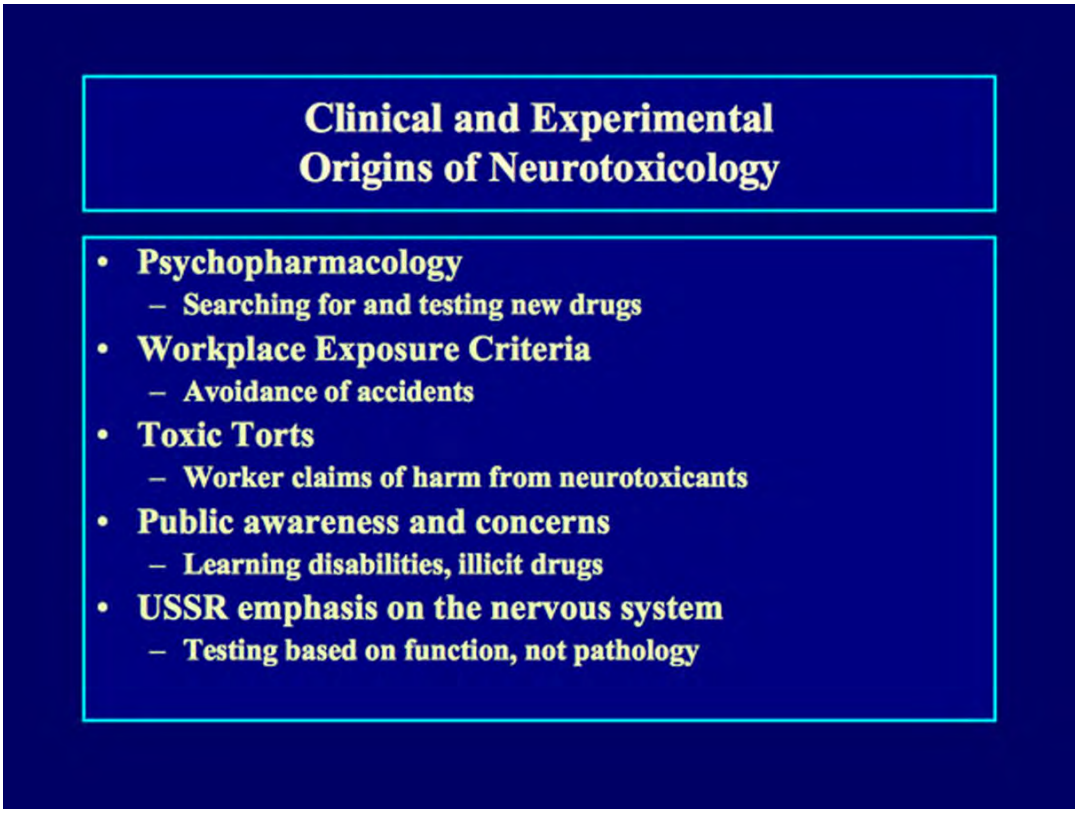

Figure 28.
Origins of neurotoxicology.

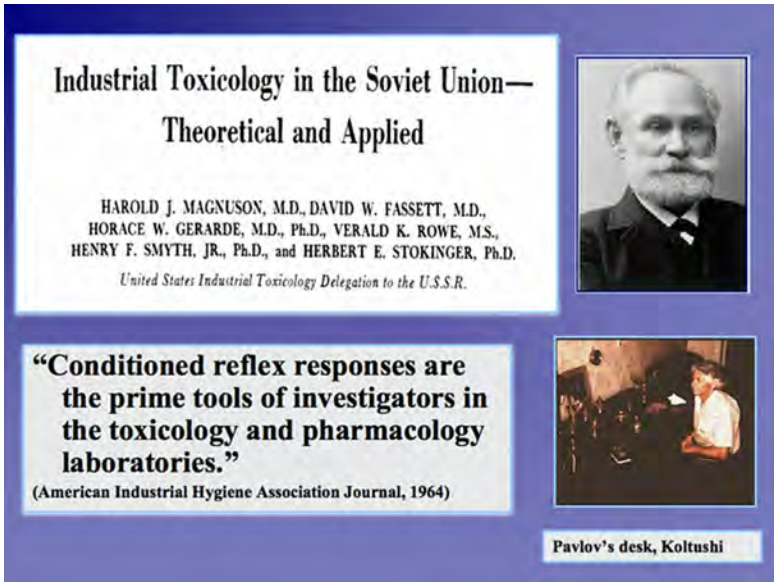

Figure 29.
Survey of USSR approach to toxicological testing.

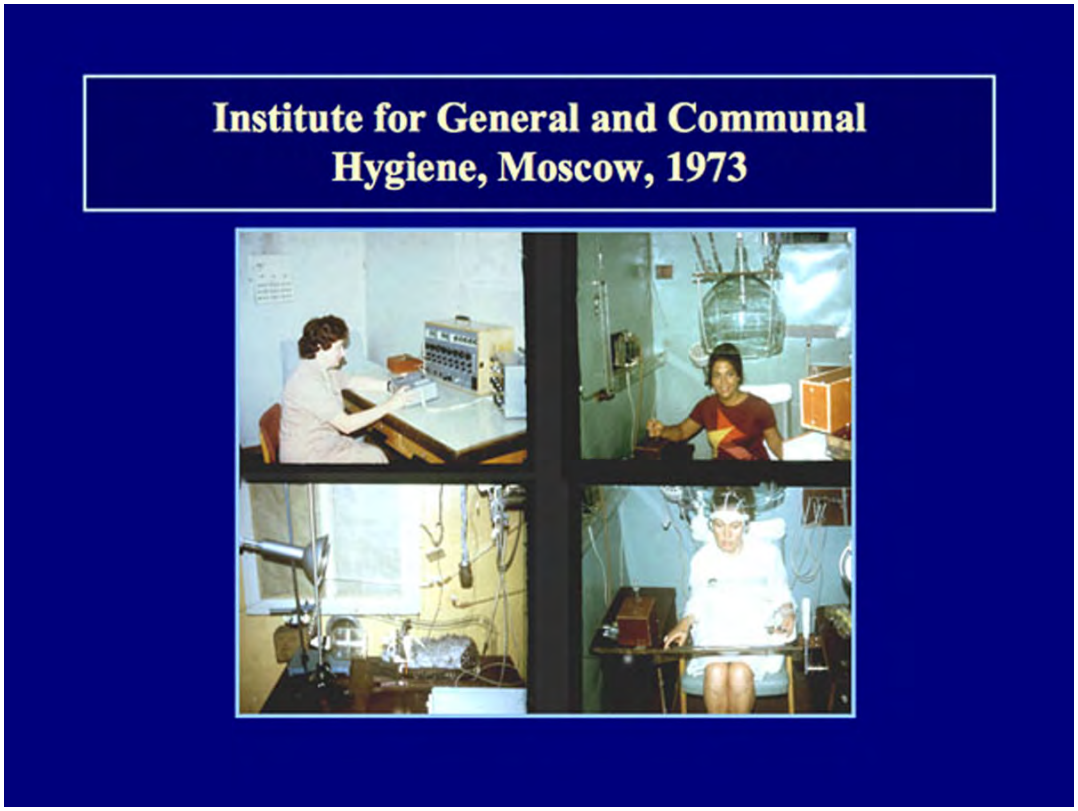

Figure 30.
Views of USSR laboratory approaches to neurotoxicology.

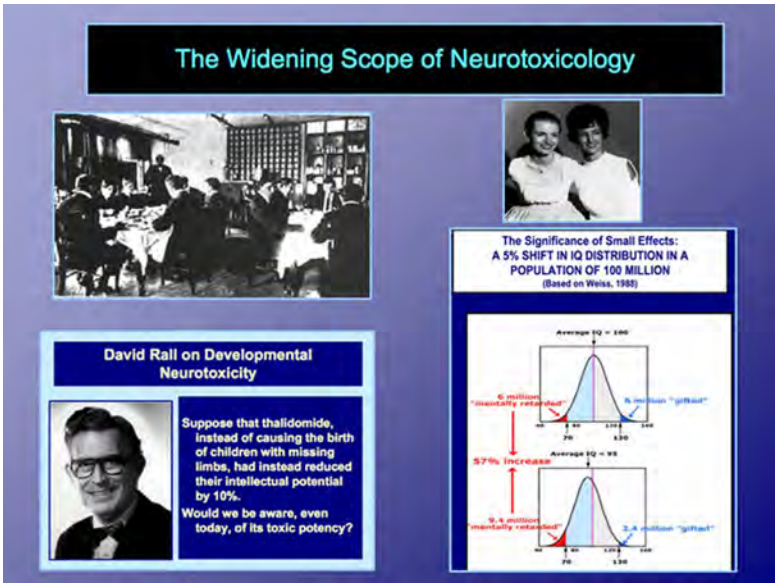

Figure 31.
Historical aspects of developmental neurotoxicology.

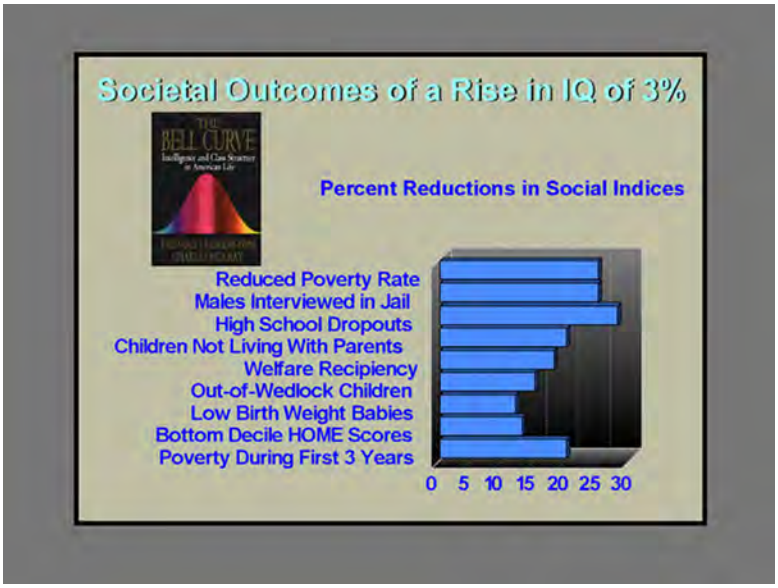

Figure 32.
Calculations based on the premises of *The Bell Curve* (Herrnstein and Murray, 1994).

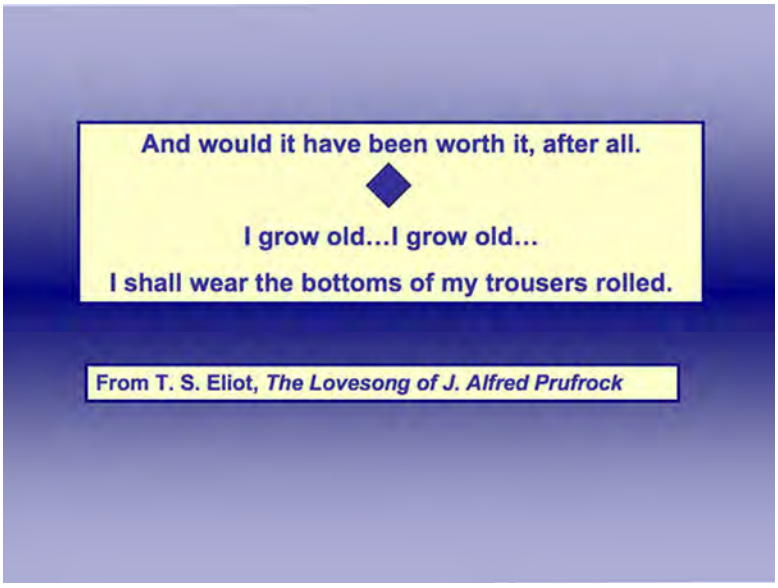

Figure 33.
The Lovesong of J. Alfred Prufrock, by the poet T.S. Eliot.

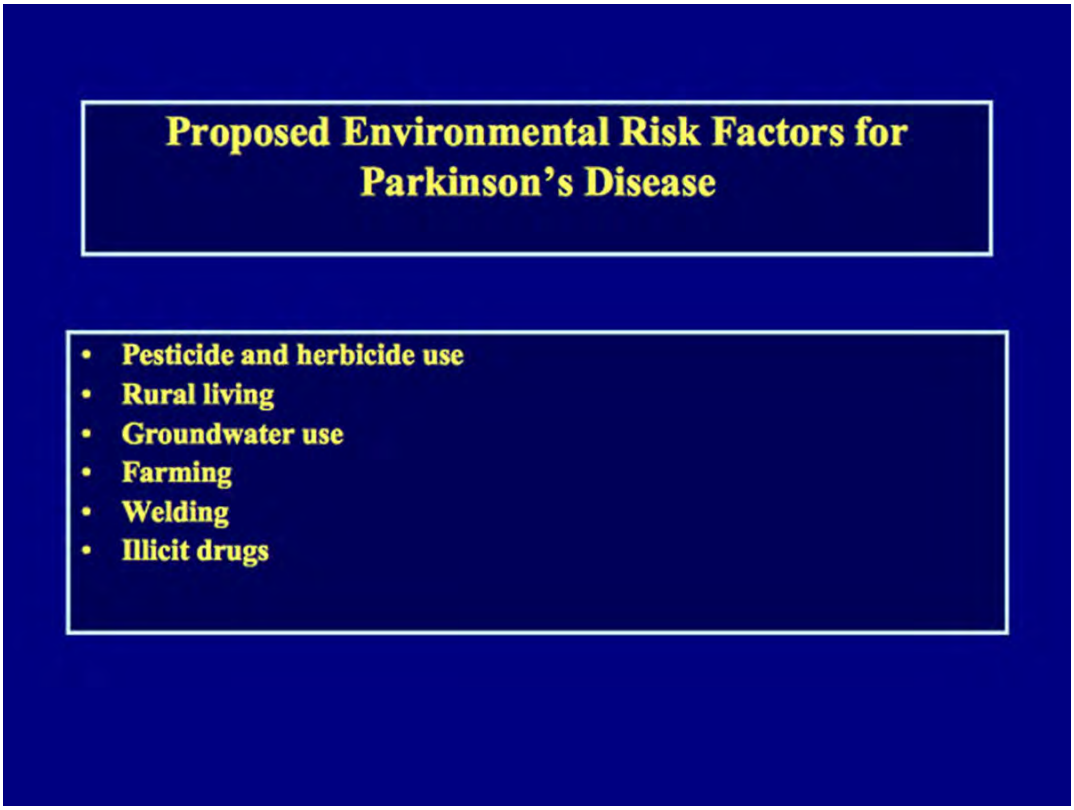

Figure 34.
Suspected risk factors for Parkinson's disease.

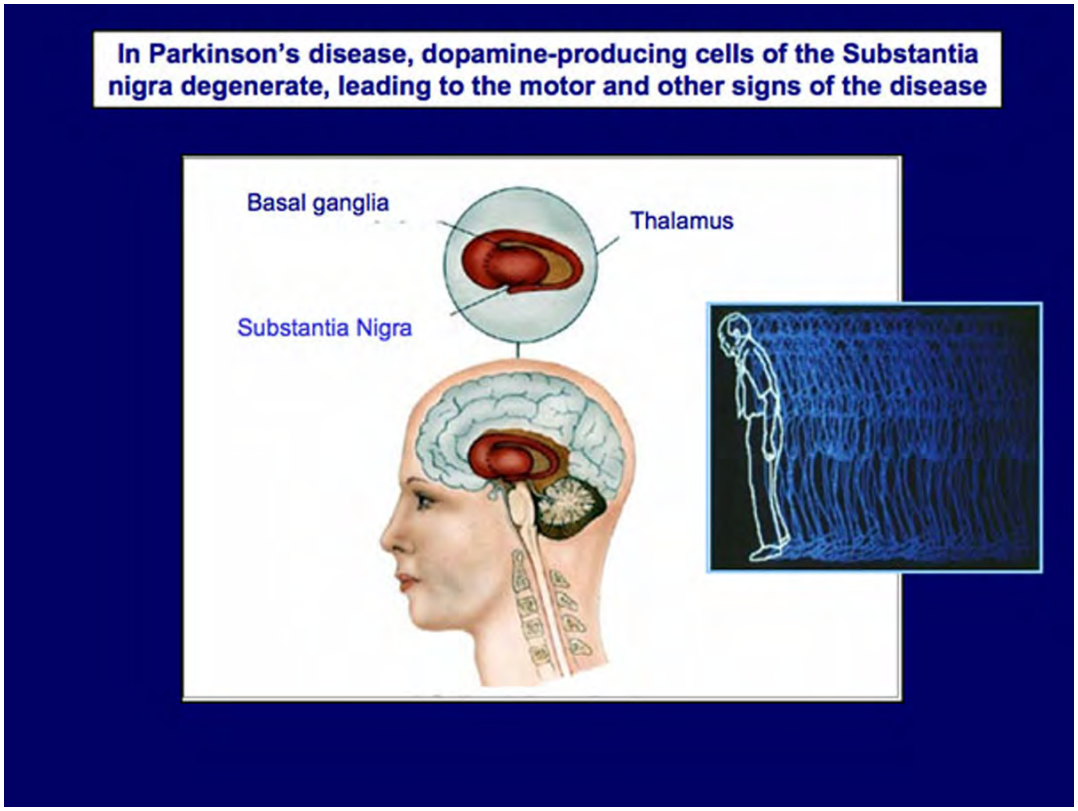

Figure 35.
Location of substantia nigra in human brain.

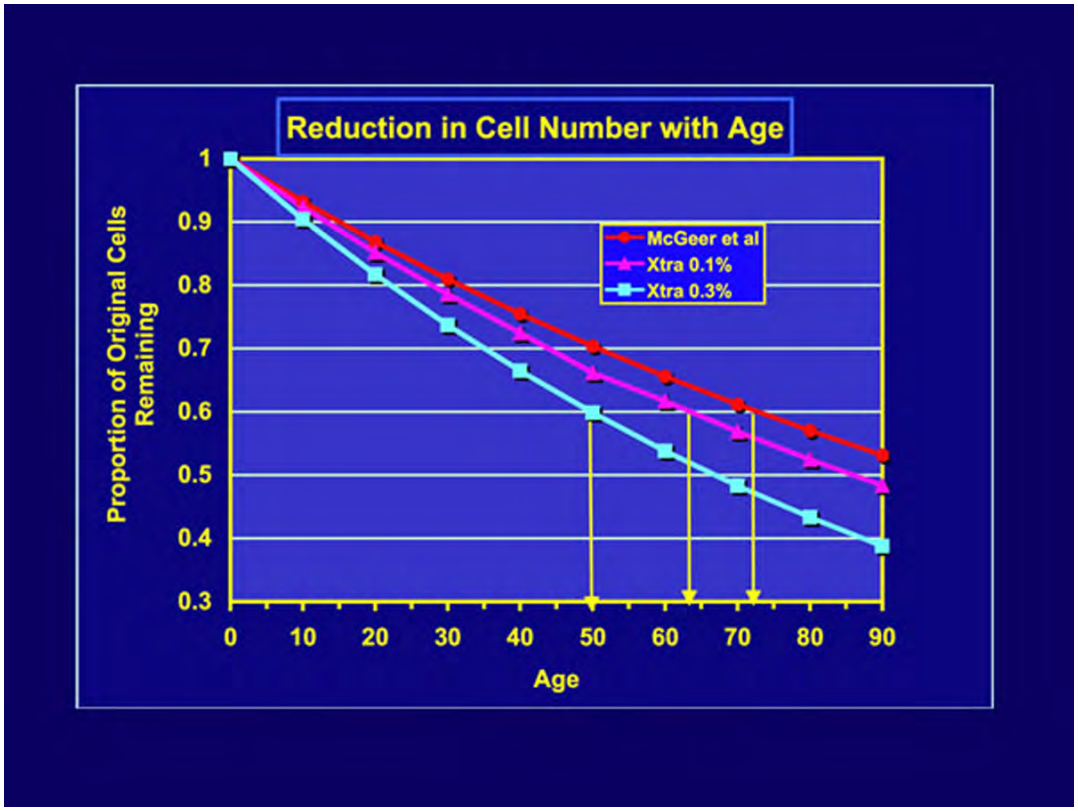

Figure 36.
Declines in substantia nigra nerve cell numbers with aging, and effects of small accelerations in rate of loss (based on McGeer et al, 1988).

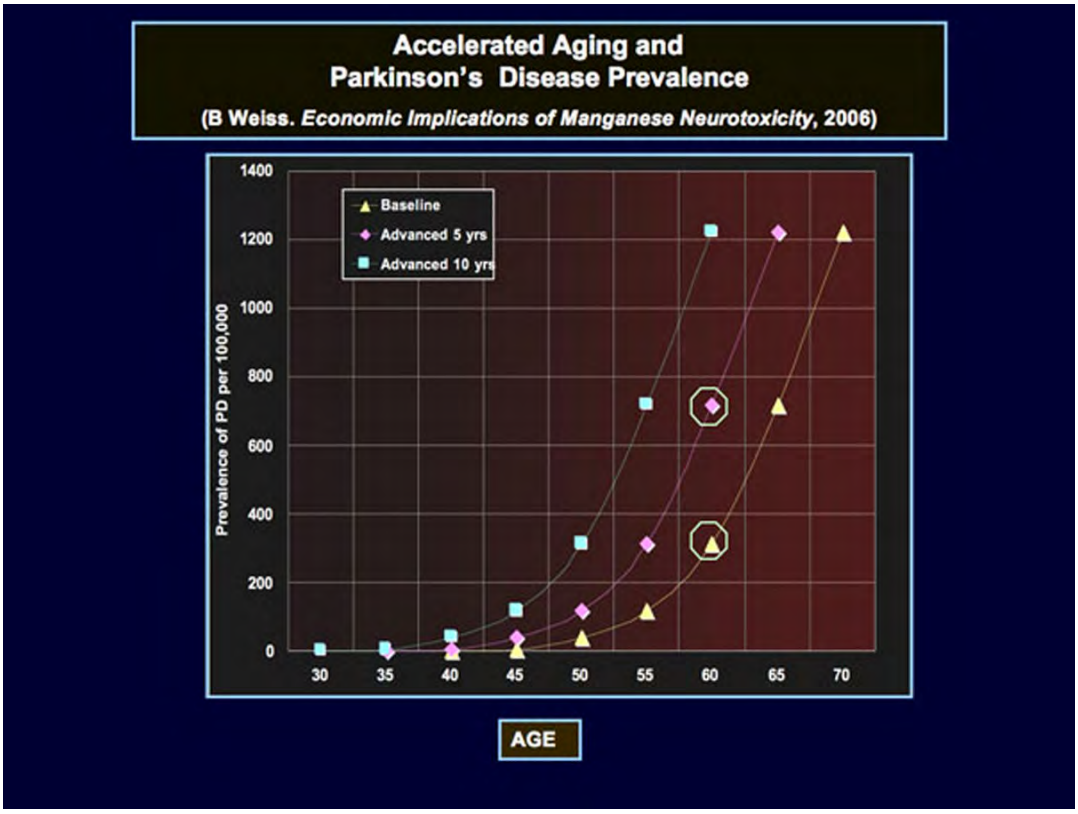

Figure 37.
Effects on Parkinson's disease prevalence of shifts in the age-prevalence function.

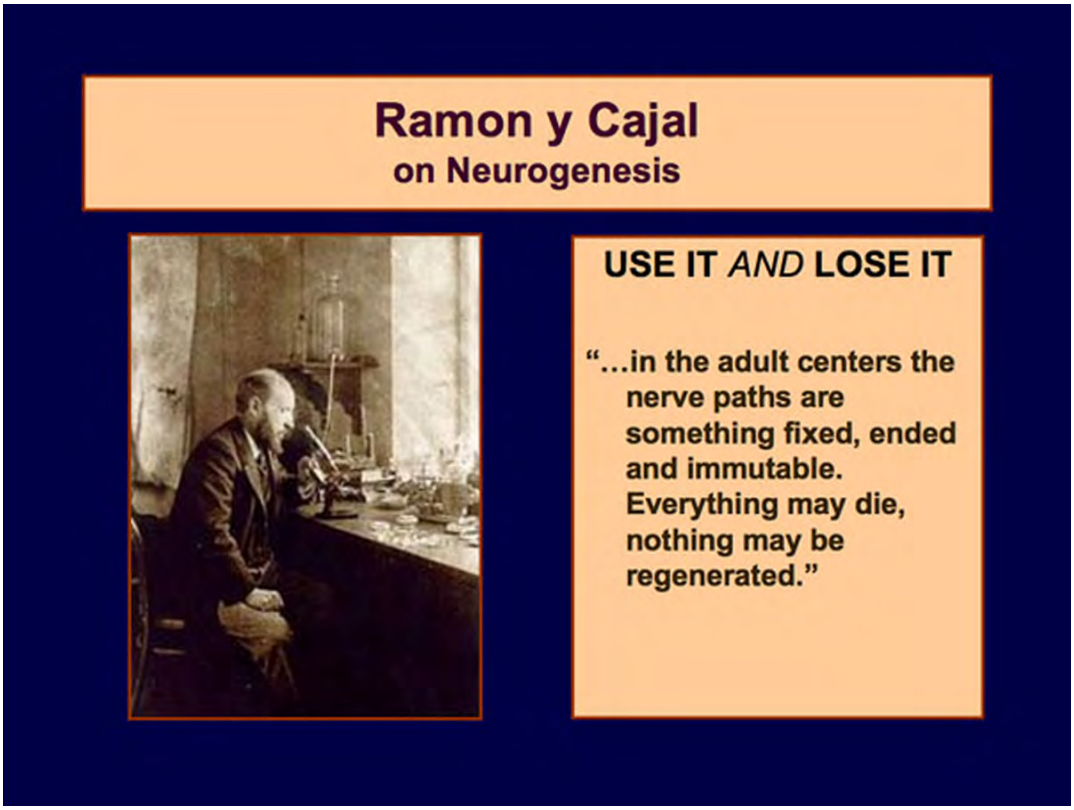

Figure 38.
Ramon y Cajal, and the doctrine of nerve cell irreplaceability.

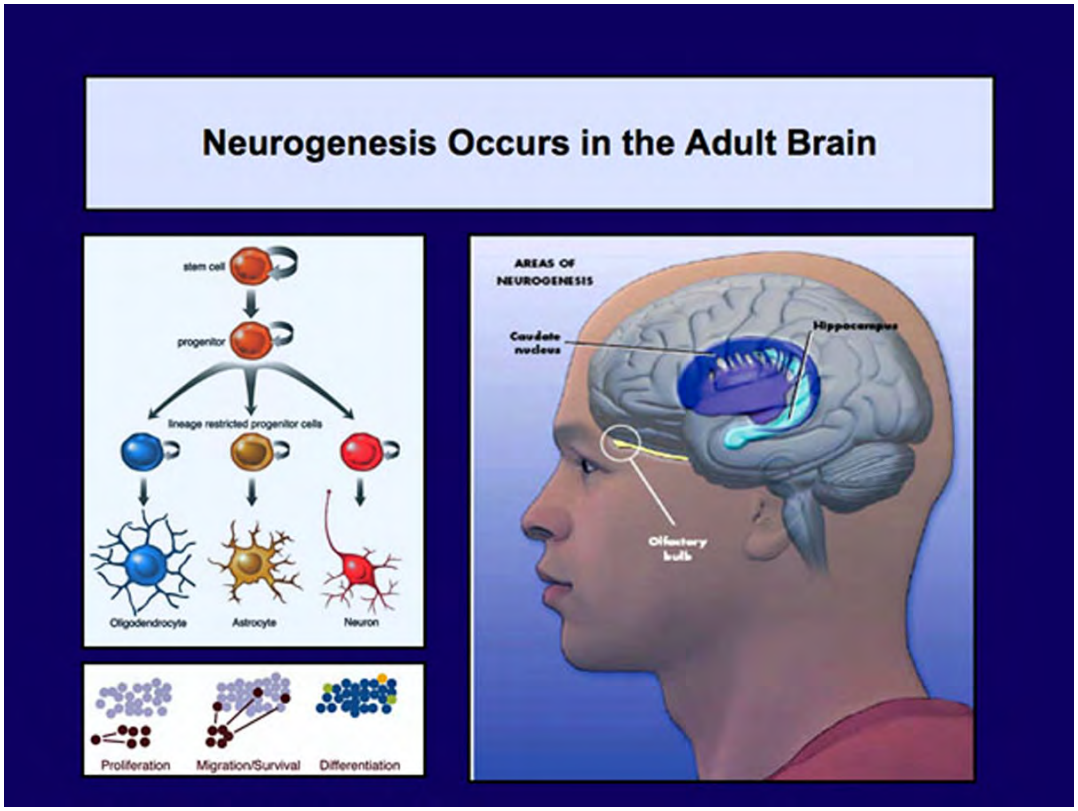

Figure 39.
Major sites of neurogenesis in adult brain.

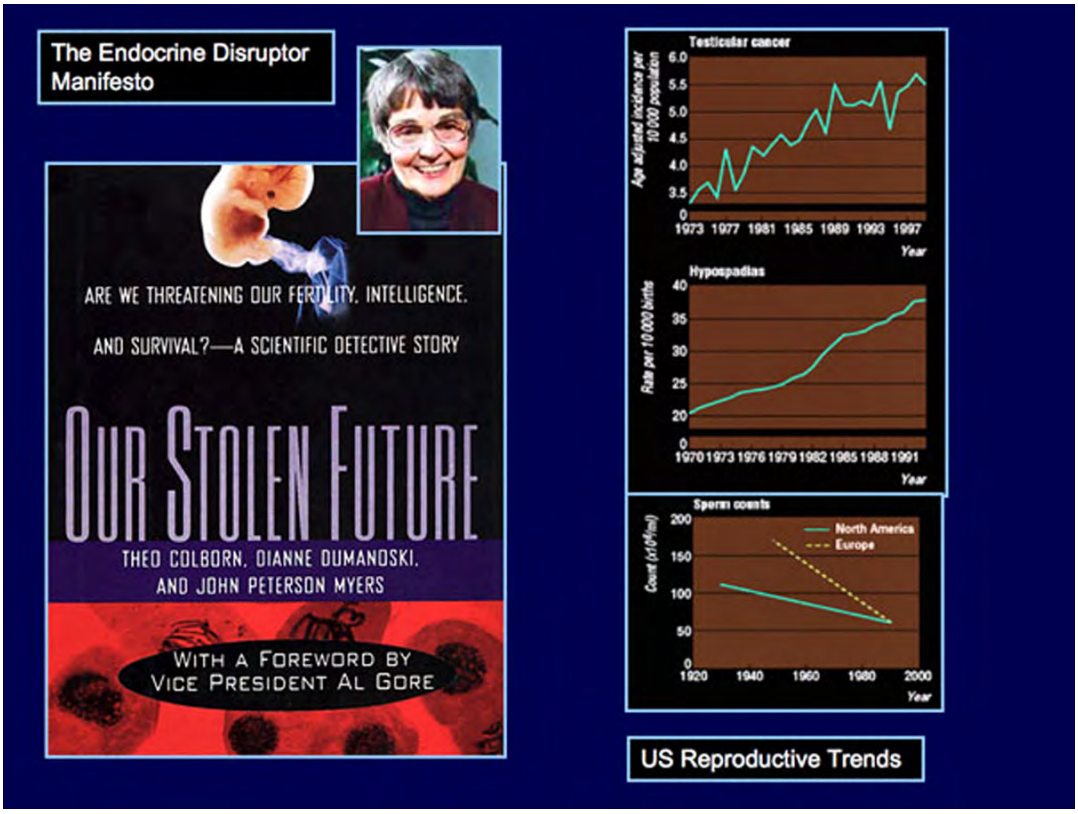

Figure 40.
Theo Colborn, the book that in essence launched appreciation of endocrine-disruption chemicals, and trends in reproductive health in males.

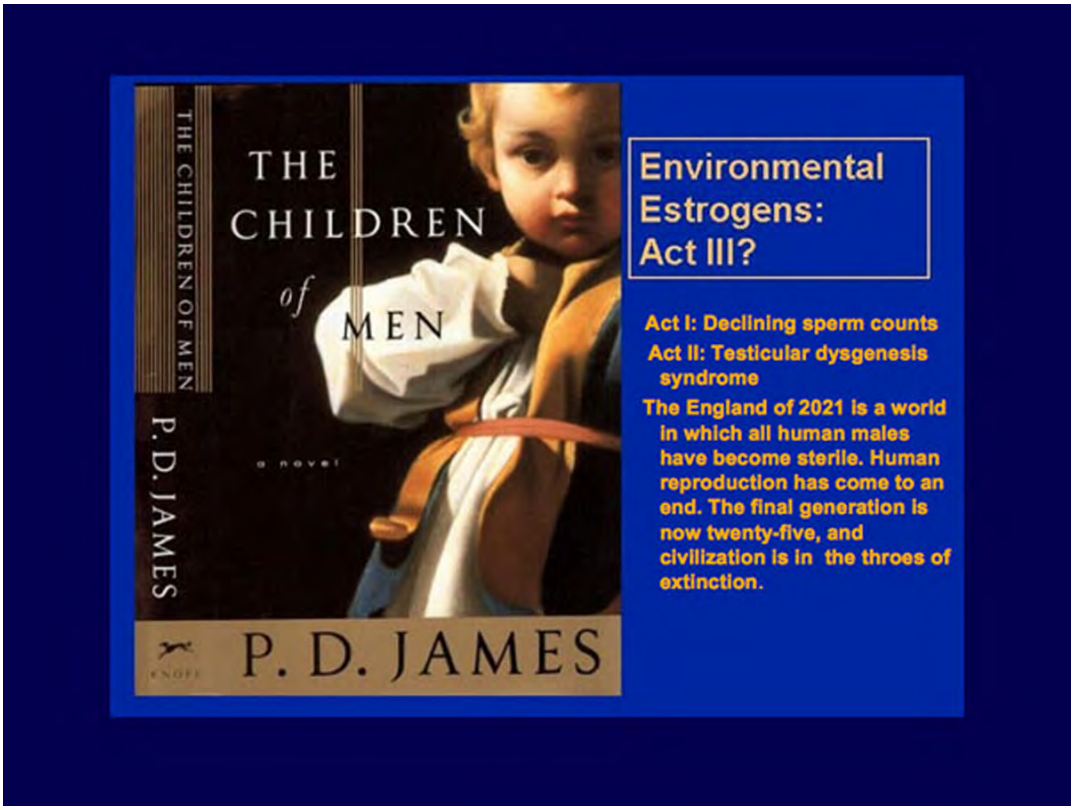

Figure 41.
A novel that translated endocrine disruption into a dystopian catastrophe.

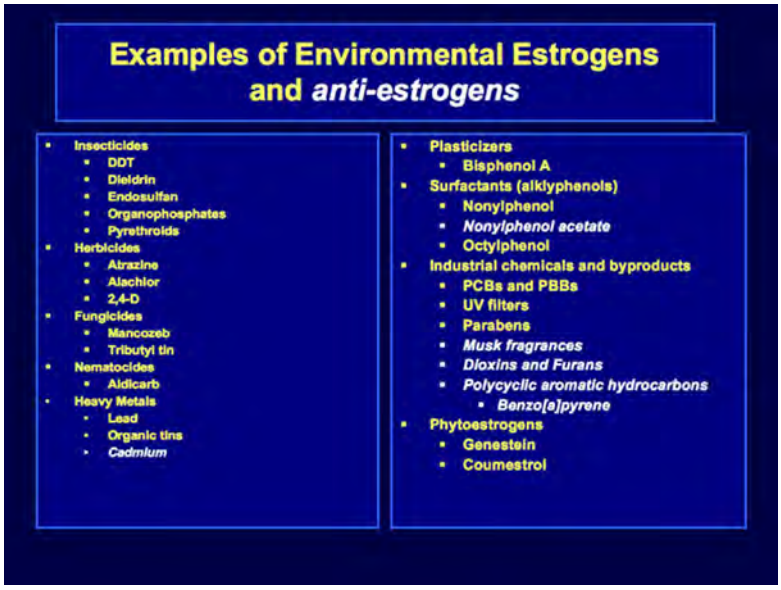

Figure 42.
Partial listing of environmental estrogens and antiestrogens so far identified.

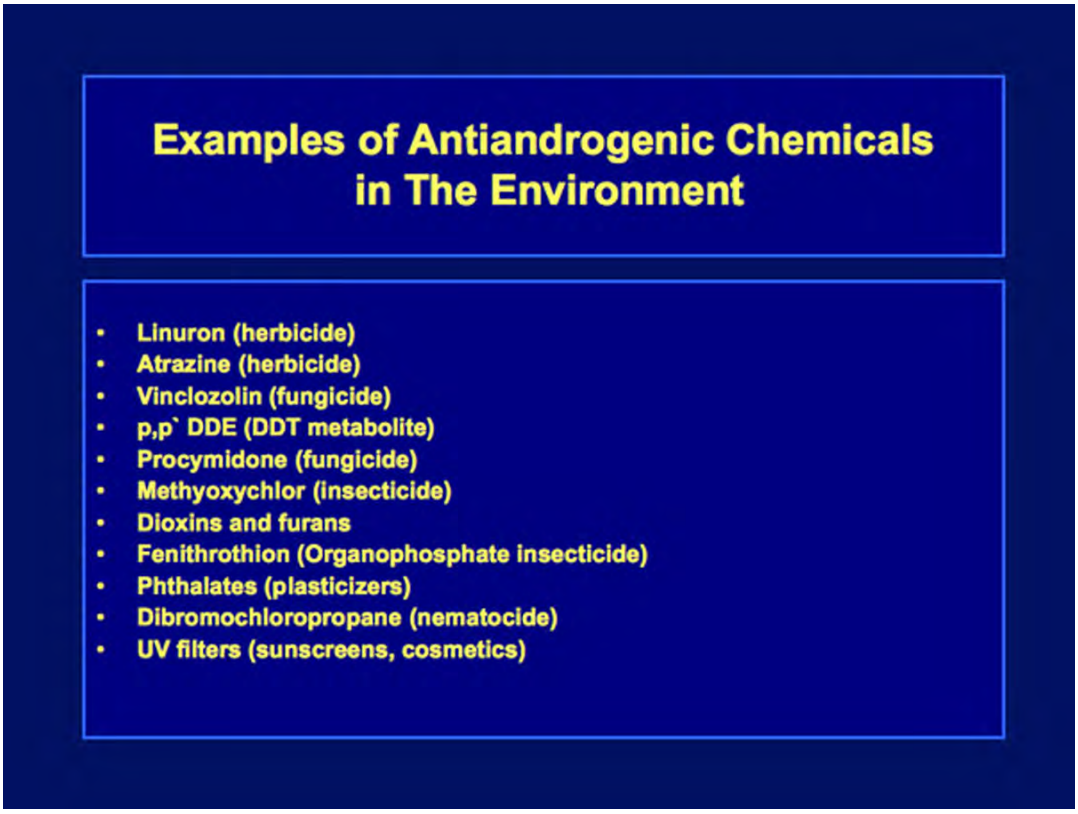

Figure 43.
Partial listing of antiandrogenic chemicals in the environment.

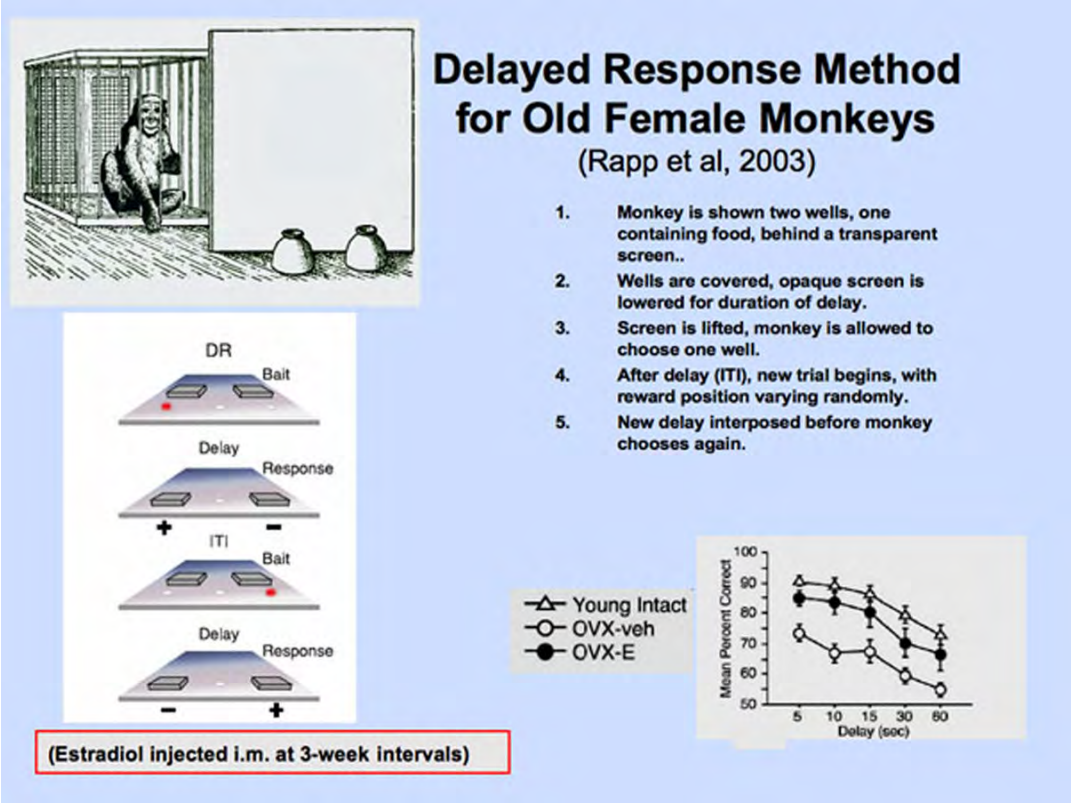

Figure 44.
Memory deficits resulting from ovariectomy can be overcome with periodic estrogen injections.

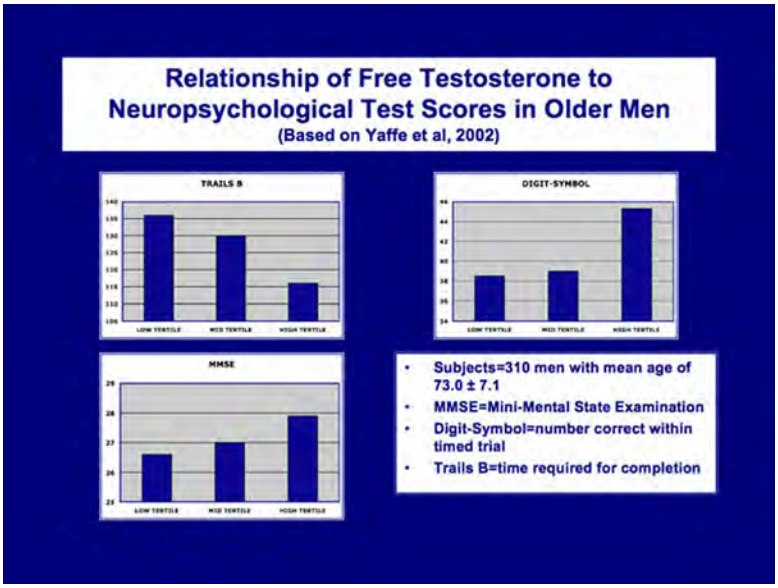

Figure 45.
Testosterone levels in older men are correlated with neuropsychological test performance.

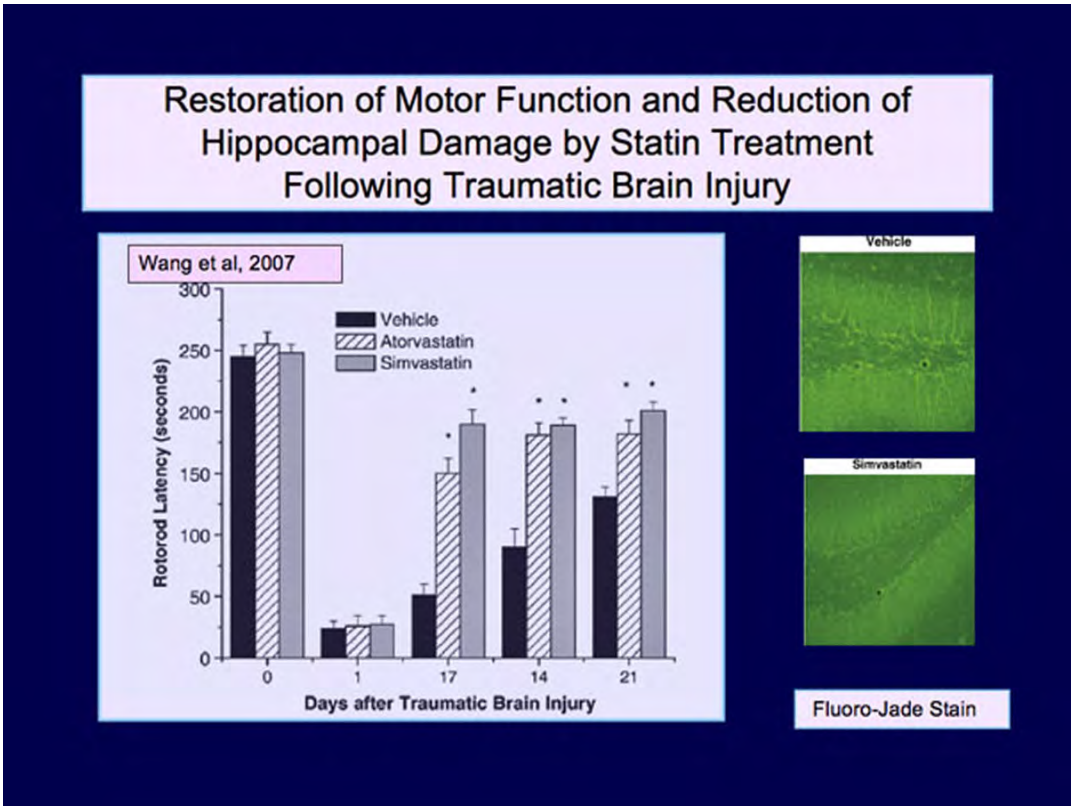

Figure 46.
Statin treatment can help restore functional and structural deficits induced by brain damage.

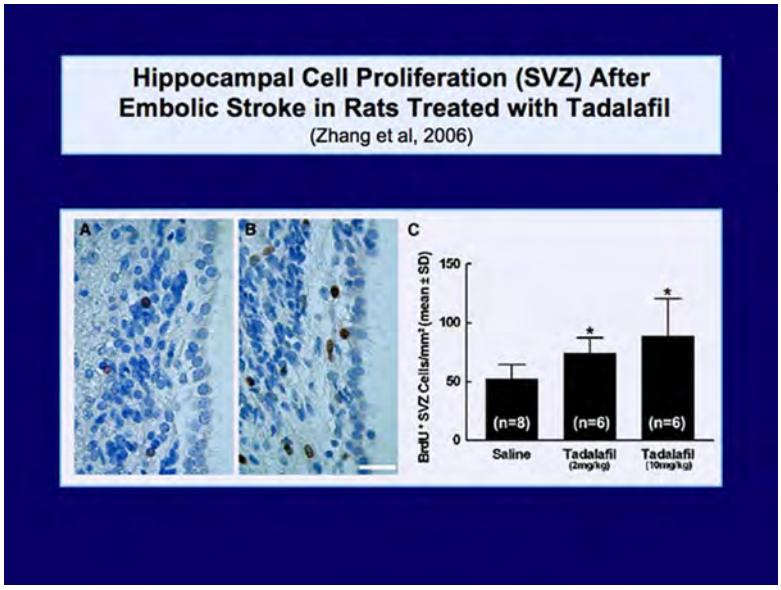

Figure 47.
Tadalafil and other phosphodiesterase-5 inhibitors can counteract damage induced by stroke.

Figure 48.
"Emergency kit" for those of advancing age at risk for heart attacks and strokes.

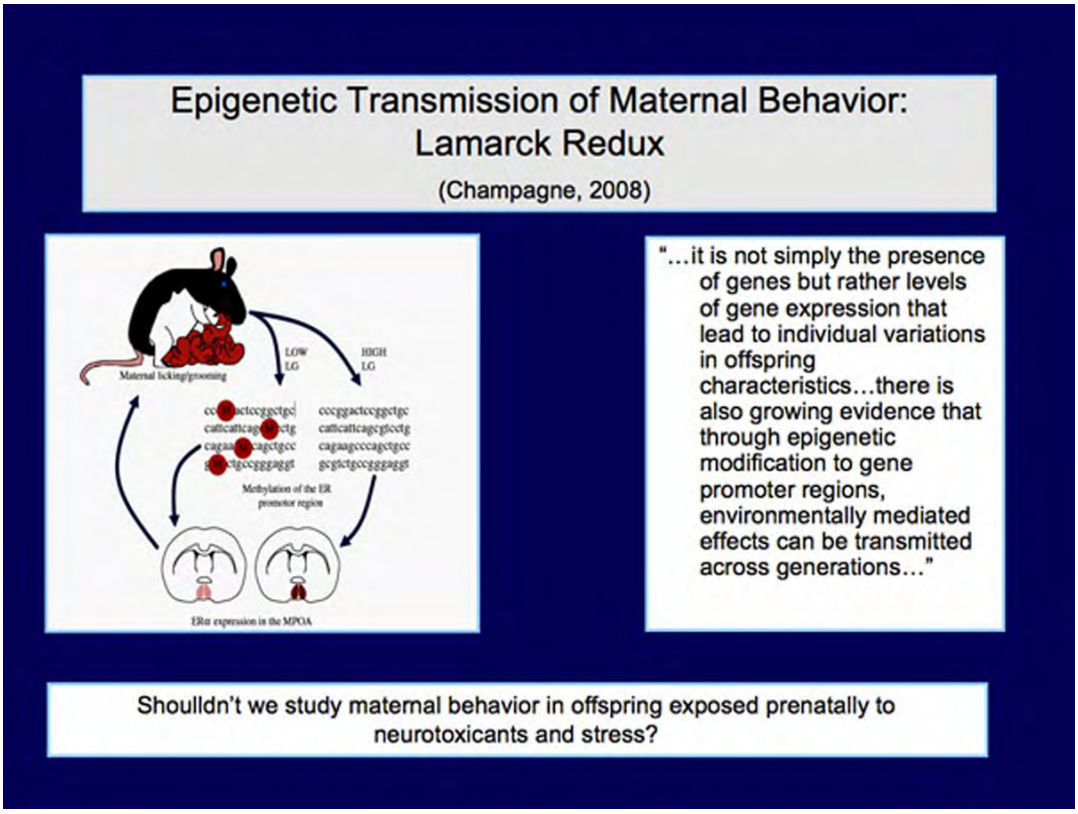

Figure 49.
Epigenetic mechanisms for transmitting maternal behavior patterns.

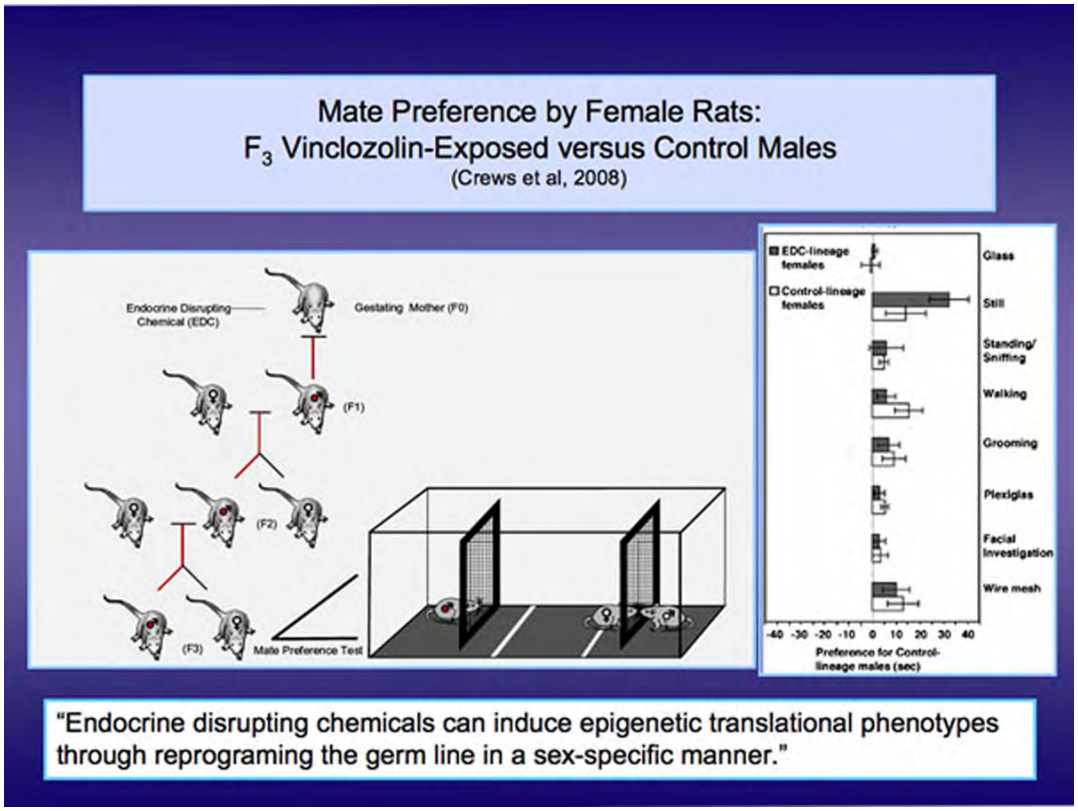

Figure 50.
Mate choice by females, a behavioral measure, may be determined by gestational exposures three generations in the past.

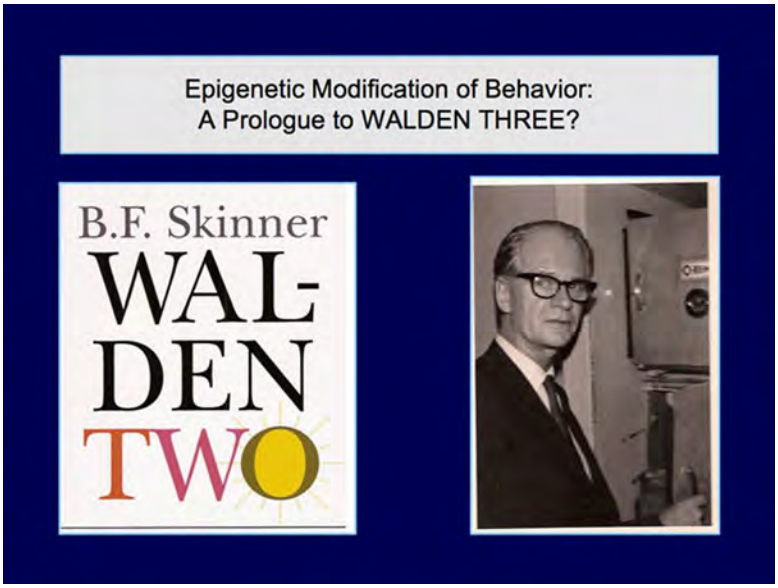

Figure 51.
B.F. Skinner and his utopian novel. The inset shows Skinner during a visit to the Rochester lab in the 1960s.

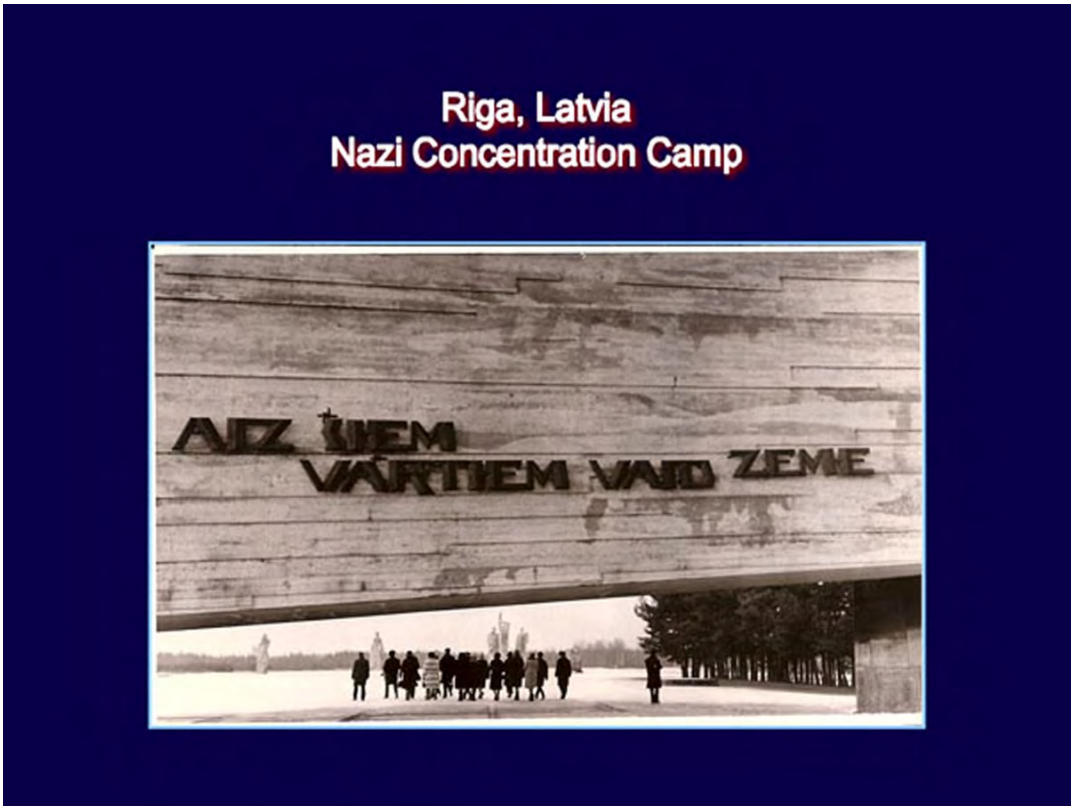

Figure 52.
Nazi concentration camp near Riga, Lativa, with participants in US-USSR Environmental Health Exchange Agreement, 1974.

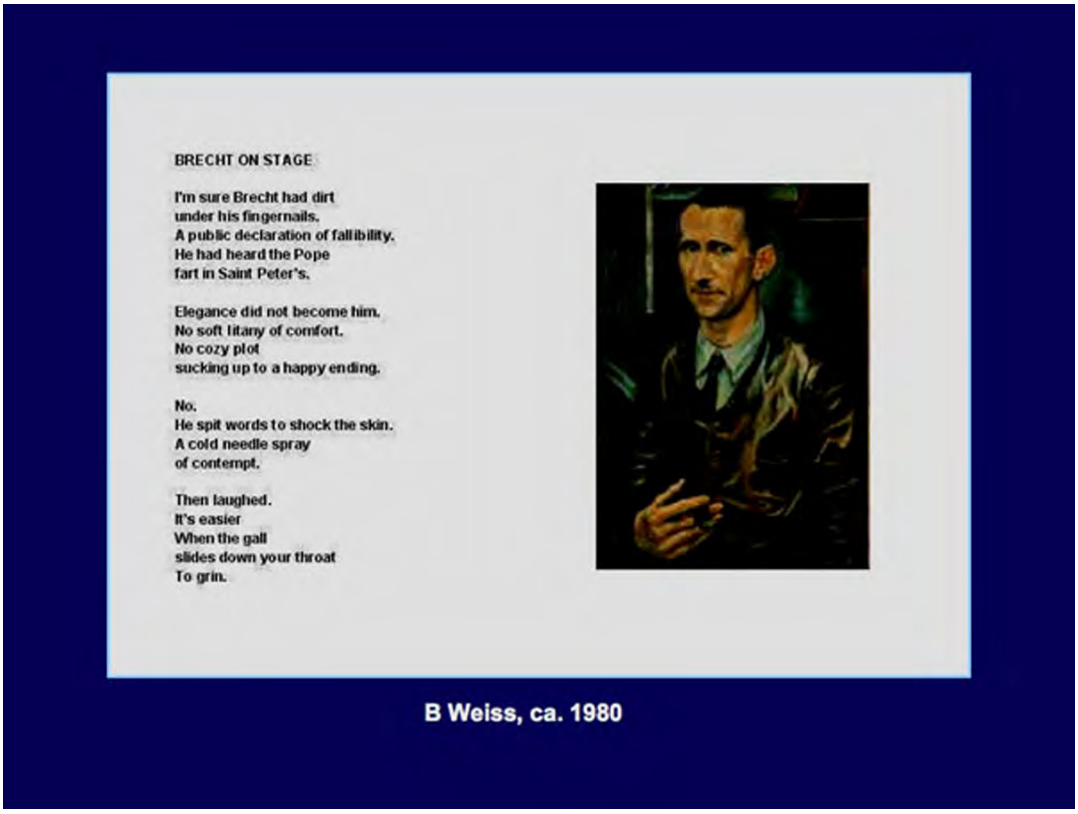

Figure 53.
Poem by the author about Berthold Brecht.

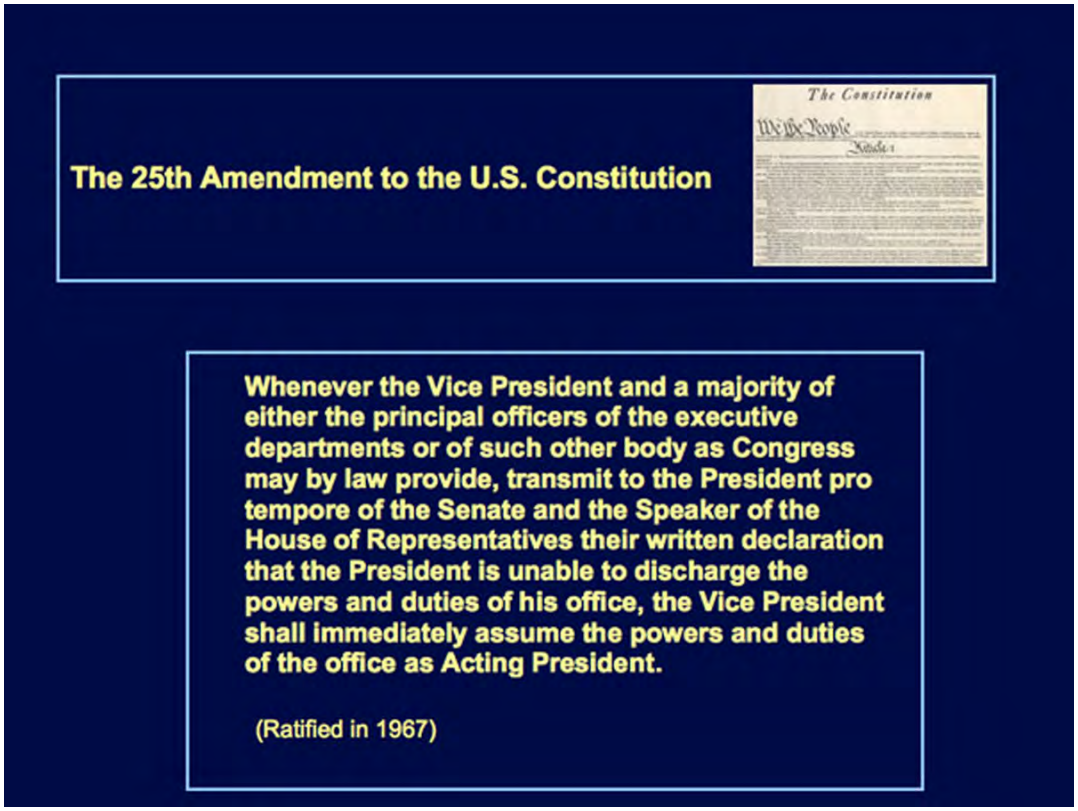

Figure 54.
25th amendment to the U.S. Constitution.

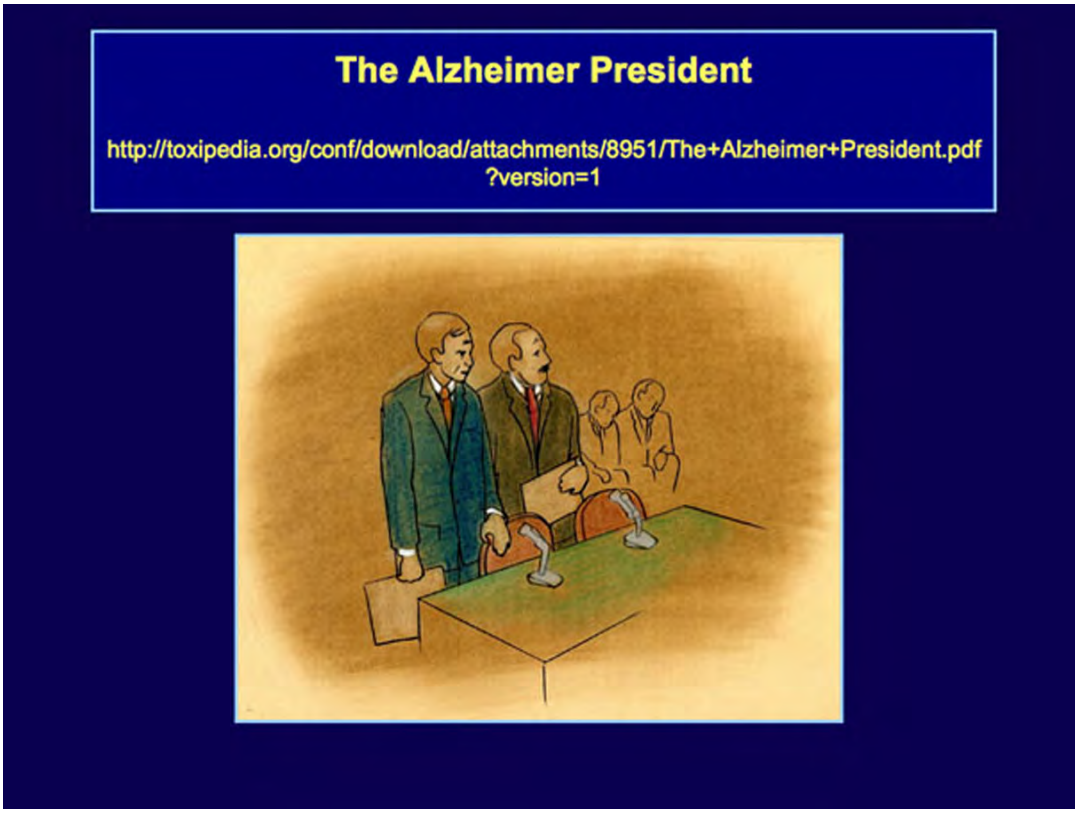

Figure 55.
Illustration for the author's novella about a president with incipient Alzheimer's disease. It shows the protagonist preparing for testimony before Congress. See: http://toxipedia.org/wiki/download/attachments/8951/The+Alzheimer+President.pdf?version=1

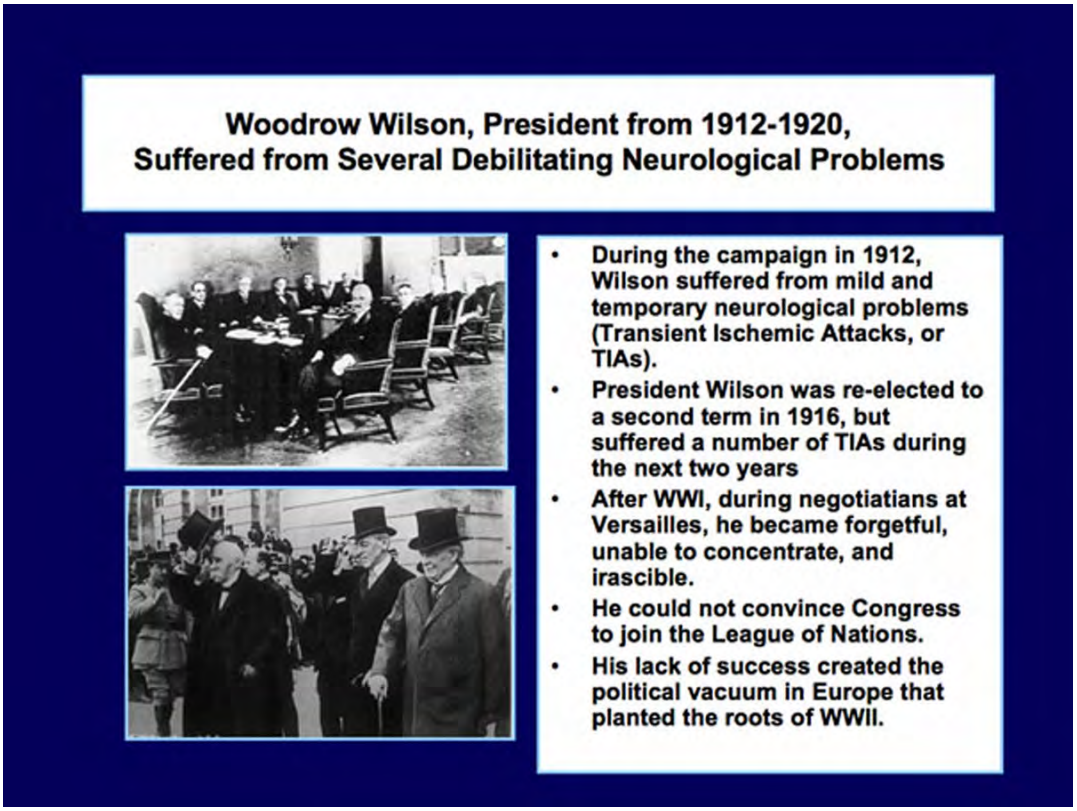

Figure 56.
History of neurological problems in President Woodrow Wilson.

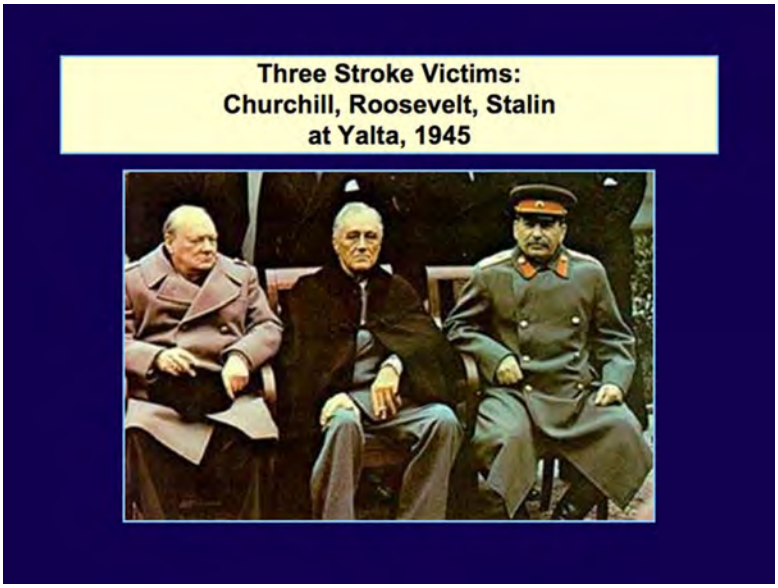

Figure 57.
President Franklin Roosevelt, Prime Minister Winston Churchill, and USSR leader Joseph Stalin at Yalta.

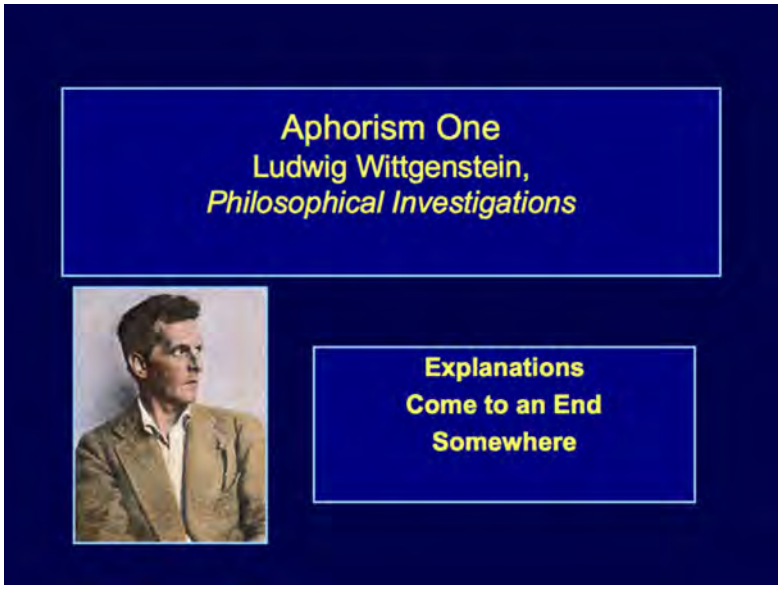

Figure 58.
Ludwig Wittgenstein, 1889–1951.

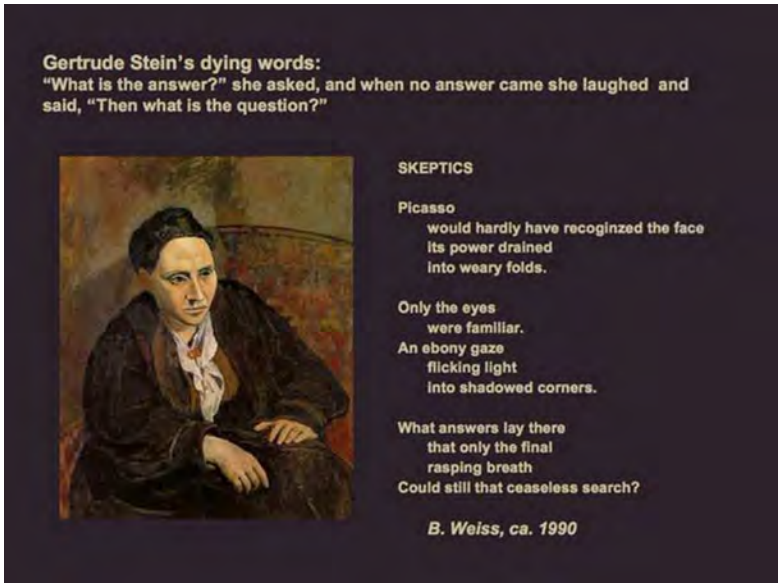

Figure 59.
The author's poem about Gertrude Stein and her portrait by Picasso.