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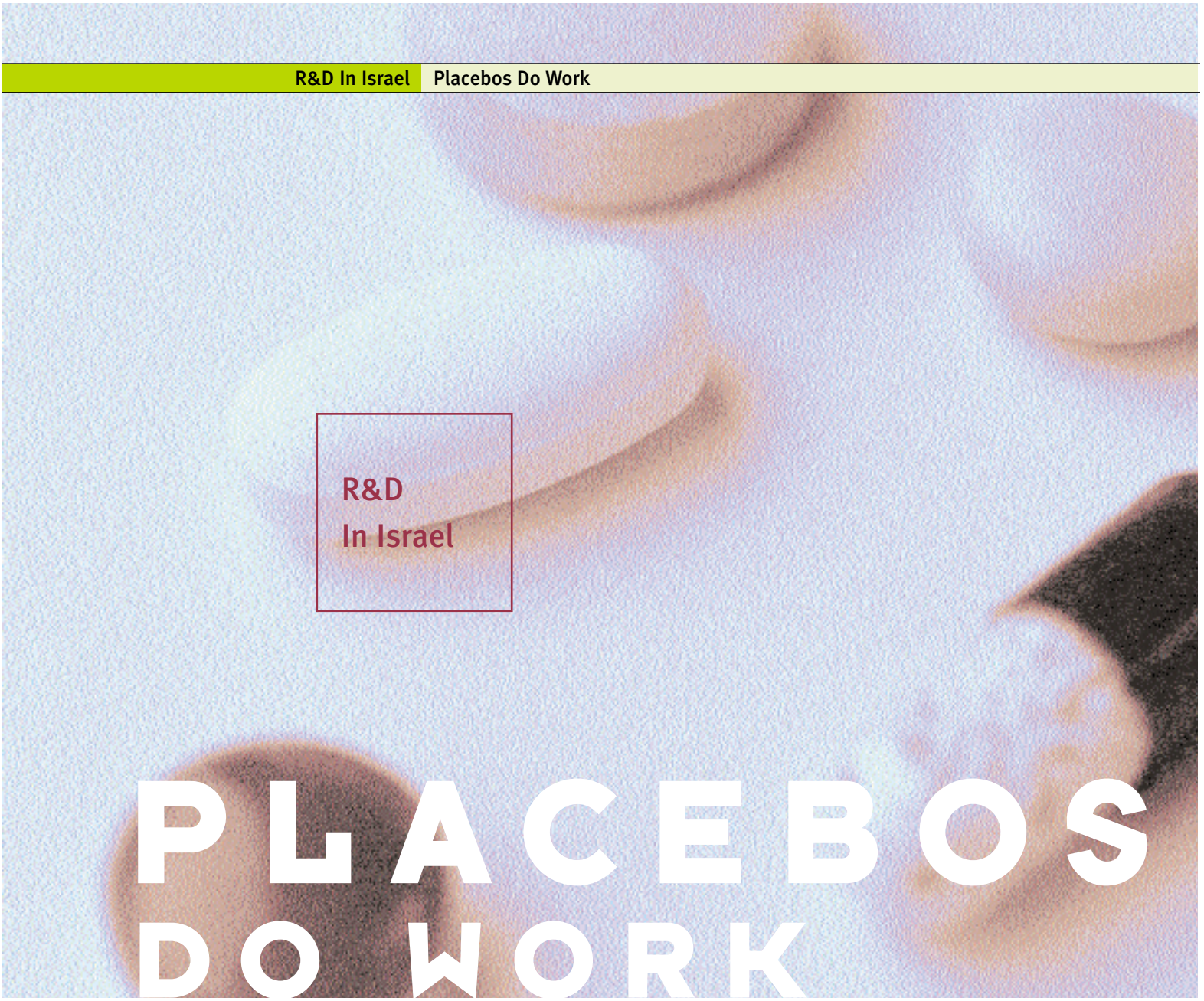


R&D
In Israel

# PLACEBOS DO WORK

**Does a sugar pill sometimes have the power of a prescription drug proven effective in double-blinded, randomized clinical trials whose manufacturer is authorized by the government to make therapeutic claims? It depends whom you ask.**

Dr. Asbjorn Hrobjartsson of the University of Copenhagen and Dr. Peter Gotzsche of the Nordic Cochrane Center in Denmark recently claimed in the May 24th issue of the – New England Journal of Medicine – and later in the journal – Science – that there was no statistical difference in the results between control groups given a placebo and those given no treatment at all. They collated data from 130 previous studies and reached the conclusion that the "placebo effect" - first documented nearly 50 years ago in a paper showing it is a harmless treatment that benefits one in three patients - doesn't exist.

The Danish team performed a meta-analysis of studies published over decades and concluded that in most cases, placebos are no more effective than no treatment at all. The only

occasional exception, they declared, was that placebos "may be better than nothing" for relieving pain partly because pain is a very subjective sensation. There is no justification for the use of placebos except in an experimental setting, Hrobjartsson and Gotzsche insisted. Results of tests involving placebos do not take into account the natural history of disease, which can wax and wane in severity, they argued.

## Israeli researchers disagree

But an internal medicine specialist at the Hebrew University of Jerusalem who has a special interest in behavioral medicine now strikes back with a new book arguing that placebos can provide true symptom relief. Prof. Raphael Melmed of the HU-Hadassah Faculty of Medicine and Hadassah-University Hospital writes in his new book *Mind, Body, and Medicine* (Oxford University Press, 2001, $49.95) that placebos – along with reduction in patient anxiety and physician belief in the medication – can produce a physiological response that results in genuine easing of symptoms. He says he has spent two decades researching the field, and the last 10 actually writing the book. Melmed aims his volume at doctors and other professionals and suggests that they may be better able to help their patients by using the mind-body connection to appreciate new ways of treating hard-to-treat diseases. One of the 20 chapters is devoted solely to the placebo effect.

**Placebos have been used by generations of doctors as a control to test whether medical treatments actually work, and many have claimed they can reduce symptoms thanks to the power of the mind.**

Placebos have been used by generations of doctors as a control to test whether medical treatments actually work, and many have claimed they can reduce symptoms thanks to the power of the mind. Justifiably or not, the burgeoning popularity of complementary medicine techniques – from acupuncture to Zen meditation – to reduce stress have won many adherents. Melmed places particular stress on the influence of doctors who convincingly communicate to their patients that a particular treatment will be effective – an aspect that was completely disregarded by the Danes. The Jerusalem physician found that the more empathetic and supportive the physician is in conveying how much a particular therapy is likely to help a patient, the more he will experience real relief, even without undergoing any conventional treatment. Melmed argues that his findings could have major implications on the way doctors interact with their patients and the need among patients to find physicians who strongly believe in the medications and treatments they are prescribing.

The other two factors that Melmed says can determine the likelihood that the placebo effect will occur either alone or together are the physiological response to anxiety reduction and the role of patient compliance. His book offers data from numerous published studies that, he says, "strongly suggest the body is capable of activating certain healing processes on its own, as long as the patient believes in the medical treatment he or she is given." When patients comply with the treatment regimen – a good sign that they have faith in it – they are more likely to experience the placebo effect, Melmed writes.

## Placebo surgery

In one double-blind study, in which neither the doctor nor the patient knew who was getting medication or not, nearly 300 patients underwent a surgical procedure cutting an artery to treat painful angina pectoris. Although this procedure was later found to be useless, 38 percent of patients whose surgeon was enthusiastic about the operation experienced "complete pain relief" that lasted for up to one year following the procedure. They felt much improved even though the basic underlying disease had not been touched. But among patients whose surgeon thought the operation was unproven, with no physiological basis for the apparently good results, only 10 percent experienced complete pain relief.

Melmed argues that the placebo effect is based on both anxiety reduction and on a physiological response in which the patient's anticipation of recovery can produce specific biological changes that lead to healing. He also presents the results of a study of patients who had survived a heart attack that was aimed at examining the number of deaths five years after patients taking a cholesterol-lowering drug or a placebo. Oddly, the results were identical for both groups of patients: in each, about 20 % of patients died within a five-year period. However, when the results were analyzed for just those patients who believed in their treatment and took their prescribed medication regularly, the death rate was 25 % lower. This percentage held true whether the patient was taking the cholesterol-lowering drug or the placebo - but few, if any, of the Danes' studies includied monitoring of patients for compliance.


# COMPLEMENTARY MEDICINE IN ISRAEL

**Young Israelis have to endure many years of medical studies and pass grueling examinations before their mothers can boast about "my son [daughter], the doctor". But anyone can hang a shingle, declare himself or herself to be a homeopath, energy healer, reflexologist, naturopath, aromatherapist, iridologist or any other practionner of complementary medicine; this person, moreover, can charge whatever he or she likes.**

Newspapers in Israel are full of advertisements placed by these practitioners, claiming to have "changed" their patients' lives, helped paraplegics to walk again, abolished pains and diseases that had thumbed their noses at licensed physicians' more conventional therapies. These ads are especially common in the ultra-Orthodox (haredi) press, whose readers in the last decade seem to have invested a great deal of faith and money in complementary treatments. Even the four public health funds (health maintenance organizations) offer complementary medicine treatments — with or without medical supervision — at a reduced price if members subscribe to supplementary health insurance plans.

The Health Ministry, in an unspoken policy of benign neglect, has taken the trouble to push through regulations that con-

trol only acupuncturists. Anyone who spins needles into acupressure points on the body must be either a physician himself or function "under a doctor's supervision." But despite the risks of blood-borne diseases, such as AIDS and hepatitis B and C, this rule is routinely ignored.

### I'll bee back

Just last May, the ministry decided to take action after a newspaper's health reporter called attention to an article in the Israel Journal of Family Practice about three patients who suf- fered serious (but not fatal) complications when a non-medical practitioner intentionally exposed them to bee stings (apitherapy). Ministry associate director-general Dr. Yitzhak Berlovich instructed his legal department to file a police complaint against the practitioner, a Tel Aviv resident and long-time bee-keeper who claimed he successfully treated hypertension, arthritis and even multiple sclerosis with hundreds or even thousands of bee stings. The apitherapist claimed he "never saw a case of anaphylactic shock" in his practice,but was aware of it and had a syringe with the antidote on hand "just in case." Berlovich noted that "practicing medicine with- out a license is a crime, even if the treatment is not invasive." The ministry investigates when it receives a complaint, but such complaints are rare. "Unfortunately, we don't have the means to actively pursue all non-doctors who advertise that they perform medical treatments. It would be something else if we had 500 or 1,000 more employees to do only this," said Dr.Yair Shamoun, the ministry's official in charge of licensing of medical professionals. He added that "even when we do file a complaint, the police usually close such cases due to 'lack of public interest.'"

Ironically,the subject of complementary medicine was investigated in minute detail over a period of three years by a high-level public commission. Prof.Menahem Elon, then a deputy president of the Supreme Court who was sympathetic to some forms of complementary medicine, issued the 26 pages of recommendations and 2,000 pages of appendices in October 1991, along with nine colleagues, among them physicians, a lawyer, scientists and a former Knesset member. The majority opinion recommended liberalization in the field to allow people who were not M.D.'s to treat patients with non-invasive unconventional medical techniques if they did not harm patients – even though they could not guarantee efficacy. Anyone harmed would be free to sue the practitioner for damages, the majority wrote. But the minority opinion on the panel argued that the major- ity's "drastic"proposals, based on the British model, was "not suited " to the Israeli reality of general disregard for many laws on the books and would "create complete lack of control... The charlatans will have a field day, and the innocent public will be thrown to the wolves."

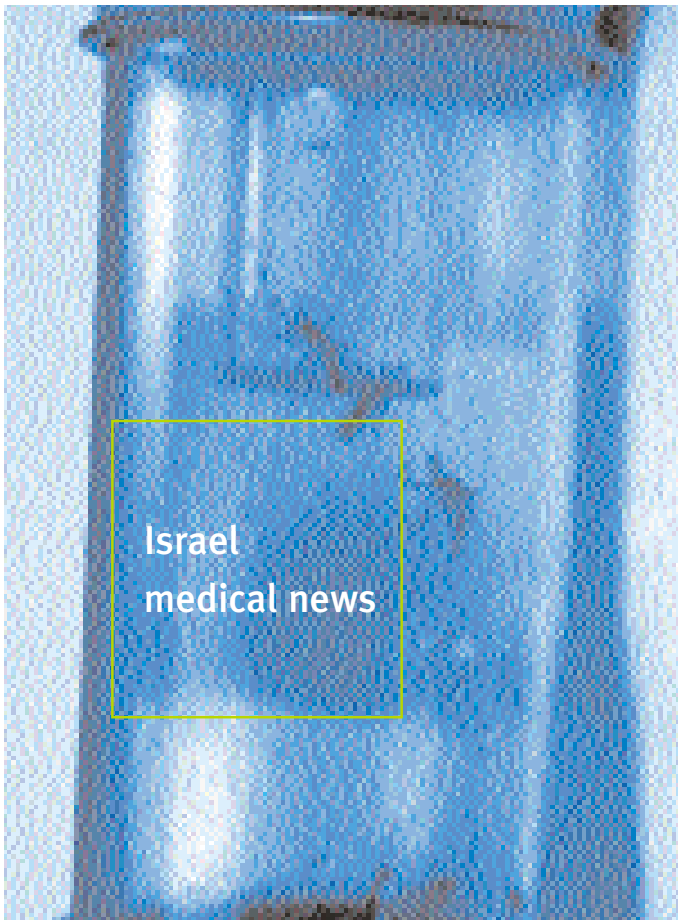
### Futile Attempt

Although then-health minister (and current Jerusalem mayor) Ehud Olmert endorsed the report's majority opinion the very same day he received it and appointed a small legal committee to "find ways to implement the majority report," that was the last anyone heard of it. Nearly a decade later, none of the recommendations has been implemented, but the Israeli public seems to believe they have, and the minority opinion's fears have become a reality. Although no single regulation or law was changed, the Elon report's publication encouraged the opening of dozens of complementary medicine "colleges" and courses, from quickie weekend lessons to curricula encompassing several years of study.

**The majority opinion recommended liberalization in the field to allow people who were not MDs to treat patients with non-invasive unconventional medical techniques if they did not harm patients — even though they could not guarantee efficacy.**

Shortly after the report's publication, a teenage Jerusalemite who contracted cancer but feared chemotherapy more than the disease itself ran away to New York and was hidden by members of a Hassidic sect, which paid for complementary medicine techniques. Feeling better, he returned home but continued to refuse chemotherapy, which his doctors said would almost certainly have cured his cancer if given in time. Just before his 19th birthday, he complained of headaches, passed blood, and died.

Asked to comment about his commission's report – yet another left by Israeli government administrators and legislators to collect dust on the shelf – Elon said recently that he was very disappointed. "We invested a great deal of time and effort in that document. It's painful just to recall it." Elon,who has since retired from the Supreme Court and is now researching constitutional matters, admitted that he hadn't been following the field of complementary medicine. "I don't know who prevented its implementation. Maybe the Israel Medical Association, but I don't want to accuse anyone," he said.




## MOSQUITOES ARE BUGGING ISRAEL'S HEALTH MINISTRY.

The problem is not the malaria spread by Anopheles mosquitoes breeding in swamps that plagued pioneers in the holy land 80 or 90 years ago; it is West Nile virus, which has become endemic to the region.

The virus, spread by ordinary mosquitoes that bite infected poultry, migrating birds and perhaps even horses, causes only self-limiting flu-like symptoms in people who are otherwise healthy. But people with weak immune systems, such as the elderly, transplant organ recipients or others with chronic diseases, can develop potentially fatal meningitis or encephalitis.
In fact, West Nile virus killed 39 Israelis and infected nearly 400 others last year, causing a scare in a population with plenty of other things to worry about. The average Israeli had never even heard of the virus before last summer and now was bombarded with daily reports of more patients hospitalized with complications. There is no preventive vaccine or cure yet, but symptoms can be relieved with supportive treatment.

The ministry, which last year announced the death of the first victim over a month after it occurred, was taken aback by the public reaction. For many weeks, health officials refused to call it even an outbreak, but as the numbers of fatalities began to mount, ministry director-general Dr. Boaz Lev described it as an "epidemic" in a radio interview. This term made then-health minister Ronni Milo so nervous that he immediately denied it for fear that it would scare away tourists. "It is not an epidemic," Milo said then. "Nile virus has been in the Middle East for decades, but that exact statistics were unavailable until last year, when reliable blood tests came on the market," he said, and any Israeli with an unexplained fever was tested for it.

The issue was further complicated when some US health authorities made claims — which were never proven — that the virus had first reached the US from Israel after an "infected parrot" was smuggled to New York. The authorities even maintained that genetic testing showed the strain of West Nile found in the US was "identical" to that in Israel.

Slow to act and appearing to be bunglers, the Health and Environment Ministries last year ordered massive spraying with pesticides in the affected areas, especially in the Sharon region north and east of Tel Aviv. Some environmentalists argued that the spraying was too drastic and too late, and that they should instead have launched a public campaign to eliminate standing water where mosquitoes breed.

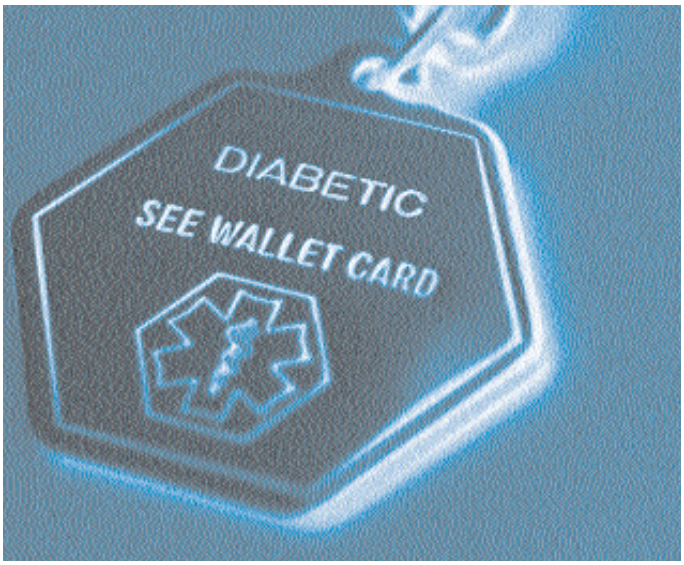
Better prepared this year, the authorities launched a public information campaign this summer, including TV ads showing a large hand smashing a mosquito. They called on high-risk people to install window screens, wear light, long-sleeved clothing, avoid going out after dusk when the bugs tend to bite and use mosquito repellents.

By mid-August 2001, there were four reported cases of West Nile virus infection, all otherwise healthy people in their 50s and 60s; they were hospitalized but quickly recovered. The Health Ministry was pleased with this very low figure, compared to 37 people who had been infected during the same period in 2000, four of whom had died. Some "credited" the extremely dry weather in 2001, which has caused Lake Kinneret (Sea of Galilee) to reach the lowest point in recorded history and many underground aquifers to dry up. The drought apparently prevented the mosquitoes from multiplying, some said, while others suggested that the incidence of West Nile runs in natural cycles.

## FIRST SPORTS CAMP FOR DIABETIC CHILDREN

Parents' "apron strings" are especially sturdy when their children suffer from juvenile-onset (type I) diabetes: Mothers and fathers are especially worried that their diabetic kids may not strictly observe the rules about food, blood testing and insulin injections whose careful observance keeps them alive and well. Apprehensive that the kids may overdo physical activity, many parents and teachers are liable to be overprotective and bar them from taking part in sports altogether.

That is the background for a rigorous sports camp for 240 children and teenagers with type I diabetes that has been held for the first time in Israel. The youngsters, aged nine to 18, learned judo and karate, swam, rowed kayaks, shot at targets and practiced other sports while their blood sugar and insulin levels were carefully monitored by nurses and young adult diabetic volunteers at the Wingate Institute for Physical Education near Netanya.




Dr. Na'ama Constantini, a senior Wingate sports medicine specialist who was involved in the youngsters' medical supervision, said that during the past 20 years, the Israel Juvenile Diabetes Foundation has sponsored summer activities. However, having the entire program filled with sports activities was unique here and unusual in the entire world.

She explained while keeping their insulin and sugar levels in balance, they should be freed from parents' "apron strings" — even for only a week — so they can enjoy themselves in a safe atmosphere while bolstering their feelings of independence and self-confidence.

Constantini added that diabetic children generally get too little exercise because of the complexity of monitoring and their schools' concern about complications. They are, in effect, wrapped in cotton wool to protect them. "They did things at the camp that they never experienced before. The physical activity significantly reduced the levels of insulin that the children had to inject, and that is very beneficial," said Constantini.

The camp showed participants that they can do virtually anything if their physiological condition is monitored, Constantini said. She added that Wingate staffers will soon conduct research on the use of insulin pumps — which regulate injections depending on their physical activity and diet — by diabetic children and the effects of sports activities on their functioning. In addition to four or five doctors and dietitians on hand, a nurse dealing solely with insulin pump maintenance was on duty at the camp to supervise 70 of the campers who wear them. About 1,000 of the 4,000 Israeli children with type I diabetes already use insulin pumps, which are included in the basket of health services provided by the public health maintenance organizations.

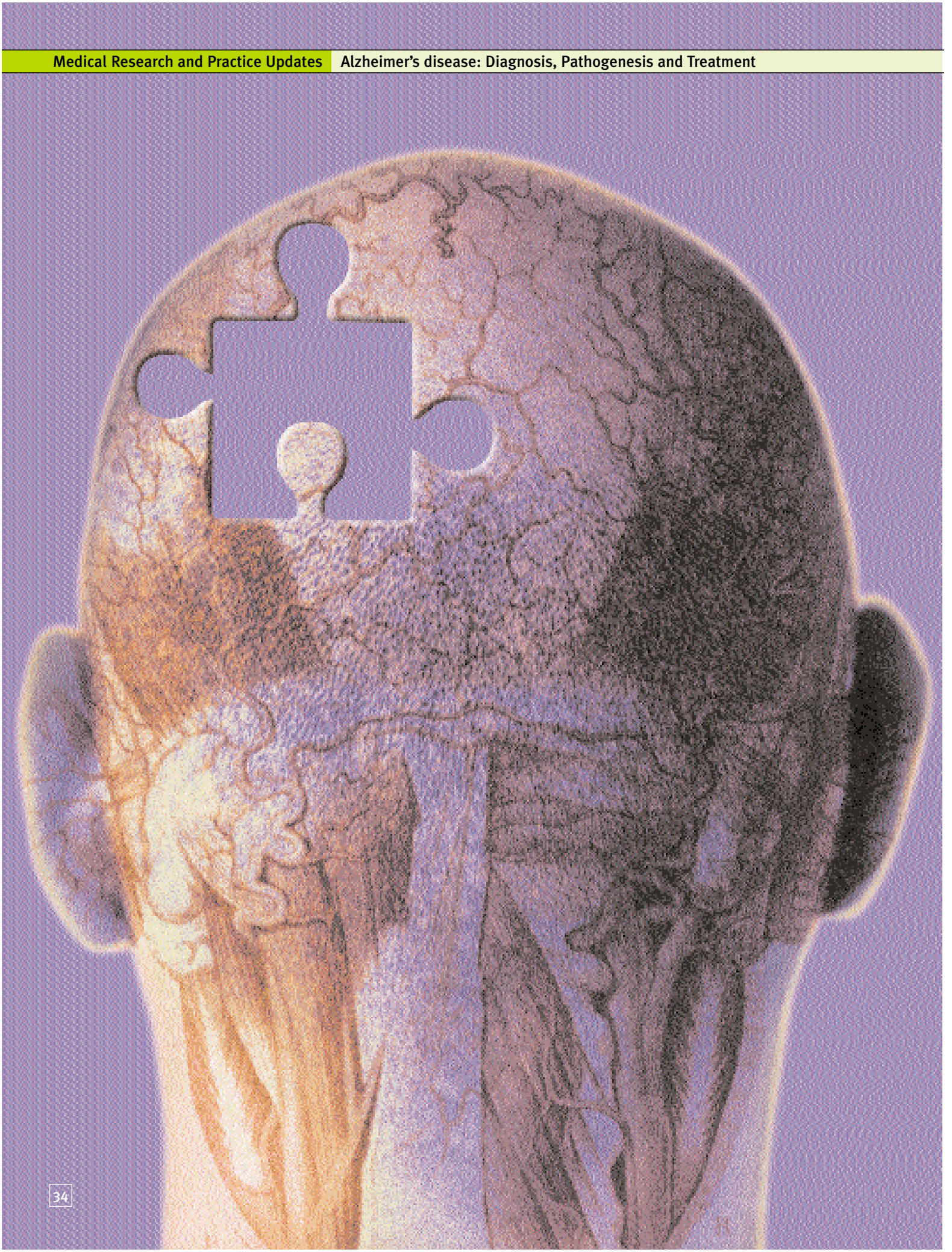
Shulamit Nuss, chairman of the Juvenile Diabetes Foundation of Israel, which organized the week-long, live-away camp, said the families paid only half the cost, with the rest of the expenses covered by the Glencor Foundation in England and the Matan Foundation of Israel. Many more diabetic youngsters wanted to participate, she said, but their number was limited by the lack of facilities; next summer, Wingate intends to run several sports camps so that more can benefit.

## CONGENITAL DEFECTS

Arab Israelis are up to 1.6 more likely to have children with congenital defects — including spina bifida, anencephalus, microcephalus, hydrocephalus, cystic kidney disease, hypoplastic left heart, small intestine atresia and limb reduction — than Jewish Israelis, according to a report issued by the Health Ministry's department of community genetics.

The authors give two reasons for this: many Arabs marry close relatives (consanguinity) to keep property in the family; carriers of the same recessive genes who marry are much likelier to hand down inherited disorders, while Arab women are less likely than their Jewish counterparts to undergo an abortion when such a disorder is diagnosed prenatally. Health authorities have tried in recent years, without much success, to reduce the rate of inbreeding among Israeli Arabs.

Fifty-five percent of Jewish women whose fetuses are diagnosed with Down syndrome have an abortion, compared to only 18 percent of Arabs; the figures are 73 percent and 43 percent respectively for spina bifida (when part of the spinal cord forms outside the vertebrae) and 90 percent and 59 percent respectively for anencephalus (when the brain or spinal cord are missing).



Marc E. Weksler, M.D.

**Alzheimer's Disease (AD) is the most common cause of memory loss and impaired cognition in the elderly human. The course of AD is prolonged, often lasting as long as 10 years, and frequently requiring institutionalization during the last years of the illness because of behavioral disturbances and the inability to perform activities of daily living.**

Medical Research and Practice Updates

# ALZHEIMER'S DISEASE:

## DIAGNOSIS, PATHOGENESIS AND TREATMENT

The disease is named for Alois Alzheimer, a neuropathologist, who reported in 1907 his finding of "miliary deposits of a peculiar substance" in the brain cortex of a demented patient.

The prevalence of AD rises exponentially from approximately 1% in persons 65 years old to more than 50% in 85-year-olds. The estimated lifetime risk of developing Alzheimer's is approximately 25% slightly higher for women, even after correcting for the longer life span of women. Not surprisingly, with the dramatic increase in life expectancy in industrialized countries from approximately 50 years in 1900 to 75 years in 2000, the number of persons over 65 years of age has increased many fold. In fact, the elderly are the most rapidly growing segment of the population of industrialized countries. AD has grown to epidemic proportions with the explosive increase in the number of elderly. In France, this year 50,000 new cases of AD will develop in comparison to fewer than 1,500 new cases of AIDS. In the USA, in the coming years, 50% of all families will include a member with AD.

In the USA, 50% of all families will include a member with AD.

Initially, and through the 1950s, most physicians believed AD was not a disease, but the fate of persons who attained old age. This view explained its then popular name "senile dementia." However, even in those days, a premature form of dementia was recognized to affect younger individuals and this "disease" was termed "presenile" dementia. The notion that senile dementia was not a manifestation of normal aging arose from two critical developments. The first was that it became clear that not all humans who reached 90 or even 100 years of age were demented, and the second was that the molecular pathology of senile dementia was established.

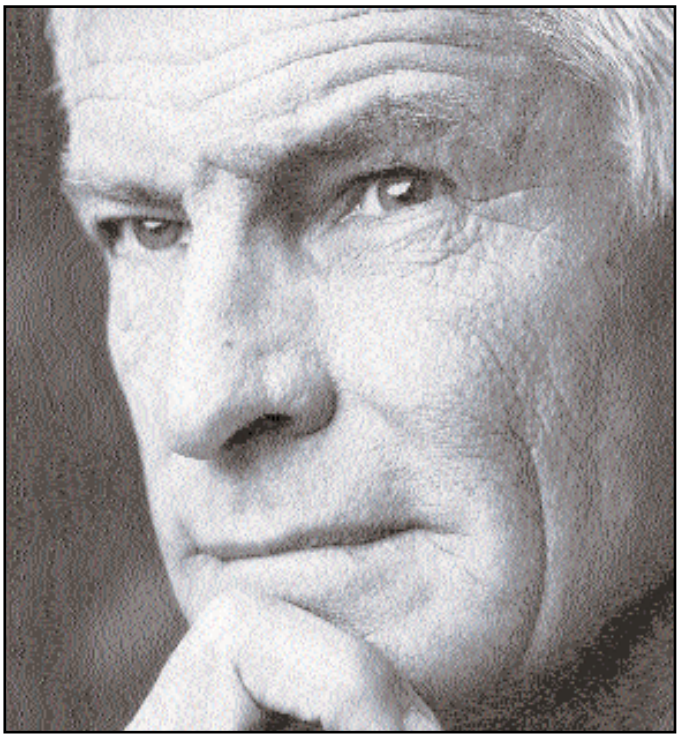
The era of molecular pathology of AD can be dated to 1984, when George Glenner's group reported that the miliary deposits first described by Alzheimer and termed senile plaques or "amyloid" plaques, because of their birefringency and staining with a Congo red dye, were composed of extracellular aggregates of a mixture of 40 and 42 amino acid peptides termed amyloid beta (Aß) peptides. Today, two additional neuropathological features, neurofibrillary tangles, made up of hyperphosphorylated tau proteins, and cortical neuron loss are the diagnostic neuropathology of AD. However, the amyloid plaque first asso-

ciated with the dementia by Alzheimer remains the key pathologic lesion in AD. Most experts in AD believe that the generation and aggregation of Aß peptides into amyloid plaques stimulate a cascade of events that ultimately result in neuron death and impaired cognition typical of AD.

### Diagnosis of Alzheimer's Disease

As brain tissue is rarely obtained for diagnosis in demented patients, the diagnosis of AD usually remains a diagnosis of exclusion. Despite this fact, the accuracy of the clinical diagnosis, based on the clinical symptoms and signs typical of AD and the lack of evidence for other causes of dementia, approaches 90 to 95%. AD is characterized by a slow progressive anterograde loss of memory, impaired cognitive function, anomia, agnosia and apraxia. The patient with AD rarely recognizes symptoms of intellectual decline. This feature is helpful in distinguishing the elderly patient with AD from the elderly patient with depression who complains of memory loss. The self-referred patient with complaints of memory loss is usually depressed. The patient whose memory loss concerns a family member is usually demented. The intellectual loss in AD patients is not associated with changes in consciousness, psychiatric, or cerebral diseases such as vascular disease, tumors, hydrocephalus or space occupying lesions, metabolic diseases including pernicious anemia, hypothyroidism, renal or hepatic failure, or infection that may cause intellectual impairment. When there is no clinical evidence of these diseases and the laboratory tests, including a complete blood count, a serum screen for vitamin B12 deficiency, renal, hepatic, or thyroid disease, and a brain scan do not suggest other causes of dementia, progressive intellectual decline over a period of six months to a year in a person more than 65 years of age is almost always due to AD.

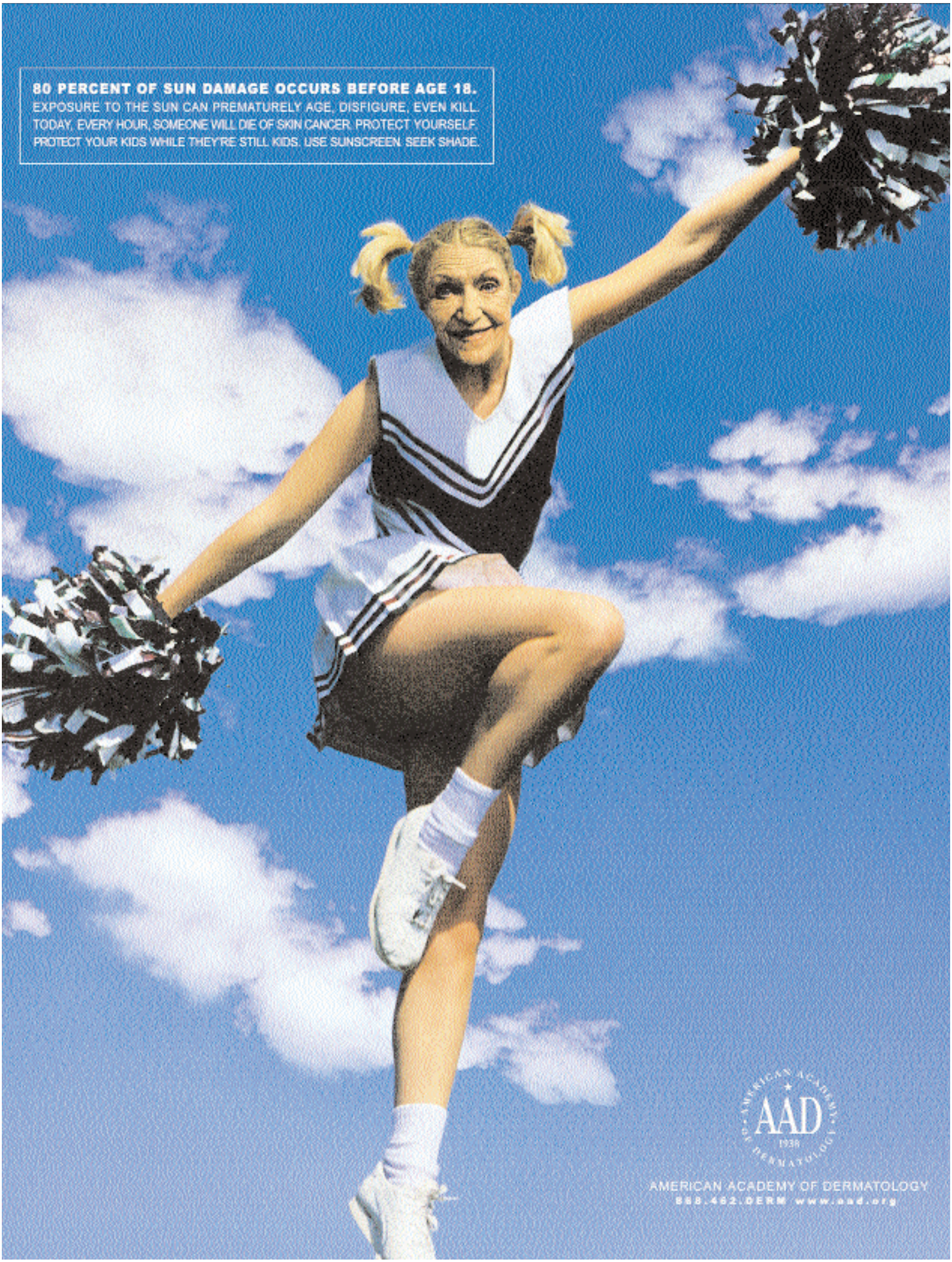
In the future, magnetic resonance imaging (MRI) may permit the positive diagnosis of AD. Thus, a recent study[1] suggested that AD is associated with a decrease in the volume of the hippocampus detectable by MRI before the clinical diagnosis of AD can be made. MRI scans were 100% accurate in differentiating normal subjects from patients with mild AD. Even more remarkable was the 93% accuracy of MRI scans in distinguishing normal subjects from individuals with memory impairments not diagnosed with AD but who subsequently developed it. The capacity to identify individuals at risk or in the earliest stages of AD will become increasingly important as effective therapies for AD are developed. Early diagnosis will be critical so that therapy can be initiated before the progression of AD results in extensive cortical neuron loss making therapeutic benefit more difficult to obtain.



### Pathogenesis of Alzheimer's Disease

The pathologic hallmark of the disease first described by Alzheimer is the amyloid plaque composed of aggregates of the 40 and 42 amino acid Aß peptides. The Aß peptides are derived from a transmembrane amyloid precursor protein (APP) whose gene resides on the human 21st chromosome. There are three molecular forms of APP, a transmembrane protein of unknown function, ranging in length from 691 to 770 amino acids. The longer APP proteins are widely expressed by neurons and non-neuronal cells throughout the body. However, the smallest form of APP is almost completely limited to neurons. There are two catabolic pathways of the APP, a pathologic and physiologic pathway. In the pathologic pathway, beta and gamma secretase cleave the APP into three fragments. One fragment is composed of the 40 or 42 amino acid Aß peptides that aggregate to form the amyloid plaque. In the physiologic pathway, an alpha secretase cleaves the APP protein into two fragments, both of which are soluble and do not aggregate.

There is a general consensus that the cascade of events following generation of the Aß peptide including aggregation followed by induction of both inflammation and neurotoxicity is the pathogenic pathway to AD causing neuron loss and producing, as byproducts, neurofibrillary tangles. Of the two Aß peptides, the Aß42 peptide is the first Aß peptide deposited in the brain, is the most likely to aggregate, and is the most neurotoxic. Thus, the Aß42 peptide appears to play the leading role in the pathogen-


80 PERCENT OF SUN DAMAGE OCCURS BEFORE AGE 18.
EXPOSURE TO THE SUN CAN PREMATURELY AGE, DISFIGURE, EVEN KILL.
TODAY, EVERY HOUR, SOMEONE WILL DIE OF SKIN CANCER. PROTECT YOURSELF.
PROTECT YOUR KIDS WHILE THEY'RE STILL KIDS. USE SUNSCREEN. SEEK SHADE.
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esis of AD. Nonetheless, other factors, including apolipoproteins and aging, certainly play supporting roles. Both age and the expression of the E4 allele of apolipoprotein E are risk factors for late-onset AD.

AD is a disease of aging, as time is necessary for the aggregation of Aß peptides and consequent destruction of sufficient neurons to attain the clinical threshold for AD. Expression of the apolipoprotein E4 gene and a recently described gene on chromosome 10 of unknown function[2] are genetic risk factors for late-onset AD. All genetic risk factors for AD lead to an increased production of Aß peptides in the brain. Thus, patients homozygous for the E4 gene have greater deposits of Aß peptide in their brain than AD patients heterozygous for the apolipoprotein E4 gene who have greater deposits of Aß peptides than patients without an E4 gene. The apolipoprotein E4 appears to increase the level of cerebral Aß presumably by decreasing its clearance from the brain.

The aggregates of Aß peptides stimulate an inflammatory response in the brain and have been shown to be highly toxic to neurons in vitro. The aggregation of the Aß peptides leads to the formation of the amyloid plaques and plays a key role in the pathogenesis of AD by causing the loss of cortical neurons. Cholinergic neurons appear to be lost preferentially in AD, especially those in the nucleus of Meyert. This results in a decline in acetylcholine levels in the brain of AD patients.

Additional evidence for the pathogenic role of Aß peptide production in AD comes from the identification of rare, genetic, early-onset, forms of familial AD that contribute to 5 to 10 percent of the cases of AD. AD in these early-onset forms occur before the age of 60 and are caused by genetic mutations and chromosomal abnormalities in the APP gene that increase the susceptibility of APP to pathologic cleavage, trisomy 21 that increases the dose of the APP gene and the production of the APP, and the mutations in the presenilin 1 and 2 genes that increase the activity of the beta and gamma secretases that cleave the APP to Aß peptides. In all these cases the genetic abnormality favors the development of AD by increasing the production of Aß peptides from APP. The most direct evidence that Aß42 peptide plays a primary role in AD is the fact that injection of non-aggregated Aß42 peptide into the rat brain is followed by the formation of Aß42 aggregates, the appearance of amyloid plaques, the induction of extensive neuronal damage, astrocytosis and microglial activation all seen in AD[3]. Thus, there is strong support for the hypothesis that cerebral accumulation of Aß peptides is an early and necessary step in the pathogenesis of AD.

## Therapy of Alzheimer's Disease

Until recently, the drugs recommended for the treatment of AD conveyed little benefit. For this reason, treatment of AD patients with hydergine, chelation therapy, n-acetyl carnitine and lecithin have been abandoned. However, recent well-controlled studies have shown the efficacy of anti-cholinesterase agents and epidemiological studies have suggested the potential utility of anti-inflammatory drugs and estrogen replacement therapy in AD.

These agents are used in the hope of maintaining neuron function and limiting neuron death (apoptosis) caused by the neurotoxic Aß peptides (Figure 1). The hope for the future is to be able to go beyond these approaches that limit damage induced by Aß peptide and slow the progression of AD by preventing Aß peptide deposition using a combination of increased clearance of Aß peptide from the brain and decreased synthesis and aggregation of Aß peptides within the brain. It may also be necessary to stimulate neuron regeneration to reverse neuron loss that occurs before the disease is recognized. It is hoped that the use of nerve growth factors or regrowth of cortical neurons from neuron stem cells can be used to achieve this goal.

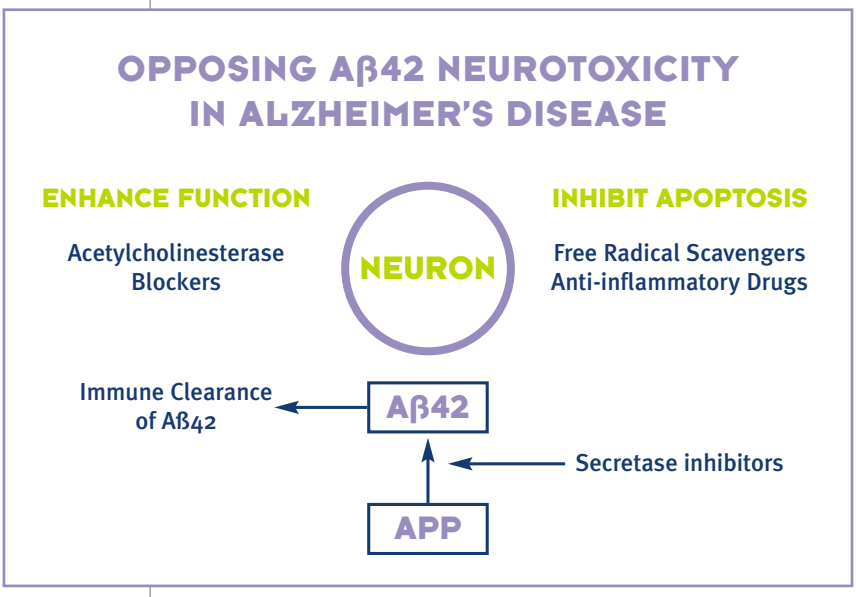


Figure 1

1. Cholinesterase inhibitors: Drugs approved in the USA for the treatment of AD include the acetylcholinesterase inhibitors, Donepezil (Aricept), Rivastigmine (Exelon), and Tacrine (Cognex). Because choline acetytransferase activity is reduced in AD, acetylcholinesterase inhibitors, by preventing breakdown of acetylcholine, can reverse, at least in part, the decreased level of acetylcholine at the postsynaptic neuron. Whatever the benefit of the selective enhancement of the cholinergic neurons, it does not correct the loss of other neurotransmitters nor prevents neuron loss.

Nonetheless, the acetylcholinesterase inhibitors are the first agents to have been shown in double-blind, placebo-controlled studies, to produce statistically significant benefits in patients with mild or moderate AD.

Aricept, a second generation anti-cholinesterase inhibitor, has largely superseded Tacrine because it can be given once a day and rarely causes the nausea or hepatotoxicity that complicate Tacrine therapy. In mild to moderately severe AD, clinical trials have shown that these agents improve cognition for 3 to 6 months in one-third of AD patients, stabilize cognitive function for 6 to 12 months in one-third of AD patients, and have no effect in one-third of AD patients. Side effects include cardiac arrhythmia and impaired urination. Follow-up studies suggest that the cognitive benefits of Aricept over placebo can be maintained in some patients for as long as two years.

**2. Disease-modifying drugs:** While no drugs have been proven to be effective in modifying the course of AD, epidemiological studies have suggested that anti-inflammatory drugs can interfere with the inflammatory reaction within the brain of patients with AD manifested by microglial activation, astrocytosis, and inflammatory cytokine production. One could envision the potential benefit of anti-oxidants, free-radical scavengers, calcium channel blockers of modulators of certain signal transduction pathways that might protect neurons from the downstream effects of the accumulation of the Aß peptide.

(A) Anti-inflammatory agents: The inflammation observed in the brain of patients with AD is characterized by the activation of cortical microglial cells, the deposition of immunoglobulins, acute phase proteins, and inflammatory cytokines in amyloid plaques as well as the deposition of complement in neurofibrillary tangles. Inflammation induced by aggregated Aß peptides may be the pathway to neuron apoptosis. The importance of cerebral inflammation in the pathogenesis of AD is supported by epidemiological studies that suggested that AD is less common in individuals who have taken non-steroidal anti-inflamatory drugs for a long period of time. Furthermore, ibuprofen, when administered to a transgenic mouse model of AD, significantly delayed the development of amyloid plaques. In humans, a small, placebo-controlled study showed that AD patients given indomethacin had a small but statistically significant improvement in cognitive function[4]. In contrast, a recently completed study of low dose of prednisone, 20 mg/day for 4 weeks and 10 mg for 48 weeks, was not effective in the treatment of AD. It is possible that the low dose of prednisone used because of the toxicity of this class of drugs was insufficient to inhibit the intracerebral inflammatory response. Presently a study is under way to measure the effect of the less toxic anti-inflammatory, cyclooxygenase-2 inhibitors on the progression of AD.

(B) Estrogen therapy: Epidemiological studies have shown that post-menopausal women who have taken estrogen replacement therapy have been reported to have a lower prevalence of AD than women who have never taken estrogen replacement therapy. However, administration of estrogen to hysterectomized women with mild to moderate AD for as long as 15 months had no significant effect on cognitive function. These apparently conflicting results may be explained if estrogen therapy were effective in suppressing the development of AD but not effective in reversing it.

(C) Anti-oxidants: Vitamin E, an anti-oxidant, promotes survival of neurons cultured with Aß peptides, and when combined with selegiline (a monoaminine oxidase inhibitor) has been reported to benefit AD patients in a placebo-controlled study. Neither agent alone benefited AD patients. An extract of ginkgo biloba, thought to have anti-oxidant effects, is approved in Germany for the treatment of dementia. Clinical trials have shown that patients with mild to moderate AD given ginkgo biloba had a modest improvement in cognitive function.

**3. Experimental therapies being tested in animal models of AD**

In the last 2 years, no approach to AD has stimulated greater interest than the use of immunotherapy to prevent or reverse cerebral amyloid deposits in APP-transgenic mice. Active immunization of APP-transgenic mice with Aß42 peptide leads to the appearance of anti-Aß antibodies in serum, the prevention of cerebral

amyloid deposition in young APP-transgenic mice, and the reversal of cerebral amyloid deposits in older APP-transgenic mice. It appears that anti-Aß42 antibodies can solubilize Aß aggregates in vivo as has been shown in vitro. Presumably, once the Aß aggregates are dissolved, they are more easily removed from the brain. This explains the benefits of another approach to AD. Small peptides that bind to Aß peptide have been shown to decrease aggregates of Aß peptide within the brain of experimental animals and decrease the histological evidence of experimental AD[3].

The capacity of this therapeutic approach to reverse cognitive impairment in experimental AD was reported in the last issue of the journal *Nature* for the year 2000. Active immunization of APP-transgenic mice with Aß42 peptide was shown to inhibit not only cerebral Aß peptide deposits in the brain but also the loss of cognitive function. Active immunization with Aß peptides is now being studied in phase one studies in humans.

Another potential target of therapeutic intervention is the identification of drugs that inhibit the beta and gamma secretase that generate the neurotoxic Aß peptides from APP. Such agents could be used to generation of Aß peptides in combination with methods to remove the Aß peptides already deposited in the brain. In summary, it is likely that new approaches to the treatment and/or prevention of experimental AD will find their place in the treatment of patients with AD. Primary prevention would involve the inhibition of Aß peptide generation. Secondary treatment would be solubilizing the Aß aggregates present in the brain and reversing neuron loss during the early course of the disease by removing aggregated Aß peptides from the brain and stimulating regeneration of neurons by the administration of nerve growth factors, perhaps in combination with injection of neural stem cells would be necessary.

Obviously, the early diagnosis of AD before neuron loss has become extensive would be essential for any successful strategy for the treatment of AD. In the future, one can envision screening techniques to assess the risks of AD in individuals: family history, genetic testing, MRI and measurement of various AD associated molecules – Aß peptides, tau protein, or other markers of AD neuropathology in CSF or even blood. Once the risk of AD is determined, individuals at high risk would be treated with novel therapies directed at interrupting the key steps in the development of AD very likely related to the pathophysiology of the APP protein: the generation and aggregation of Aß peptides, the removal of Aß aggregates already present, and regeneration of neurons killed by the neurotoxicity of the amyloid plaques first identified by Alzheimer in the form of dementia that today bears his name.

## Further Reading:

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## Abbreviations:

AD, Alzheimer's Disease;
Aß, amyloid beta;
APP, amyloid precursor protein.