

ALZHEIMER'S DISEASE: TREATMENT WITH CHINESE HERBS

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BACKGROUND

Alzheimer's disease is currently thought to contribute to about 75% of all cases of senile dementia that occur in the U.S. The disorder is marked by reduced levels of acetylcholine, development of amyloid plaques, and degeneration of brain tissue. It produces cognitive and coordinative dysfunctions with notable loss of memory. From the modern medical viewpoint, the cause of Alzheimer's disease is not yet established. There is a genetic component, since the frequency of the disease is higher in an identical twin or a child of a person with Alzheimer's disease, and the disease occurs with higher frequency in persons with the genetic disorder producing Down's Syndrome. But other factors, as yet unidentified, seem to be at least as important as genetics, based on the distribution of the disease. No infectious agent that might cause the disease has been identified, and there is no current evidence suggesting that an infection is involved.

Except for one of the rare genetic forms of the disease that causes early dementia, Alzheimer's usually does not occur in clinically obvious form before age 60. The incidence of the disorder increases with age, such that up to 30% of those over age 80 are believed to suffer from some degree of Alzheimer's disease. A recent study has suggested that early subtle signs-such as limited linguistic complexity-reveal the tendency to develop Alzheimer's disease. Such indicators may be detected before age 30. This would support the idea that the disorder has a genetic basis which yields an evident mental disease under the influence of the aging processes. It is possible, though not proven, that chemical pollutants, high fat diet, and sedentary life style may lead to the severe form of the disease.

Current orthodox medical treatment involves use of hydergine, dexedrine, and a variety of antidepressant drugs, all of which can produce modest improvements, especially in early stages of the disease. There are several experimental drugs in various stages of clinical trials that may improve the outcomes. Because of the advanced age of most sufferers, it is unlikely that even the most effective treatments would be able to produce complete remission.

In Europe, one of the main therapies for Alzheimer's disease is *Ginkgo biloba* leaf extract, which is a widely-used plant drug sold in pharmacies. This flavonoid-rich extract promotes blood circulation to the brain as well as to other parts of the body. Because a large investment in research dollars has been made in testing ginkgo extract, many people do not realize that the same or similar effects may be attained by using other herbs that are a source of circulation-promoting flavonoids.

THE CHINESE MEDICAL APPROACH

Currently, there are two treatment approaches to Alzheimer's disease in China: use of complex herbal formulas based on the traditional methods of Chinese medicine, or administration of an alkaloid drug, called huperzine A, derived from the herb huperzia. This drug inhibits the breakdown of the neurotransmitter acetylcholine, allowing more of it available for brain functions, including memory. Huperzine A has passed Phase I trials in the U.S. and it may become available as a prescription drug at the end of this decade. It is not possible to get sufficient quantities of huperzine A by simply consuming the whole herb from which it is derived, nor its crude extract in reasonable dosage. There are, however, numerous Chinese herbal formulas that may significantly increase levels of acetylcholine.

In analyzing the Chinese medical therapies for Alzheimer's, it is important to recognize the difficulty in distinguishing this condition from other cases of senile dementia, mainly atherosclerotic dementia. A firm diagnosis of Alzheimer's is made by extensive procedures that might include a CT scan, MRI, and EEG. In most cases, such procedures are not routinely done in China; therefore, the symptom pattern is used as the diagnostic

criteria. Some reversible diseases produce dementia and even severe depression may produce dementia, so the treatments that are reported to be successful for dementia might not succeed in actual cases of Alzheimer's disease.

HISTORICAL DEVELOPMENT OF IDEAS ABOUT SENILE DEMENTIA

According to the fundamental ideas of Chinese medicine, the brain is an outgrowth of and is nourished by the kidney. Therefore, brain defects and deterioration of the brain may be prevented, limited, or halted by the ingestion of kidney tonics. Rich nourishing agents such as placenta, rehmannia, and cistanche; kidney essence astringents, such as rose fruit and schizandra; and qi and blood tonics that ultimately help nourish the essence, such as astragalus, polygonatum, and tang-kuei, are frequently recommended to benefit the brain. The cognitive functions of the brain are said to be regulated by the heart: the kidney provides the substance, the heart the regulation of activity. Memory, cognition, and wisdom are believed to become disordered if the heart is agitated or if the influence of the orifices that connect the heart and brain are blocked by phlegm obstruction of the channels. The herbs zizyphus, biota, polygala, and acorus are considered important for treating heart disorders affecting memory and cognition. To benefit the function of the heart, qi tonic herbs are also used, as they enhance the energy or qi of the heart. Formulas based on the combination of heart-regulating herbs coupled with kidney and qi tonic herbs are sold in China as *Bu Nao Wan* (Brain Tonic Pills) or *Jian Nao Wan* (Healthy Brain Pills).

In the book *Jingyue Quanshu (Collected Works of Zhang Jingyue; 1637 A.D.)*, a chapter on dementia (*chidai*) describes the problem as a combination of collapse of original qi (yuanqi) and the presence of impure qi in the meridians and heart orifices. Tonification therapy is the proposed solution, as the restoration of normal qi will help to dispel the pathological qi. A formula developed by Zhang for dementia is *Qi Fu Yin*, comprised of ginseng, cooked rehmannia, tang-kuei, atractylodes, zizyphus, baked licorice, and polygala. The latter herb helps to clear the phlegm obstruction of the orifices.

In the book *Bianzheng Lu (Manual of Medical Differentiation; 1690)*, Chen Shiduo proposed that the first step in development of dementia is depression of liver qi, which is usually caused by emotional problems. This liver qi disorder might eventually lead to exhaustion of the stomach qi because the pathological qi from the liver is easily transmitted to the stomach, where it disrupts normal digestive functions. The resulting undigested food in the stomach can produce obstructive phlegm. He said that "treating phlegm is treating dementia." To accomplish the goal, he suggested that one would tonify the spleen and stomach, resolve phlegm, and clear the orifices of the heart. A formula that Chen developed is *Su Xin Tang*, comprised of ginseng, hoelen, pinellia, bupleurum, coptis, evodia, gardenia, aconite, tang-kuei, peony, and zizyphus. Bupleurum invigorates the flow of liver qi; coptis and gardenia purge the pathologic qi of the liver, while evodia disperses the liver qi that is damaging the stomach functions; pinellia and hoelen resolve phlegm. Chen devised some alternative formulas for dementia, including ingredients such as shen-chu to enhance the stomach's digestive activity, arisaema to cleanse the accumulated phlegm, and acorus to open the clogged orifices.

At the end of the 19th century, Wang Qingren, who is famous for developing the use of blood-vitalizing therapies, proposed that dementia was caused by an emptying of the material substance making up the marrow and brain, and by stagnant blood clogging the orifices. A formula he developed for this purpose is *Tong Qiao Huo Xue Tang*, comprised of red peony, cnidium, persica, carthamus, onion, musk, jujube; rice wine is added to the water when preparing the decoction. Onion and musk help to clear out the clogged orifices. The wine helps activate the blood-vitalizing properties of the formula.

The modern (post-1950) Chinese approach to Alzheimer's follows closely the ideas of Wang Qingren. Degenerative changes in tissues are usually treated by herbs that promote blood circulation-often relying on salvia in place of persica and carthamus used in Wang's time-plus tonics to treat the deficient organ. The brain is nourished with kidney tonics and qi tonics, such as rehmannia and ginseng. Many physicians still pursue the method of differential diagnosis, and the treatments may vary rather than follow a set pattern based on the disease description.

In China, a patent remedy, *Nao Li Kang* (Restore Brain Power Granules) has recently been developed. In the patent remedy application to the Sichuan Ministry of Health, it was reported that the formula was carefully tested in 31 patients with Alzheimer's disease and atherosclerotic dementia confirmed by CT scans. The formula ingredients include rehmannia, salvia, polygala, and polygonatum. Three months treatment with the formula resulted in improvements in 40% of the Alzheimer's patients and in 86% of the atherosclerotic patients. Although the improvement rate for Alzheimer's was relatively low, because this disease is so difficult to reverse, the result is still of interest.

The treatment of Alzheimer's should begin at its earliest signs, since any brain cells that have been destroyed cannot be regenerated and the fibrous and mineralized plaques that form in the brain are unlikely to be removed as a result of the ingestion of herbs. Chinese herbs can still prove useful in later stages, by preventing further degeneration or optimizing the function of the intact brain cells, but attempts to more fully resolve the disease could only meet with success in the early phases. During this earlier period, a definitive diagnosis of Alzheimer's is not always possible, but one can safely administer the Chinese tonic herbs and blood circulation agents.

USING DIFFERENTIAL DIAGNOSIS

Despite the fact that brain disorders can be described generally by the theoretical framework of traditional Chinese medicine, many physicians working in China continue to rely on differentiating cases. The particular disorder, Alzheimer's disease, may occur either from a variety of different causes or from a basic cause in a variety of constitutional situations. The primary differential categories used by Chinese doctors to describe senile dementia are:

1. Spleen qi deficiency, with phlegm and stagnating blood obstructing the orifices to the brain.
2. Liver qi stagnation, with entanglement of qi, accumulation of phlegm, and stagnating blood.
3. Hot phlegm clogging the orifices.
4. Spleen and kidney yang deficiency, with phlegm and stagnating blood obstructing the orifices to the brain.
5. Deficiency of liver and kidney yin, with phlegm and stagnating blood obstructing the orifices and with generation of internal wind.
6. Qi and blood stagnation, obstructing the orifices to the brain.

According to the category that seems most appropriate, one may tonify qi, yin, and/or yang, disperse qi and blood, and resolve phlegm accumulation. The tonic herbs to be used are the same as those commonly found in traditional formulas to treat problems of aging: ginseng, astragalus, atractylodes, dioscorea, rehmannia, lycium fruit, cistanche, and morinda. For unclogging the orifices, acorus, polygala, arisaema, typhonium, and alum are used in various combinations. Acorus and polygala are said to restore proper communication between the kidney and heart; Alum (an aluminum sulfate compound) and arisaema are considered remedies for "mental phlegm." Sedative herbs are sometimes included in prescriptions for dementia, including zizyphus, fu-shen, biota, dragon bone, and oyster shell.

According to traditional Chinese medicine, the depletion of kidney-which is the dominant cause of symptoms associated with aging-can be largely overcome by regular ingestion of either Rehmannia Six Formula (*Liu Wei Di Huang Wan*) or Rehmannia Eight Formula (*Ba Wei Di Huang Wan*). Stagnation of blood can be limited by daily ingestion of salvia wine, or some other salvia-based herbal preparation. The obstruction by phlegm can be largely overcome by reducing fat in the diet (a health-promoting strategy that is recommended by all physicians today) and by using herbal formulas that aid the digestive process, such as Six Major Herbs Combination (*Liu Jun Zi Tang*) or a formula that contains herbs such as crataegus and shen-chu. Saponins from ginseng (and from several traditional anti-aging tonic formulas) have been shown to improve memory function. Sleep disorders-which may respond to the use of herb therapies-are commonly reported among the elderly and may contribute to worsening mental function.

A report in the Shanghai Journal of Traditional Chinese Medicine (1991) describes a study with 60 patients divided into a Chinese herb group and a control group (both used Western medications as needed). Six different herb formulas were used for the study, given according to the diagnosis of the patients' underlying conditions. Eighteen symptoms other than memory functions were monitored, including headache, dizziness, tinnitus, and head fullness; poor appetite and constipation; fatigue and leg weariness; fever and sweating; and so on. The Chinese medical treatment group showed improvements in all of the symptoms except tinnitus. There were also changes in the tongue (less redness) and tongue fur (less greasiness). When the symptom changes related to mental condition were compiled, 7 of 30 in the Chinese medical group showed marked improvement and 16 more showed some improvement. Thus, about 77% showed some degree of improvement, but there was no notable difference between these results for mental capabilities and those of the Western medical control group. The patients in this study were treated with herbs in capsules or tablets, in order to obtain good compliance, not higher-dosage decoctions as would have been preferred by the physicians. The dosage used began low and was increased gradually. Treatment time was six months, and the treatment then needed to be continued to maintain the benefits.

Based on a review of the literature on Alzheimer's disease and senile dementia, a general formula would be acorus, polygala, platycodon, ginseng, atractylodes, licorice, astragalus, citrus, pinellia, crataegus, shen-chu, curcuma, gastrodia, salvia, cnidium, red peony, zizyphus, rehmannia, lycium fruit, tang-kuei, cistanche, morinda, aconite, dioscorea, and hoelen (or fu-shen). Certain herbs could be deleted or added to focus the formulation on the exact needs of the patient.

Among the contributors to aging disorders are the cumulative impact of oxidation reactions (including the accumulation of lipofuscin) and the decline of hormones (it was recently shown that estrogen aids memory in women). Numerous antioxidants have been identified and are readily available in convenient tablet or capsule form (flavonoids, carotenes, Vitamins C and E, and certain minerals, such as selenium, and amino acids, such as glutathione). Several Chinese herbs have been shown to have antioxidant effects and reduce levels of lipofuscin; these include the tonic herbs ligustrum, lycium, cuscuta, psoralea, atractylodes, codonopsis, epimedium, ganoderma, polygonatum, and ho-shou-wu. Some of these herbs function by increasing levels of antioxidant systems, such as SOD (super oxide dismutase). In addition to using Chinese kidney tonic herbs to enhance the body's production of hormones, exogenous sources of many hormones are now available, including growth hormone, DHEA (dehydroepiandrosterone), and melatonin, which could be administered along with the herbs initially to obtain more obvious early effects from the treatment.

NEW PLANT DRUG FOR ALZHEIMER'S: HUPERZINE

Huperzine, an anticholinesterase alkaloid, is divided into two chemical species, huperzine A and huperzine B, which have similar effects but differing activity levels (huperzine A being about 10 times as strong as huperzine B). Huperzine A was first isolated from the Chinese herb *Lycopodium serratum* in 1980 at the Zhejiang Academy of Medical Sciences and the Shanghai Institute of Materia Medica of the Chinese Academy of Sciences. Huperzine B was isolated five years later. The plant source, originally called *Qian Ceng Ta*, meaning thousand-layers pagoda (referring to the tall multi-leafed appearance of the plant), is also known in China as *Jin Bu Huan*, a term meaning "more valuable than gold," usually applied to plants that have potent analgesic actions. This herb should not be confused with the patent remedy called *Jin Bu Huan* made from tetrahydropalmatine. The plant has been reclassified botanically as *Huperzia serrata* from the new family Huperziaceae, rather than from the closely related family Lycopodiaceae. It is reported that the Lycopodiaceae have two medicinal genera: *Lycopodium* (now *Huperzia*) and *Phlegmariurus*. A common constituent is the alkaloid fordine, which is found in 14 species of *Huperzia* and has similar action to the huperzines.

Huperzia, as it is now called, contains a wide variety of alkaloids, including lycodoline, lycoclavine, and serratinine, as well as the huperzines. The alkaloids are of a unique structure and have been called Lycopodium alkaloids. In general, they are comprised of four rings, though one of the rings may be opened. The huperzines, like many of the other lycopodium alkaloids, contain a nitrogen within one of the rings and an NH₂ group attached to the ring structure (some of the Lycopodium alkaloids contain only a nitrogen within the ring structure).

Huperzia is not much used as a crude herb in Chinese medicine: the dominant application is for blood disorders caused by trauma or acute ailment, such as hematemesis caused by overstrain, bruises, hemorrhoids, and lung abscess. In addition to alkaloids, it contains triterpenoids. Huperzines and other isolated alkaloids are increasingly used in Chinese medicine as an alternative to crude herb preparations.

PHARMACOLOGY AND CLINICAL APPLICATIONS OF HUPERZINE

Huperzines A and B reversibly inhibit cholinesterase; huperzine A has a stronger action than huperzine B, which in turn has a stronger action than galanthamine (an alkaloid from *Lycorus radiata* that has been used for its anticholinesterase activity). Huperzine A has substantially stronger anticholinesterase activity than physostigmine or neostigmine (chinchona alkaloids obtained from *Physostigma venenosum*; neostigmine is a common drug for treatment of myasthenia at a dose of 1-2 mg by IM or 0.5 mg IV; physostigmine is also an approved anticholinesterase drug), but huperzine B is three to five times weaker than physostigmine. Huperzines A and B have greater effect on acetylcholinesterase (AChE) than on butyrylcholinesterase (BuChE). Huperzine A, because of its cholinesterase inhibiting activity, has been used in myasthenia gravis patients in China, with apparent success.

Both huperzine A and B have been shown to have memory-enhancing activities in animals. At 0.075 mg/kg for huperzine A or 0.5 mg/kg for huperzine B, IP administration to mice significantly facilitated spatial discrimination learning in a Y-maze study. At slightly higher doses (0.075-0.125 mg/kg for A and 0.6-0.8 mg/kg for B) the huperzines given prior to exposure of mice to carbon dioxide prevented hypercapnia-induced impairment of learning. Memory retention and retrieval could be enhanced in animals when the alkaloids were given immediately or 6-12 hours after training. Substantially lower or higher doses of huperzines are not effective. Huperzine has been used for Alzheimer's and senile dementia with positive results. In a double-blind trial with a group of 56 patients suffering from multi-infarct dementia or senile dementia and a group of 104 patients with senile and presenile memory loss, huperzine A was demonstrated to be effective for improving memory. It was given by intramuscular injection, 0.05 mg twice daily for four weeks to the first group and 0.03 mg twice daily for two weeks to the second group. The only side effect was slight dizziness experienced by a few patients. In rats, for example, at 0.01-0.04 mg/kg IP, speeds up conditioned avoidance responses, reverses impairment of conditioned avoidance response, and antagonizes hippocampal and cortical EEG changes induced by quinuclidinyl benilate.

Huperzine A has been evaluated at the Mayo Clinic in Jacksonville, Florida. According to Alan Kozikowski, a chemist who is heading the research there, Huperzine A is more effective and more specific than tacrine, another anticholinesterase drug. Interneuron Pharmaceuticals in Lexington, Mass. is testing Huperzine A in human clinical trials.

OTHER CHOLINESTERASE INHIBITORS FROM CHINESE HERBS

Lycorus radiata (*shisuan*) contains the alkaloids lycorine, lycoramine, lycoreine, and galanthamine. Both lycoramine and galanthamine have been shown to be reversible cholinesterase inhibitors. Lycoramine is weaker than galanthamine, but equivalent to Nivalin. Galanthamine easily crosses the blood-brain barrier. It decreases cholinesterase activity of the cerebral cortex and medulla oblongata, and at high dosage shows an anticholinesterase activity in the thalamus. Lycorine produces a marked sedative action in mice and rats, and it prolongs sleep time in animals treated with pentobarbital. Lycorine could also potentiate the analgesic effects of morphine and corydalis.

Macleaya cordata (*boluohui*) in the Papaveraceae family, contains several alkaloids including sanguinarine, chelerythine, protopine, and allocryptopine. The sulfates of these alkaloids have a more potent local anesthetic action than procaine. Sanguinarine inhibits cholinesterase. The herb is mainly used for bacterial infections and trichomonas, and for killing maggots (the alkaloids cause excitation and then paralysis and death of larvae).

Coptis chinenses (*huanglian*) contains berberine alkaloids, mainly berberine, but also coptisine, worenine, palmatine, and columbamine. Berberine is a cholinesterase inhibitor. When given to mice at 0.250 mg/kg, berberine enhances establishment of positive conditional reflex, but high dosages (10 to 20 times higher) inhibit it. Berberine exerts a dose-dependent biphasic effect on acetylcholine in animals and their isolated organs.

Berberine antagonizes acetylcholine-induced bradycardia and ST segment depression in rabbits. Tetrahydroberberine, a berberine derivative, produces analgesia, sedation and muscle relaxation, with an effect that is three times more potent than that of meprobamate. Its action may be similar to that of tetrahydropalmatine; l-tetrahydroberberine, like l-tetrahydropalmatine, appears to be a more potent tranquilizer than the d-isomer.

Berberis species (sankezhen) are another source of berberine and also provide berbamine, palmatine, isotetrandrine, and jatrorrhizine. Palmatine was shown to have strong anticholinesterase activity. Isotetrandrine (also found in *Stephania* species), antagonizes ileal contraction induced by histamine or acetylcholine. Jatrorrhizine reduces spontaneous activity of mice and prolongs the animals sleep elicited by pentobarbital; it also induces sleep in mice given subthreshold doses of pentobarbital.

Securinega suffruticosa (yiyiqiu) contains many alkaloids, mainly securinine and its derivatives. Securinine is a CNS stimulant that antagonizes the inhibitory action of meprobamate. Securinine inhibits cholinesterase activity, but it is weaker than galantamine. *Solanum nigrum* (longkui), contains solanine, salasodine, and related alkaloids. Salasodine reduces sensitivity of animals to pain. Solanine markedly decreases spontaneous activity of mice and prolongs the sleeping time induced by pentobarbital. Solanine has a strong anticholinesterase action that is attributed to its aglycone solanidine.

Most of the herbs mentioned in this section inhibit bacterial growth and are used in tumor therapy. The isolated alkaloids often have the same effect as the crude herbs for these applications and are increasingly used in clinical practice. Clearly, there is reason to hope that one or more of the plant alkaloids will prove helpful to those with Alzheimer's and that these alkaloids might be administered with the herbs used by traditional doctors for the treatment of memory disorders so as to attain superior results.

SOURCES

Except for the general information about the nature of Alzheimer's disease and its treatment with Western medicine, which is available from many sources, the information for this article was derived from three sources:

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July 1996