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GOLD AND ITS RELATIONSHIP TO NEUROLOGICAL/GLANDULAR CONDITIONS

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Despite increasing sales of gold supplements, and claims of benefits for neurological and glandular conditions, gold has received little attention in modern medical literature except as a drug for rheumatoid arthritis. Historically, however, gold had a reputation as a "nervine," a therapy for nervous disorders. A review of the historical literature shows gold in use during the 19th century for conditions including depression, epilepsy, migraine, and glandular problems such as amenorrhea and impotence. The most notable use of gold was in a treatment for alcoholism developed by Keeley (1897). In the modern medical literature, gold-containing medicines for rheumatoid arthritis are known to have occasional neurotoxic adverse effects. There are also a few studies suggesting a role for gold as a naturally occurring trace element in the reproductive glands. One small recent study demonstrated a possible positive effect of gold on cognitive ability. There is a need for more experimental and clinical research of the neuropharmacology and neurochemistry of gold, and for the exploration of gold's possible role as a trace element.

Keywords glandular, gold, history, neurological, trace element

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The modern use of gold-containing medicines focuses primarily on rheumatoid arthritis, with some recent attention to other anti-inflammatory uses of gold, and to new anticancer and antimicrobial gold drugs (Fricker, 1998). Otherwise, in mainstream medicine, gold has been seen as a metal with little biological relevance. In contrast, the benefits suggested for gold-containing supplements, widely available in health food stores and over the Internet, address a variety of conditions including alcoholism, depression, and gland function (e.g., http://www.colloidalgold.com, 2001; http://www.topsilver.com, 2001). The present review asks if there is any support for a neuropharmacologic effect of gold.

Although there is very little modern research on these applications for gold, historically one notable use of gold was as a "nervine," a substance that could revitalize people suffering from nervous conditions, a term we would today call neurological and psychiatric disorders, such as epilepsy and depression. This article reviews the historical use of gold as a healing agent for the nervous and glandular systems, and looks at recent literature pointing to a biological role in these systems for gold.

Goodwin and Goodwin (1984) have addressed what they term the "tomato effect," a rejection of highly efficacious therapies. The analogy is with the long-held belief that tomatoes were poisonous, despite evidence to the contrary. The tomato effect contrasts with the placebo effect, where a positive (but spurious) response causes therapies to be accepted which are later shown to be useless or harmful. The Goodwins use gold as an example of the tomato effect. The original rationale behind the use of gold for rheumatoid arthritis was its effectiveness as an antibiotic for tuberculosis (with the assumption that rheumatoid arthritis was a related infectious disease). When, by 1945, the infectious theory of rheumatoid arthritis was discarded, gold therapy fell into disfavor, despite its proven effectiveness. "Gold started to regain its former popularity only when the medical community accepted both the evidence of gold's efficacy and medicine's ignorance of gold's mechanism of action. The fact that gold now has an unknown mechanism of action—is a truly idiopathic medicine—is no longer an impediment to its use, because rheumatoid arthritis has become an idiopathic disease" (p. 2389).

The intent of this article is to explore a similar situation for gold and neurological/glandular disorders. Neither the causes of the disorders nor the mechanism of gold is known, yet there are reports pointing to a possible involvement of naturally-occurring gold in the nervous and glandular systems, and evidence from historical sources of a possible efficacy of gold in therapy for neurological disorders.

HISTORICAL REVIEW OF GOLD AS A NERVINE

Gold has a therapeutic history in both Eastern and Western traditions. Mahdihassan (1985) has explored the historical use of gold in Eastern traditions. The Chinese were the first to prepare and use red colloidal gold as the alchemical drug of longevity. The word alchemy derives from two Chinese words: Kim (gold) and Yeh (juice). Kimyeh (gold juice) entered the Arabic language as kimiya, and with the definite article, al, the Arabic word for red; colloidal gold was alkimiya, which in the Western world gave the word alchemy. The procedure for the preparation of red colloidal gold is still in use today in India, prescribed by Ayurvedic physicians for rejuvenation and revitalization in old age under the name of Swarna Bhasma (red gold).

There is modern scientific support for at least one effect of Eastern gold preparations on the nervous system. Bajaj and Vohora (1998) studied the analgesic activity of gold preparations used in Ayurveda and Unani-Tibb, two Indian medical traditions. Two calcified gold preparations were compared to the modern antiarthritis gold drug auranofin in rats using four types of noxious stimuli. Both the Indian drugs and auranofin exhibited analgesic activity. The analgesic effects of the two Indian drugs could be partly blocked by pretreatment with naloxone (an opiate antagonist), but not the effects of the auranofin. The authors feel that this suggests involvement of an opioidergic mechanism for the Indian drugs.

The use of gold in Western medicine as a nervine has a long history as well. The medieval alchemists, like their Eastern counterparts, probably drew on the traditions of Eastern alchemy and sought a form of gold that could be internally consumed: "potable gold," as

the elixir of life. Paracelsus, in the 16th century, recommended preparations of gold in his therapy for epilepsy (Temkin, 1971). By the beginning of the 17th century, alchemists were clearly able to produce the soluble salt gold trichloride (Higby, 1982). By the mid-17th century, gold was in use as a nervine.

"A gold cordial could be found in the new pharmacopoeias of the 17th century and was advocated by Nicholas Culpepper for the treatment of ailments caused by a decrease in the vital spirits, such as melancholy, fainting, fevers, and falling sickness [epilepsy]" (Fricker, 1996). This is notable because it includes a grouping of what today would be called neurological/psychiatric disorders (e.g., depression, epilepsy).

By the beginning of the 19th century, gold had become a recognized (although probably not very effective) treatment for syphilis, a disease causing dementia among other serious symptoms. In 1821 the Frenchman J. A. Chrestien published "Researches and observations on the effects of preparations of gold in the treatment of many diseases and notably in syphilitic maladies" (Niel & Chrestien, 1821). Chrestien was a notable physician of the time, with a degree from the University of Montpelier, and memberships in the Royal Academy of Paris, the Royal Academy of Medicine of Madrid, and many other learned societies. His interest in gold came from the observation that it had milder side effects than mercury (the common treatment for syphilis at the time). He was also apparently the first to notice that in occasional cases treatment with gold produced an increase in vitality and intellectual faculties, and had a stimulating effect on the glands and sexual functioning. Chrestien and those who followed him used gold trichloride as their form of gold.

In 1879, James Compton Burnett published a lengthy treatise on the use of gold in medicine. Burnett was a medical doctor, a homeopath, and a prolific author (27 books listed in the National Library of Medicine catalog). Burnett traced the modern use of gold back to Chrestien's first book in 1811, but gave credit to earlier figures as well. He noted that the ingestion of gold is mentioned in the Bible (Exodus 32:20), and that the Chinese were using it in 2500 BC, according to Wiegleb's *History of Alchemy* in 1777. He traced its use in a diversity of disorders, including neurological and glandular problems such as epilepsy, sterility, and diseases of the

uterus, to the publication of *De Auri Tinctura sive Auro Potabili Vero, etc.* by Glauber in Amsterdam in 1651. He also noted that "Hahnemann [Samuel Hahnemann, the originator of homeopathy] mentions nearly thirty authors (1698–1730) who praise gold as a valuable remedy in various diseases such as melancholia . . ." (p. 91).

According to Burnett, Chrestien's use of gold was at first opposed by the medical profession, which had abandoned the use of gold in medicine. However, after Chrestien's publication, gold regained its popularity. Burnett cites Legrand's (1828) account, *the Medicinal Properties of Gold,* in which he lists 80 medical men of the time who became known as "auralists," who were exploring the use of gold. Burnett says, "Gold is an *excitant.* . . . The patients feel an *indescribable sense of well-being, they feel themselves lighten* (as they express it), so that we may say that Gold possesses hilariant properties. The *intellectual faculties* are *more active.* It has been known to produce *frequent erotic salacity going on to painful priapism.* M. Legrand, however, states that he has not used it as an aphrodisiac, but it has been used as such with success" (p. 49). Burnett also says, "Some are of the opinion that Gold belongs to that class of noble metals, such as silver and copper, which exert a powerful influence on the nervous system. Of this opinion is Vogt (Pharmaco-dynamik)" (p. 57).

Burnett was also well aware of the toxic effects of high doses of gold. He identifies himself as a homeopath, but has a different philosophy from many homeopaths. In traditional homeopathy, the remedy is an extremely high dilution of a substance, so high that not even a single molecule remains. It was Hahnemann's alternative to "heroic" medicine, which involved high doses that were frequently toxic. Burnett took a middle course, resembling the approach of 20th century medicine. He preferred low dilutions, as opposed to high ones. Thus, his recommended dosage of gold is 3/100 or 9/100 of a grain. Since a grain is 65 milligrams, this would range from 1.95 mg to 5.85 mg. This is very close to the range of daily dose of modern antiarthritic drugs, e.g., the 6 mg per day (1.74 mg of gold, at 29% gold) standard dose of auranofin. It seems possible, then, that Burnett did find an effective dose of gold with relatively low toxicity.

By the end of the 19th century and in the first half of the 20th century, gold was listed as a treatment for nervous disorders in sources ranging from medical texts to the first Merck manual.

In discussing the treatment of asthma, for example, Eichhorst (1886) in his *Handbook of Practical Medicine* says, "In nervous individuals, resort should be had to the nervines: bromide of potassium, valerian, arsenic, auronatrium chloratum [gold sodium chloride], zinc, copper, and silver preparations, etc." (p. 236). Bromide of potassium and valerian are still used for treatment of nervous disorders, and arsenic came into use in the early 1900s as a treatment for syphilis, which has neurological manifestations.

Potter (1894), in his *Materia Medica*, based on the *U.S. Pharmacopoeia of 1890*, describes the effects of small doses of gold: "The Salts of Gold promote appetite and digestion, stimulate the cerebral functions, and produce a marked mental exhilaration, a sense of well-being. Continued, they induce aphrodisiac effects in both sexes, and in women an increase of the menstrual discharge . . . Amenorrhea and Impotence, of the functional kind—may be cured by it." He is also well aware of the toxic effects of too large a dose, resembling those of mercury, and including "nausea and vomiting, glandular irritation . . . violent gastroenteritis, mental disturbance, convulsions, priapism, trembling, paralysis." This recognition of both kinds of effects is significant, since later in this article the adverse effects of gold are discussed as a possible indicator of areas particularly sensitive to the therapeutic effects of lower doses of gold.

The 1899 *Merck's Manual* lists gold under "aphrodisiacs" (p. 187). Gold bromide is an "anti-epileptic, anodyne, nervine," used for "epilepsy, migraine, etc., said to act, in small doses, quickly and continuously, without bromism" (p. 38). Bromides, particularly potassium bromide, were first used as nervines in the mid-19th century to treat epilepsy, insomnia, nervous excitement, and irritability (Leake, 1975). They were the first effective antiseizure medicine. It is not clear exactly when gold bromide began to be used, but it appears that it was found to be effective in a smaller dose than potassium bromide used alone. For example, the standard dose of gold bromide was given in *Merck's Manual* as 1/10 to 1/5 grain, 2 to 3 times daily. This can be contrasted with a standard dose of potassium bromide, of 5 to 60 grains (Gerber, 1942), or of sodium

bromide (10–60 grains, Garber, 1942; 5–30 grains, Dorland, 1908). Ryan and Baumann (1999) give modern guidelines for bromide dosage in epilepsy—might gold bromide allow a lower dose to be effective?

Hare (1912), in his *Text Book of Practical Therapeutics*, notes "it [gold sodium chloride] is said to act as a powerful sexual stimulant and to be of service in impotence dependent upon inability to obtain an erection or when there is deficient glandular action" (p. 274). Page 900 in Hare lists a standard dose of "gold and sodium chloride" as 1/20–1/10 grain (3–6 mg), and "gold bromide" as 1/8–1/2 grain (8–30 mg).

Fomon (1920) in his book *Medicine and the Allied Sciences*, in the section on Materia Medica and Therapeutics: Agents Producing Changes, says gold (as chloride of gold sodium) "stimulates the nervous system," "stimulates the sexual organs," and is employed in therapeutics as an aphrodisiac, an alterative in chronic diseases, and in the Keeley cure for alcoholism and opiumism.

Even as late as 1942, *Stedman's Practical Medical Dictionary* (Gerber, 1942) lists gold bromide as employed in epilepsy, headache, and as a nerve sedative. Double chloride of gold and sodium is listed as an alterative (a medicine that produces a favorable change in the processes of nutrition and repair, Dorland, 1908) and tonic. Finally, *Stedman*'s notes the Keeley cure or gold cure, "a secret method of treatment of alcoholism, said to be by the administration of strychnine and gold chloride." Actually, based on Keeley's own writings (Keeley, 1897), strychnine is unlikely to be a component of Keeley's cure.

The most interesting use of gold in treatment is the gold cure of Leslie E. Keeley, M.D. (1832–1900). Keeley's great discovery was that the chloride of gold and sodium (prepared by mixing gold chloride and sodium chloride) was an effective treatment for addictions, including morphine/opium and cocaine addiction, as well as alcoholism. In the 19th century, a variety of medications were used in an effort to ease withdrawal symptoms and cure addictions. Most, such as atropine and strychnine, were so toxic that they were of little use. Even gold chloride was too caustic for internal consumption. Keeley found that he had to carefully monitor patients for toxic effects. Then, however, he discovered that mixing gold

chloride with sodium chloride and a substance which he kept secret produced a cure for addiction that "accomplishes this quietly and mildly, without any shock or reactive effects" (Keeley, 1897, p. 82).

Keeley was well aware of the history of gold in medicine, citing numerous researchers who had worked with gold in the treatment of diseases including syphilis and tuberculosis, but noting the problems with gold toxicity (that his discovery had solved). Keeley had excellent powers of observation. For example, in the course of treating addictions, he noted: "In opium patients whose bodies are covered with nodulations, sores, pimples, blotches, tumors, and ulcers, resulting from the poison of the 'drug,' remarkable effects have been produced by the use of gold. The sores rapidly heal up and pass away, even without the use of any liniment or local application whatever" (p. 84). Gold medications are now a recognized replacement for steroids in treating serious skin conditions (Thomas, 1987).

Included in Keeley's book is a copy of an editorial from the *Chicago Tribune*, February 13, 1894. The editorial discusses Keeley's remarkable record, citing a recent summary of 1000 cases, of which over 90% seemed to have achieved a long-term cure of their addictions. Other evidence of the efficacy of Keeley's gold therapy includes the testimonial of Clark (1893), who wrote a detailed description of his own experiences in Keeley's program, and a historical discussion of the Keeley League by Barclay (1964).

Higby (1982) cites an estimate as high as 100,000 patients treated with gold by Keeley, and notes that by the mid-1890s, over 30,000 former Keeley patients joined clubs, "dedicated to the twin goals of mutual support and spreading the gospel of Dr. Keeley's marvelous gold treatment" (p. 138). Unfortunately, Keeley's exact formula was kept a closely guarded secret, and the use of gold in treatment of alcoholism at Keeley Institutes ceased with Keeley's death. Higby calls for more historical research on the Keeley gold cure, since Keeley probably administered more medicinal gold than anyone before or since. Despite the absence of formal scientific study, Keeley's success in treating addictions such as alcohol and morphine is impressive historical evidence of the potential of gold as a nervine, given that these problems are still very difficult to treat.

The use of gold as a therapy not only for alcoholism, but for a variety of neurological and glandular disorders, continued into the

1940s in the work of Edgar Cayce. Callan (1979) in the first editorial addressing holistic medicine in the *Journal of the American Medical Association*, credits Cayce with the origin of holistic medicine in America. Cayce followed the philosophy evident in Barnett: very small doses (<1 mg) of gold chloride taken orally. The gold was buffered with either sodium bicarbonate or sodium bromide, presumably to reduce toxicity. Although there were testimonials to the efficacy of Cayce's treatments (Cayce, 1993), no controlled studies of the use of gold were conducted in his time.

Nineteenth century microscopists also discovered an application for gold in exploration of the nervous system. Gold salts have been employed in neurological staining for light microscopy since Cohnheim in 1866 (Clark, 1983). Ramon y Cajal (1995) notes that Gerlach in 1871 stained with gold chloride and was able to enhance the distinction between white and gray matter in sections, and to obtain an unprecedented degree of contrast. Gurr (1962) lists several stains in modern use containing gold chloride, for neuroglia fibers, astrocytes, nerve fibers, sheaths and cells, and even for nerve fibers of planarians.

The affinity of gold for the nervous system and the implications of this for the treatment of nervous disorders was remarked on by Keeley (1897): "The use of gold by the histologist to develop microscopical nerves may, perhaps, be said to indicate that nerve fibre has a peculiar affinity for that metal. The application of it in solution brings out nerves which otherwise would be invisible. When the fact is recognized that absorption by lifeless fibre is quite unlike assimilation or reconstruction of that which is vitalized, then the development of lifeless microscopic nerves by a solution of gold may be in part owing to some of the recondite forces which cause the gold, taken into circulation, to reconstruct living ones" (p. 82).

A similar approach to drug discovery was held by Paul Ehrlich (1854–1915). "Ehrlich's earliest observations dealt with the staining of tissues for microscopic examination, and so with the processes by which particular dyestuffs combined with and were fixed to specific components of the tissues. Ehrlich supposed that the action of drugs in bodily organs was likely to involve similar fixation. . . . As an early test of this thesis, he treated a small number of malarial patients with the dye methylene blue, which was known to stain

(that is, be fixed by) the malaria parasite, and he showed that it had a modest therapeutic effect" (Weatherall, 1993, p. 925).

Taylor (1985), in a review of therapeutic uses of trace elements in neurological/psychiatric disorders, notes that while metal compounds have been administered for several centuries, the scientific basis for treatment with trace elements began with the use of gold compounds, initially in patients with tuberculosis and later those with rheumatoid arthritis. He points out the other important uses of trace elements, including "the central nervous system where the use of lithium has provided spectacular results in the treatment of affective and other disorders." Lithium carbonate is a simple metal salt with major effects; the same may be possible for gold salts. It is interesting that the first use of lithium in medicine was lithium bromide in the 19th century (Scott, 1992); gold bromide was also used, for epilepsy.

To summarize the relevance of the historical uses of gold, it is clear that there is a long tradition of gold as a nervine. But there were no multicenter clinical trials; that is a modern phenomenon. There were only observations and reports of individual cases. Keeley's work stands out in this regard, but there is no other scientific support for his claims; as with most of 19th century medicine, there are only testimonials. Yet this work can be seen as a source of hypotheses for testing with present day methods.

As 20th century medicine developed, gold disappeared from the pharmacopoeias, except in the case of rheumatoid arthritis. Forestier (1935) demonstrated its effectiveness in arthritis, although the popularity of gold and belief in its effectiveness has waxed and waned (Goodwin & Goodwin, 1984). Yet there appears to be no early 20th century literature on the efficacy of gold for neurological and glandular conditions, either pro or con. And the possible biological role of gold as a naturally-occurring trace element was not explored at all until recently.

THE BIOLOGICAL ROLE OF NATURALLY-OCCURRING GOLD

There is a continuum of effects with increasing concentration in the biological activity of elements, from beneficial physiological effects

as trace elements, to pharmacological effects, to toxic effects at high doses (Mertz, 1998). As described above, the pharmacological and toxic effects of gold were well known historically, although the pharmacological application is more limited today. But very few studies of trace elements in the body have included gold. However, those few studies have shown that naturally-occurring gold is found concentrated in glandular and reproductive tissues, and, in the female, its concentration cycles with the reproductive cycle.

Alexiou et al. (1977) measured trace elements, including gold, in human placenta and newborn liver at birth. They found gold in significantly higher concentrations (3-fold higher) in placenta than liver tissue. Because some essential trace elements (zinc, cobalt, and selenium) were found in higher concentrations in the liver tissue, Alexiou et al. concluded that gold is a nonessential trace element. An alternative may be that gold is specifically involved in reproductive glandular activity, as discussed below.

Hagenfeldt et al. (1977) measured trace elements, including gold, in the human endometrium and decidua, looking for cyclic variations, including those during pregnancy. It had been previously established that there are significant cyclic variations in major elements with known importance, such as sodium, potassium, and copper. Using uteri from women undergoing hysterectomy, they found that the levels of gold were similar in the endometrium and the decidua. There were cyclic variations in gold (as well as a number of other elements), which were significant at the $p < .05$ level. They reported that the levels of gold were slightly lower around midcycle than at other stages of the cycle, but the physiological significance of these changes is unknown.

In the male reproductive system, Skandhan and Abraham (1984) measured gold in semen, and noted that "this is the richest source of gold reported in biological materials" (p. 587). They also speculated that since gold was not seen in one pathological sample with asthenozoospermia, that may be an indication that reduction of this trace element led to this pathology.

Kauf et al. (1984) measured the amounts of a number of trace elements in the hair of newborn infants. They noted, "The investigation of trace elements in the hair of babies resulted in the remarkable observation that in the first three months of life zinc, copper and gold contents shows a considerable increase to multiple levels

of the birth values, followed by a decrease. . . . It must be emphasized that gold, although classified as a nonessential trace element, behaves in the hair of infants just like the physiologically important essential trace elements zinc and copper" (p. 299).

One major source on trace elements in neurological disease is the work of Gooddy et al. (1974). The 1974 study, which summarizes the results of several studies by previous researchers, does not give values for gold. They do, however, point out the importance of many trace elements in enzyme systems. The discovery of the biological activity of these elements has largely depended on the development of technology for measuring them at very low levels. They point out the great metabolic importance of copper, and note that the vertical neighbors of copper (in the periodic table of elements indicating some similar properties), silver and gold "are known medically almost as curiosities, with some rare therapeutic and toxic properties" (p. 330). Given this observation, it is not clear why they failed to measure these elements in their study.

El-Yazigi et al. (1984) looked at both silver and gold, as well as a variety of other trace elements, in cerebrospinal fluid (CSF) of patients with cerebral neoplasms (brain tumors). The concentration of silver was markedly increased in patients with malignant tumors, the malignant tumor/control patient concentration ratio was 2.31. They state that the biochemical mechanism of this increased concentration is unknown. Interestingly, though there was no consistent relationship between gold and tumor vs. control subjects, for the single patient with *pinealblastoma* the concentration of *gold* was about twice the concentration for the controls or other tumor types.

El-Yazigi et al. (1990) also looked at other trace elements in the CSF, in particular, platinum. They note that there are no previous values in the literature for platinum in the CSF. They found that platinum, in the opposite direction from silver, is *depleted* in patients with tumors. Platinum is known to react with DNA, and has treatment uses in cancer, as well as mutagenic properties. Platinum is also adjacent to gold in the periodic table of elements (the highly neurotoxic mercury is on the other side of gold, and toxic lead is close by). The platinum concentrations in the control group were 11.4 (SD 1.7) micrograms/liter. This is about 1/3 of the concentra-

tion of gold from the other study. In patients with tumors, the platinum concentration is about half this level.

Are there dietary sources of this gold? This can be an important issue, since dietary factors may be responsible for many of the reported inconsistent and divergent findings in trace element research (Nielsen, 1985). Warren (1989) looked at potential sources of gold in the diet. He noted that in 1981 gold was found in honey bee pollen in amounts as high as 0.9 ppm (dry weight). He found two plants (in British Columbia, Canada) that conceivably could provide gold in the diet, either to honeybees or perhaps directly—*Phacelia sericea and Dryas drummondi*—which carry 25–50 times as much gold as any other plants with which they are associated. Mahler et al. (1970), in a study of trace metals including gold, in fingernails and hair note the importance of differences in environmental sources of gold in different areas. Anderson et al. (1998) have shown that "hyperaccumulator" plants, such as Indian mustard (*Brassica juncea*), can uptake and store large amounts of gold, up to 100 times that found in most plants. Any study of naturally-occurring gold needs to address dietary sources.

These few reports show that naturally-occurring gold is found in nervous and glandular tissue, behaves in some cases like an essential trace element, and may change in concentration in correlation with certain diseases.

THERAPEUTIC GOLD AND THE NERVOUS/GLANDULAR SYSTEMS

Adverse effects of drugs can be an indicator of related therapeutic effects at lower dosages. The therapeutic and adverse effects of gold in living organisms are varied and paradoxical. Several different gold salts are currently in use: gold sodium thiomalate and gold thioglucose, both administered by injection, and auranofin, a complex organic gold salt taken orally. The primary therapeutic use of gold is in the treatment of rheumatoid arthritis (Kean et al., 1985), but there are many other less common uses, e.g., as a steroid replacement in asthma and skin disorders, and as an anticancer substance (Fricker, 1996). The primary adverse effects include skin and

gastrointestinal reactions (Locke & Smith, 1985). Yet gold-containing drugs have numerous rarer side effects, and can cause or exacerbate the same disorders for which they are effective in therapy. Gold-containing drugs have been used in place of steroids in therapy for asthma (Bernstein et al., 1996; Nierop et al., 1992), but in other cases have been responsible for respiratory disorders and even death (Blackwell & Gossage, 1995; Blancas et al., 1998). Similarly, gold is used in dermatological therapy (e.g., for pemphigus) (Thomas, 1987), yet skin disorders are a common side effect of gold medicines, and gold has also been found to cause pemphigus (Usuba et al., 1989). As another example, gold may be useful in treating lupus erythematosus (Weisman et al., 1983; Dalziel et al., 1986), yet gold may also induce lupus (Korholz et al., 1988). The mechanism of action for these effects is not known (Liebfarth & Persellin, 1981).

Neurological adverse effects of gold-containing drugs are rare, but diverse. They include both peripheral and central nervous system effects. At first one might think that toxic side effects are evidence *against* the utility of gold as a nervine. However, there is a therapeutic-toxic continuum with all drugs; this was clearly recognized in the 19th century by such gold therapists as Burnett (1879) and Keeley (1897). The effects may be related to specific gold compounds, dosage, mode of administration (oral, parenteral), and individual idiosyncratic responses. Toxicity can often be a pointer to a therapeutic use at a lower dose.

Three forms of gold-induced neurological side effects have been recognized: (1) painful neuropathy, sometimes accompanied by insomnia and anxiety; (2) peripheral motor neuropathy; and (3) encephalopathy with symptoms including depression, delirium, and exogenous psychoses (Schlumpf et al., 1983). Some of the case studies are mentioned below; they contain references to many other cases.

The variety of peripheral neuropathies includes various forms of polyradiculoneuropathy, a general term referring to peripheral disorders involving multiple nerve roots. These can include both sensory and motor symptoms, with both overactivity and paralysis. They include Morvan's fibrillary chorea, a form of spontaneous muscular activity (e.g., Vernay et al., 1986), and a Guillain-Barre-like syndrome with weakness and paralysis (e.g., Schlumpf et al.,

1983). Some of the reports of adverse effects of gold are simply reported as peripheral neuropathy. Weiss et al. (1982) report a case that was characterized by weakness and numbness of the hands and feet in association with hyperalgesia of the palmar surface of the hands. With cessation of gold therapy (aurothioglucose), recovery was slow but complete. In general, patients typically recover, but slowly, from gold-induced neuropathy.

Microscopic descriptions of peripheral neuropathy include marked loss of myelinated nerve fibers. In one patient, a nerve biopsy revealed, "a chronic polyneuropathy with predominant features of regeneration. Such features are clustering of myelinated fibers and the onion bulb-like arrangement of Schwann cells around and within such clusters" (Schlumpf et al., 1983). This observation is especially interesting, since one of the claims for gold as a nervine is for the regeneration of nerves.

Encephalopathy is the general term used for damage to the brain, as opposed to the peripheral nerves. Gulliford et al. (1985) report a case of gold-induced encephalopathy, as do McAuley et al. (1977) and Perry and Jacobsen (1984). Fam et al. (1984) describe a case of gold-induced encephalopathy with cerebral and cerebellar white matter lesions, reversible on withdrawal of gold therapy. Erhardt et al. (1978) report a case of cerebro-organic syndrome related to gold therapy, consisting of delirium, dementia, and amnestic and cognitive disorders.

Schlumpf et al. (1983) note that it is not surprising that neurological complications can be caused by gold because experimental work in animals has shown that gold localizes in nervous system tissue. Gold thioglucose, the medicine Solganol used for rheumatoid arthritis, is a well-known neurotoxin in rodents, used in studies of obesity to destroy the ventromedial hypothalamus, the part responsible for control of eating behavior and metabolism. In addition to obesity, it appears to become concentrated in other glandular tissue such as the pancreas (Blech et al., 1986) and the thymus and adrenals (Atkins et al., 1975). It can also cause generalized hypothalamic lesions in the chicken and duck (Hopper & Satterlee, 1984). In humans it is interesting that people who develop neurological adverse effects from gold sodium thiomalate can be successfully changed to gold thioglucose for rheumatoid arthritis therapy (Hill et

al., 1995). Clearly there are species differences in response to gold compounds, as well as pronounced individual differences and dose-related effects.

The question of whether gold affects glandular function in humans is still open. Chipman et al. (1982) tested the hypothesis that gold therapy enhances endogenous cortisol secretion, using juvenile rheumatoid arthritis patients. Their preliminary data suggested stimulation of cortisol secretion, but the results of the more complete study were ambiguous. Cortisol secretion was significantly greater in gold-treated patients than in similar patients not receiving gold. However, when untreated patients were restudied after initiation of gold therapy, there was no significant change in cortisol secretion. Gold therapy also did not significantly alter secretion of the peptide hormones or DHEA-S. Their conclusion is that gold does not appear to influence endogenous adrenal hormone secretion.

In summary, there are diverse neurological and glandular side effects occasionally observed in response to gold-containing medications. These effects are further evidence suggesting that gold may play a role in these systems.

HOW MUCH GOLD IS NECESSARY FOR A PHARMACOLOGICAL EFFECT?

Conventional gold therapy uses rather large doses, typically more than 1 mg per day. But there is some evidence that very low doses of gold can have pharmacological effects.

The gold drugs used in rheumatoid arthritis are typically administered in very large doses. Yet the relationship between dosage and response is not simple. Speight and Holford (1997) say, "Dosages as low as 10 mg/week appear to be no different from 50 mg/week, which in turn is as effective as 150 mg/week" (p. 1129). Given that toxicity is often seen at high doses, how little gold can still produce a therapeutic effect?

Effects have occasionally been seen with very low doses of gold. Mulherin et al. (1997) examined the hypothesis that gold rings might protect against erosion of the finger joints in rheumatoid arthritis. They found that there is less articular erosion at the left-hand ring

finger joints, and perhaps adjacent joints. Their hypothesis is that gold could pass from a gold ring through the skin and local lymphatic to nearby joints in sufficient quantities to delay articular erosion. Since metallic gold has been seen as virtually inert in biological systems, especially when present only at the skin surface, a therapeutic effect is surprising. But there is some historical support for this notion. In 14th century England, "cramp rings" were used to relieve muscular pains or spasms, and particularly epilepsy. Gold coins were placed by the king on a church altar, removed, and made into rings (Bloch, 1961). We have no reliable information concerning their effectiveness.

Belt and Kaarela (1998) and Bolosiu (1998) have expressed skepticism of the low-dose gold hypothesis. But gold has been measured in significantly greater concentrations in fingernails nearer gold rings by Kanabrocki et al. (1968), a fact apparently unknown either to Mulherin et al. or to Bolosiu et al. Kanabrocki et al. noted, "Only speculation can be made on the mode of transport of gold from wedding bands to the fingernail," a situation that is still the case.

Klinkhoff and Teufel (1995), in an article entitled, "How low can you go?" explored the minimum effective dose of gold for rheumatoid arthritis. They identified a group of patients with sensitivity to both the beneficial effects and the side effects of gold. They found that doses as low as 2 mg every 4 weeks could result in major improvement, and concluded that the minimum effective dose is not known. (This contrasts with the standard daily dose of 10 to 50 mg/week for parenteral gold, and of 6 mg/day for oral gold (Goodman et al., 1990)). This is still far more than the dose of gold available from a gold ring, but is further evidence that physiological effects do not require large doses of gold. Interestingly, it is similar to the amount of gold in prescriptions for neurological and other disorders by Cayce in the early 20th century (Cayce, 1993).

THE MODERN USE OF COLLOIDAL GOLD AS A NERVINE

Although gold is not in use as a nervine at present in mainstream medicine, its use has recently been explored in alternative medicine.

Instead of the modern gold-containing drugs, or the gold chloride used historically, colloidal gold has become popular. Colloidal gold is very fine particles of metallic gold (from 2 nm to 150 nm), suspended in water. As discussed earlier in the historical section, colloidal gold may have been the first form used as a nervine, as far back as the ancient Chinese and Indian alchemists (Mahdihassan, 1985). According to Abraham (1996) it is not toxic, but little is known about its physiological effects. In mainstream medicine, colloidal gold is generally thought to be biologically inert, and is used in electron microscopy studies for that reason. By attaching it to macromolecules such as antibodies, these molecules can be tracked to the locations where they are active without affecting their functions. Polak and Varndell (1984) note, "Fortunately, upon adsorption, full biological activity of the macromolecules is preserved." Yet Abraham reports that colloidal gold can have significant biological effects.

Abraham and Himmel (1997) used colloidal gold to treat rheumatoid arthritis. They studied 10 severe cases, orally administering 30 mg of colloidal gold per day. There was no clinical evidence or laboratory evidence of toxicity in any of the patients. The effects of the gold on the tenderness and swelling of joints were rapid and dramatic. Evaluated individually, 9 of the 10 patients improved markedly after 24 weeks of colloidal gold.

Abraham et al. (1998) explored the potential of colloidal gold as a nervine. Encouraged by pilot work suggesting improved cognition and well-being (Abraham, 1996), they conducted a study to see whether gold could improve cognitive functioning. They tested cognitive ability using the Wechsler Intelligence Scales (WAIS-R) before and after four weeks on colloidal gold at 30 mg/day. After four weeks on colloidal gold, there was a 20% increase in IQ scores. The effect of the colloidal gold persisted in three subjects after one to two months off gold, whereas in two subjects who took the test three months after stopping the gold, IQ scores were down to baseline levels. While a study of this small size is very preliminary, it is encouraging evidence of the potential of gold as a nervine, and as a demonstration of a nontoxic preparation.

DIRECTIONS FOR FUTURE RESEARCH

Future research could focus on two aspects of gold: exploring the effects of gold supplementation on neurological conditions, and establishing whether naturally-occurring gold is an essential trace element with functions in the nervous/glandular systems.

Two approaches might be taken in exploring the effects of gold supplementation. The first consists of attending to the side effects of gold medications in cases where there is comorbidity of rheumatoid arthritis and a neurological, psychiatric, or glandular disorder. For example, one could ask, do patients with epilepsy, depression, or adrenal insufficiency who may be receiving gold for arthritis show any improvement in neurological/glandular symptoms? Although neurological adverse effects are rare, beneficial side effects might be found.

The second approach is to administer gold with the intention of affecting a neurological or glandular condition. This is more challenging, since little is known about effective or toxic doses. The bioavailability of different gold compounds is an important consideration in exploring the effects of gold supplementation. There are substantial differences in the efficacy and side effects of the organic gold salts used for rheumatoid arthritis, and individual idiosyncrasies in response. As noted previously, it has been difficult to establish a dose-response relationship for gold (Speight & Holford, 1997). Gold chloride, a favorite in the 19th century, is now used primarily as a test for allergic skin reactions, not internally, so nothing is known about its metabolism. And colloidal gold, as noted above, should have very little physiological interaction at all, although Abraham and Himmel (1997) present evidence to the contrary. An advantage to using colloidal gold is that is has no known adverse effects. Animal studies with gold chloride as well as the current gold medications might also be productive.

Establishing gold as an essential trace element is another challenging task. The few studies cited here are encouraging. A systematic exploration of the concentrations of gold in cerebrospinal fluid, blood, and neurological and glandular tissue could be performed.

The results would be interesting in neurological disorders and tumors (e.g., El-Yazigi et al., 1984), glandular disorders (e.g., Skandhan & Abraham, 1984), and developing infants (e.g., Kauf et al., 1984). But much further research will be needed to confirm these observations and determine gold's biological role. There are thousands of studies on such elements as chromium and boron, which have only recently been suggested as essential nutrients (Nielsen, 1990). It takes on the average about 30–40 years for the general acceptance and application of the discovery of a new essential trace element (Mertz, 1998). Studies in both animals and humans will need to address specific physiological roles, effects from deficiencies, and interactions with metabolic stressors.

This research has the potential for re-establishing gold as a significant therapeutic agent in a much wider range of disorders than those for which it is currently used. And it could help in sorting out valid from invalid claims of benefits from supplementation.

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