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FOCUS ON INFLUENZA

With this issue, we begin a two-issue series focusing on pandemic influenza. In this issue, see Influenza: Lessons for the clinic from 1918, below, and Cytokines and Herbal Therapeutics in Influenza on page 5. In our next issue, we will feature three clinical articles: Influenza prevention, Therapeutics for acute febrile illness, and Therapeutics for the acute cough.

Influenza: Lesson for the clinic from 1918

by Paul Bergner

Abstract: Avian influenza and the potential threat of a major influenza pandemic have been among the top news stories over the past year. Public health concern is high because of the high human mortality rate associated with bird flu and fears of the potential for emerging strains to spread from human to human. Coupled with the news stories are accounts of the deadly 1918 influenza pandemic. The "superbug" theory of pandemic influenza generally attributes all excess mortality to the strength of the pathogen and ignores all other factors involved in host resistance. This theoretical stance does not withstand close critical examination, particularly in light of what is historically known about the 1918 pandemic. Factors such as urbanization, micronutrient malnutrition, poor diet, vitamin D deficiency, and host-weakening iatrogenic disease may have contributed significantly to mortality in the 1918 pandemic, and these factors may have been as important as the pathogenic potential of the virus. An examination of these factors from 1918 leads to recommendations for prevention or treatment during future pandemics.

By their very nature, viruses constantly mutate and evolve, partly in response to host resistance in general, but also in response to the specific host carrier. Influenza viruses mutate and evolve in human, bird, and pig hosts, and spread between these hosts in agricultural areas. Viral strains may evolve characteristics that make them more or less lethal to humans, with more or less facility of transmission, and mortality may vary somewhat from season to season. The contemporary concern of public health authorities is that a strain with unusual lethality could develop, killing millions of people worldwide and causing widespread social and economic disruption through secondary effects. Of special concern is the current epidemic of Avian Influenza H5N1, which primarily infects birds. Bird-to-human infection has a high mortality rate – estimated at about 50% of those hospitalized with the disease (Wong and Yuen). Actually lethality may be much less, because asymptomatic, subclinical, or mild illness is unlikely to come to the attention of authorities, and only those most severely affected are hospitalized. Whether the virus will mutate to allow human-to-human transmission – and whether such a mutation will retain the lethality of the current bird virus – is a matter of serious concern.

Typical seasonal influenza infections are one of the leading causes of death in the United States. Of the 30,000 to 70,000 influenza-related deaths per year, most involve the elderly or those with compromised immune systems. In North America, mortality of these typical viruses is 1/10,000; in the 1918 flu pandemic, mortality was 2/1000, about 20 times normal. Mortality in 1918 among Native American populations was extremely high. Up to 80% died in some Eskimo villages, and 10% of the entire population died in the state of Chiapas, Mexico. This phenomenon among Native Americans may be similar to the plagues of Western diseases that decimated native peoples around the world following first European contact, with a large percentage of the native population lacking innate immunity to influenza and other Eurasian diseases (Barry; Killingray; Newman). No such lethal epidemic of influenza had been recorded previously, or since, and this has become the reference point for most discussions of unusually deadly organisms.

HOST FACTORS

An examination of the social and public health conditions of the Western urbanized societies in the early twentieth century offers alternate explanations for the lethality of the 1918 epidemic. Urban social and public health conditions may have contributed significantly to

the epidemic, and these factors tend to modify the preeminence of pathogen strength as the sole cause of excess mortality. It was established during the 1918 epidemic that a large percentage of the population either did not get infected, or experienced only subclinical symptoms. In several trials at the time, subjects were unable to become infected even though experimentally exposed. In these cases, their host resistance was able to withstand exposure or generate immunity without producing symptoms. In an experiment with prisoners in a U.S. Navy brig in Boston, researchers were unable to infect any of 100 "volunteers," despite exposing them to infected individuals and to their mucous secretions (Rosenau). None had shown any previous signs of having contracted the virus between the outbreak of the epidemic and the experiment. The following account summarizes the procedures used:

> *"Then we proceeded to transfer the virus obtained from cases of the disease; that is, we collected the material and mucous secretions of the mouth and nose and bronchi from cases of the disease and transferred this to our volunteers. We always obtained the material in the following way: The patients with fever, in bed, have a large, shallow, traylike arrangement before him or her, and we washed out one nostril with some sterile salt solution, using perhaps 5 c.c., which is allowed to run into this tray; and that nostril is blown vigorously into the tray. That is repeated with the other nostril. The patient then gargles the solution. Next we obtain some bronchial mucous through coughing, and then we swab the mucous surface of each nares and also the mucous membranes of the throat."*

Two similar experiments in other localities had identical results (Kolata). These results are inexplicable given the high mortality rates of the virus in other settings. The only possible explanation is host resistance.

HOST FACTORS IN THE 1918 PANDEMIC

Any infectious disease is the result of interaction between the infectious agent and the host resistance to it. Some agents are weak enough that anyone with strong host resistance will not acquire the disease; others may be so powerful that only a very few will be able to resist infection and disease. Most influenza strains are intermediate in strength, and some individuals with strong host resistance can avoid infectious symptoms and develop immunity without acquiring symptomatic illness. Those with moderate host resistance may acquire the illness without serious consequences, while those with weakened immunity are most likely to have the most severe, and potentially lethal, symptoms.

This equation of balance between host immunity and pathogenicity is almost universally ignored in discussions of potent new strains of influenza. From a public health perspective, this balance should be the primary topic of discussion because measures to increase resistance are easier and cheaper to implement on a mass scale than the measures required to develop and administer vaccines and pharmaceutical drugs. Compared to the costs and logistical problems involved in major medical campaigns, measures such as public education, improved nutrition, and environmental modifications are a cost-effective way to increase host resistance on a large scale. Even if vaccines become more effective than those available at present, or if drugs are developed that do not ultimately promote drug-resistance, these other measures to improve host resistance to influenza will continue to be effective on an individual, practice-level, or broad social scale. They may also increase the effectiveness of vaccines and antiviral drugs. See the accompanying article Influenza Prevention.

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An examination of the social conditions in industrialized countries in 1918 may reveal that specific factors profoundly influenced host resistance, especially in the younger generation. The 1918 epidemic came after several decades of urbanization in North America, involving a major population shift from farm to city, and to the conditions of labor and diet in the city. During this same period, sugar and white flour became available as staple foods rather than specialty foods, and they became a major portion of the diet. Flour used during this period did not contain the vitamins in whole grains that are lost during processing, and it was many decades before the advent of fortified processed foods. The resulting deficiencies included reduced intake of many immune-supporting nutrients such as zinc, vitamin A, vitamin C, vitamin E, selenium, iron, and essential fatty acids (See accompanying article Influenza Prevention). As a result, as the population of North America increasingly relied on processed grains, the general health, constitution, and immunity of the population weakened over time. By 1900, white sugar consumption had grown to exceed 100 lbs of sugar per capita in the United States – or 4 to 5 ounces per day – with most of the consumption occurring in urban areas. Sucrose or its derivative glucose are known to be immuno-suppressive in the amounts consumed by urban dwellers in 1918. In one study, 3 ounces of sucrose at one sitting reduced the ability of phagocytes to engulf bacteria and other invaders by

about 40%. The effect started within 30 minutes and lasted more than 5 hours (Sanchez et al 1973; Ringsdorf et al 1976). Another trial showed that only 2 ounces of glucose suppressed the activity of B- and T-lymphocytes (Bernstein 1977).

While researchers have proposed that the young died in greater numbers than the old during the 1918 epidemic because they had healthier immune systems and could mount a more powerful self-destructive cytokine storm than older patients (See the accompanying Cytokines and Herbal Therapeutics in Influenza), observers at the time noted that the young were in fact weaker and more sickly than their elders during the decade of the epidemic. In the 1916, dentist and nutritional anthropologist Weston Price was stricken by the phenomenon of sickly, urban youth in Cleveland, Ohio – particularly those from families with robust farm-raised parents and grandparents. In response to this phenomena, he pursued worldwide studies linking modern dietary changes to physical degeneration, with documentation by photograph in his classic *Nutrition and Physical Degeneration* (Price). The photographs showing the deterioration of the health of children relative to their parents or to others following a traditional rather than modern diet. One photograph shows an older Scottish brother, eating a traditional diet, with robust health, while the younger brother, freely eating pastries and sugar, with his bone structure and teeth deteriorated. The same degeneration of the constitution was noted by nature cure physician Henry Lindlahr in Chicago. In 1913, Lindlahr described a generation of healthy grandparents, "anemic" parents, and "sickly children subjected to the full horrors of urban life". (Lindlahr). Child labor also peaked in the U.S. during the first decades of the twentieth century (CLPEP) and many children were not only malnourished but were also subjected to dawn-to-dusk working conditions. It is possible that the pandemic struck this younger generation like a forest fire among insect-infested trees.

VITAMIN D

The new urban labor conditions in 1916 North America kept factory workers, including children, indoors and out of the sun for most or all of the day – with an epidemic of Vitamin D deficiency as the result. The role of vitamin D in defense against influenza cannot be overestimated (for a full review see the Cannell article in the references). The seasonality of influenza correlates precisely to the darkest seasons of the year in both the Northern and Southern temperate zones and during cloudy monsoon seasons in the tropics. One role of Vitamin D is to promote immuno-competent peptides in the immune cells of the respiratory tract; another is to blunt the severity of inflammation during infection. Together these two functions are the perfect combination to prevent influenza infection or to modify excessive inflammation from cytokine effects and render the infection less lethal. In intervention trials, vitamin D given as cod liver oil has shown much better results for prevention of respiratory infection during flu season, or reduction of severity of symptoms, than influenza immunizations (Cannell). Cod liver also contains vitamin A and essential fatty acids, both may benefit host resistance. In one cited study, the vitamin D dose for children equivalent to 4,000 IU in an adult completely prevented all respiratory infection over a winter in a group of children who had experienced three or more infections the previous year.

IATROGENIC INJURY

Many recorded features of the 1918 flu do not match the natural course of the disease, but are common side effects of methods used to treat the infection at the time. Aspirin was a new drug at the time, as were several medications similar to acetaminophen with poorly defined toxicity. Two recorded sample prescriptions for influenza during the epidemic follow (Anonymous):

Prescription 1

Aspirin	1300 mg
Phenacetine	650 mg
Salol	1300 mg

Prescription 2

Aspirin	1300 mg
Acatanilid	260 mg

Phenacetine and N-phenylacetamide are in the drug class with acetaminophen. Salol yields about 60% salicylic acid. These combinations of aspirin and non-steroidal anti-inflammatory drugs (NSAID) are in line with what might be recommended today for febrile illness, but similar doses have been found to be immuno-suppressive in viral respiratory illnesses, including influenza. In 1975, a pair of double-blind trials administered either aspirin or placebo to volunteers experimentally infected with rhinovirus, the most common virus to cause the common cold. Aspirin reduced the symptoms somewhat, but caused a "highly significant" increase in virus production. The authors stated that such treatment could worsen viral illness and contribute to its spread (Stanley et al.). In 1990, other researchers tested the effects of aspirin and acetaminophen on experimental rhinovirus infection. The use of either drug suppressed antibody response to the virus and prolonged the time that infected cells produced new virus (Graham et al.). In 2000, researchers tested the effects of antipyretic therapy with aspirin or acetaminophen on experimentally produced influenza A virus. The authors noted a "striking" prolongation of influenza infection in the patients who

took either aspirin or acetaminophen (Plaisance et al.). It would seem that the routine administration of these drugs during the epidemic weakened resistance to the illness, prolonged the illness, and may have made it more infectious. In addition, the combination of aspirin and NSAID may have made matters worse. Today standard references warn against giving aspirin in doses higher than 325 mg if accompanied by an NSAID. Note that treatment of fever with NSAID is standard treatment today in H5N1 infection despite the above research, and this treatment approach may contribute to the reported lethality of the disease. Treatment of advanced complications of H5N1 with immuno-suppressive corticosteroids has also been standard until recent recommendations against it (WHO).

Besides weakening host immunity, aspirin may have also contributed to the distorted presentation of the 1918 pandemic. So many patients demonstrated hemorrhagic symptoms, that it is now often included as a symptom of that pandemic, even though it is not part of the normal course of influenza (Barry). Aspirin can cause such symptoms, sometimes even at low doses. One contemporary trial found that 200 mg of aspirin per day taken chronically causes major bleeding events in about 4% of patients (Peters et al.) Aspirin had only been available to the medical profession and the public for about 20 years before the epidemic, and its toxicity was not well known. In 1918, there are reports of doctors giving as much aspirin as a patient could tolerate, and doses up to 6.5 grams for several days in a row (Winston). Aspirin and other medications were available over the counter in an era when safety warnings were absent and prescriptions were not required for any medications. Other side effects of aspirin overdose also overlap with symptoms of epidemic influenza, including respiratory collapse and shock. High doses of aspirin may also explain some of the mortality in the younger generation through the effects of Reyes syndrome. Reyes syndrome is associated with multiple organ failure in individuals under the age of eighteen with viral illness who take aspirin.

Besides weakening host immunity, aspirin and other drugs may have also distorted the clinical presentation of the 1918

The other two drugs in common prescriptions, Acetanilid and Phenacetine, are no longer sold because safer alternatives are available. Phenacetine has a depressant action on the heart, where it can disrupt electrolyte activity. Its use has been discontinued due to potential carcinogenicity with chronic administration. Acetanilid (N-phenylacetamide) can cause a rapid and sudden drop of fever, which may be also accompanied by cardiovascular collapse (Osol and Farrar). In acute poisoning, acetanilid causes cyanosis with subsequent prostration and collapse. Traditionally, and at the time of the 1918 epidemic, acetanilid was given with caffeine, which increases its toxicity (Osol and Farrar). Notably, cyanosis and sudden circulatory collapse were two symptoms often noted in the 1918 flu epidemic (Barry). We wonder if these and some of the unusual symptoms reported for the 1918 influenza were not, in fact, side effects of the medications routinely given. For example, an account from a military hospital in Massachusetts indicates that the patients

".... start with what appears to be an ordinary attack of . . . influenza, and when brought to the hospital they very rapidly develop the most viscous type of pneumonia that has ever been seen. Two hours after admission they have the mahogany spots over the cheek bones, and a few hours later you can begin to see the cyanosis extending from their ears and spreading all over the face, until it is hard to distinguish the colored men from the white. It is only a matter of a few hours then until death comes, and it is simply a struggle for air until they suffocate. It is horrible. One can stand it to see one, two or twenty men die, but to see these poor devils dropping like flies sort of gets on your nerves. We have been averaging about 100 deaths per day, and still keeping it up. " (Leavitt)

The 1918 epidemic normally had a mortality rate of about 3%; it appears that whatever treatment was given in the above hospital was killing the patients because cyanotic symptoms are not part of the natural course of influenza. Because all of these medications were available over the counter in 1918, some individuals who self-medicated likely took overdoses of the drugs, possibly before entering the hospital. It seems likely that then, as now, some individuals overdose when self-medicating with aspirin — aspirin overdoses are the fourth most common drug overdose in conventional emergency care. It would take only a few percent of patients over-medicating with these drugs to produce much of the excess mortality noted in the epidemic.

VACCINES

Further iatrogenic injury may have contributed to excess mortality in the 1918 epidemic. Vaccines and antitoxins to various non-influenza diseases were routinely given to patients with acute influenza. Typhoid vaccine was a common prescription, and "others poured every known vaccine into patients in the hopes that they would somehow boost immunity" (Barry). While neurological complications of vaccines are common, the neurological complications of influenza patients in 1918 were attributed entirely to the virus.

DIGITALIS

Hospitalized influenza patients were administered digitalis as a matter of course; this was a standard treatment at Johns Hopkins. In 1918, the drug was administered as powdered leaf of the digitalis plant. Accurate dosing of dried plant material is difficult, as the active constituents in the plant degrade rapidly in powdered material (Osol and Farrar). In addition, dosing is complicated by the fact that the toxic dose is very close to the therapeutic dose. In standard practice, the herb dose was administered until its strengthening effects on the heart and pulse were noted, and then the dose was increased again until nausea appeared. Nausea and vomiting are the first signs of toxicity. Headache, fatigue, malaise, and drowsiness are the next signs to appear, and all are indicators for a reduction of the dose. Because these signs of toxicity overlap almost completely with typical signs of acute influenza, the possibility of overdosing the patient and inducing heart arrhythmia and cardiac collapse was great.

OPIATES

Other drugs routinely given were heroin hydrochloride, codeine sulphate, cocaine hydrochloridum, opium, morphine sulphate, elixer terpin hydrate (a concoction of terpentine, alcohol, and nitric acid), paregoric elixer (made with powdered opium, benzoic acid, camphor, oil of anise, and glycerin diluted alcohol), and morphine

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Acute and chronic opioid administration is known to have inhibitory effects on humoral and cellular immune responses including antibody production, natural killer cell activity, cytokine expression, and phagocytic activity. Opiate receptors modify immunity by action on the central nervous system, the autonomic system, and directly on immune cells (Vallejo et al; Molina). Opiates also specifically depress the numbers of circulating natural-killer cells, which are responsible for attacking virally-infected host cells (Weed et al.). Opiates are suspected to increase susceptibility and to decrease resistance to the spread of viruses such as HIV and the hepatitis-C Virus Cabral; Zhang et al). Opiates also increase susceptibility to bacterial infections in burn patients (Schwacha et al.).

LESSONS FOR THE CLINIC

- Increase host resistance with diet and lifestyle approaching flu season.
- Take 4,000 to 10,000 IU of vitamin D during winter season.
- Don't suppress fever or immunity with aspirin, NSAID, or other medications.

Cytokines and Herbal Therapeutics in Influenza

By Paul Bergner

One theory for the higher mortality of Avian Flu H5N1and of the 1918 influenza strain is that an excessive immune response contributes to the pathology and lethality of the disease (Cheung et al). Immune cells pour out inflammatory cytokines in an attempt to destroy invading pathogens, and this may occur more or less intensely depending on the influenza strain. According to this "cytokine storm" theory, lymphocytes and macrophages may produce a sustained and massive cytokine response in response to a "superbug," leading to severe systemic inflammation and destruction of tissues, especially in the lungs (Hseih et al). According to the theory, an individual with a strong immune system would be more likely to die than an individual with a weak immune response. This theory has been put forth as an explanation for why the 1918 epidemic struck young patients with more virulence than the old, reversing the typical epidemiology of the disease (Loo and Gale). This theory also raises questions about the wisdom of using herbal medicines that stimulate immunity during influenza infection.

The cytokine storm theory for the lethality of some influenza strains is by no means settled science. Alternative explanations for the elevated lethality in flu "superbugs" have been put forth in the scientific literature. Although more than one phenomenon may contribute to overall mortality at the same time, the ability of the H5N1 avian influenza virus to escape the respiratory epithelium and to produce a widely-disseminated systemic infection may be more important to pathogenesis of the disease than exaggerated cytokine response. Influenza infection is normally restricted to the upper respiratory tract.

Another alternate theory suggest that vitamin D status may be a critical determinant of total cytokine effects, and not only determines susceptibility to influenza infection, but also the severity of symptoms (Cannell et al). The Cannell article is part of a significant body of recent scientific literature establishing widespread vitamin D deficiency as a major root pathology in many contemporary diseases. One of the chief physiological roles of vitamin D, an immuno-modulator steroid hormone, is to put a brake on inflammatory cytokine responses, and thus the deficiency may play a role is pathological cytokine excess. Note that in 1918, the world was entering into a period of rapid urbanization, with new factory working conditions which often kept the individual out of direct sunlight 6 days a week – conditions which pro-

mote profound vitamin D deficiency. Typical seasonal influenza is closely and inversely related to average vitamin D status of humans, peaking throughout the world at local times when vitamin D status is at its lowest.

CYTOKINES AND SUDDEN DEATH

A characteristic of the 1918 influenza was the sudden death of some of its victims. Anecdotal accounts tell of four men sitting down to play a card game in the evening, with only one of them left alive in the morning. Another tells of several individuals dying on a streetcar within several blocks, including the conductor. From the natural course of influenza infection, it is unlikely that these individuals died at first onset of the illness. More likely is that they left their sick beds too soon. The typical course of influenza infection, as measured by the presence of cytokines, is 1 full week. Different cytokines surge or peak at different times over this period, but peaks may occur as late as Day 6. The initial fever of influenza often recedes between Days 2 and 4 as the levels of one set of cytokines decreases. On Days 4 to 6, as patients may begin to feel some relief from symptoms, cytokines associated with lower respiratory infection may surge (Hayden et al). The symptoms are less dramatic, but the complications and lethality of a lower respiratory infection and inflammation may nevertheless be quite severe. It is common in contemporary times for patients to leave their beds and return to work when the fever of influenza first subsides. In one recent year, the author had six patients with influenza, all of whom felt better by Day 3. They were cautioned to rest for a full seven days, but two of them went back to work on Day 4 of their infections. Both relapsed with viral pneumonia and were hospitalized on Day 6 of the infection. Similar behaviors in the 1918 epidemic may have led to the high incidence of sudden death as those who left their beds too early died in public of lower respiratory infection and inflammation.

Doctors at John's Hopkins medical school conducted a retrospective analysis of which patients did better or worse with various medical treatments in the 1918 pandemic. The analysis found only that those who "went to bed the earliest, stayed there the longest, and had the best nursing care survived the best" (Barry).

HERBS AND CYTOKINES

Physician-level treatment of influenza with herbal medicines has been recorded at least since the 18th century in North America (Lloyd and Lloyd). Several of the most common herbs used, *Sambucus nigra, Eupatorium perfoliatum,* and *Echinacea spp.*, have been shown through scientific investigation to enhance host immunity (Brush et al; Zakay-Rones et al; Wagner et al; Wagner and Jurcic). A critical question in light of the cytokine theory in the pathology of influenza is whether an herbal agent that enhances host resistance may also increase pathological expressions of cytokines. Many herbal medicines with reputation as immuno-stimulant actually have immuno-modulating effects, enhancing some inflammatory cytokines while moderating their effects by stimulating secretion of inhibitory cytokines along with them.

ELDERBERRY

Sambucus nigra, elderberry berries or flowers, are used in traditional herbalism to treat respiratory infections, including influenza. Clinical trials over the last decade have demonstrated a powerful effect of an elderberry extract syrup on the course of influenza (Zakay-Rones et al. 1995, 2004). The extract has also been shown to inhibit influenza virus replication in ten strains of the virus in vitro (Zakay-Rones 1995). Notably, elderberry extracts have been shown to enhance both inflammatory and anti-inflammatory cytokines in human cells in lab experiments (Barak et al). In one lab study, an extract of the flowers inhibited all pro-inflammatory cytokines measured (Harokopakis) and in another showed at least partial inhibition of inflammatory cytokines (Yesilada et al).

ECHINACEA AND BONESET

Echinacea species, used a hundred years ago in the treatment of influenza, and remaining a common treatment today may enhance immunity and also have a moderating effect on excessive inflammation (Sharma et al.; Randolph et al., Brush et al.; Zwickey et al.) One trial of the use of a combination of Echinacea and *Eupatorium perfoliatum* found no net inflammatory effect produced by cytokines in humans at the dose tested (Elsasser-Beile et al.) Eupatorium has been one of the frequently used herbs in the treatment of influenza in North American history (Lloyd and Lloyd).

In the absence of specific evidence that herbs traditionally used in the treatment of influenza aggravate the condition by overstimulating cytokines, there appears to be no reason to avoid their use for this speculative reason.

LESSONS FOR THE CLINIC

- Promote healthy vitamin D levels in patients as a preventive in the face of an approaching pandemic.
- Consider megadoses of vitamin D acutely at exposure or onset of symptoms in patients whose status is likely to be low.
- Treat acute infections with herbs according to historical usages, unless specific evidence emerges that they may exacerbate the symptoms or pathology of a hew pandemic influenza strain.

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Influenza prevention

Immunization and Tamiflu are not enough

by Paul Bergner

ABSTRACT

Vaccination and antiviral drugs are the standard public health measures available for pandemic influenza; these will be insufficient to provide protection for the great majority of individuals affected. Other methods of increasing host resistance may be available with dietary changes, nutritional supplementation, and herbal medicines. Research supporting the efficacy of such measures is reviewed.

Influenza pandemics occur in regular cycles, and judging from previous history, we are due for another at any time. A pandemic is a global disease outbreak that emerges when a new influenza virus emerges for which people have little or no immunity, and for which there is no vaccine. The disease can spread within populations and from country to country very rapidly.

Pandemics occurred during the 20th century in 1918, 1957, and 1968. The occurrence of a pandemic does not necessarily imply excess deaths beyond those caused by regular seasonal influenza. The 1918 Spanish flu resulted in approximately 500,000 deaths in the U.S, whereas in the 1957 Asian flu about 70,000 patients died, and in the 1968 Hong Kong flu, the number was about 33,000. Non-pandemic seasonal influenza epidemics in the U.S. cause about 36,000 deaths annually in the current era.

Once a pandemic appears, world public health agencies engage in a race to produce a vaccine to the new influenza strain before the disease is widely circulated. In the 1957 pandemic, a new strain was identified in February of that year, and the new vaccine was in production by May. It was available in limited supply by August (USHHS). The epidemic began in earnest in September, three months earlier than most seasonal outbreaks. This early seasonal appearance is typical for new strains, and may be followed by several more waves of the epidemic over the next six months. The gap between identification of the new strain and the availability of a vaccine today still may be 6-9 months or more (CDC b). Once administered, vaccines then take about two weeks to confer immunity. Millions of North Americans will be exposed to any new pandemic virus weeks to months before a vaccine is available and will need to rely on other methods to increase host resistance to the infection.

Influenza vaccines have mixed effectiveness. A vaccine well-matched to the influenza strain may prevent 80% of cases in normal healthy adults. Because of difficulty matching vaccines to the exact annual strain of influenza, and because the virus can mutate in the midst of an epidemic, typical seasonal vaccines reduce incidence in healthy adults by only about 50%. It appears that vaccines mainly prevent influenza in those who will not develop severe symptoms anyway — among healthy adults, the percentage of individuals in a vaccinated population who develop severe disease, miss days at work, or require hospitalization is the same as in an unvaccinated population, and a meta-analysis in 2004 reached the conclusion: “There is not enough evidence to decide whether routine vaccination to prevent influenza in healthy adults is effective (Demicheli; Jefferson).” Another recent meta-analysis of influenza vaccination in elders reached the conclusion that immunization does not reduce mortality in that age group (Simonsen). Simonsen and his co-authors challenged the conclusion of some studies that routine influenza immunization in nursing homes reduced overall winter mortality. Their study, published in The Lancet, found that mortality from influenza in individuals over seventy years old (who account for about 75% of all influenza mortality) remained unchanged or actually increased between the years 1980 and 2002. During that period, the percentage of elders over age seventy who were immunized rose from 15% to 65%. Vaccines may also cause major health problems in some individuals — vaccines for the Swine Flu in 1976 caused significant morbidity, and were eventually withdrawn for this reason. More than 1000 individuals were paralyzed by the vaccine before it was removed from the marketplace.

DRUG THERAPY

Influenza is treated today with two classes of drugs: adamantanes (amantadine and rimantadine) and neuraminidase inhibitors (oseltamivir/Tamiflu; and

zanamivir/Relenza). Adamantanes are only active against A strains of influenza, and not B strains. Influenza strains that are resistant to adamantane drugs emerge rapidly in epidemics where the drug is used. Up to 30% of patients treated with amantadine may shed resistant viruses, sometimes as early as day two to three after treatment. Such adamantane-resistant viruses can readily be transmitted to contacts. Most North American influenza viruses are already resistant to adamantanes. Neuraminidase inhibitors are put forth as the best treatment for those infected in a future pandemic. These are active against seasonal strains of either A or B influenza viruses. Trials have shown that Tamiflu reduces the severity of influenza in these cases, but the drug must be given early in the course of infection (within 48-60 hours). A recent review suggests that Tamiflu is much less effective for H5N1 Avian influenza (Crusat and deJong) also rapidly promotes development of viral resistance — 25% of patients in one small study (de Jong et al.) Future strains of epidemic influenza will likely become rapidly drug-resistant in any epidemic where the drug is widely used.

The most important micronutrients for immunity are zinc, vitamin A, vitamin C, vitamin E, selenium, iron, and essential fatty acids.

Vaccination and antiviral drugs are the only public health measures available for pandemic influenza, and will be insufficient to provide protection for the great majority of individuals affected. Other methods of increasing host resistance may be available with dietary changes, nutritional supplementation, and herbal medicines.

NUTRITION

General immunity is highly dependent on nutritional status; many individuals who are not overtly malnourished have micronutrient deficiencies that contribute to reduced resistance to infection. For some nutrients, their status in the system or consumption in clinical trials has been directly correlated with susceptibility to influenza infection and disease severity. Several nutrients have been demonstrated to increase the host response to influenza immunization. For an excellent review of the roles of specific nutrients in general immunity, a free full-text journal article is available through the PubMed service of the National Library of Medicine (Field et al). The most important micronutrients are zinc, vitamin A, vitamin C, vitamin E, selenium, iron, and essential fatty acids. The first five of these comprise the ZACES formula, developed in Southern Africa as a treatment for AIDS. The formula (see Table 1) is combined with a whole foods diet and other lifestyle modifications, and is now part of standard treatment for AIDS throughout Zimbabwe, South Africa and neighboring countries. The director of an AIDS treatment center in Harare, Zimbabwe, stated in an interview that the ZACES formula with lifestyle changes can "prolong the progression of HIV infection to AIDS almost indefinitely, and get the AIDS patient out of bed and back to work (James). HIV infection is clearly not influenza, but the formula apparently works by correcting any underlying deficiencies of the nutrients essential to optimal immune response, and might be useful in any viral infection.

The ZACES formula itself has not been tested in clinical trials of HIV infected individuals, but each of its components has been studied in HIV infection or AIDS, and found to be beneficial in intervention trials. This includes trials of zinc (Bobat et al; Wellinghausen et al), Vitamin A (Semba et al.2005), combinations of vitamins A,C, and E (Fawzi et al; Villamor et al.), combinations of vitamins C and E (Allard et al.), vitamin E alone (de Souza et al.), and selenium (Burbano et al; Shor-Posner et al; Kupka et al; Hurwitz et al.) Notably, each of these nutrients has also been successfully tested in intervention trials, mostly among the elderly, specifically for influenza and other respiratory infections, and to improve response to influenza vaccines. This includes a generic multivitamin (Wouters-Wesseling et al), zinc and selenium (Girodon et al), vitamin E (Hara et al), and vitamin C (Gorton et al.) See Table 2 for a description of the doses in a successful intervention trial in the elderly with a ZACES-like formula. Doses at a small fraction of those used in Africa were moderately successful in preventing respiratory infections and immunity to influenza in elders. Larger doses might be much more successful.

DEFICIENCIES IN THE POPULATION

Supplements will not necessarily increase immunity if the nutrients are not deficient in the host, but deficiencies of immunity-related nutrients are common in populations of industrialized nations. A recent study found in an Italian population of elders about 50% of the individuals were deficient in selenium, nearly 50% in zinc, and more than 20% for vitamins A and E (Ravaglia et al). A recent study in France concluded that about 70% of females were deficient in iron, and 66% deficient in vitamin C (Touvier et al). Statistics are similar in North America.

ZINC

In 2003 in Canada, the percentage of the population with inadequate zinc intake ranged from 9% of adult males aged 31 to 50 years old to 43% in male elders over the age of seventy. The figures for women were 15% of those aged 19 to 31 years and 30% of elders over seventy. (Mendelson et al) In the United States, the third National

Health and Nutrition Examination Survey found that only 50% of women over age nineteen and 50% of men over age 70 met the criteria for recommended daily intake of zinc. In the United States, only 50% of men aged 71 and over and of women aged 19 and over had adequate zinc intakes, using the Recommended Dietary Allowance as the criteria (Briefel et al). Positive responses to zinc intervention trials in the United States also suggest a widespread sub-clinical zinc deficiency in the population (Hambridge).

VITAMIN A

The prevalence of vitamin A deficiency among adults in the United States is low — about 1%. Deficiency in children is much higher, more than 30% in some groups of young children tested (Ballew et al.) Even mild vitamin A deficiency can cause a higher incidence of respiratory disease and a higher rate of mortality from infectious disease (Field).

VITAMIN C

A study by the U.S. Department of Agriculture in 1996 found that 18% of US adults consumed less than 30 mg per day of vitamin C. The recommended dietary allowance is eight times this, or 240 mg. (Hampl et al).

VITAMIN E

Gross vitamin E deficiency is rare in North America, suboptimal intake is almost universal. The National Health and Nutrition Examination Survey III in the early 1990s found that 18% of white participants, 41% of African Americans, and 28% of Mexican Americans had blood levels of vitamin E less than 20 mmol/liter, the level at which cardiovascular disease risk increases. Using the current recommendations for vitamin E intake, a 2004 survey found that more than 90% of the population fails to consume the recommended dietary intake (Ahuja et al).

SELENIUM

Optimal serum levels of selenium have not been officially established. A recent survey found an average serum level of 1.58 micro-moles/liter. Other research indicates that selenium related disease may be present at levels at or below 1.5 micromoles/L. About half the U.S. population appears to consume sub-optimal levels of selenium (Semba et al. 2007).

IRON

Iron deficiency is generally low in the U.S. population, affecting about 2-5% of males. It is much higher in females, however — nine to twenty two percent depending on age and race. Deficiencies are highest in Black and Hispanic women (CDCa). Because iron is pro-oxidant, and because excesses are readily stored in the tissues, it should not be supplemented unless a deficiency is identified by blood analysis. When deficient, effects on immunity may be profound (Field).

ESSENTIAL FATTY ACIDS

Because the Food and Nutrition Board of the National Academy of Science has not issued an official recommended daily intake of essential fatty acids, it is difficult to assess deficiencies in the population. Historical trends, however, indicate profound and deepening deficiencies in the U.S. since 1900 (Hibbein). Throughout the countries bordering the North Atlantic Ocean, seasonal consumption of cod liver oil to prevent colds and flu in winter is an established cultural phenomenon. Several intervention trials have demonstrated that cod liver oil can profoundly reduce the incidence of respiratory infections (Cannell et al). In one trial, a group of children who had experienced frequent infections in the previous year was completely infection-free during a season of taking cod liver oil. Cod liver oil provides essential fatty acids, vitamin A, and vitamin D, each of which can improve general immunity.

CHOLECALCIFEROL

Vitamin D, or cholecalciferol, is of special interest in the face of an influenza pandemic. Cholecalciferol is not actually a vitamin, but a steroid hormone with profound effects on the immune system. In human history, the primary source of this hormone has been sunlight — ultraviolet radiation acting on cholesterol in the skin produces a precursor to the hormone. Mid-day or summer exposure of the whole body (a normal exposure throughout the year in human evolution near the equator) generates the equivalent of about 10,000 IU of cholecalciferol, a level difficult to achieve with diet. Human migration out of tropical regions, and modern work and lifestyle conditions have created a situation where winter norms of serum cholecalciferol are about 20% of the levels that would be attained from tropical sunlight exposure.

Vitamin D expert John Cannell has recently published an article reviewing the specific roles of cholecalciferol in preventing influenza infections or moderating its severity (Cannell et al.) Cholecalciferol promotes immune competence specifically in the respiratory tract by assisting in the production of immune-peptides in the white blood cells there. The hormone also has anti-inflammatory effects, and specifically has a moderating influence on the production of pro-inflammatory cytokines. Part of the pathology of highly virulent influenza strains is the overproduction of such cytokines, which, in excess, may cause more damage to the system than the virus itself. Cholecalciferol may thus prevent influenza infection or moderate its severity. Supplementation with Vitamin D3 in a dose of 4000 IU per day will restore near-normal serum levels over a period of months. Higher doses to

Table 1

The ZACES formula

zinc	20 mg
beta carotene	25000 iu per day
vitamin C	2 grams twice a day
vitamin E	200 IU per day
selenium	100 mcg twice a day

Also recommended: 3-5 cloves of garlic per day, multiple vitamin containing B-complex, plus local herbs.

Note on Influenza:

double the dose if taking antibiotics,suffering from a cold, influenza, infection, or stress.

ref:SAT

Table 2

ZACES ELDERY INTERVENTION

zinc	10 mg
vitamin C	120 mg
beta-carotene	6 mg/5000 iu
alpha Tocopherol	20 iu
selenium	100 mcg

The doses here are much lower than the traditional ZACES formula, but still reduced respiratory infections. The benefits were due mainly to the minerals. C was found to be highly protective taken at onset; it reduced symptoms more than 80% compared to controls who received pain killers and decongestants.

Girodon et al.

more rapidly achieve optimal serum levels may be warranted in the face of a spreading pandemic. Although the official upper safe limit of vitamin D is 2000 IU/day, this has been revised upward by leading vitamin D researchers in the last twelve months. Hathcock et al provided evidence in January of 2007 that the safe limit should be raised to 10000 IU/day. In a study published in September 2007, researchers gave doses greatly in excess of 10000 IU/day for many months, and found no evidence of vitamin D toxicity (Kimball et al.) In order to rapidly raise serum levels toward normal, up to 40,000 IU/day might be safely given for a period of six weeks, followed by daily doses of 4000-10000 IU. Increased calcium in the serum and/or urine are the defining symptoms of vitamin D toxicity. An individual taking supplements in excess of the official upper safe limit of 2000 IU might out of prudence have serum and urine calcium measured periodically. Because vitamin D production in the skin is moderated by serum levels, Hathcock et al suggest that serum levels cannot be raised above the normal upper limit with doses of 10,000 IU/day. Except in certain uncommon genetic conditions, that dose should never produce serum levels sufficient to produce toxicity.

HERBAL MEDICINES

Taken in conjunction with nutritional support and lifestyle changes, herbal medicines may also help to prevent respiratory infections or moderate their severity. The principle of prevention in traditional herbalism is: what is good for treatment is also good for prevention, but in smaller doses.

ECHINACEA

Although echinacea species have been tested in clinical trials for their ability to prevent upper respiratory infections in general, or the common cold caused by rhinovirus in particular, they have not been tested for their ability to prevent or treat confirmed cases of influenza, a condition with a severity and a course very different from the common cold. However, the herb appears to work by increasing host anti-viral resistance, which may very well help to prevent influenza or moderate its severity if contracted.

A number of small clinical trials of echinacea for prevention of upper respiratory infections have been conducted with only mixed results. Most have had small numbers of participants, however, and when analyzed in several meta-analyses, actually show very good results for preventing colds. Combining data from fourteen previous clinical trials, one group of authors demonstrated that echinacea reduced the odds of having the common cold by 58% while taking echinacea, and the duration of colds that did occur was a day and a half shorter in the groups taking echinacea than in the groups that did not (Shah et al). The other meta-analysis demonstrated that echinacea protected against experimental infection with the rhinovirus (Shoop et al).

GARLIC

In herbal traditions throughout the world, from ancient Egypt, to China, to the folk traditions and medical herbalism of North America, garlic *(Allium sativa)* has been used to prevent or to treat respiratory infections (Bergner 2001) A number of trials have demonstrated that garlic can increase general immunity in animals or humans, and specifically strengthen components of the immune system that increase resistance to viral infection and cancer (Sumiyoshi; Bergner 1995). In a well-designed clinical trial for prevention of respiratory infections, a single capsule of a garlic product provided strong protection. The group receiving garlic had 64% fewer colds than the control group, had fewer than 30% of days sick with a respiratory infection, and duration of symp-

toms averaged 1.5 days in the garlic group compared to 5 full days among the controls (Josling).

BONESET

Boneset *(Eupatorium perfoliatum)* has been used to treat influenza and other viral respiratory infections continuously in North America since before first contact with Europeans. A review of this history was published by the Lloyd Brother pharmaceutical company in 1918 (Lloyd and Lloyd). The review describes the use of a strong boneset tincture to prevent influenza during the 1918 pandemic.

> *"Eupatorium was employed both in the course of treatment of the disease, and as a preventive. Five employees in one manufacturing establishment were afflicted in one day. At once, a prescription was filled and given to each of the large force remaining, with the direction to begin taking it immediately. None were thereafter afflicted."* (Lloyd and Lloyd)

Boneset has also been used traditionally as a topical treatment for herpes viral infection. Despite its fame, little scientific investigation of the plant has been conducted. Two trials have shown an increase in the activity of immune cells from various constituents extracted from boneset, including the water-soluble polysaccharides (Wagner et al; Wagner and Jurcic). In the latter trial, boneset polysaccharides were more potent than those of Echinacea.

AMERICAN GINSENG

Several clinical trials have found a proprietary extract of American ginseng *(Panax quinquefolium)* to be effective in preventing influenza and other respiratory infections among elders in a nursing home. In one trial, the participants took 200 mg of the preparation in a capsule a day for four months, beginning in September. Initially there was little difference in respiratory infections between the groups. By November and December, however, the frequency and duration of acute respiratory infection during the first two months of the group taking ginseng had about half the rate of respiratory infection as the placebo group. About a third of the ginseng group had infections, versus two-thirds of the placebo group. The difference in duration of symptoms was also dramatic – 5.6 days on average in the ginseng group versus 12.6 days in the placebo group (McElhaney et al 2006). None of these patients had influenza.

The same researchers had earlier tested the same ginseng protocol for its ability to prevent confirmed influenza in a nursing home (McElhaney 2004). Only one of ninety-seven patients in the ginseng group contracted influenza, compared to seven of 101 subjects in the placebo group. Data were similar for infection with respiratory syncytial virus – only one patient in the ginseng group was infected, versus 9 in the placebo group. The overall relative risk of acquiring a respiratory infection of any kind was 89% lower in the ginseng group. Significantly, about 90% of the populations being tested had received annual influenza vaccinations during the years of the trial – the ginseng greatly enhanced any effectiveness of the vaccines.

A DAILY SUPPLEMENT PROTOCOL FOR OPTIMAL IMMUNITY

Vitamin D	4,000 to 10,000 IU vitamin D3
Zinc	40 mg
Vitamin C	1000-2000 mg
Vitamin E	100-200 IU
Selenium	200 mcg
Cod Liver Oil	1 Tablespoon
Vitamin A	25,000 IU as beta-carotene
Iron.	10 mg/day, only when a diagnosed deficiency is present.

Lifestyle factors

Avoid Sleep debt

Avoid sugar and high glycemic foods.

EMPIRICAL TREATMENTS

In North American herbalism, a general application for prevention of influenza is to administer the herbs or formulas that might be used to treat it, but in lower doses. A scientific review concludes that the overall support for this method is slight, due mainly to a lack of investigation rather than to negative outcomes of trials (Guo et al.). The following empirical treatments, employed in the clinic and school community of the North American Institute of Medical Herbalism may be useful in increasing general host immunity. Although recommended doses are given, the intensity of preventive applications should depend on the degree of exposure. The busy clinician exposed frequently will naturally take a higher dose than an individual without significant contact with the sick. Higher doses may also be warranted if co-workers or family members contract influenza.

Immune tincture

Equal parts of:

Echinacea *Echinacea angustifolia*

Boneset *Eupatorium perfoliatum*

Osha *Ligusticum porteri*

Red root *Ceanothus americanus*

½ part of Licorice *Glycyrrhiza spp*.

½ part of Ginger *Zingiber off.*

The proportion of the herbs might be adjusted to match the patient, and synergist herbs other than licorice of ginger might be substituted or added.

Dose: 10-20 drops, 2-3 times a day for prevention.

Immune tincture #2

Equal parts of:

Echinacea *Echinacea angustifolia*

Oregon grape *(Mahonia spp.)*

Western red cedar *Thuja plicata*

Wild Indigo *Baptisia tinctoria*

¼ part Cayenne *Capsicum spp*

Dose: 10-20 drops, 2-3 times a day for prevention.

Elderberry syrup

Samubcol(TM) is an elderberry product widely available in health food stores. It has been successfully tested in clinical trials for influenza, but not specifically for prevention. Sambucol contains sugar or xylitol, and a more natural alternative elderberry syrup based on glycerin is available from the Herb Pharm company (Williams,OR).

Dose: 1 tsp twice a day.

Astragalus and codonopsis

These common Chinese herbs may be added to soups and stews, or brewed as teas to increase general host resistance, especially in cold weather. 1-2 sticks of each per quart of soup or tea is a good dose for prevention.

SMUDGES

Incense and smudging have been used throughout history to treat or prevent the spread of respiratory route infections. Because the influenza viral infection is normally restricted to the upper respiratory mucous membranes, smoke from medicinal incense or smudge may deliver medicinal properties directly to the tissues involved. Note that incense typically delivers four to five times the amount of particulate matter to the air as tobacco (Mannix et al). In one clinical trial in China, a traditional incense was as effective at removing bacteria from the air as conventional allopathic disinfectants (Yan et al). Common disinfectant smudges used in the community of the North American Institute of Medical Herbalism include artemisia species, salvia species, frankincense, and myrrh. One method for the practitioner, family member, or coworker who thinks they have been exposed is to take a "smudge shower." Using an appropriate smudge, close the bathroom and take off the clothes, and make the room thick with smudge. Inhale deeply, and also rub the smoke all over the surface of the body. This might be enhanced by steaming the room with a hot shower first.

SAUNA

Saunas, sweat lodges, and other methods of applying heat to the body and mucous membranes may be useful for prevention. The influenza virus normally cannot live above about 96 degrees, a condition that keeps it on the surface of the physiology, in the membranes, rather than penetrating into the hotter core. Applying hot air from without, and breathing deeply to heat the membranes, may effectively disinfect them.

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Medical Herbalism

A Journal for the Clinical Practitioner

Volume 16, Number 1 Spring 2009

Influnza: Treatment of Acute Febrile Disease

by Paul Bergner

We are continuing our series on the treatment of influenza. The two chief therapeutic considerations in influenza are the fever and the dry cough. I describe the treatment of a normal febrile illness in an otherwise healthy older child or adult. Note that fevers and influenza can be dangerous in children under one year old, in elders, and in those with compromised immune systems; these may require the care of a physician.

PHYSIOLOGY OF FEVER

Fever is a beneficial rise in the body s metabolism which permits the urgent manufacture of antibodies and white blood cells, with increased circulation to the surface defenses and increased elimination. Antibody production increases about 20-fold. The mistaken concept that fever is itself a disease (rather than a vital response for fighting off a disease) has led to overmedication and suppression of fever much to the detriment of hundreds of millions of patients. Chronic suppression of fever can lead to injury of the vital structures of the body, resulting in chronic fatigue, chronic immune weakness, and other vital derangements.

During fever, the body-temperature set point of the hypothalamus is elevated, much like the thermostat on a furnace being turned up. In the first stage, the normal body temperature feels cold; there is shivering, aversion to cold and wind, and closing of the pores to prevent sweating and heat loss, resulting in paleness. Shivering raises the metabolism and generates heat. In the second stage, the temperature peak of the set point is reached (102 104 °F is healthy), optimizing antibody production. The skin may be hot and dry, and the pulse fast. The patient is drowsy. Muscle tissue is broken down to make amino acids available for immune component manufacture and tissue repair, resulting in body aches. Gut motility decreases and the natural appetite disappears at a temperature of about 99 °F. Blood concentrations of iron and zinc are reduced, possibly denying food to pathogens. In the third stage of fever, the set point is lowered back toward normal; now the patient feels hot and sweats to reduce the temperature. During the daily cycle of a fever after it reaches its peak, it is normal for the body to cycle between the second and third stage intermittently. The fourth stage, from a clinical standpoint, is a recovery period about equal to the length of time of the fever.

The chief concern for higher fevers (over 104 °F) is dehydration or metabolic exhaustion in elderly or debilitated patients. High fever in cardiac patients may put lethal strain on the arterial plaque, leading to heart attack or stroke from plaque rupture.

TEMPERATURES

96.5 °F morning to 99 °F evening is common normal range. Upper range is more variable in children.

Normal temperature may reach 104 °F under vigorous exercise.

98 99 °F: influenza virus dies.

99.5 °F: the digestive system shuts down.

104 °F: upper range at which most bodily functions are not altered.

104 °F: gonococcus is killed. *Poliovirus* replication is reduced by a factor of 250.

106 °F: threshold for possible seizure activity. Normally human body temperature does not rise above this.

106 °F: pneumococcus dies. Spirochetes die.

106 110 °F: malignant cells are selectively killed.

108 °F: brain damage may occur due to denaturation of proteins.

110 °F: human cells begin to die.

Rectal temperature is usually 0.5 1 °F higher than oral temperature.

Armpit temperature is usually 0.5 1 °F lower than oral temperature.

In infants aged 1 month, 101.4 °F may be a critical temperature. This rises to 102 °F at 2 months of age.

SUPPRESSION OF FEVER

In an animal trial, rabbits infected with pneumococcus had a 29% mortality rate. One group had their fever lowered by 1.5 degrees with salicylates, and had 100% mortality. In a related trial, suppression of fever resulted in 2.5% faster replicaion of pneumococcus in cerebro- spinal fluid. In human trials with salicylates or other non-steroidal anti-inflammatory drugs, lowering the fever increases severity of subjective symptoms and length of infection. In viral infection in babies, salicylates may cause fatal Reye s syndrome (a rare condition). The benefits are primarily in severely debilitated patients with weak vital force facing metabolic exhaustion by the heightened demands of the fever.

Febrile seizures in children are not correlated with the severity of the fever. The cause is generally unknown. They affect 3 5% of children in the U.S. and about 15% in some countries. Giving antipyretic drugs does not reduce the incidence of future seizures in children. Most seizures disappear by age five, and most do not indicate a serious cerebral disease.

THERAPEUTIC STRATEGY

Support the vital force according to its expression in the stages of the fever. Avoid pharmaceutical antipyretics or plants with antipyretic pharmaceutical properties. The fever is the ally, not the enemy.

Fasting during fever is critical. Henry Lindlahr, the nature cure master of the early twentieth century, said Not so much as a drop of milk until the fever falls below 99 degrees. I have followed this practice, for myself and my patients, since the mid-1970s. The natural appetite disappears although the neurotic appetite may not, and the cravings of the latter have to be resisted. One rationale is that in normal physiology, about half of the protein production during the day is for digestion or regeneration of the gut wall. Feeding during a febrile illness will reliably increase the patient s discomfort and extend the period of the fever. Some care and patience needs to be taken as the fever begins lowering toward normal, to wait until it has truly returned to normal.

First stage strategy: the skin is cold or cool, the pulse may be weak. Support the body s need to warm up. Warm bath. Warm blankets. Warm room. Warming stimulant diaphoretics, such as hot yarrow tea, garlic, cayenne. Hot teas. Fast.

Second stage strategy: skin is hot and dry, the pulse full, strong, fast. Use relaxing diaphoretics such as boneset or elder. Ventilated room. Cool Melissa water. Plenty of liquids. Tepid bath (warm to the feel, never cool or cold). Lukewarm teas rather than hot. Short hot stimulating showers.

Third stage strategy: rest, hygiene, avoid exposure to cold or wind. No food until the fever goes below 99 °F.

Fourth stage strategy: nourishment, tonification, rest. Don t go back to work or daily duties too rapidly. The period of recovery should be at least the length of the fever itself. In influenza, a longer recovery period (five to seven days after the end of the fever) is necessary. A poorly managed recovery period may lead to extended lingering flu-like symptoms for weeks or months, or to a permanent state of chronic fatigue.

MATERIA MEDICA

For Materia Medica, we consider diaphoretics / sudorifics and antipyretics. Although the words diaphoretic and sudorific both imply an increase in sweating, these herbs are not necessarily used therapeutically to increase the volume of sweat in fever. While the body may decrease heat through sweating, a larger amount of heat is lost through ventilation. As the capillaries below the thin epidermis of the skin are opened up through herbal action, more of the hot blood comes to the surface where the heat can be radiated out into the room. Opening up the surface circulation may drop the temperature of the fever a degree or two, even without extensive sweating. The physiomedicalist physician William Cook described the right use of diaphoretics as until the skin regains its normal moisture rather than for stimulating heavy sweating as a cooling mechanism. This understanding is critical because dehydration must be strictly avoided in fever. Also, in some cases or stages of fever, exhaustion can lead by itself to excessive sweating.

HOT STIMULATING DIAPHORETICS

Referring to diaphoretics as hot or cold can be misleading. Some have an initial heating effect which causes blood to move to the surface, ultimately cooling the fever. So are they hot or cold? The initial effect is warming and the secondary effect is cooling. Even ginger, an herb that is unequivocally warming, can open the surface and lead to cooling. The hot stimulating diaphoretics are best matched to the stage(s) of fever when chills are present.

RELAXING DIAPHORETICS

Relaxing diaphoretics do not have any heating qualities at all. They open the surface by relaxing the peripheral resistance in the capillaries, and the blood leaks out to the surface and promotes cooling through ventilation.

SOME PATTERNS IN THE DIAPHORETIC MATERIA MEDICA:

Most stimulating diaphoretics are also emmenagogues and carminatives.

Many diaphoretics are also expectorants.

Most relaxing diaphoretics have some antispasmodic effects.

Many diaphoretics exhibit those properties in a warm and weaker infusion, while showing diuretic effects in a stronger cold infusion.

ANTIPYRETICS

The term antipyretic may be used to describe herbs that, through the activities of their constituents primarily salicylate- or berberine-containing plants. In a Vitalist paradigm, where we view the fever as a healing response rather than a disease, such a strategy should be used with caution. There is also an open question in herbalism about whether these bitter herbs act to cool the system through the pharmacological effects of their most famous constituents, or through the effects of their cooling, drying, draining bitter principles on the humoral system.

Stimulant diaphoretics

Capsicum spp. Cayenne

Asarum canadensis Wild ginger

Eugenia caryophyllus Clove

Xanthoxylum americanum Prickly Ash

Monarda spp. Horsemint,Cornmint

Thymus spp. Thyme

Milder stimulants

Achillea millefolium (warm tea) Yarrow

Tanacetum parthenium Feverfew

Zingiber officinale Ginger

Mixed stimulating and relaxing effects

Melissa officinalis Lemon balm

Nepeta cataria Catnip

Mentha x piperita (more stimulating) Peppermint

Mentha spicata (more relaxing) Spearmint

Relaxant diaphoretics

Eupatorium perfoliatum (warm tea, or tincture)

Sambucus spp. Elder berry, flower

Lobelia inflata Lobelia

Dioscorea villosa Wild Yam

Asclepias tuberosa Pleurisy root

Corallorhiza spp. Coral root

Verbena hastata (warm tea) Vervain

Antipyretics

Salix alba Willow bark

Berberine-containing plants *Mahonia, Berberis*

Usnea spp. Old man's beard

FORMULATION

It is generally not practical to devise a new formula for each stage of the fever, and most classic pairs and formulas contain a combination of stimulant and relaxant diaphoretics, with a bias toward the milder stimulants.

CLASSIC COMBINATIONS

Mentha and *Sambucus*

mild stimulant, mild relaxant (Edward Shook)

Sambucus and *Achillea*

mild relaxant plus mild stimulant

Achillea and *Mentha*

mild mixed relaxant and stimulant

Eupatorium 1 part, *Asclepias* 2, *Scutellaria* 1

add 1 part *Capsicum* if chills are predominant

two relaxants plus a sedative; astimulant (Clymer)

Eupatorium, Thymus, Nepeta

relaxant, stimulant, neutral (Tommie Bass)

Lobelia and *Zingiber*

relaxant mild stimulant (Cook)

Nepeta and *Zingiber* for children

mild mixed stimulation and relaxation

(Priest and Priest)

SOME MATERIA MEDICA SPECIFIC FOR INFLUENZA

Two of the relaxant diaphoretics above also have specific benefits in influenza beyond their cooling properties.

ELDER (SAMBUCUS NIGRA)

Recent research from Israel and Panama has demonstrated that elderberry juice not only stimulates the immune system, but also may directly inhibit the influenza virus (Zakay-Rones et al., 1995; Mumcuoglu, 1995). The trials used the juice of the berries, made into a syrup. The

syrup has less of a tendency to induce sweating, but is considered effective in most of the same conditions as the tea of the flowers (Grieve 1931). The syrup of the berries will cause nausea if taken in large doses. Israeli researcher Madeleine Mumcuoglu, Ph.D., of the Hadassah-Hebrew University Medical Center in Ein Karem, Israel, performed the initial research, and found that elder seems to be designed as a specific weapon against the flu virus. This virus forms tiny spikes, called hemagglutinins, which are laced with an enzyme called neuraminidase. The enzyme helps the virus to penetrate the cell membranes of a healthy organism. The virus then sets up shop in the cell, reproducing more viruses. The active ingredients that Mumcuoglu discovered disarm the neuraminidase enzyme within 24 48 hours, halting the spread of the virus.

Although this effect was seen *in vitro*, and may or may not occur in the living system, clinical trials show that elderberry is in fact very effective against influenza infection patients who took the elderberry juice syrup reported fast termination of symptoms. Twenty percent reported significant improvement within 24 hours, 70% by 48 hours, and 90% claimed a complete cure after three days. Patients receiving the placebo required six days for recovery. As proof that elder has more to it than the enzyme-neutralizing constituents, researchers found that the patients who took it also had higher levels of antibodies against the flu virus. Elderberry syrup has been proven effective against eight different influenza viruses. This may solve the perennial problem of the mutating flu (Zakay-Rones 1995; Mumcuoglu 1995). Use the tea or the juice rather than the tincture. A syrup of the juice the same one used in the Israeli clinical trial is available in health foods stores as Sambucol®. Versions come made with either sugar or xylitol as a sweetener. Herb Pharm sells an excellent *Sambucus* syrup made with glycerine.

BONESET *(EUPATORIUM PERFOLIATUM)* FOR ACUTE OR LINGERING CONDITIONS

For a review of the historical uses of boneset in multiple influenza epidemics, see: Bergner, P. Boneset and Influenza. *Medical Herbalism*. Fall 2003;13(4):16-19.

As a hot infusion, boneset was traditionally used to induce sweating and/or vomiting. A standard hot infusion is an ounce of the herb in a quart of boiling water; cover and let cool a bit. This is not one to take by the cupful; the dose is 1 3 oz., or less than half a teacup. Cook says to repeat the dose until the desired objects are obtained, which means sweat or vomit. Emetic therapy has almost passed completely out of Western herbalism and medicine, and boneset s emetic properties may have helped to kill the plant s reputation. Those properties are easy to avoid by sticking to lower doses.

Echinacea seems to work best for colds and flu if taken when the first signs appear. Boneset works the same way, but unlike Echinacea, it seems to work very well to clear up a mid-stage flu. Boneset also helps complicated colds, flus, and other feverish conditions, and is useful as well after the acute stage when influenza lingers. Here in an anecdote from herbalist Sasha Daucus in Missouri:

The most recent case was a thirty-eight year-old woman, a registered nurse, who came to the clinic after having been unable to work for nearly two weeks. The symptoms had begun with nausea and vomiting and extreme fatigue. At the point I saw her, she was past the acute stage but was still seriously fatigued and had a poor appetite. She had been prescribed antibiotics by an M.D., which she had taken for the full ten day course with no sign of improvement. I recommended 10 drops of boneset immediately, and then four times daily for five days. I expected she would feel significantly better after a few doses, and told her to call me the next day to check in. When she did, she was delighted. she said: After the first dose, I felt `normal for the first time since I got this. I d been feeling unreal like I was isolated from the world behind some kind of wall. That s gone and I feel like I ve returned to myself again.

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Medical Herbalism

A Journal for the Clinical Practitioner

Influenza: Treating the dry irritable cough

by Paul Bergner

The most universal presenting symptom of influenza is the dry irritable cough. The natural host cell of the influenza virus is the epithelial cell in the bronchial tract and trachea. The infected cells are inflamed by the body s attempt to remove them, and mucous secretions may be deficient. Many herbal *stimulant expectorants* that are useful in moist coughs with accumulated or stuck mucous work by irritating the tissues slightly to produce new mucous. These usually are ineffective in the dry cough of influenza and may aggravate the cough. The two categories most useful for the acute dry irritable cough are *relaxant expectorants* and *demulcents*. In most cases of acute cough in influenza, a primary demulcent strategy is most successful. Especially useful may be demulcent drinks. A tea of demulcents with a smaller amount of relaxant expectorants may be diluted, one cup per liter of water, with a small amount of honey, and taken as the beverage during the acute stages. This may improve the patient s sleep during the night when the cough disrupts rest.

Wild Cherry Bark

The use of wild cherry bark (Prunus serotina) was learned by the British colonists from the Eastern Indian tribes, including the Cherokee, and the Iroquois. Other tribes throughout North American have used various wild cherry species in the same way. The use became very popular throughout the United States in the nineteenth century. Wild cherry bark is still recorded as a cough remedy in the folklore of the Amish, New Englanders, and residents of the Southwest. It is also used in contemporary North American and European medical herbalism. Wild cherry cough drops are still available in stores today, although they are now made with artificial flavors instead of wild cherry bark. The bark s constituent prunasin reduces the cough reflex, and for this purpose it combines well with lobelia. Prunasin is a potentially toxic compound, but not for adults in the quantities taken in a tea of the bark. Besides its prunasin content, wild cherry has expectorant and demulcent properties, so it is like a cough formula in itself, with three activities rolled into one plant. Wild cherry bark is especially suited to dry, irritable coughs, and combination with another demulcent will improve its effects. In the following formula, it is combined with licorice root.

QUICK COUGH SYRUP

Place a tablespoon licorice root in a pint of water. Boil for five minutes, take off the heat. Let cool 10 minutes, add a tablespoon of wild cherry bark ½ cup of honey, and then let sit until it cools to room temperature. The dose is a quarter cup.

LONGER PREPARATION SYRUP FROM (WILLIAM COOK, M.D.):

Moisten five ounces of coarsely powdered prunus with cold water, and let it stand twelve hours, (or six hours in warm weather;) transfer to a percolator, and gradually add water till a pint of liquid has been obtained; to this add two pounds of refined sugar, in a bottle, and shake occasionally till the sugar is dissolved. This is the process of the U. S. Pharmacopoeia, except a reduction of the time of maceration from twenty-four hours. It is an elegant preparation, but requires to be kept in a very cool place (Cook).

Slippery elm

Slippery elm (Ulmus fulva) bark has a slimy mucilaginous texture that is soothing to inflamed tissues in the mouth and throat. It also promotes the flow of soothing fresh mucous in the bronchial tract. It is ideally suited to the dry cough and sore throat of influenza. It was an official cough remedy in the United States Pharmacopoeia from 1820 until 1930.

QUICK RECIPE

Into a pint of boiling water, stir an ounce of slippery elm bark powder and three tablespoons of honey. Turn off heat. Let stand for a half hour. Strain and take as desired.

Licorice

Licorice root (Glycyrrhiza glabra) has been used for coughs an bronchial problems in many traditions throughout the world. It was an official medicine in the U. S. Pharmacopoeia from 1820 until 1975, as a flavor-

ing agent and a demulcent and expectorant for cough syrups.

QUICK RECIPE

Directions: Cut an ounce of licorice sticks into slices, pour a quart of boiling water over them, and steep for twenty-four hours. Use as a drink throughout the day, adding honey to taste.

Relaxant expectorants

Use for coughs, whether wet or dry, when they are irritable, prolonged, producing much tension in the body, interfere with sleep, etc.

LOBELIA LOBELIA INFLATA

Combines powerful cough relaxant properties with relaxing expectorant effects. Relaxes and moistens at the same time. Useful for sedating the cough reflex

PLEURISY ROOT ASCLEPIAS TUBEROSA

A nearly pure relaxant with affinity for all the membranes. It is cooling and soothing to the irritable cough. Combine with gentle circulatory stimulants such as ginger.

LUNGWORT STICTA PULMONARIA

Soothes the cough reflex.

WILD CHERRY BARK PRUNUS SEROTINA

Often listed with multiple actions. The primary action is as a relaxant. See detailed discussion in the accompanying article.

THYME THYMUS VULGARIS

Mixed effects Traditionally used for the spasms of whooping cough. May have some stimulant expectorant properties.

Demulcent herbs

Useful for dry irritable coughs with little expectoration

MARSHMALLOW *ALTHEA OFF*

Almost pure demulcent, moistens the membranes without stimulating them.

LICORICE *GLYCYRRHIZA GLABRA*

Effective demulcent and moistener can counteract irritating effects of the milder stimulant expectorants in formulas. Taken in excess as tea or powder, may increase force of a cough through tonifying effects.

SLIPPERY ELM *ULMUS FULVA*

Other elms might be substituted

COLTSFOOT *TUSSILAGO FARFARA*

Mixed demulcent and expectorant properties. Combines well with a cough reflex sedative

Media for delivering coughs formulas

HONEY AND SUGAR

William Cook, M.D: Demulcent, and at the same time moderately stimulant to the respiratory mucous membranes. These are common components of cough syrups, and because of their gentle expectorant action, many cough preparations can be given in syrup form. .

Basic onion syrup: Chop 5 or 6 white onions and place them in a double boiler. Add ½ cup of honey and the juice of 1 lemon and cook on lowest heat possible for several hours. Strain the mixture and take by the tablespoon from every ½ hour to every few hours as needed.

VINEGAR, LEMON, LIME

William Cook, M.D. Promotes the secretions of the throat and respiratory tract membranes Cook states that the action of vinegar tinctures are mostly restricted to the respiratory passages and stomach.

Stimulating expectorants

Avoid in the acute cough of influenzaunless balanced by demulcents or relaxants. May be useful in later stages with secondary bacterial infection. Used for conditions with copious or stagnant mucous, primarily to dislodge the mucous.

GARLIC *ALLIUM SATIVUM*

Also antimicrobial and immune stimulating

SPIKENARD *ARALIA RACEMOSA*

Reputed to be ginseng analogue, but its stimulating and drying effects are too pronounced for general tonic use.

ELECAMPANE *INULA HELENIUM*

Equally valuable in cold moist conditions of the digestive tract. Useful in recovery phase of influenza if mucous is present.

HOREHOUND *MARRUBIUM VULGARE*

Common in patent remedies for coughs in the US for more than 100 years. Expectorant and also somewhat astringent.

GUMWEED *GRINDELIA SPP.*

Excellent general purpose mild stimulant expectorant

OSHA *LIGUSTUCM PERTERI*

May be irritating unless combined with a demulcent. Combines well with honey or licorice.

MULLEIN *VERBASCUM THAPSUS*

Listed as a demulcent in many books, but this probably refers to the flowers. Will reliably cause aggravation of a dry irritable cough. Most useful for unproductive cough, to loosen the mucous secretions.

Formulas for influenza

Demulcent drink

4 parts Althea officinalis (Marshmallow)
2 parts Ulmus spp. (Slippery elm; Siberian elm)
1 part licorice

Make as tea, simmer 20 minutes, add one cup with 3 TBLS honey per liter of water. Drink as beverage.

Cough relaxant tincture

1 part lobelia Lobelia inflata
1 part Prunus spp. Wild cherry bark
1 part licorice

Dry cough syrup

Simmer 4 oz fresh Zingiber (ginger) root and 2 oz Glycyrrhiza (licorice) in 4 pints of water over low heat until the mixture has been reduced to 3 pints. Strain again and add 3 cups of honey and 1/2 c each lobelia vinegar and Asclepias tuberosa (pleurisy root) tincture, and the juice of one lemon. Skim any froth that forms on the top and add 1 dram each anise and thyme essential oils when cool. Adults may use 1 tbl 5 or 6 times a day, children 1 tsp. May use hourly for acute respiratory problems. (Stansbury, J.)

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