FROM: ACKERMANN-VIRUS LIFE IN DIAGRAMS

HERPESVIRIDAE

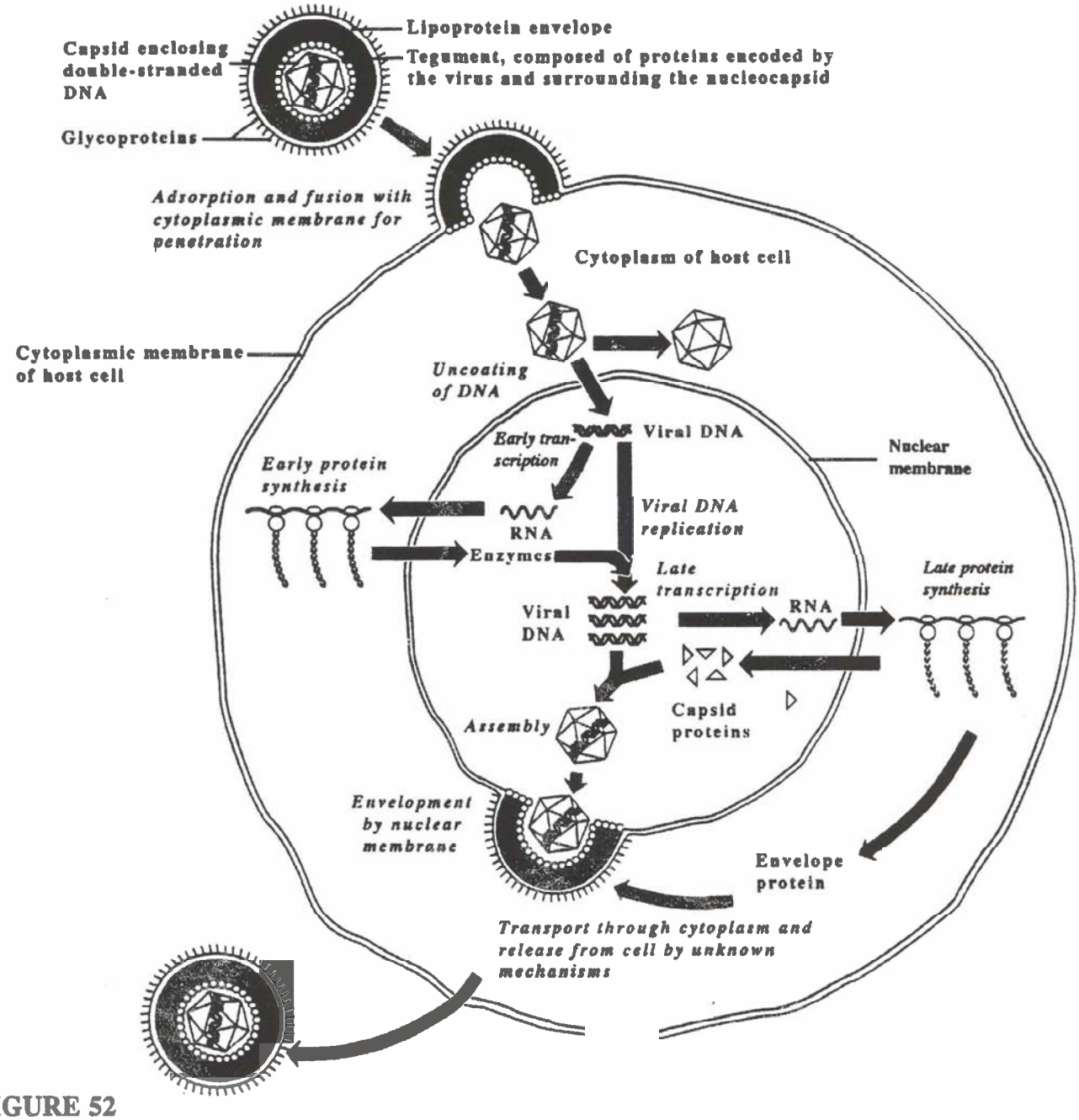

FIGURE 52

Replication of herpes simplex virus. Specific glycoproteins in the viral envelope are essential for adsorption on host cell receptors in the cytoplasmic membrane. Envelope and cell membrane fuse and the viral nucleocapsid is released into the cytoplasm. Viral DNA is then uncoated and transported to the nucleus. Early transcription and mRNA are apparently catalyzed by host enzymes. The resulting early viral enzymes are used in DNA replication. Further RNA transcripts are responsible for synthesis of viral capsid and envelope proteins as well as glycoproteins in the nuclear membrane. The structural proteins enter the nucleus to participate in the assembly of novel viral nucleocapsids. The latter are enveloped by budding through the nuclear membrane and complete viruses are released by unknown mechanisms. (Modified from Pelczar, M.J., Chan, E.C.S., and Krieg, N.R., *Microbiology — Concepts and Applications*, McGraw-Hill, New York, © 1993, 428. Reproduced with permission of The McGraw-Hill Companies.)

CHAPTER 15

Herpes Simplex Virus Infection

David Rakel, M.D.

PATHOPHYSIOLOGY

Herpes simplex virus (HSV), a member of the family Herpesviridae, has troubled the human race for more than 2000 years. The term *herpes* comes from the Greek language meaning "to creep or crawl." Two types of virus most commonly cause these creeping eruptions: herpes simplex virus type 1 (HSV-1) and herpes simplex virus type 2 (HSV-2). HSV infection can cause symptoms anywhere on the body, but HSV-1 is generally associated with outbreaks above the waist, particularly around the lips in the form of cold sores, and HSV-2 with symptoms below the waist, specifically the genital area. HSV infection preferentially affects these mucous membranes, where the skin is thin. Other common dermal areas of infection are those that are overly moist or where the natural protection has been compromised by injury or disease.

The first episode of HSV infection (primary herpes) is usually the most severe and starts after an incubation period of 4 to 6 days, but onset may be seen 1 to 26 days after exposure. The classic progression of symptoms involves pain, inflammation, and erythema followed by the formation of clear vesicles on an erythematous base. The clear fluid may then become pustular, followed by scab formation. Scarring is rare. Healing occurs over a 1- to 6-week period. After the primary infection, HSV has a unique ability to migrate up the peripheral sensory nerve to the dorsal root ganglia, where it lies dormant until reactivated (Fig. 15–1). How the virus is triggered to reactivate is unknown, but clinical correlation can be seen with a number of different stimuli (Table 15–1).

The function of the immune system plays an important role in the severity of disease and the frequency of recurrences. Persons with immune deficiency are at higher risk for complications. It is interesting to observe that many more people have been exposed to HSV than show symptoms or recurrences. In one study, 72% of persons with antibodies to HSV-2 shed virus when they were without symptoms.[1] What makes some people more or less susceptible to the potential effects of this virus is a point for further study and invites an integrative therapeutic approach to reduce the severity of the disease once exposure has occurred.

INTEGRATIVE THERAPY

Lifestyle Considerations

Personal Contact

Avoiding exposure to persons experiencing outbreaks of either HSV-1 or HSV-2 infection is warranted but does not ensure against contracting the disease. Use of condoms while limiting the number of sexual partners will help reduce the prevalence of infection. Oral sex should also be avoided because genital herpes can cause oral lesions, and vice versa.

> **NOTE**
>
> *As many as 90% of persons infected with genital herpes are unaware of their infection and may unknowingly shed virus and transmit infection.*[2]

Autoinoculation

The patient should be educated on how to prevent transmission to other parts of the body during an outbreak. For example, after bathing, patting dry with a towel instead of rubbing should be encouraged. The transmission of vesicular fluid to other parts of the body must be avoided.

Trauma to the Skin

HSV is more prone to causing recurrence and primary infection if the skin is traumatized or exposed to ultraviolet radiation. The patient should be encouraged to use sun protection to help prevent recurrence of HSV-1 infection, should avoid traumatic intercourse, and should prevent chapping of the lips. Using zinc ointment on the lips not only protects against ultraviolet light exposure but may also help to suppress HSV growth.

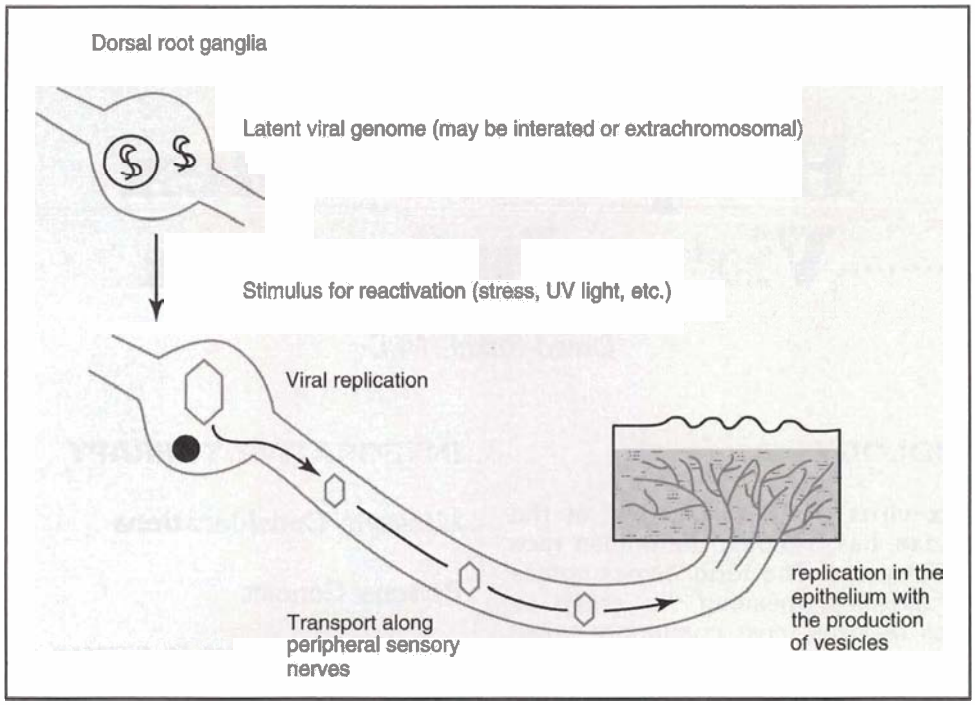

Figure 15–1. Schematic diagram of herpes simplex virus latency and reactivation. UV, ultraviolet. (From Whitley RJ: Herpes simplex virus infections. In Goldman L, Bennett JC [eds]: Cecil Textbook of Medicine, 21st ed. Philadelphia, WB Saunders, 2001; 1810–1814.)

Table 15–1. Potential Triggering Factors for Reactivation of Herpes

HSV-1–Specific Triggers
Ultraviolet light
Immunodeficiency
Stress, depression, anxiety (chronic)
Poor sleep
Trauma to mucosa
Cold, windy, or dry weather
Hot food or lip biting
Food allergy
Fever
HSV-2–Specific Triggers
Immunodeficiency
Stress, depression, anxiety (chronic)
Poor sleep
Food allergy
Trauma to genital mucosa
Menses (usually 5–12 days before onset)

Sleep

Poor sleep hygiene can result in fatigue, which may lead to an increased frequency of recurrence. The clinician should specifically inquire about sleep habits to help the patient make changes that will result in an improved sleep cycle.

Nutrition

Lysine- and Arginine-Containing Foods

A diet that promotes lysine-rich foods and reduces arginine-containing foods has become a popular recommendation for helping patients reduce recurrence of HSV infections. Evidence from in vitro studies supports this approach. The replication of the virus requires proteins rich in arginine, and arginine itself may be a stimulator of HSV replication. Lysine exerts antiviral effects by blocking the activity of arginine.[3] Clinical studies show mixed results.[4, 5] One argument is that inadequate doses of lysine were used. In one study, 52 people with recurring oral and genital HSV infections were assigned to receive either L-lysine 1 g 3 times daily or placebo; they also avoided nuts, chocolate, and gelatin (arginine-rich foods). After 6 months, 74% of persons receiving lysine reported their treatment as either effective or very effective, versus 28% of those receiving placebo. The mean number of outbreaks was 3.1 in the lysine group, compared with 4.2 in those taking placebo.[6]

There is some concern that taking supplemental lysine for prolonged periods of time may increase the risk of atherosclerosis, possibly by increasing levels of low-density lipoproteins.[7] Accordingly, adjusting

Table 15–2. Arginine-Containing and Lysine-Rich Foods: Dietary Recommendations for Prophylaxis of Herpes Simplex Virus Infection Recurrence

Foods to Avoid (High Arginine Content)	Foods to Include (High Lysine Content)
Chocolate	Vegetables
Peanuts	Beans
Almonds	Fish
Cashews	Turkey
Sunflower seeds	Chicken
Gelatin	

the amount of arginine in the diet by reducing arginine-rich foods may be the safer approach (see Table 15–2).

Food Allergy

Although there is limited research to back the claim that food allergies trigger recurrences of HSV infection, a trial of an elimination diet should be offered to persons with frequent recurrences (see Chapter 82, on elimination diets).

Good Nutrition

The most important nutritional factor in prevention of HSV infection is a balanced diet with 7 or 8 servings of fruits and vegetables a day, to help support a healthy immune system.

Mind-Body Medicine

It has been a common belief that isolated stressful events may lead to recurrent HSV outbreaks, although research has not supported this association. One study of 64 people with HSV infection found no correlation between acute stressful events and a later outbreak.[8] On the other hand, chronic or persistent stressors have been found to correlate with an increased frequency of recurrence.[9] This correlation is consistent with findings showing a decrease in HSV immunity in caregivers of dementia sufferers[10] and a decrease in herpes zoster immunity in persons with depression.[11] Therapeutic focus should be on helping the patient find a balance of lifestyle demands and on learning techniques to reduce day-to-day stress in persons with frequent recurrences.

> **NOTE**
>
> *Chronic rather than isolated stress has been found to result in more frequent HSV outbreaks.*

Relaxation Exercises

Teaching the patient a simple relaxation exercise that can be used on a regular basis or when needed for recurring stressful events can empower the patient to learn how to reduce stress (see Chapter 91, Prescribing Relaxation Techniques).

Meditation

For persons with chronic recurring stress, practice of meditation can help to reduce the stimulation of the adrenal gland. Overactivity of the adrenals can lead to suppression of the immune response and increase susceptibility to recurrent HSV infection (see Chapter 94, Learning to Meditate).

Supplements

Vitamin C

When used early in the prodrome of an outbreak, vitamin C 1000 mg with the addition of 1000 mg bioflavonoids taken 5 times a day for 3 days after recognition of symptoms was found to reduce blister healing time in herpes labialis, from 10 days in the placebo group to 4.4 days in the treatment group.[12]

Zinc

Zinc has been found to inhibit HSV replication in vitro and enhances cell-mediated immunity to help reduce HSV infection recurrence. Oral compound of 25 mg of zinc with 250 mg of vitamin C was given twice a day for 6 weeks, which resulted in either complete suppression of an outbreak or resolution of HSV-1 eruptions within 24 hours.[13] Topical application of a zinc sulfate solution of 0.01% to 0.025% concentration has also been found to be helpful in healing HSV-1 lesions and in inhibiting recurrence.[14] Use of zinc and vitamin C supplementation constitutes an inexpensive option for the patient with frequent recurrences.

Dosage. Zinc 25 mg a day with vitamin C 250 mg a day for recurrence prophylaxis.

Precautions. In prescribing zinc supplementation, the clinician should be aware that zinc competes with copper, calcium, and iron absorption. The patient should not take more than the recommended dose and should not take calcium and iron supplements with zinc. Doses greater than 50 mg per day have been found to be associated with reduction in serum copper levels.

Lysine

As discussed previously under "Nutrition," lysine exerts antiviral effects by blocking the activity of arginine, which promotes HSV replication. Although the results of research are mixed, a trial of 1 g of lysine daily to prevent recurrences, increased to 1 g 3 times a day during an outbreak, seems reasonable.

Dosage. L-Lysine 1 g daily for prevention, 1 g 3 times a day for acute outbreaks.

Precautions. Diarrhea and abdominal pain have been reported in persons taking doses of more than 10 g a day. There has been a single case documented of tubulointerstitial nephritis progressing to renal failure.[15] Lysine may cause a modest rise in low-density lipoprotein levels.

Vitamin E Oil

Topical application of vitamin E oil has been found to help reduce the pain of oral herpetic lesions within 8 hours and to result in more rapid healing.[16, 17]

Dosage. Squeeze the contents of a vitamin E capsule (*d*-alpha-tocopherol) onto a cotton swab and apply directly to the lesion every 8 hours as needed.

Precautions. Local skin reaction is possible but is rare.

Botanicals

Lemon Balm

Lemon balm (*Melissa officinalis*) is the most common botanical used for treatment of herpes infections. Lemon balm ointment consists of a 70:1 lemon extract concentrate. The preparation has been found to be helpful for the treatment of active HSV outbreaks. In one large study involving three German hospitals and a dermatology clinic, when lemon balm was used to treat the primary infection of HSV-1, not a single recurrence was noted. This finding suggests that lemon balm may help to prevent recurrences if used during an initial infection. The cream has also been found to reduce the healing time for both genital and oral herpes lesions.[18]

Dosage. 70:1 lemon extract cream, applied fairly thickly (1 mm) to herpetic lesions 2 to 4 times a day.

Precautions. Toxicology studies have found lemon balm to be safe and suitable for long-term use.

Licorice Root

Licorice (*Glycyrrhiza glabra*) is well known for its anti-inflammatory properties and has also been found to be of benefit in inhibiting both the growth and cytopathic effects of HSV.[19] Topical application of licorice root preparations is an option to help reduce duration of outbreaks and severity of oral herpes lesions.

Dosage. Apply tincture of licorice with a cotton swab, or drop directly onto the lesions, three times a day until resolution.

Precautions. Local allergic reaction may be seen with topical application.

Tea Bags

A folk remedy that has been found to be an inexpensive and easy-to-prepare treatment for oral HSV lesions is to steep an ordinary tea bag (preferably Earl Gray tea), cool, and then apply to lesions. This measure is thought to speed healing and to prevent recurrence, although there are no studies to support this. Tea contains catechins that have been found to enhance the immune function and may be a component of its therapeutic benefit.

Dosage. Steep a tea bag, cool, and apply directly to lesions for 20 minutes 1 to 3 times a day.

Pharmaceuticals

Antiviral medications effective against HSV work by inactivating DNA polymerase, which inhibits viral replication. In order for these medications to be effective, they need to be started soon after symptoms appear because viral replication may end as early as 48 hours into an infection.

Oral antiviral medications should be used with caution in persons with underlying kidney disease or when given with other nephrotoxic drugs. As with any antimicrobial, regular use can result in viral resistance.

Treatment for Primary Genital Herpes Infection

- Acyclovir (Zovirax) 200 mg 5 times daily for 10 days
- Famciclovir (Famvir) 250 mg 3 times daily for 10 days
- Valacyclovir (Valtrex) 1 g twice daily for 10 days

Although more expensive, valacyclovir has the advantage of reduced frequency of dosing.

Treatment for Episodic Recurrences

Research has shown only a minimal benefit with treatment of recurrences with antiviral medications, and some experts may question the need for episodic treatment. Best results are obtained if the drug is started at the prodrome of the recurrence, when the patient notices itching, burning, or erythema.

- Acyclovir (Zovirax) 800 mg twice daily for 5 days
- Famciclovir (Famvir) 125 mg twice daily for 5 days
- Valacyclovir (Valtrex) 500 mg twice daily for 5 days

Pharmaceutical Prophylaxis

Prophylaxis is generally reserved for persons who have more than 6 outbreaks in a year. For patients with frequent recurrences, the practitioner should look holistically at other potential factors such as chronic stress, suboptimal nutrition, and decrease in perceived level of well-being before simply prescribing prophylactic antiviral medication. If pharmaceutical prophylaxis is started, therapy should be discontinued once a year to see whether continuation is necessary, and the patient should be encouraged to titrate down to the lowest effective dose.

Short-term prophylactic therapy for oral herpes

has been shown to reduce severity but not recurrence following ultraviolet light exposure in skiers.[20]

- Acyclovir (Zovirax) 400 mg twice daily
- Famciclovir (Famvir) 250 mg twice daily
- Valacyclovir (Valtrex) 1 g once daily
- Aspirin 125 mg daily

In a small pilot study, aspirin was found to reduce the rate of active infection by nearly 50%.[2] This inexpensive therapy may prove fruitful if more research supports this claim.

> **NOTE**
>
> *Topical acyclovir is generally not highly effective for the treatment or prevention of oral herpes infections. Topical application of acyclovir every 2 hours was found to reduce healing time by just 1 day.[22]*

Other Therapies to Consider

Monolaurin

Monolaurin (Laricidin) is a monoglycerol ester of lauric acid, a saturated fatty acid found in breast milk and coconut oil. It has been found to destroy the fatty coating of certain viruses that allows them to adhere to cells, causing infection. It is thought to help protect breast-feeding infants from viral infection. Monolaurin is currently being studied for its potential use in treating infections due to lipid-coated viruses including HIV. There is a lack of evidence to recommend its use at this time, but patients have reported clinical benefit from this inexpensive therapy.

Dosage. At the first sign of infection, the patient should take 1800 to 3600 mg (6 to 12 300-mg capsules) daily for 4 days and then reduce the dose to 600 to 1200 mg (2 to 4 300-mg capsules) daily until lesions have resolved.

Precautions. Animals fed monolaurin in amounts up to 25% of their diet showed no signs of harm after weeks.[23] Human studies are limited.

Homeopathy

Homeopathic remedies are given until resolution of lesions occurs. Examples of remedies used for genital HSV infection are sepia, graphites, rhus (toxicodendron), and dulcamara. Hylands #27 is a common homeopathic remedy for oral HSV infection.

— THERAPEUTIC REVIEW

Prevention of HSV Infection Recurrences

Lifestyle
- *Avoid trauma to genital and oral mucosa.*
- *Use sun protection.*
- *Encourage 7 to 8 hours of sleep a night.*

Nutrition
- *Encourage 7 or 8 servings of fruits and vegetables a day while increasing lysine-rich foods and reducing arginine-rich foods (see Table 15–2).*
- *Consider an elimination diet (see Chapter 82).*

Mind-Body Medicine
- *Make lifestyle changes to reduce chronic stress and anxiety.*
- *Educate regarding relaxation techniques such as breathing exercises and meditation.*

Supplements
- *Zinc 25 mg and vitamin C 250 mg a day*
- *If no reduction in frequency of recurrences is obtained after 3 months, consider replacing with or adding lysine 1 g daily.*

Botanical Medicine
- *Apply lemon balm extract cream 2 to 4 times a day for primary outbreaks of HSV infection*

Pharmaceuticals
- *Prophylactic therapy is reserved for persons who have not responded to a holistic therapeutic approach and who experience more than 6 outbreaks in a year.*
- *Acyclovir (Zovirax) 400 mg twice daily*
- *Valacyclovir (Valtrex) 1 g once daily*

THERAPEUTIC REVIEW continued

Acute Treatment of HSV Infection

Supplements

- *L-Lysine 1 g 3 times a day until resolution*
- *Topical vitamin E oil: Apply oil from capsule to oral HSV lesion 3 times a day.*

Botanicals

- *Lemon balm (70:1 lemon extract cream): Apply to herpetic outbreak 2 to 4 times a day.*
- *Licorice root tincture: Apply to lesions 3 times daily until resolution.*
- *Tea bag: Steep tea bag, cool, and apply directly to oral lesions for 20 minutes 1 to 3 times a day.*

Pharmaceuticals

For primary infection:

- *Acyclovir (Zovirax) 200 mg 5 times daily for 10 days*
- *Famciclovir (Famvir) 250 mg 3 times daily for 10 days*
- *Valacyclovir (Valtrex) 1 g twice daily for 10 days*

Efficacy of treating episodic recurrences remains to be established, but the following can be tried:

- *Acyclovir (Zovirax) 800 mg twice daily for 5 days*

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Herpesviruses

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GLOSSARY

capsid The protein coat or shell that contains the nucleic acid genome of the virus particle.

capsomere Represents the individual morphological units (or sides) on the surface of the capsid.

envelope The lipid-containing outer membrane that surrounds the entire virus particle. The envelope arises from budding of mature herpesvirus particles through the nuclear membrane.

icosohedron Geometric shape with 20 equal sides or capsomeres (similar to a soccer ball). The herpesvirus capsid is an icosohedron.

latent infection The virus persists in an quiescent (occult or cryptic) form most of the time with very little viral replicative activity. Also characterized by intermittent flare-ups of clinical disease.

nucleocapsid Includes the capsid and the enclosed nucleic acid.

I. INTRODUCTION

The Herpesviridae represent a large group of viruses that are pathogenic for many vertebrates. The name is derived from the Greek word "herpein" meaning "to creep" such as the chronic, latent, and recurrent infections associated with herpesviruses. Diseases resulting from infection with a member of the herpesviruses vary widely according to the virus. Several members of the family cause lifelong infections in humans that are characterized by periods of quiescence followed by reactivation and expression of clinical symptoms. The pattern of infection de-

pends on the portal of entry or site of infection and the immune status of the host. In neonates and immunocompromised individuals, primary infection by herpes simplex virus (HSV), for example, results in severe infection that can lead to encephalitis. Resolution of the primary infection in healthy individuals is accompanied by the establishment of latency. For HSV, the development of latency means that virions reside "quietly" in neural tissues without causing disease. Periodic reactivation of the latent virus is frequently accompanied by clinical symptoms and the development of herpetic lesions. Other members of the family have been associated with mononucleosis, lymphoproliferative disease, lymphomas, and Kaposi's sarcoma.

II. VIROLOGY

A. Characteristic Structure

Herpesviruses are large DNA viruses. The diverse members of the family share similar architectural details and are morphologically indistinguishable. Each member has a double-stranded DNA toroid core (DNA spooled around a cylinder of protein) that is encapsulated within an icosahedral capsid. The capsid is composed of 162 capsomeres and is itself within a lipid envelope. This envelope is formed from the nuclear membrane of an infected cell from which progeny viruses bud. Within this nuclear–lipid envelope are virus-encoded glycoproteins or "spikes" about 8 nm long. An additional feature of the herpesvirus family is a tegument, which is an amorphous, asymmetrical structure located between the capsid and envelope. The entire virion measures 120–200 nm and the naked capsid is approximately 100 nm in diameter.

B. Characteristic Genome

The genome of herpesviruses is double-stranded linear DNA with a molecular weight of $95–150 \times 10^6$ or 120–230 kbp. Herpesviruses have a characteristic arrangement of their DNA sequences; their genomes have terminal and internal repeat sequences that are bounded by a unique long (UL) and a unique short (US) region. These repeats allow some members of the family to undergo genomic rearrangement of their unique regions, giving rise to different genomic isomers. Because of the high incidence of rearrangement, spontaneous deletions occur, and defective viral particles are common. Thus, there is little DNA homology among different herpesviruses except for herpes simplex virus types 1 and 2, which show 50% sequence homology, and herpesvirus 6 and 7, which share 30–50% homology. Digestion of the genome with restriction endonucleases yields a characteristic fragment pattern specific for each family member. This allows for rapid epidemiologic tracing of a given strain. The genome of the typical herpesvirus is large and encodes for at least 100 different proteins, many of which (>35) are structural in nature. Several virus-specific enzymes, including DNA polymerase and thymidine kinase, are synthesized in infected cells, but no virus-specific enzymes are incorporated into the mature virus particle.

C. Subclassification

Over 100 different herpesvirus have been identified, including eight human isolates. The entire family of herpesviruses is subdivided into three subclasses based on modes of replication and sequence similarity.

1. Alphaherpesviruses have a broad host range; they replicate rapidly in many types of cells. Although these are highly lytic viruses, members of this subclass can establish latency in neurons and glial cells. This group includes human herpes simplex virus type 1 and type 2 (HSV-1 and HSV-2), human varicella-zoster virus (VZV), and bovine herpesvirus type-1 (BHV-1).
2. Betaherpesvirus have a restricted host range and grow slowly in tissue culture. Infection typically causes cells to swell. These members can establish latency in hematopoietic progenitor cells and can cause persistent infections of epithelial and glandular cells. Includes human and murine cytomegaloviruses (CMV), human herpesvirus 6, and human herpesvirus 7.

3. Gammaherpesvirus have a restricted host range. These members can replicate in epithelial cells and establish long-term latency in lymphocytes. In addition, some of these viruses can transform or immortalize their host cell. Includes Epstein–Barr virus (EBV) and Kaposi's sarcoma-associated human herpes virus (also called human herpesvirus type 8).

D. Virus Replication

Viruses are obligate intracellular parasites; as such, members of the Herpesviridae must interact with a host cell for survival. These viruses recognize potential host cells through specific interactions between a host cell receptor and a viral membrane glycoprotein. Some herpesviruses bind to host cell surface glycosaminoglycans such as heparan sulfate. Other herpesviruses recognize immunoglobulin supergene family members; EBV recognizes a specific complement receptor and human cytomegalovirus recognizes β_2-microglobulin, whereas HSV-1 binds to a member of the tumor necrosis factor/nerve growth factor (TNF/NGF) receptor family. In addition to these common receptors, other glycoproteins have also been implicated in herpesvirus recognition of host target cells.

After binding, the virus enters the host cell by fusion with the cell membrane. The capsid is transported through the cytoplasm to a nuclear pore. Once inside the nucleus, uncoating occurs and the viral DNA forms a circle immediately upon release from the capsid. Host macromolecular synthesis is shut off early in infection; normal cellular DNA and protein synthesis virtually stop as viral replication begins.

Expression of the viral genome is regulated tightly and ordered sequentially in a cascade fashion. Immediate early genes are expressed, yielding α proteins (those that are produced in the absence of prior virus gene expression). α Proteins permit expression of the early set of genes, which are translated into β proteins (those that are expressed before DNA replication). Viral DNA replication begins and late transcripts are produced that give rise to γ proteins (those that are expressed after DNA synthesis). Many of the α and β proteins are enzymes or DNA-binding proteins, whereas many of the γ proteins are structural in nature.

Herpesvirus DNA is synthesized by a rolling circle, or concatameric, mechanism that appears seemingly endless. Huge amounts of viral DNA are transcribed throughout the replicative cycle by *cellular* RNA polymerase II. The length of the replication cycle varies from about 18 h for herpes simplex virus to over 70 h for cytomegalovirus. Although host cell polymerases are required for viral DNA replication, many virus-derived cofactors are involved. This distinguishes the herpesviruses from other nuclear DNA viruses in that they encode a large number of enzymes involved in DNA synthesis. The newly synthesized viral DNA is packaged into preformed empty nucleocapsids in the cell nucleus.

Maturation occurs by budding of nucleocapsids through the inner nuclear membrane. Enveloped viral particles are then released from the cell through tubular structures that are continuous with the outside of the cell or from vacuoles that release their contents at the surface of the cell. Cells infected productively with herpesvirus are invariably killed.

E. Overview of Diseases Caused by Herpesviridae

As there are over 100 different types of herpesviruses, it is not surprising that they can cause a wide variety of diseases. As their subclassification into α, β, and γ herpesviruses suggests, primary infection and possible latency may involve different cell types and present a widely different set of symptoms and clinical disease.

1. *Herpes Simplex Viruses*

HSV are extremely widespread in the human population and exhibit an ability to replicate in many host tissues. They also infect other animals. There are two main forms of the herpes simplex viruses: type 1 and type 2. Both viruses grow rapidly and are extremely cytolytic. Typically, these viruses infect epithelial cells found in mucosal tissue and establish latent infections in peripheral neurons. HSV-1 has been classically associated with oropharyngeal lesions characterized by recurrent fever blisters. HSV-1 is spread by contact, usually involving infected saliva. HSV-2 has been associated with recurrent genital herpes and is usually transmitted sexually or from

maternal genital infection to a newborn. Both viruses can cause neurologic disease with HSV-1 being the leading cause of sporadic encephalitis in the United States. Both HSV-1 and HSV-2 can cause severe primary infections in newborns.

Latent infection followed by recurrent disease is the hallmark of these viruses. HSV-1 and HSV-2 reside in latently infected ganglia in a nonreplicating state with only a few viral genes being expressed; the infectious virus cannot be isolated during latency. Persistence of the viral genome within a latently infected cell lasts for the lifetime of the host. Following a reactivating stimulus, the virus follows axons back to the peripheral site and replication proceeds in the epithelial cells. Spontaneous reactivation occurs despite HSV-specific immunity. More than 80% of the human population harbors HSV-1 in a latent form, but only a small proportion experience reactivation. The molecular basis for reactivation is not completely understood. Herpes simplex viruses are also called human herpesviruses 1 and 2.

2. *Varicella-Zoster Virus*

VZV or human herpesvirus 3 is highly contagious and a very common virus. The typical route of infection is the mucosa of the upper respiratory tract. After primary replication in the mucosal epithelium, the virus enters the circulation and eventually localizes to the skin where it causes two distinct syndromes. Upon primary infection, usually in children, it causes chicken pox (also called varicella), which is characterized clinically by a generalized vesicular eruption of the skin and mucous membranes. However, VZV subsequently establishes a latent infection and, on reactivation, the virus causes shingles (also called zoster). Shingles is a sporadic, incapacitating disease of adults or immunocompromised individuals that is clinically characterized by a rash that is limited in distribution to the skin innervated by a single sensory ganglion. The lesions are similar to varicella.

3. *Epstein–Barr Virus*

EBV or human herpesvirus 4 causes infectious mononucleosis (heterophile test-positive) and is a factor in the development of nasopharyngeal carcinoma, Burkitt's lymphoma, and other lymphoproliferative disorders in immunocompromised individuals. EBV is commonly transmitted by infected saliva (hence the nickname "the kissing disease"). Primary infection involves epithelial cells of the oropharynx and parotid gland. Viral shedding occurs for weeks to months after infection. Following replication in epithelial cells, EBV infects B cells and quickly becomes latent. Continuous or immortalized cells lines are produced when EBV transforms human B lymphocytes. EBV blinds to the B cell through the C3d component of the complement cascade (CR2 or CD21).

4. *Cytomegalovirus*

CMV or human herpesvirus 5 infects respiratory epithelial cells or epithelial cells within salivary glands or the kidneys. CMV is an important cause of congenital defects and mental retardation in more than 5000 infants in the United States per year. CMV is the largest herpesvirus with a genome of approximately 240 kbp. Infection is characterized by massive enlargement of infected cells. Primary CMV infections in immunocompromised hosts are more severe than in normal hosts.

5. *Human Herpesvirus 6 and Human Herpesvirus 7*

These viruses were first recognized in 1986 and 1990, respectively. Both viruses were isolated from cultures of peripheral blood mononuclear cells (T lymphocytes). Currently, their association with any known human disease has not been established. These two viruses share significant sequence homology however, they are antigenically and immunologically distinct.

6. *Human Herpesvirus 8*

This virus is also known as Kaposi's sarcoma-associated herpesvirus and was originally isolated in 1995. It is present in all forms of Kaposi's sarcoma and in primary effusion lymphomas. HHV-8 expresses a number of cellular regulatory genes that the virus appears to have pirated from mammalian cells as a way of defeating host defense mechanisms. This virus represents the first known human member of the genus *Rhadinovirus*.

7. B Virus

The B virus is highly pathogenic for humans, although transmissibility of the virus from its normal host to humans is limited. Typically, B virus infects Old World monkeys and is enzootic in rhesus, cynomolgus, and other macaque monkeys. B virus infections in the natural host seldom cause overt disease, but latency is established and B virus is easily reactivated under stressful conditions. Infection of humans usually results from monkey bites and is associated with a high rate of mortality due to an acute, ascending myelitis and encephalomyelitis.

F. Herpesvirus Proteins

Herpesviruses differ widely in their protein expression. HSV type 1 encodes approximately 72 proteins (which is average for most herpesviruses, although over 100 proteins are not uncommon).

1. Structural Proteins

The mature virus particle typically contains about 20 proteins, of which many are capsid proteins. A single major capsid protein (≈150 kDa) constitutes the pentons and hexons of the icosohedron. Several other minor capsid proteins (VP19, VP22a, VP23, VP24, and VP26) play roles in packaging of the DNA and the toroid core, although their functions are largely unclear. In the envelope of the virus are eight major virus glycoproteins, some of which form "spikes." These proteins are immunodominant and offer targets for virus-specific neutralizing antibodies.

2. Nonstructural Proteins

These proteins are subclassified into three groups depending on the time during viral replication that they are expressed. α proteins, or immediate-early proteins, are produced prior to viral DNA synthesis. Each of these proteins has regulatory roles that take over the macromolecular machinery of the host cell and thus enable production of subsequent proteins. β proteins are also called early proteins. Their production follows that of the α, but the expression of β proteins does not require DNA synthesis either. Among the proteins in this group are the DNA polymerase, DNA helicase, and DNA synthesis origin-binding proteins. Many β proteins are required for replicative function. γ proteins are also called late proteins as they are produced after DNA replication has begun. These late proteins are mostly structural in nature, forming the capsid and envelope glycoproteins. The majority of proteins that constitute the mature virion are γ proteins.

III. IMMUNOBIOLOGY AND RECURRENT DISEASE

The course or natural history of a herpes viral infection is influenced by the site of viral entry and host defenses. Primary infection with a herpes virus induces both innate and adaptive immune responses, which result in the termination of viral replication and cessation of clinical symptoms. However, unlike acute viral infections in which a successful immune response leads to elimination of the virus, infection with herpesviruses frequently leads to latency and thus the opportunity for episodic recurrent disease.

A. Innate Immunity

All mammals are born with a genetically inherited resistance to infectious microbes that is termed innate or natural resistance. Expression of natural resistance does not require previous exposure to the viral antigen (as does the adaptive immune response). The primary function of natural resistance during a viral infection is to restrict the early spread of the virus prior to the induction of virus-specific T- and B-cell responses. Experimental studies have demonstrated that cellular components of natural resistance are activated following infection with HSV-1. Macrophages, natural killer (NK) cells, and killer cells mediating antibody-dependent cellular cytotoxicity (ADCC) all have a role in restricting the early spread of the virus. Infection by members of the Herpesviridae is also accompanied by the expression of genes encoding the interferons, which impart resistance to uninfected cells surrounding an infected cell. These natural resistance mechanisms are very important in the early phase of an HSV infection as this virus has been shown to downregulate the expression of HLA class I molecules (which limits

recognition of infected cells by $CD8^+$ T cells). Loss of HLA class I molecules, however, targets the cell for elimination by NK cells, thus limiting spread of the virus.

B. Adaptive Immunity

Most infections with members of the Herpesviridae result in the induction of virus-specific humoral (antibody) and cell-mediated immune responses. Immunological memory also follows primary infection; however, neither the successful termination of virus replication during primary infection nor the establishment of immunological memory prevents reactivation of latent virus and the development of recurrent lesions. Clearly, a primary infection with HSV, whether asymptomatic or symptomatic, results in the production of virus-specific antibodies (both binding and neutralizing). These antibodies play multiple roles in mediating resolution of the primary infection through direct viral neutralization, viral lysis (in combination with complement), and lysis of infected cells by an ADCC mechanism. Virus-specific T cells are also very important during infection; individuals with cell-mediatated immunodeficiency suffer severe herpetic disease. Detailed sequential biopsy studies of the pattern of cell acquisition and cytokine gene expression have shown at 24–48 h that herpetic lesions contain $CD4^+$ T cells expressing a broad range of cytokines (including IL-2, interferon-γ, IL-12, IL-4, IL-5, IL-10, and IL-13). Clearance of virus from the lesions correlates with the presence of $CD8^+$ T cells with virus-specific cytolytic activity.

C. Recurrent Disease

Whether the time to reactivation of latent virus is weeks to months (as is the case for HSV) or years to decades (as is the case for VZV), it is clear that immune memory, which results from the resolution of a primary infection with these viruses, offers little or no protection against recurrent diseases. The development of recrudescent lesions is a two-step process. The first step occurs at the cellular/molecular level and involves the regulation of viral and host transcription factors influencing the state of expression of the latent viral genome. The balance between positive and negative transcription factors determines whether the genome will be reactivated, and this process is mediated by numerous hormonal and growth factor signals. These signals may result from many different stimuli. Psychological stress, physical trauma, UV irradiation from a sunburn, or hormonal fluctuations of the menstrual cycle have all been associated with reactivation of latent virus.

The period of time that the reactivated virus gets to replicate, and thus cause clinical symptoms, is mediated immunologically (and represents the second step in the process). Healthy adults generally limit clinical symptoms during a recurrence to a couple of days or less, whereas individuals with diminished cell-mediated immunity, as seen in the acquired immunodeficiency syndrome (AIDS), often develop severe disease that lasts much longer.

IV. STRESS AND HERPESVIRUS REACTIVATION

The capacity of latent herpesviruses to reactivate and replicate is essential for completion of the viral life cycle. During the latent phase of herpesvirus infection, virus gene expression is highly restricted; only latency-associated transcripts (LATs) are expressed. Reactivation of herpesvirus from ganglia results in the appearance of infectious virus at the site of the initial primary infection. However, the genetic elements that determine reactivation have not been identified thoroughly. The limited knowledge of the molecular pathogenesis of herpesvirus latency and reactivation was generated from studies in laboratory animals, including mice, guinea pigs, and rabbits. In these models, reactivating stimuli range from mechanical and pharmacological to immunological alterations of cells and surrounding tissues. It is thought that the altered expression of cellular factors in the host cell leads to the induction of herpesvirus gene expression, resulting in reactivation. Accordingly, it is commonly thought that psychological stress may be one of the contributing factors to reactivation of herpesvirus.

The impact of psychological stress on immune function is well documented in the literature, sup-

porting the hypothesis that both physical and psychological stressors can have an impact on the pathophysiology of disease. Accordingly, there are numerous studies in humans documenting the reactivation of HSV-1 and HSV-2 with psychological stress. Several studies have shown that the reactivation of latent HSV infections was more frequent in individuals who experienced traumatic life events, such as the death of a family member, the stress of interpersonal problems, or work-related difficulties. Similar relationships between psychosocial stress and reactivation of other herpesviruses, including EBV and VZV, have also been reported. It is thought that the physiologic alterations that ensue during stress alter the cellular microenvironment and serve as reactivators of latent herpes infections.

In mammals, stressors typically activate a specific set of core stress responses, including the hypothalamic–pituitary–adrenal (HPA) axis and sympathetic nervous system (SNS). Activation of the HPA axis results in increases in glucocorticoids such as cortisol, and activation of the SNS results in increases in circulating and tissue levels of catecholamines such as epinephrine. Each of these alterations in the host physiology has been linked to herpes reactivation. For example, a model for *in vivo* reactivation has been established in the rabbit with the eye as the site for shedding. Epinephrine induces reactivation and recovery of mature infectious virus in the tears. In this model, it was found that expression of LATs was required for reactivation; however, its role in reactivation is unknown.

Glucocorticoids have also been implicated in reactivation. For example, in the presence of antiviral drugs, primary cell cultures established from latently infected mouse trigeminal ganglia provide a model to test reactivation *in vitro*. Glucocorticoids such as cortisol or dexamethasone can drive viral replication in these latently established ganglion cultures. Other stressors, such as the protein synthesis inhibitor cyclophosphamide, UV irradiation, and transient hyperthermia, can also cause recrudescence. However, in no model are the events that occur between stress and production of infectious HSV-1 completely understood. Therefore, important biological knowledge remains unknown concerning reactivation.

V. CONCLUSION

The herpesviruses represent a diverse group of viruses that have evolved unique relationships with their hosts. Members of this viral group have been associated with diverse disease manifestations ranging from malignant transformation to latency and reactivation. Herpes infections occur from the cradle (neonatal HSV encephalitis) to the grave (shingles caused by reactivation of VZV in the later decades of life). They affect healthy individuals (CMV, mononucleosis) and immunodeficient individuals (human herpes virus type 8, Kaposi's sarcoma in AIDS). Reactivation of the latent members of the herpesvirus family has been associated with multiple forms of stress (from physical stressors such as UV irradiation to psychological stress such as social conflict). However, detailed knowledge of molecular steps that trigger reactivation is lacking. Furthermore, the inability to contain these viruses with the traditional approaches of vaccination and/or drug treatment makes research on the development of new prevention and treatment strategies a high priority for *Herpesviridae*.

See Also the Following Articles

CANCER; CYTOKINES; HIV INFECTION/AIDS; HPA AXIS; IMMUNE RESPONSE

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CHART I Reflexology Points

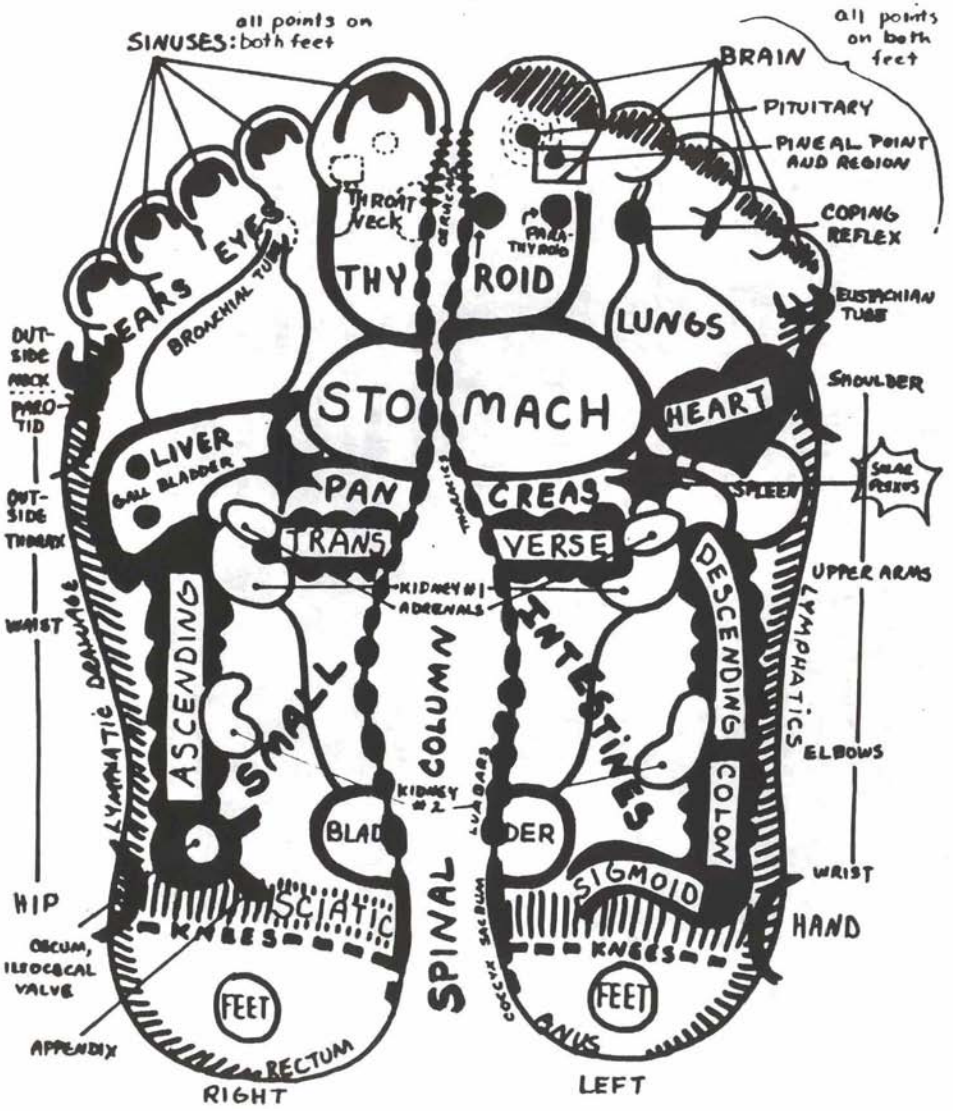
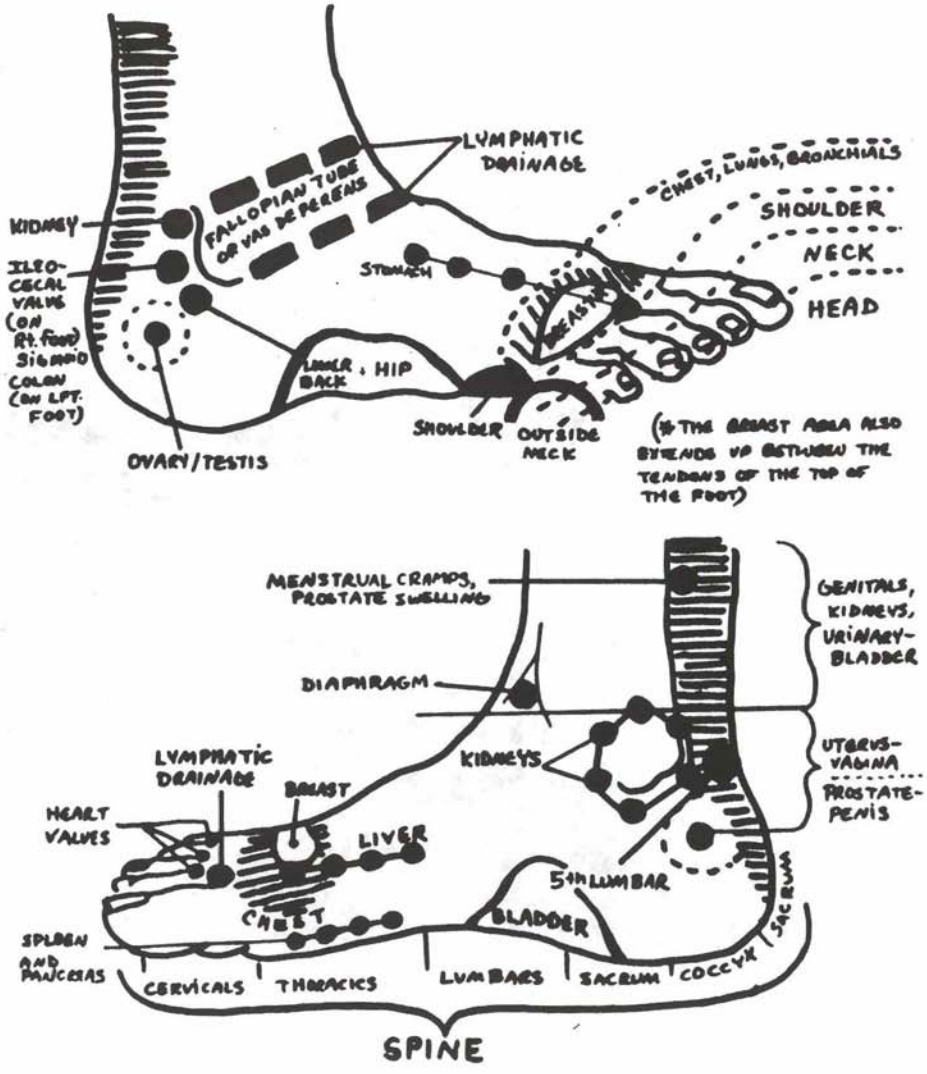
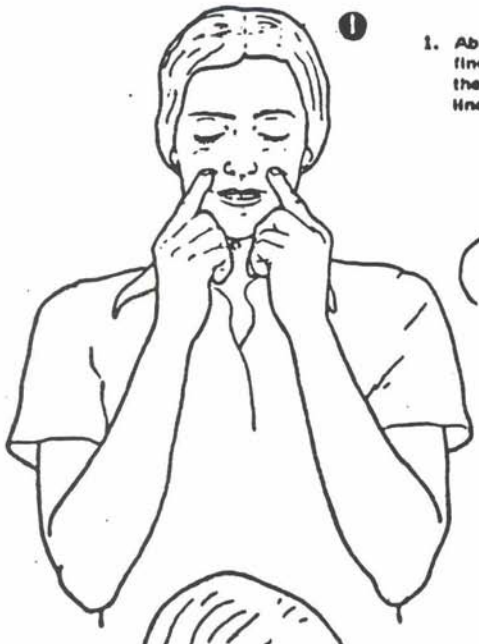


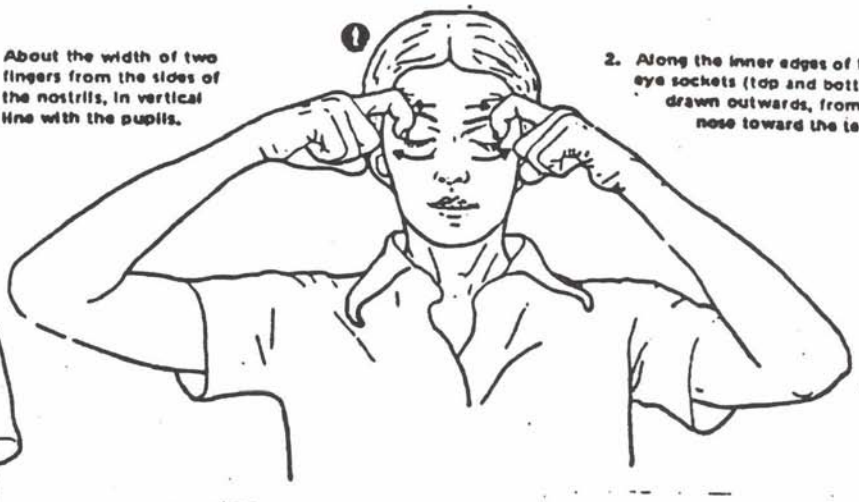
CHART II



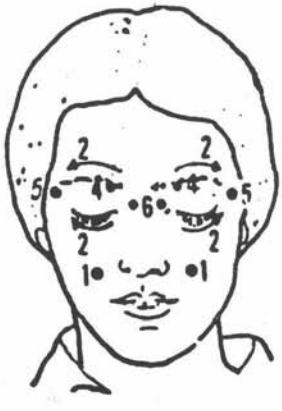
THE CHINESE ACUPRESSURE EYE EXERCISES



1. About the width of two fingers from the sides of the nostrils, in vertical line with the pupils.

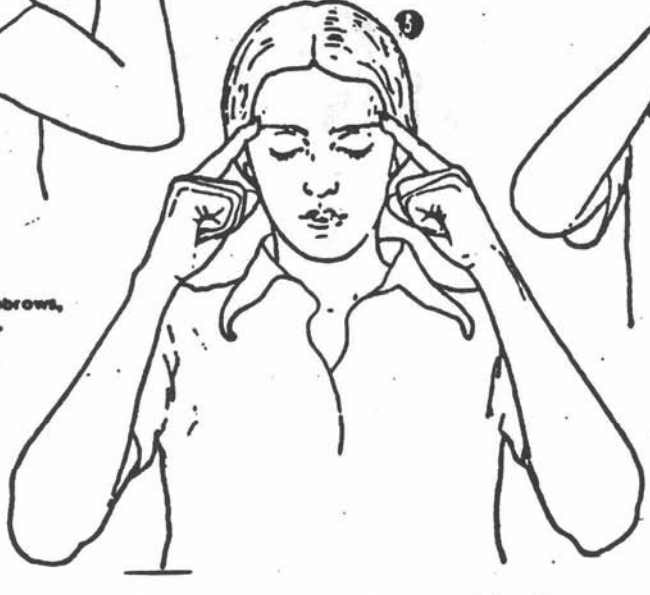


2. Along the inner edges of the eye sockets (top and bottom), drawn outwards, from the nose toward the temples.



5. At the outer edges of the eyebrows, in the soft spots found there.

6. In the inner corners of the eye (cantharis).



3. In the webbing, between the thumb and index finger on the back (top) of the hand.

4. Under the inside corners of the eyebrows (best way to stimulate these is to put tips of fingers along hairline, tips of thumbs in the tender spots at inner corners of eye socket and massage like a "spider doing pushups.")

These exercises should be performed daily (as done by the schoolchildren in China) to improve and maintain good eyesight. They take less than a minute to do after you memorize the G-Jo points. They may be performed in any sequence, to an "eight-count." That is, stimulate each point eight times before moving on to the next point or exercise.

Deep pressure should be used—deep enough to feel aching pain on the point you are stimulating. This discomfort will disappear as soon as you finish triggering the point.

You should notice results—in the form of improved eyesight—within several weeks. It is not unusual to notice an occasional minor headache, nausea or other possible symptom of sight disorder—especially if you wear glasses. This is because, as your eyes begin improving, your existing glasses may become "too strong." These exercises were brought to America by The U.S.—China Peoples' Friendship Assoc. (Berkeley, CA) and refined by Ralph Alan Dale, Ph.D., of The Acupuncture Education Center (Miami, FL). If problems persist, see your doctor.

weeks

2

8 amniotic cavity — bilaminar disc

9 lacunae appear — primitive yolk sac

10 implantation complete

11 Primitive placental circulation established.

epithelium growing over surface defect

12 extraembryonic mesoderm — coelom

13 primary villi

14 dorsal aspect of embryo — prochordal plate — embryonic disc

3

15 first missed menstrual period

16 primitive knot — primitive streak

17 embryonic mesoderm — trilaminar embryo

18 neural plate — primitive streak — length: 2-3 mm

19 neural fold — notochord — embryonic coelom

20 brain — neural groove — somite — Thyroid begins to develop.

21 neural groove — somite — Heart tubes about to fuse.

4

22 Heart begins to beat — Neural folds fusing.

23 anterior neuropore — primordia of eye and ear present. — posterior neuropore

24 heart bulge — 2 pairs of branchial arches

25 otic depression — 3 pairs of branchial arches

26 arm bud — indicates actual size

27 4 pairs of branchial arches, arm & leg buds present.

CR = crown-rump length.

28 CR: 4-5 mm

5

29 CR: 6-7 mm

30 Lens vesicles, optic cups, nasal pits forming.

31 developing eye — nasal pit — primitive mouth

32 Hand plates (paddle-shaped)

Atrium dividing

Lens vesicles and optic cups formed.

33 CR: 8-11 mm

34 Head much larger relative to trunk.

Digital rays visible in hand plates.

Foot plates (paddle-shaped)

35 CR: 11-14 mm

6

36 Oral & nasal cavities confluent.

37 CR: 14-16 mm

38 Upper lip formed.

39 CR: 17-20 mm

40 Arms bent at elbow.

Fingers distinct but webbed.

Notched toe rays.

Palate developing.

41 ventral view

42 CR: 21-23 mm

(weeks)

7

43

44 Stage 18 begins

45 Tip of nose distinct

Toe rays appear

Ossification may begin

46 Loss of villi

Smooth chorion

47 genital tubercle — urogenital membrane — anal membrane — ♀ or ♂

48 Stage 19 begins

Trunk elongating and straightening

49 CR: 18 mm