Pathogenesis of Rashes in Virus Diseases

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INTRODUCTION

Observations on the rashes accompanying infectious diseases date back to ancient times, a rash being one of the most characteristic and readily observed signs of disease. Most of these exanthemata are seen in the course of virus infections. In spite of unprecedented expansion in our knowledge of animal virology many questions regarding the pathogenesis of rashes in virus diseases remain unanswered, and little progress has been made since the work of von Pirquet, Councilman, Mallory, Findlay, and others. For instance, there is still no explanation for the basic differences in distribution of the rashes of chickenpox and smallpox, and it is not known whether measles virus, to produce the rash, grows in the skin, and, if it does, in which cells it multiplies.

Advances which have taken place in certain fields of research during the past 5 years seem to make a fresh approach to the problem of rashes worthwhile. The rapidly advancing field of immunology is providing a sounder basis for evaluating the role of cellular and humoral immune events in the production of skin lesions, and recent work on the inflammatory response is also giving important information. The electron microscope reveals the ultrastructural background against which events in the skin must be considered, and the fluorescent-antibody method, by identifying infected cells, makes an analysis of virus growth in the skin possible at the histological level.

Rashes will be discussed from three aspects: first, the method by which virus arrives in the skin; second, the sites at which virus growth occurs; and, third, the mechanism by which lesions are produced. For the most part, rashes will be discussed as if the virus concerned did
localize and grow in the skin, although this may not be so in prodromal rashes, for instance, or in the rashes seen in certain arbo- and enterovirus infections. Because their pathogenesis and pathophysiology are better understood than in many virus infections, and because very striking rashes are produced, rickettsial diseases will also be considered. Some aspects of the pathogenesis of virus-induced skin lesions have already been discussed in Platt's excellent short review (108).

**Virus Route to Skin—Primary Lesion**

For viruses which give rise to skin lesions by localizing and growing in the skin, it is convenient to distinguish the lesions initiated by viruses that penetrate the skin from the outside from those in which virus reaches the skin from the inside after spreading through the body of the infected host; in other words, to distinguish between primary and secondary skin lesions. In much of the experimental work to be described, the primary lesions produced at the site of the injection of virus into the skin have been studied. Also, some viruses, such as those responsible for warts and papillomas, produce a skin lesion only at the site of infection and fail to spread through the body. A separate discussion of primary lesions, at least of the early stages in their pathogenesis, is thus necessary. Although the skin is usually infected via injuries or biting vectors, the possibility of infection through unbroken skin will also be considered. A later section deals with virus infection through the skin in relation to the feeding methods of blood-sucking arthropods, a subject of some significance in arthropod-transmitted virus diseases.

**Unbroken Skin**

The skin is rightly regarded as protecting the body, both mechanically and chemically, from invading microorganisms. When bacteria are placed on normal human skin, they are rapidly inactivated, the relative roles of acidity, desiccation, fatty acids, or other factors probably differing with different bacteria (116). These antibacterial factors might also be expected to help prevent skin infection with viruses, but the only report which could be found on this topic dealt with influenza virus (101), and this virus would not be expected to infect the skin.

Results of some experiments have indicated that virus particles are able to penetrate the skin of normal animals. Keller (68) reported that, when the tail or abdominal skin of normal mice was atraumatically placed in contact with fluid containing $10^{10}$ plaque-forming units (PFU) of *Bacillus megaterium* phage per milliliter, irregular amounts of phage were recoverable from the blood at 0.5 to 2 hr later. The amounts represented an exceedingly small proportion of the phage present at the skin surface. Nevertheless, if these experiments are valid, the phage particles not only penetrated normal skin, but they subsequently entered dermal blood vessels. However, normal skin probably cannot accurately be described as unbroken at the microscopic level, and, in any case, under normal circumstances such large amounts of virus are not likely to be locally available at the skin surface. There have been occasional reports of infection with viruses or rickettsiae through apparently unbroken skin, but these infections have occurred under conditions where scratching and rubbing of the inoculation sites have often not been controlled (8). Skin can be broken without visible injury or bleeding, and particles can thus be placed in contact with living cells.

**Virus infection through truly unbroken skin**

The skin infection through apparently unbroken skin probably involve minute local injuries. Deliberate local injury will be considered as a method of infection, first, because it is the classical method of vaccination against smallpox, and, second, because it is the method used in much of the experimental work on the primary lesion produced by viruses. In the multiple pressure method of smallpox vaccination, it seems necessary only to split open the epidermis and allow virus to encounter epidermal or dermal cells. An increasing amount of evidence suggests that many viruses infect cells by being phagocytosed (20), often after an initial specific attachment to receptors on the cell surface. Put another way, cells infect themselves. Epidermal cells, for instance, are able to ingest particles of carbon introduced into the skin of the guinea pigs' foot (107). Roberts (114), using the fluorescent-antibody technique, showed that epidermal cells were infected in the first cycle of growth after the controlled intradermal inoculation of ectromelia virus into the skin of mice. This certainly implies an initial uptake of virus by epidermal cells.
Inevitably, viruses scratched or injected into the skin enter dermal lymphatics. This is particularly true for intradermal injections, and, in saying that “every intradermal injection is an intralymphatic one,” Hudack and McMaster (60) drew attention to the very rich superficial plexus of lymphatics in the skin of man, as well as of the mouse (59). When large amounts of ectromelia virus are injected intradermally and subcutaneously into mice, virus is detectable in local lymph nodes within a few minutes (Mims, unpublished data). The lymphatic system, although extensive, does not deal with all the injected particles in this way, and the rest have the opportunity to infect dermal cells. If the infecting virus grows in these cells, its spread in the dermis is almost assured. If it fails to grow, it may be restricted to the initial site of growth in epidermal or other cells, as is probably the case in wart or papilloma virus infections. Roberts (114), in his immunofluorescence study of ectromelia virus infection in mouse skin, found that, after scarification of virus into the dermis, the first infected dermal cells appeared to be macrophages, and the focus then spread through the dermis by means of the infection of neighboring cells.

**Biting Vectors**

When biting vectors transmit virus diseases mechanically, there being no multiplication of virus in the vector, the contaminated mouthparts introduce virus into epidermis and dermis, as discussed in the preceding sections. This is true of the transmission of swinepox by the pig louse (123), for instance, and the best studied example is the transmission of myxoma virus by mosquitoes (38).

When transmission is said to be biological, this means that the virus multiplies in the vector and, after an incubation period, is transmitted by the saliva during a blood feed. A discussion of the process of infection must take into account the mechanics of blood feeding. Mosquitoes, in the act of feeding (49), probe in dermal tissues, emitting “puffs” of saliva as they do so. If the proboscis enters a blood capillary, it is “threaded” along the vessel, and further ejections of saliva take place during the ingestion of blood. The infected saliva is thus introduced into dermal tissues, and often directly into the vascular system. Ticks are exclusively “pool feeders”; i.e., they pierce the skin with their cutting mouthparts, suck up the pool of blood which accumulates, and periodically eject saliva into the wound throughout the feed (72). Virus infection by ticks is, therefore, the counterpart of a minute intradermal injection.

Thus, the mechanically transmitted poxviruses encounter epidermal and dermal cells, and it is in these cells that they grow. Rickettsia, too, probably grow in these cells, and striking local lesions or eschars are often produced. These viruses and rickettsiae also have the opportunity to spread systematically, because they enter dermal lymphatics. The biologically transmitted or arboviruses, however, do not give rise to local lesions, in spite of the fact that infected saliva is introduced into the dermis. Conceivably, they do not grow in dermal or epidermal cells, and infection takes place only after virus particles have entered the lymphatic or vascular system.

**Virus Route to Skin—Secondary Lesion**

Secondary skin lesions occur in the course of generalized virus diseases and will be considered as due to the localization and growth of virus in the skin. As will be discussed at a later stage, rashes can quite probably arise by allergic mechanisms without the localization and growth of virus in the skin. It is because even less is known about such rashes that discussion will be restricted in the first place to lesions produced by the growth of virus in the skin. With rare exceptions, virus reaches the skin via the blood, during a viremic stage of the disease.

Viremias can be classified into those in which virus is cell-associated, and those in which virus is free in the plasma (91), although viremias sometimes are of mixed character. The essential primary event for the production of a skin lesion is for free virus or an infected leukocyte to localize in small blood vessels in the skin, and in many generalized virus diseases, such as varicella (135), alastrim (83), and myxomatosis (64), a vascular lesion is the earliest event in the development of a skin lesion. To understand this vascular localization of virus in skin, one must first discuss the behavior of inert virus-sized particles when they are introduced into the blood, and also the evidence for the passage of leukocytes through the skin blood vessels of normal animals.

**Vascular Localization of Circulating Inert Particles**

In certain virus diseases with rashes, such as those produced by enterov- and arboviruses, virus is free in the plasma. Foreign particles, viral or nonviral, are cleared from the blood by reticuloendothelial cells, particularly those lining the liver and spleen sinusoids, and larger particles tend to be removed more rapidly than smaller ones (91). Large particles, indeed, would
be cleared by reticuloendothelial cells before there was much opportunity for localization elsewhere, unless capillary reactivity was altered. Small particles, on the other hand, with a longer circulatory half life, could more easily localize in small skin blood vessels.

Do particles introduced into the blood, in fact, localize in skin vessels? Convincing evidence for localization is usually obtained with the electron microscope, and particles in blood vessel walls are likely to be seen in sections only when they are very numerous. Thus, in most experiments, inflammatory changes have been induced in vessels, so that particles would localize in them on a grand scale. After histamine or serotonin treatment of rat scrotal tissues, for instance, intravenously injected colloidal mercuric sulfide was detectable between the endothelial cells of capillaries and postcapillary venules (84). Particles appeared to be held up by the basement membrane but later were seen in the cytoplasm of pericapillary phagocytic cells. It was noted that an occasional particle was seen in vessel walls in untreated animals. Alksne (1) made similar observations on dermal capillaries in the skin of the mouse, and he also saw occasional particles in capillary walls in untreated mice, in areas where the hair had been clipped just before the mercuric sulfide injection. One weakness in such evidence is that very large numbers of particles were suddenly introduced into the blood, whereas in a virus infection there would be a more gradual entry of particles into the blood. Localization in skin or other blood vessels might then be less common. There is also the theoretical possibility that the large injections of colloidal particles could lead to local histamine-mediated changes in blood vessels, as in the anaphylactoid response.

Apart from these observations, there is very little direct information about the vascular localization of circulating virus-sized particles in the skin of normal animals. However, it can reasonably be assumed that minute injuries or infections occur regularly in the apparently normal skin of animals. Small-scale inflammatory changes might then take place, and, however transient these changes, circulating virus particles could localize in small blood vessels. There are certain other physiological circumstances under which particles localize in skin vessels. Capillaries which are regenerating after injury have been shown to have temporary gaps between endothelial cells, and deficiencies in the basement membrane, so that circulating inert particles localize in, and leak from, these vessels (119). During hair growth cycles there are changes in the capillary networks supplying hair follicles, both in man (34), and in animals such as the mouse (142). The actively growing capillaries around follicles which are resuming activity might then differ from normal capillaries in their reaction to circulating particles. Finally, the microcirculatory changes in the skin which are known to take place after changes in environmental temperature might affect the localization of blood-borne particles, and perhaps even the vasodilation of reactive hyperemia could act in the same way.

There is also some important indirect evidence indicating that circulating particles might localize in the skin vessels of normal animals. Grotte (52) injected different molecular species of dextran intravenously into dogs, and determined the concentration in lymph from the leg. Dextran of molecular weight 300,000 was found in the lymph, and Grotte concluded that these molecules, of effective diffusion diameter 225 Å, leaked through capillary walls to enter lymphatics. Courtice and Garlick (19) estimated concentrations of different lipoproteins in the serum and in the lymph from the foot of hypercholesterolemic rabbits. The particle size of the lipoproteins was determined by electron microscopy, and the authors concluded that smaller particles passed through capillary walls more rapidly than larger ones. Even particles 600 to 700 Å in diameter were readily recoverable in lymph. Although the rabbits were anesthetized and their legs were immersed in warm water to promote lymph flow, these experiments could mean that particles the size of small viruses leak through capillary walls under normal circumstances. Such events might not be common enough to be detected in sections by electron microscopy. The site of leakage in the foot is not known, but is likely to be in the skin.

Vascular Localization and Diapedesis of Leukocytes

In the viremas of myxomatosis, mousepox, measles, rinderpest, and distemper, for instance, virus is associated with leukocytes (91). Platelets, lymphocytes, monocytes, or polymorphs may be infected. Healthy cells which bear virus particles, or are at an early stage of infection with leukocyte-pathogenic viruses, would be expected to move through small blood vessels like normal leukocytes, and could thus carry infection through to extravascular tissues. The ultrastructural details of this diapedesive have now been carefully studied (86). Platelets would not be expected to pass through blood vessel walls, but the adherence of platelets to vascular endothelium, an early response to mild damage or inflammation, could enable platelet-borne viruses to infect vascular endothelium.
If, as discussed earlier, small-scale inflammatory events occur in apparently normal skin, these may lead to leukocyte localization and diapedesis. There is direct evidence that leukocytes leave blood vessels in the skin in normal animals. Yoffee and Drinker (160) reported that small numbers of leukocytes were present in afferent lymph from the limbs of normal cats and dogs. In these experiments, the animals were anesthetized and the limbs were massaged to promote lymph flow. In more physiological studies, Hall and Morris (60) cannulated afferent lymphatics in the legs of sheep, and found that afferent lymph contained up to 3,000 leukocytes per mm³, about 80% of these being mature lymphocytes. The sheep were maintained in pens and the cannulas remained in position for many weeks. It must be assumed from these experiments that leukocytes leave blood vessels in the skin and perhaps the muscles of normal animals. This is also in accord with current beliefs about the wanderings and recirculation of lymphocytes.

It is now necessary to see to what extent these considerations about free particles and leukocytes apply to the vascular localization of circulating viruses.

Vascular Localization of Viruses

As discussed above, there is some experimental precedent for the localization of free or cell-associated viruses in skin blood vessels. There are numerous testimonies to the localization of virus lesions in provoked skin areas, and an inflammatory response, or an increased vascularity, can usually be invoked as the cause of this localization. Much of this evidence was reviewed, in relation to the “stickiness” and permeability of capillary endothelium, by Findlay (39). Experimentally, it has been usual to record the development of lesions in treated skin areas after intravenous injection of large doses of virus. For instance, fowlpox lesions localize at the site where feathers have been pulled out (13), and vaccinia lesions where the skin of rabbits has been plucked, shaved, scarified, treated with histamine, or even where vasodilation has been produced by sympathetic nerve section (15, 16, 39, 140).

Some viruses localize in the unprovoked skin of apparently normal animals after intravenous injection. When large doses of vaccinia were injected intravenously into rabbits, lesions were seen 4 days later on the untreated skin of the lips and nose, and also on the tongue and on the general body surface (26, 76). Downie (27) injected cowpox virus intravenously into normal rabbits and recorded skin lesions on the lips, eyelids, ears, and tongue. Platt (109) injected herpes simplex virus intravenously into normal male guinea pigs and observed a blotchy rash on the perineum 2 to 4 days later. When cowpox virus is injected intravenously in large doses into mice, nearly all of the virus is taken up by reticuloendothelial cells, but it also localizes and grows in the skin of the tail, ears, snout, anogenital regions, paws, and tongue (93). Fluorescent-antibody studies have revealed that the injected virus localizes in small dermal blood vessels and then grows in dermal and epidermal cells. The skin becomes bright red on the 3rd or 4th day, so that a confluent rash is formed on the hairless areas. It is not known whether free or cell-associated virus localizes in the skin in these instances, but free particles would have to localize in spite of rapid clearance from the blood by reticuloendothelial cells.

In the secondary skin lesions which localize in irritated areas in the course of exanthematous virus diseases, infected leukocytes may be concerned rather than free particles, although free virus may also be present in the blood. Varicella can localize under strips of adhesive tape or napkins, and in areas affected by acne (112), or secondary syphilis (132). The rash in measles may be more profuse in “mottled” skin areas (77), at the site of intradermally injected tuberculin (118), or in other irritated areas (137). Ricketts (111) drew attention to the localization of smallpox lesions in irritated skin areas, and Fenner (37) localized mousepox skin lesions in shaved areas. Some of the experimental findings on the localization of foot-and-mouth disease virus may also involve local vascular changes (108), but it seems probable that genuine differences in the reactivity of the epidermis are sometimes equally important. Also, the ability of an already localized virus to infect dermal and epidermal tissues and produce a macroscopic lesion may well depend on nonvascular regional differences in the skin.

In summary, skin lesions may appear in irritated skin areas, but lesions also arise in apparently unprovoked skin, both experimentally and in the course of exanthematous virus diseases. Either each lesion arises in a subclinically inflamed area, or there is localization in normal blood vessels. Most of the evidence concerns viruses which are associated with leukocytes during their viremic stage. The possibility that viruses in the plasma, whether exanthematous or not, localize in skin vessels, will be discussed more fully later.
GENESIS OF THE LESION

The essential first act in the genesis of the skin lesion, the localization of virus in blood vessel walls, has been discussed. The skin lesion may then develop as a primarily vascular one or, alternatively, as a result of the spread of infection into other tissues in the skin (see Fig. 1). Broadly speaking, a lasting local dilation of subpapillary dermal blood vessels produces a macule. If there is also edema and an infiltration of cells into the area, the macule becomes a papule. There may be secondary changes in the epidermis leading to desquamation or changes in pigmentation, but a primary involvement of the epidermis usually results in vesculation, ulceration, and scabbing.

Primary Vascular Lesions

Viruses growing in cells of the blood vessel wall could damage these cells directly, and thus initiate an inflammatory response. There is direct evidence that vascular endothelium is infected in certain virus diseases, because specific inclusion bodies (73, 124, 135), or viral antigen (18, 57, 165) have been observed in the endothelial cells of small blood vessels. At a later stage, antigen-antibody reactions could contribute to the pathological changes (see below) There might be edema, vasodilation, and cellular infiltration, giving rise to a visible skin lesion, or even thrombosis and hemorrhage if damage to the vessel was severe.

In some instances, the infection may not proceed far beyond the blood vessel wall. Indeed, the infectious process would be automatically restricted to the vessel wall if there were no infected emigrating leukocytes, and if at the same time neither dermal cells nor perivascular phagocytic cells could be infected.

Primarily vascular lesions are seen in a number of different virus diseases. For instance, there is a primarily vascular lesion in equine viral arteritis, leading to medial necrosis of smaller arteries (66). In African swine fever (wart-hog disease) and hog cholera, distinctive changes in the dermal blood vessels provide the basis for the observed skin lesions (89, 124), and the skin lesions in sheep pox have been attributed largely to the effects of vascular thrombosis (110).

Hemorrhagic rash as an unusual complication.

Hemorrhagic manifestations, including petechial rashes, are seen occasionally in a number of virus diseases, including varicella (87), variola, and measles (61). Almost nothing is known of the pathogenesis of these hemorrhagic rashes, except that an altered host reactivity must be important. The very rare instances of measles complicated by purpura appear to be thrombocytopenic in origin. Hemorrhagic chickenpox is seen particularly in tropical countries, where differences in nutrition and the presence of parasites and other infections may play a part. It may be relevant that hemorrhage can be induced around established vaccinia lesions in the skin of rabbits by the intravenous injection of endotoxin (50, 71).

Mosquito-borne hemorrhage fevers. Hemorrhagic manifestations and petechial rashes are seen more regularly in certain arthropod-transmitted virus diseases. These were classified by Gajdusek (45), who distinguished between those transmitted by mites or ticks and those transmitted by mosquitoes.

The mosquito-borne fevers with hemorrhagic manifestations include dengue and yellow fever, and in many outbreaks of these two diseases hemorrhages from small blood vessels have been reported. In hemorrhagic yellow fever it is difficult to assess the importance of primary vascular damage, because the liver lesions lead to deficiencies in prothrombin and other coagulation factors (90, 133), and this contributes to the production of hemorrhages. Skin hemorrhages are occasionally seen. In hemorrhagic dengue, there are also coagulation defects and often thrombocytopenia (98), but here vascular damage is of primary importance. The outbreaks of hemorrhagic dengue in Thailand have been carefully studied from a physiopathological standpoint (54), and it is evident that there is a primary injury to small blood vessels. This leads to increased capillary fragility, as indicated by a positive tourniquet test (46), and a leakage of plasma from the blood, with hemoconcentration and possible shock. Hemorrhages are seen in various parts of the body, and there is often a petechial rash.

Maculopapular rashes have also been reported in dengue outbreaks. Sabin (117) infected volunteers with dengue virus, and biopsies of the rash showed an endothelial swelling of small blood vessels, perivascular edema, and a mononuclear infiltration. It is clear that in dengue small blood vessels in the skin are damaged, and this may give rise to a maculopapular, or even petechial rash, the tendency to hemorrhage perhaps being increased when there is a coagulation defect or thrombocytopenia. What is not clear is whether the vessel damage is due to a direct destructive effect of the virus. Sabin could not inhibit the rash locally with intradermally injected immune serum, and, curiously enough, the rash spared the site of initial infection in the skin, whether this had been by needle or by mosquito bite.
It seems unlikely that circulating toxins cause the blood vessel damage, but mechanisms involving the immune response are easier to visualize (see below). Dengue virus growing in capillary endothelium may do very little direct damage, but, if antigen is present there at the time that free antibody appears in the serum, there would be an antigen-antibody reaction with pathological consequences in the vessel walls. Little is known about the pathogenesis of hemorrhagic dengue, and the hemorrhagic manifestations are not usually seen in occidental patients, but the possibility of a hyperergic host response is prominent in much of the current thinking on the subject (54).

Mite- and tick-borne hemorrhagic fevers. Some of the hemorrhagic mite- and tick-borne fevers have also been investigated from the physio-pathological point of view. Here, too, damage to small blood vessels is one of the primary pathological changes, resulting in capillary leakage, increased capillary fragility, and hemorrhages (74). Patients may have lasting flushes or mild rashes, as well as petechial rashes (33). Greisman (51) made direct observations on small blood vessels in the nail-fold bed, and described prolonged dilatation and hemorrhage in patients with Korean hemorrhagic fever. As is the case with mosquito-borne hemorrhagic fevers, we are ignorant about the relative importance of direct viral damage, toxins, and immune reaction in the pathogenesis of the vascular lesions.

Rickettsial rashes. Rickettsia can be observed directly in vascular endothelium in the lesions of Rocky Mountain spotted fever (143), typhus, and scrub typhus (144, 145), and very striking rashes are seen in these diseases. When rickettsiae are injected intravenously in large doses to mice or rats, they produce widespread capillary endothelial damage, and animals die in shock as a result of the leakage of plasma through capillaries (138). Death occurs within hours, and there are no gross pathological changes in vessels. Infectious particles, not toxins, are responsible for the effect. Rickettsiae, clearly, have a primary pathological action on vascular endothelium. Equally clearly, when patients with rickettsiae in blood vessel walls produce circulating antibodies, antigen-antibody reactions will tend to damage these vessel walls. This could account for the vascular lesions, for there need be no classical Arthus reaction. Allen and Spitz (2) suggested that the hyperergic state was important in the pathogenesis of the vascular lesion in scrub typhus and other rickettsial diseases. Intraepidermal vesicles are seen in the skin lesions of one rickettsia disease, and these are sufficiently like chickenpox (25, 62) to have led to the distinctive name of rickettsialpox. But it is not known whether rickettsiae grow in the epidermis to produce these epidermal lesions, which are also described in the early development of the scrub typhus eschar (2).

Thus, in most rickettsial diseases, the rash appears to be produced by rickettsiae growing in blood vessel walls, and then reacting with circulating antibodies and perhaps with immune cells. The evidence does not warrant conclusions about the relative importance of direct damage by rickettsiae, and damage mediated by the immune response.

**Extravascular Involvement**

The infectious process may spread to extravascular tissues, either after the infection of perivascular cells and release of virus into surrounding tissues, or by way of migrating leukocytes. Unfortunately, although the possibilities can be discussed in this way, it is not often possible to say exactly what happens in any particular virus disease. In any case, if dermal fibroblasts or macrophages become infected, a spread of the infection through the dermis is possible. At this stage, the quality of the ground substance of the dermal connective tissue might play an important role.

**Role of the ground substance.** Do viruses spread extracellularly in the skin? The ground substance is viscous and normally offers considerable resistance to the passage of foreign material (81). However, when very large numbers of colloidal gold particles were injected subcutaneously into mice, electron microscopic examination showed that at least some particles spread significantly through the dermis (47). But standard injection techniques, in which comparatively large volumes are introduced under pressure, are grossly unphysiological compared with the normal process of infection through skin, and even more so compared with the evolution of hematogenous lesions in the skin. The changes in the ground substance that occur under some circumstances increase the difficulty with which inert particles spread in the dermis. At the same time, smaller skin lesions are produced by certain viruses, and with greater difficulty (127). During pregnancy, for instance, rabbits develop smaller skin lesions at the site of inoculation of myxoma virus (126). There might be increased opportunity for the spread of free particles in edematous tissues, through which dyes are known to move more rapidly (67, 80). Hyaluronidase, the spreading factor, has been shown to have pronounced effects on the movement of particles within the skin, and on the production of skin lesions by poxviruses (31). Although the
physiological role of hyaluronidase in tissues like the skin is still unsettled, the fact that it has such effects when injected locally shows that the consistency of the ground substance can be important in the development of virus skin lesions.

Thus, the ability of free particles to spread through dermal connective tissue, although probably limited, can be influenced by certain physiological changes. To what extent would this be important during the genesis of virus skin lesions? It would seem that virus particles released locally and in small numbers are likely to be taken up at an early stage by phagocytic cells. Later on in the evolution of a lesion, if there was edema, or a larger scale release of virus particles, there might be an opportunity for significant spread of free particles. But the spread of virus extracellularly is probably unimportant compared with spread by the movement of infected cells or by the infection of successive cells, either of which could in turn be influenced by changes in the ground substance.

Dermal response to infection. In the dermis, vasodilation, edema, and cellular infiltration combine to produce pathological changes which are not often very characteristic for different viruses. The type of cellular infiltration may depend on the relative importance of nonspecific inflammatory and delayed type hypersensitivity responses. There are also likely to be changes in the quality of the ground substance.

Many features of the dermal response are discussed elsewhere, but the characteristic lesions caused by myxoma virus and the Yaba poxvirus will be mentioned here. In rabbits infected with myxoma virus, the skin lesions contain large amounts of mucicarmine staining extracellular fluid. This mucinous or myxomatous fluid appears to be produced by fibroblasts, some of which transform into myxoma cells (64). The closely related fibroma virus, while it may lead to the production of a similar material in newborn rabbits (32), induces the formation of a more solidly cellular tumor in the dermis of adults. Fibroblasts are known to be capable of forming mucin, and they do so regularly in young embryos, as well as in certain rare mucinous tumors. The fact that a virus infection may specifically induce this change in the secretory activity of fibroblasts is of some interest, but such aspects of the infection have not been investigated experimentally. The Yaba poxvirus is mentioned because it induces an unusual response in the dermal histiocytes of monkeys. These cells, which are infected, multiply to produce "histiocytomas," and, if India ink is injected with the virus, the dermal nodules are seen to consist of ink-laden cells (125).

Involvement of epidermis. Once infection has spread into dermal connective tissue, the surface epidermis, hair follicles, and sebaceous glands may in turn be infected (Fig. 1). Although the entire body surface is covered with a sheet of epidermis, in nearly all mammals most of the epidermis is in fact below the body surface, for it is embedded in the dermis in the form of hair follicles and glands. Hair follicles and sebaceous glands, indeed, are selectively affected in certain virus diseases, the severe scarring following attacks of variola major, for instance, being a result of the destruction of deep-seated sebaceous glands (12).

A submicroscopic (350 Å) membrane sheet separates basal epidermal cells from the dermis (121). This membrane is thinner and different in appearance from basement membranes elsewhere, and, although metabolites must pass through it to nourish the epidermis, perhaps by way of the vesicles described by Odland (100), it might be expected to act as a barrier to the spread of free particles into the epidermis. Platt (107) found that iron dextran introduced below the epidermis of guinea pigs did not pass through into epidermal cells, except in injured areas and in certain parts of the body. The latter comprised the tip of the tongue, ears, feet, belly, and prepuce, and the possibility that in the normal animal minute undetectable traumata were always occurring at these sites was discussed. He drew attention to differences in the phagocytic activity of epidermal cells, but pointed out that differences in the integrity of the basement membrane, and thus in the passage of particles across it, may have played a part. Selby's material (121) included skin from the footpad of rats, but there have been no studies of regional differences in completeness of the membrane at the dermo-epidermal junction. Gerard and Tyler (47) found that when colloidal gold was injected subcutaneously into mice some of the particles spread into the dermis, and some came to lie adjacent to the basement membrane. But they generally failed to pass into the epidermis, except for occasional particles which were seen between epidermal cells.

It can be concluded that free particles in the dermis, although capable of passing through the basement membrane and thus encountering epidermal cells, do so uncommonly. Thus, in Rob-erts' (114) careful immunofluorescence study of the infection of the mouse skin with ectromelia virus, the primary dermal lesion was shown to spread laterally through the dermis and occasionally to reinfect the epidermis to produce "island foci" which were separate from the primary epidermal focus. The reinfection of the epidermis
from the dermis did not take place regularly but only in occasional places. Perhaps in certain parts of the body and in injured areas the passage of particles across the basement membrane is more easily accomplished, but evidence on this matter is not available. Virus-bearing cells might theoretically pass from dermis to epidermis, but except during inflammation this is not thought to be of importance.

Once particles are in the epidermis, they may be taken up by epidermal cells. Platt (107) showed that when carbon, saccharated iron oxide, or carmine particles were injected intradermally into guinea pigs, they were taken up into stratum Malpighii cells around the needle tract within 12 hr. Roberts (114), in his immunofluorescence study of the early stages of infection of the mouse skin with ectromelia virus, found that epidermal cells in the neighborhood of the scarification lines, as well as dermal macrophages, were the first cells to be infected.

If the epidermis is infected, there are no special barriers to the spread of the focus in epidermal cells. It can be assumed that only the living cells in the stratum Malpighii are infectable. These cells accumulate keratin, die, and become more horny scales as they move toward the surface. Many factors influence the time taken for basal cells to reach the surface of the skin, but fully keratinized cells may contain virus after infection some days earlier in the stratum Malpighii.

**Role of melanocytes.** Besides epithelial cells, the epidermis of all mammals contains melanocytes, and these cells arise during embryonic development from the neural crest. Between 1 in 4 and 1 in 10 of the cells in the basal layer of the human epidermis are melanocytes (129), and the dendrites of each melanocyte are in contact with a number of epidermal cells. If infected with virus, the melanocytes could play an important part in the spread of the epidermal lesion (10). They might hand over virus particles to epidermal cells in the way that they appear to hand over melanin granules, and with their branching dendritic system could spread virus more rapidly than would be possible by the stepwise involvement of epidermal cells. In the one report on the infection of melanocytes by a virus (82), pigmented multinucleated melanocytes containing intranuclear viral inclusions were described and figured in a recurrent herpes simplex skin lesion from a Negro. In this case, in-
clclusion bodies were "confined almost entirely to the pigment carrying cells," and this raises the interesting possibility that melanocytes play an important part in recurrent herpes and perhaps even in zoster. The cornea, a site for recurrent herpes, also appears to contain melanocytes (Langerhans' cells) which impart a slight pigmentation to the cornea in some animals. The only experimental evidence concerning the role of melanocytes in the development of virus skin lesions comes from the work of Roberts (114). He examined fluorescent antibody-stained epidermal strips from developing ectromelia skin lesions in mice, and could find no evidence that melanocytes facilitated the spread of infection. He was unable to determine whether the melanocytes were, in fact, infected.

Melanocytes, therefore, because there are many of them in the skin of all mammals, could theoretically play an important part in the development of epidermal lesions. In one instance where their role was investigated, they did not appear to be important, but information is scarce, and usually it is not even possible to say whether they are infected by viruses growing in the skin.

Differences in susceptibility of epidermal cells. Although there are no special barriers to the spread of infection in the epidermis, there is the possibility that the epidermal cells themselves, in certain areas or under certain circumstances, are more susceptible to infection. Thus, more actively mitotic epidermal regions, epidermal cells round hair follicles during the active stages of hair growth, or epidermal cells in exposed regions like the mouth, paws, prepuce, or udders, might be more readily infected. Where lesions appear in certain areas of skin in generalized infections, a difference in the ability of circulating virus to localize in skin blood vessels must also be considered. It is difficult, as Platt (108) has pointed out, to decide whether there are also local differences in the susceptibility of epidermal cells. For instance, it might be simply the vascular localization of virus which leads to the initiation of smallpox lesions in sebaceous glands and hair follicles, just as vascular localization accounts for the appearance of vaccinial lesions in the shaved skin areas of intravenously injected rabbits. Genuine differences in the behavior of epidermal cells are therefore more readily revealed when primary lesions are studied.

Platt (106) showed that when foot-and-mouth virus was injected into the skin of guinea pigs there were marked regional differences in susceptibility. The metatarsal pads were highly susceptible, the ear less so, and the trunk almost insusceptible. Skin from metatarsal pads, however, when grafted onto the chest, was much less susceptible to directly inoculated virus. The change in susceptibility was not regularly related to alterations in mitotic activity in the grafted skin, and changes in skin temperature were not thought to be important. Platt suggested that there was a change in the susceptibility of the epithelial cells themselves.

Kidd and Parsons (70) reported that local injections of Shope papilloma virus produced lesions in the skin, but not in the mucous membrane inside the mouth or urogenital tract of domestic rabbits. In this case, lesions are produced by the proliferative response of epidermal cells, and, although the findings are of considerable interest, they do not lead to any firm conclusions about the development of the infectious focus in epidermal cells. Friedewald (42) found that, when the skin of rabbits was made hyperplastic by treatment with certain chemicals, it became more susceptible to intradermally injected or scarified papilloma virus. Whiteley (140) showed that the same virus, inoculated by scarification into the skin of rabbits, produced much larger tumors in skin with actively multiplying epidermis, 5 and 10 days after plucking. Here again, it is only possible to say that tumors are more readily induced, and once established grow faster, in thick, actively mitotic epidermis. In a similar experiment with vaccinia virus, there was no great difference between the lesions produced in active and in quiescent skin (140).

Finally, the growth of viruses in the skin can almost certainly be directly affected by temperature. There are various observations suggesting that this occurs, but where, in generalized virus infections, skin lesions are reduced in cooled extremities, the results may be attributable to poor vascular localization in cool skin. More direct evidence is available from the work of Roberts (115). He injected ectromelia virus into the footpads of mice kept in the cold and at normal temperatures, and compared virus growth curves in the inoculated feet. From the start, less virus was produced in the feet of mice kept in the cold. When virus was injected into the hairy and therefore warmer skin of the back, there was no difference in skin titers at the site of injection. Although the results might have been due to changes in the susceptibility of cells as a result of reduced blood flow, the probable explanation is that in the feet of mice in the cold the cells, particularly those in the epidermis, were at a suboptimal temperature for virus growth (115). In an experiment with an attenuated strain of myxoma virus, Roberts (personal communication) made parallel titrations intra-
dermally on the freshly clipped and on the normal furred sides of a rabbit's back. End points, as judged by the appearance of a lesion, were 100-fold higher on the clipped side. This recalls the work of Thompson (131), who showed that rabbits in the warm room, with skin temperatures several degrees higher than control rabbits, developed very much smaller tumors after the intradermal injection of fibroma virus. Rabbits in the warm room were also less likely to develop skin lesions when injected intradermally with myxoma virus (102). The most acceptable explanation for the above observations is that myxoma and fibroma viruses grow better at lower temperatures (88), although, strictly speaking, the difference could be more in skin reactivity than in virus growth.

**Epidermal response to infection.** A few general features of the pathogenesis of the epidermal lesion will be mentioned. Infected epidermal cells, like other cells infected with cytopathic viruses, tend to swell and become vacuolated, and they may degenerate. The first signs of infection are seen in the living cells of the stratum Malpighi (see Fig. 1). Affected cells often swell, and may develop intranuclear or intracytoplasmic inclusions, depending on the virus. Cells may become vacuolated and necrotic, with nuclear disruption, and, when a focus of such cells has developed, a hole is produced in the epidermis. In response to the cell damage, inflammatory fluid inevitably appears, and the hole becomes a vesicle (variola, vaccinia, foot-and-mouth disease). Sometimes intercellular edema is pronounced, and a fluid-filled cavity appears as the cells are parted or degenerate; vesicles may arise in this way without substantial cell necrosis. Since vesicles arise primarily in the stratum Malpighi, there is a roof of stratum corneum and often of granuloom or prickle cells of the stratum Malpighi. The floor may consist of basal epidermal (stratum germinativum) cells or sometimes, when these are destroyed, the dermis itself. Vesicles may become pustular as leukocytes accumulate in them. In some instances, intraepidermal vesicles are small and do not unite, and a macroscopic vesicle is never seen, as in measles (85), extremely mild smallpox, or malignant fulminating smallpox. Inevitably, vesicles are striking features in thick or thickened epidermis, where a good roof is available. For instance, human smallpox lesions in the palms and soles, where the stratum corneum is particularly thick, may not disappear until after all lesions elsewhere in the body have healed. On the other hand, in the mouse, where the epidermis is thin and the stratum Malpighi is only about two cells deep, visible vesicles do not easily develop, and papules give rise directly to ulcers (37). In mucous membranes, although the development of lesions is basically the same as in the skin, the roof of vesicles, being sodden, breaks down early to produce an ulcer (herpes simplex); one result is that infectious virus is liberated at an earlier stage than from the skin.

In lesions caused by many viruses, epidermal cells proliferate, so that the epidermis becomes somewhat thicker (sheep-pox, smallpox, cow-pox). In some cases, the infected cells perhaps respond by proliferating (fowlpox), but in other cases it seems likely that nearby but uninjected epidermal cells react in this way, as indicated by the work of Roberts (124) on ectromelia skin lesions in mice. The proliferating cells at the edge of enlarging lesions are themselves eventually infected and may become necrotic. Sometimes the proliferative response in the epidermis is gross, so that tumors are produced. For instance, in the rabbit papilloma (132) or the human wart (66), cells in the stratum germinativum are initially infected and respond by mitotic activity. The viruses causing these lesions perhaps have a slow growth cycle in epidermal cells, and virus particles are not common until the cells are becoming imperfectly keratinized as they ascend to the epidermal surface, presumably a few days after their infection. These atypically keratinized cells come to form most of the dry horny papilloma or wart.

**Part Played by the Immune Response**

In discussing immune responses, it is customary to distinguish between the part played by circulating antibodies and that played by an altered cellular response or delayed type of hypersensitivity. This distinction may prove to be less meaningful in the last analysis, but it is nevertheless a valid one, and the immune response will be dealt with under these headings. The possible role of virus allergens in rashes must also be considered. Immune damage will then be contrasted with direct damage by viruses, and, finally, the factors responsible for the regression of virus rashes will be discussed.

**Delayed type hypersensitivity.** A hypersensitivity reaction to viral materials is sometimes demonstrable in animals recovered from virus infections. As usually tested for by the intradermal injection of viral antigens, this consists of a slowly evolving cellular infiltration of the skin. This allergic or delayed type of hypersensitivity reaction can be elicited after infections with a number of nonviral microorganisms, including tuberculosis, brucellosis, glanders, leprosy, and lymphogranuloma inguinale, all of which are
intracellular parasites involving especially macrophages. It is also seen after certain poxvirus infections [variola, vaccinia, ectromelia (37)] and mumps (35). All that need be said about it here, and indeed almost all that can be said about it, is that it is a specific cellular response to an antigen.

Fifty years ago, von Pirquet (136) suggested that an altered host reactivity to virus material played an important role in the development of vaccinia, and perhaps also measles, German measles, and chickenpox skin lesions. Von Pirquet studied the skin responses of unvaccinated patients to daily inoculations of vaccinia virus at different skin sites. He found that the evolution of individual lesions proceeded independently until 8 to 11 days, and then at the same time around each lesion an inflammatory zone developed. From these and similar studies on vaccinia virus, and from related observations in tuberculosis, serum-sickness, and other conditions, he concluded that the exanthem is produced as a result of the changed reactivity of the host. He suggested that circulating antibodies react with the virus in the skin to produce a toxic substance which gives rise to the inflammatory events in the lesion. Pincus and Flick (104) confirmed and extended von Pirquet's observation on vaccinal skin lesions. With the virus preparations used by these workers, an allergic response could be detected as early as the 4th day after inoculation, and their evidence indicated that the subsequent evolution of the lesion, including vesicle formation, was attributable to the allergic response.

For many years, von Pirquet's idea remained interesting but ill-defined. Ledingham (73) found that the intradermal injection of India ink locally inhibited the reaction of allergy to vaccinia virus in rabbits, and that it also prevented the development of the local lesion produced by primary infection with vaccinia virus. The effect was sharply confined to the India ink injection site, and a typical vaccinial lesion once developed just outside the edge of the ink mass. These findings were confirmed by Widelock (141), who also showed that the ink injection did not affect virus multiplication in the skin. It would be interesting to know whether a smallpox eruption fails to involve tattoo marks. Presumably, the effect involves a generally changed reactivity of blood vessels, because there is also no inflammatory reaction to pneumococci or oil of citronella in the ink injection site (4). The experiments, therefore, do no more than indicate that for the development of any of these responses there must be an extravasation of fluid and cells into the skin.

In his far-reaching survey of the pathogenesis of virus diseases, Burnet (14) drew attention to von Pirquet's work and gave a more up-to-date interpretation of the measles exanthem in terms of von Pirquet's hypothesis.

A few years ago, the subject of the role of allergy and delayed type hypersensitivity in the development of viral skin lesions was reopened by the observations on patients with agammaglobulinemia, and by a number of interesting laboratory experiments with vaccinia virus. Pincus and Flick (103) found that, when an antimononuclear cell serum was injected intradermally into guinea pigs, the lesions produced by vaccinia virus injected into the same site failed to evolve in the normal way. An erythematous area developed in the first few days, but neither papules nor vesicles appeared. Serum hemagglutination inhibiting antibody titers appeared as in control animals, indicating that the guinea pigs had indeed been infected. The delayed type hypersensitivity response to dinitrochlorobenzene could be inhibited in the same way, and it was concluded that this response was essential for the normal evolution of the vaccinial skin lesion. Impressive confirmatory evidence was obtained when rabbits were made immunologically tolerant to vaccinia, and then injected intradermally with virus (41). In contrast to control animals, skin reactions were either completely absent or else abortive, with slight redness and scabbing but without vesicle formation. These rabbits failed to produce antibody to vaccinia virus, and many died with generalized visceral infection. Virus can be assumed to have grown in the skin, because typical vaccinial inclusion bodies were seen in epidermal cells in the lesions, just as in Widelock's (141) India ink experiments, where epidermal cell swelling and hyperplasia occurred as usual, in spite of the fact that typical lesions failed to appear. There is strong evidence, therefore, that in vaccinal skin infections much of the dermal swelling and edema, and even vesicle formation in the epidermis, are mediated by a delayed type hypersensitivity response. Vesicles are also produced in the delayed type hypersensitivity response of contact dermatitis, and sometimes when a tuberculin patch is applied to the skin of sensitized subjects.

There are a few observations suggesting that host responses play an essential part in the development of the measles rash. Hecht's giant cell pneumonia appears to be an atypical response to measles virus infection, and in three patients from whose lungs virus was isolated postmortem there had been neither Koplik spots nor rash (36). Each patient had an underlying chronic
disease, and it seems possible that the absence of the rash was associated with a failure in host reactivity to virus growth.

**Antibodies.** During the normal evolution of a primary vaccination lesion in man, an erythematous area appears round the central zone after 7 or more days, depending on the amount of virus inoculated. This coincides with the appearance in the blood of circulating antibodies, and can be attributed to an antigen-antibody reaction in the lesion. If viral antigens are present in blood vessel walls and circulating precipitating antibody appears, then antigen-antibody complexes may be precipitated in vessel walls and an Arthus-type reaction is generated with primary damage to these vessels. Antigen-antibody reactions may also occur extravascularly and lead to an increased capillary permeability, as seen in the passive cutaneous anaphylaxis response. In retrospect, the "allergy" referred to by von Pirquet in his observations on primary vaccinal skin lesions probably consists of an antigen-antibody mediated response. Similar observations on the evolution of myxoma virus skin lesions in rabbits have been made (Marshall, personal communication), and clear evidence about the role of circulating antibodies was obtained in the following experiment (Mims and Roberts, unpublished data). A rabbit was given 40 intradermal inoculations with 10^4 LD50 of a virulent strain of myxoma virus, and on day 3, when the lesions were slightly raised reddish papules, 40 ml of myxoma-immune rabbit serum were injected intravenously. Within 1 hr, the skin lesions developed a deep red zone at their edges, so that the lesion came to resemble those often seen with attenuated virus strains after 8 or more days. This is taken as good evidence that antibody plays a part, at least in the later stages in the development of skin lesions.

Although antibodies may be responsible for the erythematous zone around established lesions, there is evidence that antibodies do not otherwise play a part in the evolution of the vaccinal skin lesion. X-irradiation, which suppressed circulating antibody formation but not the development of delayed type hypersensitivity, failed to affect the development of vaccinia skin lesions (41, 43). Again, agammaglobulinemic patients who are unable to produce antibodies, or at least have greatly reduced ability to do so (5), nevertheless generally develop typical skin lesions on primary vaccination and give immune responses to revaccination (48).

Thus in the case of the best-studied viral skin lesion, that produced by vaccinia virus, it seems that a delayed type hypersensitivity response plays an important part in the early evolution of the lesion. Although, as discussed earlier, the swelling and vacuolation of cells and the formation of microvesicles may be a purely cellular response to infection, there is evidence that vesicle production in the gross sense is mediated by the delayed type hypersensitivity response. Later, the appearance of circulating antibody may give the lesion an added inflammatory character. However, it may often prove difficult to distinguish between the parts played by the separately characterizable components of the immune response. Skin-sensitizing antibodies would be of possible importance in viral skin lesions, but nothing is known about these antibodies in virus diseases.

**Allergic rashes.** Certain clinically observed allergic rashes should be mentioned. They are fairly well characterized, but usually have no counterpart in experimental animals, and their pathogenesis is not understood. They may nevertheless be important in understanding the pathogenesis of viral rashes. These allergic rashes are seen in a number of human diseases and skin sensitivity can often be demonstrated, but the allergen has clearly not been locally introduced into the skin at the site of the rash. For instance, urticarial erythematous or vesicular rashes are seen in serum sickness, in food and other allergies, in helminth infestations, in drug eruptions, and in the trichophytids of fungus infections. The agent responsible for the eruption must be assumed to be blood-borne. Presumably antigens or allergens enter the circulation, localize in skin blood vessels, and an immunological reaction which occurs at some stage gives rise to the rash. The rash may be restricted in distribution, even to a localized skin area in the fixed drug eruptions; it may appear in showers, and may tend to be symmetrical. Whatever the pathogenesis of these rashes, or the factors responsible for their localization, their possible occurrence in virus disease must be considered. The fleeting prodomal rashes sometimes seen in chickenpox, smallpox, or measles might well be rashes of this sort. The definitive rashes in certain enteroviral and arbovirus infections (Table 1) may also come into this category. Even in the case of measles, there is no good evidence that infectious virus rather than viral allergen localizes in the skin to produce the rash, although Debre, Bonnett, and Broca (22) showed that intradermally injected immune serum locally inhibited the development of the measles rash, and the closely related distemper virus has been shown by fluorescent-antibody staining to grow in the skin of intranasally infected ferrets (79).

Soluble viral antigens can certainly be liberated into the blood in generalized virus infections.
Rivers and Ward (113) demonstrated noninfectious precipitinogen in the serum of rabbits infected with myxoma virus. Using the precipitin reaction, Hughes (63) demonstrated soluble antigens in the serum of monkeys infected with yellow fever virus, and, more interestingly, the experiments of Davis (21) indicated that the antigens in such sera can induce anaphylaxis in passively sensitized animals.

In summary, some of the rashes seen in virus diseases may well be allergic in nature, with circulating materials localizing in the skin to give rise to immediate or delayed reactions. Such rashes have usually been described in man, and, although comparable skin reactions are recorded in animals, for example, in fungus infections in the guinea pig (56, 128), they may prove to be of significance in man rather than animals.

Direct damage by viruses. In spite of the fact that the immune response may be important in the genesis of skin lesions produced by certain poxviruses and perhaps by measles virus, the role of direct cell damage by viruses should not be underestimated. For instance, viruses growing in blood vessels may damage cells to produce endothelial swelling, extravasation of fluid and leukocytes, or even hemorrhage and infarction with consequent anoxic changes in tissues. At any stage, the products of cell destruction may themselves generate nonspecific inflammatory responses. Thus, in spite of the fact that the immune response cannot be important in the lesions produced by vaccinia virus on the chorioallantoic membrane of chick embryos, necrosis, vacuolation, edema, and hemorrhage are nevertheless prominent features. The role of the direct destructive action of viruses on skin is perhaps more clearly separable from that of secondary reactions in the primary lesions in foot-and-mouth disease. In Platt's (105) experiments on guinea pigs, where epidermal necrosis with papules and even small vesicles were visible as early as 24 to 48 hr after infection, it would seem unlikely that the immune response could have made a notable contribution.

The possible role of direct damage by toxins may be mentioned. In the Schick test for example, Corynebacterium diptheriae toxin injected into the skin of nonimmune subjects gives maculopapular lesions. In scarlet fever, circulating streptococcal toxins localize in the skin to produce erythematous lesions, but in this case hypersensitivity to the toxin perhaps plays a part. Soluble viral toxins that are active in animals have not been demonstrated but they remain a possibility.

Finally, it should be pointed out that, even if viruses can sometimes produce lesions in the skin without the help of the immune response, this cannot occur if infected cells show no cytopathic changes. Thus, in carrier mice congenitally infected with LCM virus, a state of immune tolerance permits the growth of virus in cells and tissues throughout the body (92). This virus, moreover, is completely noncytopathic for infected mouse cells, and carriers remain well in spite of the fact that all tissues are heavily infected. Foci of infection in the skin are seen by fluorescent-antibody staining, involving dermal and epidermal cells, but infected skin areas are completely healthy and show no pathological changes.

Regression of lesions. The part played by antibody and delayed type hypersensitivity in the regression of virus skin lesions merits brief discussion. Antibodies may not be important, because vaccinal skin lesions regress normally in most agammaglobulinemic patients, and also in X-irradiated animals which fail to produce detectable antibodies (43). The fact that passively administered antibody may cause regression of lesions, and that in immune animals antibody prevents the formation of lesions, does not mean that antibody is responsible for the regression of lesions under normal circumstances. There is also evidence that delayed type hypersensitivity does not contribute to the regression of primary vaccinal skin lesions (134). If this is true, at least for vaccinal lesions, it may be asked what, in fact, limits the growth of the primary lesion and prevents its spreading and covering a large part of the body surface. There is good reason to believe that interferon, which is present in vaccinia skin lesions (97), may be of primary importance (44). It has been suggested that interferon is concerned in the recovery from primary virus infection, and antibody is involved in the resistance to reinfection (6). Unfortunately, there are few studies that permit clear-cut conclusions. For instance, in vaccinia gangrenosum, a rare complication of smallpox vaccination, there is indeed a progressive enlargement of the primary lesion. Although antibodies are usually not demonstrable, and most cases heal after the administration of immune globulins, this is not always so, and in two instances the advance of the lesion was finally halted by the local injection of immune leukocytes (69, 99). In most cases, interferon production was not investigated. It is difficult to draw clear conclusions, because these patients may have had different and multiple deficiencies. Although lesions usually regressed when antibody was given, this does not mean that antibodies normally perform this function, and there may have been an accompanying
failure in interferon production, or in other resistance factors.

**Factors Affecting the Occurrence of Rashes in Virus Diseases**

Rashes are seen in only a small proportion of all generalized virus diseases, and it is of some interest to attempt to account for the presence or absence of a rash in different virus infections (see Table 1). Why do so many viruses, in spite of the fact that they circulate in the blood, fail to produce rashes? Unfortunately our basic ignorance about rashes permits no more than a few general observations and speculations.

First, the following classification of the exanthematous virus diseases can be made. There are two sets of viruses which grow in the dermis and epidermis and which, therefore, produce local lesions when injected into the skin. The first set comprises the poxviruses, herpes simplex-varicella, and probably the measles-distemper-rinderpest group. These viruses are all large, are associated with leukocytes when in the blood, and can be thought of as being carried out of dermal blood vessels by leukocytes, to infect dermal and epidermal cells. The second set includes the foot-and-mouth disease-vesicular exanthem group, and probably coxsackie A<sub>6</sub> and A<sub>16</sub> (3). These viruses are all very small, none being larger than 30 μ in diameter. They are probably free in the plasma of infected animals, and they probably all grow in dermal or epidermal cells. Particles of this magnitude are perhaps capable of leaking through small skin blood vessels in normal animals (19, 52), and lesions can then be produced if they grow in dermal or epidermal cells.

Other exanthematous viruses, including certain arboviruses and echoviruses, rubella, and infectious mononucleosis, can be thought of as failing to progress beyond the stage of vascular or perivascular infection. They are, therefore, unlikely to produce local lesions when injected into the skin. They may even produce lesions by way of allergic responses rather than by the growth of virus in the skin.

Thus, any circulating virus, free or cell-associated, which localizes in a skin blood vessel, has the opportunity to infect the vessel wall and give rise to a vascular lesion. The infectious focus could spread to involve dermal and epidermal cells as well, if they were susceptible. Even if virus fails to grow in blood vessels, leukocytes might carry it through, or, if small, it might leak through to extravascular tissues, where it would again have an opportunity to produce a lesion by growing in dermal or epidermal cells.

If localization in vessel walls takes place according to the size of virus particles, the mechanisms which localize exanthematous viruses would also localize viruses which never give rise to skin lesions. Thus, if the rash in echo 16 or West Nile infections is a result of the localization of virus in the skin, it can be asked why there are no rashes in poliovirus or yellow fever virus infections. In these last two diseases, circulating virus is known to localize in small blood vessels in the brain (polio) and liver (yellow fever) to produce lesions. Circulating virus is probably free in the plasma in each of these four infections, and it would seem unlikely that there is anything characteristic of echo 16 or West Nile virus particles which makes them localize in the skin, or about polio and yellow fever virus particles which makes them localize in the brain and liver. More probably, in each case virus particles localize in the same way according to uptake by reticuloendothelial cells and lodgement in capillaries and venules as discussed earlier. But West

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**Table 1. Occurrence of cutaneous eruptions in generalized virus diseases (75, 139)**

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<tr>
<th>Present&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Absent or not recorded</th>
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<td>Coxsackie A&lt;sub&gt;6&lt;/sub&gt;, A&lt;sub&gt;16&lt;/sub&gt;, (B&lt;sub&gt;1&lt;/sub&gt;, B&lt;sub&gt;3&lt;/sub&gt;, B&lt;sub&gt;5&lt;/sub&gt;) Echo 9, 16, (4, 6, 18) Vesicular exanthem Foot-and-mouth disease (Reoviruses 2) Arboviruses: group A (Chikungunya, O'nyong-nyong), group B (West Nile, Dengue) Measles-distemper-rinderpest Pox viruses Infectious mononucleosis Rubella Vesicular stomatitis Varicella-zoster-herpes simplex (Adenoviruses 1, 2, 3, 7)</td>
<td>Coxsackie (most) Echo-(others) EMC Polioviruses Reoviruses (most) Arboviruses: group A (most), group B (most), group C and miscellaneous Fowl plague, mumps, Newcastle disease virus Cytomegaloviruses Infectious hepatitis Rabies Adenoviruses (most) African horse sickness Panleucopenia of cats Polyoma, simian virus 40, K virus Avian leucosis - sarcoma complex And many other virus diseases of animals</td>
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<sup>a</sup> Those in parentheses are less well established.
Nile virus, for instance, although lodged in Kupffer cells, cannot initiate infection in the liver, just as poliovirus in small blood vessels in the skin cannot give rise to a lesion. This does not exclude a possible affinity of certain viruses for vascular endothelium in general, or for the endothelium in certain vascular beds. Coxsackie A virus might localize specifically in striped muscle blood vessels, or mumps virus in the blood vessels of certain glands. This explanation of the facts must have at least a limited validity.

In summary, the production of a rash by leukocyte-associated viruses may depend on their ability to grow in dermal and epidermal cells. Circulating free virus particles perhaps localize nonspecifically in skin blood vessels according to their size, and only those which grow in vessel walls or pass through vessel walls to grow in extravascular tissues produce rashes. Obviously, there are likely to be major differences in the ability of different viruses to grow in vessel walls and in dermal and epidermal cells. With so little evidence, the above speculations may prove to be unfounded; indeed, all that can be done with complete safety is to invoke the “dermotropism” of certain viruses, just as Levaditi did 40 years ago.

**DISCUSSION**

In this survey of the pathogenesis of virus rashes, attention has been drawn to general principles governing the development of skin lesions. Certain aspects of the subject have not been dealt with very thoroughly. For instance, virus-induced tumors of the skin have received no more than brief mention, and on the subject of the zoster rash, there seemed little to add to Downie’s (28) survey. The subject of rashes needed reviewing, if only to restate the old problems in modern terms, to bring together relevant information, and, in doing so, perhaps to have a clearer insight into the gaps in our understanding of the behavior of the skin in virus diseases. Without a doubt, a full understanding of the pathogenesis of rashes awaits advances in our basic knowledge of the skin and its responses.

Generally, skin lesions produced by viruses which grow in the skin when injected locally have been well studied, compared with those that produce rashes but no local lesion. Thus, experiments with poxviruses are often discussed at length, whereas remarks about arbo- or enterovirus rashes are largely speculative. It is no accident that nearly all observations and many of the experiments concern man. It might be expected that the skin of man, so closely observed by patient and physician for centuries, would for this reason alone yield more information. Even the most minute blemishes are clearly visible on human skin because it is naked, and they are more clearly visible on white than on black skin. But there is another important reason why the human skin figures so prominently in any discussion on rashes. Human skin is unique. In taking the place of fur, it still has to be both an instrument of isolation from, and of communication with, the outside world. One important consequence is that the skin of man must be thicker for mechanical protection, and this involves differences in structure and cell renewal rates, as well as a change in activity for the oily skin glands. Also, because the sensory function of hairs was largely lost, a revised distribution of skin sense organs was necessary. Finally, and most important, the skin became a thermoregulatory organ of great significance. To a greater extent than most mammals, man controls the rate of radiant heat loss from the skin by controlling the flow of blood through the skin. This has led to a very elaborate network of superficial blood vessels, together with a delicate but equally complex system of nervous and humoral control. Finally, in a poorly understood general way human skin tends to reflect the state of the central nervous system. This is not only true for more obviously psychogenic responses like blushing (every blush is a fleeting rash), but it is also true for the influence of the mind on the skin, as illustrated in any textbook of psychosomatic medicine. A Mantoux reaction can be inhibited by direct suggestion under hypnosis, presumably by an effect on the vascular contribution to the response (11).

Thus, the nakedness of man has given his skin important protective, sensory, and thermoregulatory adaptations which, taken together, make human skin unique. Interestingly, the skin of the domestic pig has points of resemblance to that of man, but there are at the same time fundamental differences, both in vasculature and in skin glands (95). Human skin, in constant close touch with the outside world, is both sensitive and reactive, and it has been graphically described as a “turbulent tissue” (94). It is this turbulent reactivity, perhaps, which often makes human skin respond more vigorously than the haired skin of animals to virus infections, as well as to other disease agents. Skin lesions are of course a feature of many virus diseases of animals, but these lesions tend to be on exposed hairless areas where the skin has the human properties of thickness, sensitivity, and vascular reactivity. Hence, although rashes may involve the general body surface of animals, it is udders, scrotums, ears, preputes, teats, noses, and paws that are
more regular sites for lesions. For instance, the closely related diseases of measles, distemper, and rinderpest can be compared. In rinderpest, areas of red moist skin, perhaps representing a confluent eruption, with occasional vesiculation, are sometimes seen on the udder, scrotum, and inside of the thighs. In distemper, the exanthem is said to be seen on the abdomen and inner aspect of the thighs in 50% of cases, but there has been some uncertainty as to whether it is in fact due to the virus (23, 29). Yet, in human measles one of the most florid and characteristic rashes known occurs, involving the general body surface. Even in susceptible monkeys, the same virus produces skin lesions sparingly and irregularly.

Mucous membranes are also a site for lesions, and are important in shedding infectious virus, but human mucosae do not differ in any important way from those of most other mammals. Accordingly, enanthems are equally a feature in animal and human virus diseases.

The mucosal lining of the alimentary canal, like the skin, is an epithelial structure, and, because it is composed of naked living cells, it is in some ways even more intimately exposed to the external world. The localization of circulating viruses in intestinal epithelium would presumably take place according to the same general principles as those discussed for the skin. The intestinal epithelium is probably often infected during virus diseases, but there may be no signs of infection until the appearance of gross symptoms like diarrhoea, which is seen, for instance, in distemper in dogs (30), in cattle infected with rinderpest virus (120), and even in measles (96). Little is known about the development or incidence of these enteric lesions. Doubtless the thinness of the epithelial surface, the high rate of cell shedding, the ubiquity of other microorganisms, and the mucus-lined, fluid surroundings, would give such lesions their special character.

The above comparisons of lesion sites in man and in animals highlight our ignorance of the factors governing the distribution of skin lesions in different virus diseases. This lack of understanding can be illustrated when we ask why foot-and-mouth disease virus, even when it infects man, produces lesions on the feet, hands, and mouth (40), or why the agent of Fort Bragg fever gives skin lesions almost restricted to the pretribal region (130). Attention is thereby drawn to the importance of local differences in the skin and hairs, sebaceous glands, vascularity, dermo-epidermal junctions, or epidermal thickness, which may vary widely in different regions (104). Any of these differences could lead to differences in the localization of virus, the growth of virus, or the production of lesions. For instance, Lewis and Harner (77) charted in a child's leg the local variations in vascular activity which are the basis for skin mottling, and they were able to show that a measles rash involved the areas where blood vessels were more dilated.

The work of Lewis on the vascular responses of human skin (78) illustrates forcibly the power and importance of clinical observation. Important facts and clear clues to principles may emerge from such observations, as has been seen in the recent work on agammaglobulinemia (48). Clinical observations have already provided many clues whose significance we have so far failed to understand. For instance, it is known that tuberculosis is activated by measles, that tuberculin-positive patients become tuberculin-negative for 1 or 2 weeks after a measles eruption (17), and that a measles rash appears early and severely at the site of a recent positive tuberculin skin test (118). In both diseases, macrophages play an important part and giant cells are formed. May not important principles lie hidden in observations such as these? Again, it has been reported that when lepers are vaccinated there is a generalized activation of leprous skin lesions, and the vaccinia skin lesions themselves are particularly severe (24, 55). Also, why is it that the pyrexias of smallpox, tuberculosis, primary atypical pneumonia, and brucellosis fail to activate latent herpes simplex and give cold sores (9)? The clinician, as well as the biochemist, pathologist and immunologist, will assuredly remain of fundamental importance in advancing our understanding of rashes.

**Summary**

The subject of the pathogenesis of rashes in virus diseases has been surveyed and discussed. Although this is an old and at present unfashionable subject, recent advances in immunology, experimental pathology, and the pathogenesis of virus diseases seemed to justify a collecting together of information and a restatement of problems in modern terms.

A preliminary section deals with the initiation of infection in the skin, including the mechanisms of infection by biting arthropods.

The localization of circulating viruses in skin blood vessels is discussed at some length. Circulating inert particles appear to localize in blood vessels in the apparently normal skin of animals, and leukocytes pass through vessel walls into tissues during the normal course of their wanderings. The localization of free and leukocyte-associated viruses in skin blood vessels is surveyed in the light of these findings. The characteristic distribution of skin lesions in different virus
exanathema remains a mystery, although there is some understanding of the mode of action of localizing factors.

The spread of the infectious process after the initial localization of virus in dermal blood vessels is discussed. In some infections, the lesion remains restricted to the vicinity of the blood vessel, and the pathogenesis of the hemorrhagic fevers is surveyed. The part played by the ground substance in the spread of infection through the dermis is examined. Infection of the epidermis is discussed, the possible role of melanocytes is considered, and the pathological response in the epidermis is briefly referred to.

A large section is devoted to the role of the immune response in the pathogenesis of skin lesions. Recent work appears to support some of the suggestions made many years ago, but in most viral rashes it is still not possible to assess the relative importance of direct cell damage by viruses, nonspecific inflammatory changes, viral toxins, and the immune or allergic response.

In a speculative attempt to account for the absence of rashes in many generalized virus infections, those infections with rashes are briefly classified and the pathogenesis of the rashes is surveyed.

In the discussion differences between the occurrence of rashes in man and in animals is commented on in relation to the uniqueness of human skin. The production of lesions in mucous membranes and in the epithelium of the alimentary canal is referred to. Finally, our basic ignorance about rashes is reaffirmed, and, since rashes are seen in man rather than in animals, attention is drawn to the continued importance of clinical observations.

LITERATURE CITED


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