all the others, and, on the whole, for good reasons. The average health of the single is probably lower than that of the married, and may in itself be the reason for remaining single. The expectation of life for a married man 25 years of age is nearly five years more than for a bachelor of the same age.

It may sometimes happen that the family physician is consulted with respect to the marriage of a patient who has had a psychosis. As a general rule it should be regarded as a most unwise adventure, for a psychosis may be of the periodic variety, known as the manic-depressive psychosis, in which attacks will occur throughout life with complete remissions between. It is these very remissions which make marriage a great peril in the neuropathic. An isolated attack may occur, especially after a great shock, and will not repeat itself even after many years. In a person who has had such an attack and is in obviously good physical health, with no definite stigmata of degeneration, such as cranial anomalies, deformities of the pinna and palate, and marked hyperextensibility of the ligaments, it would seem unnecessarily hard to refuse sanction.

Trauma would appear to be an almost negligible cause of mental disease, so rare is its occurrence. It is more likely to be followed by a neurosis, and even in this respect its liability is grossly exaggerated by the public. The experiences of the war proved the extraordinary resistance of the brain to external injury; and, indeed,

the highly skilled art of the brain surgeon, for which art I have the greatest respect and admiration, has proved it again and again. He has shaved off portions of the cortex, incised the substance of the brain, probed it, extracted neoplasms from it, and even blown air into it. Notwithstanding all these things, he has the satisfaction of seeing his patient recover from the anaesthetic with a sane mind. It is only when the cortex is affected widely, usually in some insidious manner by a toxin, that we get symptoms of mental disease.

This short paper cannot hope to cover all the ground in the causation of mental trouble. The psychogenic causes have been omitted purposely, for, as a rule, they are not within the province of the family physician. I have tried to bring before you certain physical disabilities which are at least very common accompaniments of mental disorder, and which I believe to be of the greatest importance in its production.

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VIRUSES AND SKIN DISEASES*

BY

R. T. BRAIN, M.D., M.R.C.P.

ASSISTANT PHYSICIAN, ST. JOHN'S HOSPITAL FOR DISEASES OF THE SKIN;
 CLINICAL ASSISTANT, SKIN DEPARTMENT, LONDON HOSPITAL
 (From the Freedom Research Laboratory, London Hospital)

The investigation of virus diseases is beset with peculiar difficulties. Viruses are either ultra-microscopic or if anything particulate is seen its nature is disputed. With one possible exception no virus can be grown apart from living cells, and therefore the cultural and biochemical methods of bacteriology are unavailable for the study of viruses. This essential association with living cells makes difficult the conclusive proof of life in these minute or unorganized agents, and a further difficulty is that in many cases a suitable experimental animal is not available either. It is not surprising, therefore, that the earliest direct evidence of the existence of viruses came from pathological studies of plants and animals, although Pasteur had suggested that agents of this type might be the aetiological factor in certain diseases, as hydrophobia. Iwanowsky (1891), working on the mosaic disease of tobacco plants, was the first to demonstrate the infectivity of a bacteria-free filtrate of an extract of diseased leaves, and Loeffler and Frosch (1898) obtained corresponding results in the case of foot-and-mouth disease, even though their filtrate was culturally sterile and contained no visible micro-organisms. Evidence has accumulated to the effect that more than a hundred diseases of animals and plants are now attributable to disease-producing agents, which have the following peculiarities.

PECULIARITIES OF VIRUSES

1. They are either ultra-microscopic or may be recognized as minute particles up to 0.25μ in diameter. The smallest discrete particles are called elementary bodies, but larger forms possibly occur. In the case of psittacosis virus, at any rate, Bedson and Bland (1932) have demonstrated a cycle of development in which the particles vary greatly in size so that forms larger than some bacteria occur and masses of aggregated particles or of undivided virus produce plasmodial forms.

* Read in opening a discussion in the Section of Dermatology at the Annual Meeting of the British Medical Association, Dublin, 1933.

2. Dependent upon the minuteness of the particles is the property of filterability as compared with the bacteria. Obviously the larger forms of viruses would not be filterable; on the other hand, some of the leptospira are.

3. A peculiar histological feature is commonly associated with virus infections. This is the presence in the lesion of curious intracellular bodies—the so-called “inclusion bodies”—which occur either in the cytoplasm or in the nucleus.

4. The inability to grow in cultures in the absence of living tissue cells.

Some of these points are worthy of discussion. In the first place, it is still a matter of dispute as to whether the minute particles described are actually the virus or whether they are non-specific granular-cell products on which the virus, something unorganized, is adsorbed. Recent experimental work has strongly supported the identity of these minute bodies with the virus. Woodruff and Goodpasture (1929, 1930) demonstrated the infectivity of isolated and washed Bollinger bodies—the inclusions of fowl-pox—which consist of collections of elementary bodies; and Ledingham (1931) showed that these elementary bodies, and those of vaccinia too, could be flocculated in the presence of specific antiserum. Bedson (1932) has found that it is possible, by means of high-speed centrifugation, to concentrate and wash the elementary bodies of psittacosis, controlling the operation by direct observation, and then demonstrating their infectivity, specific agglutination, and ability to fix complement specifically. This is very strong evidence that the minute bodies are the virus. One can only escape this conclusion by assuming that the virus is adsorbed on tissue particles, but against this must be placed the observation of Bedson that the particles do not react specifically with an appropriate anti-tissue serum. Further, these experiments strongly support the conception that viruses are living organisms, and it is not proposed to discuss the more elaborate thesis of Sanfelice (1914) that a virus is a non-living poison produced by living cells which is capable of attacking new cells. Suffice it to say that viruses exhibit the essential characteristics of living organisms—for example, multiplication, adaptability, preservation of identity, antigenic properties, and sensitivity to antiseptics.

Filterability was originally the essential criterion of a virus, and as this implies a simple grading according to the size of the particles there is at first sight much to commend it. Inconsistent results were, however, not infrequent, and whereas some visible organisms were found to be filter-passers, smaller virus particles were sometimes retained in the filter, presumably by adsorption. In spite of complicating factors there remains no better approach to the investigation of a suspected virus disease than by the historical route of filtration. If a culturally sterile bacteria-free filtrate of an extract from a suspected lesion can reproduce a similar lesion in a susceptible host then the inference of a virus infection is a very strong one.

INCLUSION BODIES

Much attention has been paid to the inclusion bodies which characterize many virus lesions. These bodies consist of intracellular masses of hyaline or granular material—usually acidophilic, but in some cases basophilic. Three theories are put forward to explain their nature:

1. That inclusion bodies represent a stage in the life cycle of viruses analogous to certain protozoa (Calkins, 1904). The work of Bedson and Bland (1932) gives some support to this view.

2. That the minute bodies are the virus and that the larger inclusions are cellular products (Paschen, 1908).

3. That they represent colonies of virus (minute bodies) which, as a result of the cellular reaction excited by their presence, become enveloped in some plastic material produced by the cell (von Prowazek, Lipschütz, da Rocha-Lima).

Goodpasture (1929) discusses this problem in detail with special reference to the group of animal poxes (variola, vaccinia, sheep-pox, fowl-pox, and molluscum contagiosum). He concludes that the infective agent is a minute rounded, uniform micro-organism, presumably capable of invading cells and growing in them, and that the inclusion bodies consist of masses of these small bodies suspended in a hyaline matrix which is either the product of the cell or of the virus itself. Ludford (1924-5) draws attention to a point which it is well to bear in mind when endeavouring to interpret virus lesions in epithelium. The epidermis is largely avascular, and consequently its cells are unable readily to get rid of waste products. Added to this, these cells are undergoing keratinization, with consequent nuclear and cytoplasmic degeneration. These factors result in epidermal cells containing a host of granules of different kinds, which may readily mislead the unwary in search of virus bodies. The greatest caution must be exercised in the interpretation of the histological picture presented by such lesions.

Typical cytoplasmic inclusions occur in the animal poxes and in ectromelia, a contagious disease of mice. The intracellular virus masses occurring in psittacosis, though not presenting the characteristic picture of the typical inclusion, are probably of the same nature. Nuclear inclusions occur in herpes, zoster, varicella, and other virus diseases; variola gives rise to inclusions in both cytoplasm and nucleus. Little more need be said about the inability to cultivate viruses apart from living tissues. The fact has been established for many typical viruses, and the organism of bovine pleuro-pneumonia is the only unequivocal exception. This organism is readily filterable and has the minuteness of typical viruses, yet it may be cultured on horse serum without difficulty. It may be added that the failure to grow viruses on ordinary media is the greatest possible handicap to their study.

RESPONSES OF CELLS TO VIRUS INVASION

It will be inferred from these observations that a virus is essentially a parasite of a cell rather than of an individual, and it is of interest to note the various and peculiar responses of cells to the invasion. Once the

minute virus particle has penetrated the cell it may multiply in the cytoplasm or nucleus, or in both. Goodpasture (1929) has summarized the cellular changes which different viruses give rise to, and he points out the wide range of responses between the rapid necrosis of ectodermal cells in an herpetic infection of the rabbit's cornea and the slow and prolonged proliferation of epidermal cells induced by the virus of the common wart. Cells may be stimulated to a slightly increased rate of proliferation by one virus whilst another may provoke violent reproductive activity. In other cases the metabolism of cells may be altered and the stages of degeneration marked by changes in the nucleus. Again, another virus may alter specifically the morphology of cells, affecting their size and shape, and that these changes are due to the presence of the virus in the cell and not to secondary inflammatory effects has been shown by a number of workers. For example, in molluscum contagiosum the lesion in the epidermis may attain maturity without a reaction in the corium (Goodpasture).

As a rule, each virus has a predilection for one type of cell, and this has led to the use of the term "tropism" in relation to virus infections. Thus zoster may be said to be neurotropic whilst varicella and molluscum are epidermotropic.

Since the effects of a virus infection upon a cell may be seen as a degeneration or as a hypertrophy so two types of skin lesion may result:

1. *Toxic*.—The lesion may be an erythematous macule which becomes purpuric as in typhus, or urticarial as in measles, or papular and vesicular as in varicella and herpes. The vesicle may dry up or proceed to pustulation, and end in crusts or scales.

2. *Hypertrophic*.—Here the proliferation of cells produces a papule, nodule, or tumour, as in the case of warts and molluscum contagiosum.

FOUR DERMATOLOGICAL LESIONS

At present there are only four strictly dermatological conditions which are definitely established as virus diseases (herpes, zoster, molluscum contagiosum, and warts), and their well-known clinical features will be ignored, attention being directed to those facts and observations which justify their inclusion in this paper.

Herpes.—Experiments have demonstrated beyond doubt that bacteriologically sterile vesicle fluid after filtration is infective, producing characteristic lesions clinically and histologically in susceptible animals, and the condition can be passed in series. In the Freedom Laboratory of the London Hospital we have a strain of herpes which has survived more than a hundred passages in the guinea-pig. The virus is evidently ubiquitous, and human carriers are numerous. Direct evidence of this has been obtained by Levaditi, Harvier, and Nicolau (1922) and by Busacca (1924, 1925), who demonstrated the presence of the virus in saliva and in the conjunctival sac. Indirect confirmation of the carrier rate has been obtained by the discovery of herpetic antibodies in human serums. Using the technique described by Bedson and Bland (1929) I have shown (1932) that the complement-fixation reaction is a reliable test for the presence of herpetic antibodies in serums, thirty positive reactions being obtained in a group of thirty-two individuals having a definite history of herpetic infection, whilst entirely negative results were obtained in a group of sixteen individuals with no history of herpes. Out of fifty-two unselected cases 45 per cent. gave a positive fixation with herpes, and, as it is unlikely that a transient and trivial lesion of this type would account for the persistence of herpes antibody in the blood, a simple explanation is that the positive cases are carriers of the virus. Possibly a more sensitive test for the presence of virus antibody in serum is to mix the serum with a living virus suspension and after an interval to titrate

the virulence of the mixture in an animal. If specific neutralizing bodies are present in the serum the infective titre of the virus will be appreciably diminished or lost. Neutralization tests, as they are called, have been employed with herpes virus and normal serums, and the results reported are given below:

		Percentage giving Neutralization
Zinsser and Tang	Normal adults, 17	58
ditto	.. children, 23	43
Andrewes and Carmichael ...	.. adults, 28	75

These figures suggest that 50 to 75 per cent. of normal individuals are carriers of herpes virus. Immunity against herpes is doubtful in man, but usually marked in other animals. The pathological picture is typical of a virus infection, and it resembles that of the vesicular lesions of varicella and zoster. Minute acidophil intranuclear bodies occur in epithelial cells, and they have also been noted in the cells of the cornea, central nervous system, liver, testicle, and ovary. Apparently these small bodies increase in size and coalesce, and finally occupy the greater part of the nucleus, forming the so-called inclusion body. Some of the affected cells become swollen and show a reticular degeneration, whilst others, possibly irritated by the virus, are transformed by a process of amitotic nuclear division into large multinuclear cells. The affected epidermis and the adjacent inflamed dermis become infiltrated with leucocytes, and a serous exudation dissociates cells and collects beneath the stratum corneum, forming the vesicle.

Zoster.—Owing to the lack of a susceptible animal, transmission experiments with zoster have been confined to human subjects, but adequate proof has been obtained that a bacteria-free culturally sterile vesicle fluid can produce typical histological lesions in a high percentage of healthy children, and incidentally a few of the positive "takes" developed clinical varicella. The disease is infectious, for numerous cases have been reported of zoster contacts developing chicken-pox, and much evidence has now accumulated to the effect that the two diseases are caused by the same virus.

A brief summary of the supporting evidence now follows:

1. Kundratitz (1925), Seigl (1927), and Bruusgaard (1932) produced clinical and histological chicken-pox by the inoculation of zoster vesicle fluid into young children. Several healthy contacts of these cases developed clinical chicken-pox after the usual incubation period. Further, children who had had chicken-pox were insusceptible to the inoculation of zoster vesicle fluid, and those who had recovered from the experimental zoster infection were found to be immune to inoculation with chicken-pox vesicle fluid.

2. Using the crusts of zoster and chicken-pox as antigens Netter and Urbain (1931) have investigated the serums of convalescents from these diseases for specific antibodies by the complement-fixation reaction, and their findings suggest that all cases of zoster (idiopathic and symptomatic) and varicella are due to the same virus.

With different antigens (vesicle fluids) and with a different technique I have confirmed the work of Netter and Urbain (Brain, 1933) but of course these serological tests do not furnish direct evidence, although they suggest the close relationship and possible identity of the viruses of zoster and varicella.

It has been suggested that the mechanism of infection from a case of zoster is that the virus reaches the mucous membrane of the upper respiratory tract of the contact, and from there it more readily invades the blood stream than the central nervous system, thus producing chicken-pox rather than zoster. Probably a number of individuals carry the virus dormant in the central nervous system,

where it is activated by nerve injury and, reaching the skin via the affected nerves, produces an eruption in the area supplied by them. The histological changes in the skin are exactly similar to those seen and previously described as occurring in herpes. Acidophil inclusion bodies, "Zoster körperchen," are present in the nuclei of the cells of the vesicle epithelium, and also in connective tissue cells and capillary endothelial cells of the dermis (Lipschütz). The characteristic lesions in the central nervous system have been recognized since the brilliant description of them by Head and Campbell of the London Hospital in 1900. The immunity against zoster is usually solid and lasting.

Molluscum Contagiosum.—The infectious nature of this disease was first demonstrated by Paterson (1841), and this has been amply confirmed. Juliusberg (1905) showed that the infective agent could pass through a Chamberland filter, and the experimental incubation period was fifty days. Filterability with other types of filter was later reported. The disease is pathogenic only in the case of man, infection probably occurring at baths and in schools, and possibly through the agency of parasites. The incubation period varies from five weeks to six months. Growth is very slow, four to six months being the usual time for a lesion to attain 1 mm. in diameter. The lesions are probably disseminated by auto-inoculation. Nothing has been reported of its immunological reactions, but by means of the complement-fixation reaction and using suspensions of elementary bodies prepared from curetted mollusca I have demonstrated the presence of antibodies in the serum of a patient with multiple lesions. The agglutination reaction was negative. The experiments await publication. Peculiar histological features were noted by Henderson (1841) and Paterson (1841), who were the first to describe certain large oval hyaline bodies which were seen in the superficial layers of the epithelial nodules. These molluscum bodies were thought to be protozoal in nature. In the development of a molluscum the first cellular changes are seen in the deepest cells of the stratum mucosum. In the cytoplasm of these cells numerous small vacuoles appear with minute peripheral granules (about 0.25 μ), and it would appear that these granules are the elementary virus bodies (Lipschütz), for they become numerous and fill the vacuole, and ultimately fuse to form an oval hyaline body which fills the cell and displaces the nucleus. Smears from these hyaline bodies show that they consist of aggregations of minute bodies, and Goodpasture (1927) considers that these elementary bodies are morphologically consistent with a living filter-passing micro-organism developing about and within cytoplasmic vacuoles which may be regarded as the cellular response to the invader. The affected cells and their nuclei become enlarged, and degenerative changes finally destroy their identity, leaving collections of molluscum bodies alone; but before this happens a cellular proliferation occurs producing blunt, lobulated downgrowths of the epidermis, which elongates and compresses the papillae so that eventually the latter are represented as thin, fibrous septa between the lobules. In the fully developed lesion a cavity appears near the surface at the centre of the nodule, and gradually extends downwards into each of the lobules; this cavity contains the hyalinized "molluscum bodies." The lesion is surrounded by a layer of fibrous tissue, and inflammatory changes are slight or absent.

Warts.—It is believed that the common wart, with its plane, digitate, and filiform variations, the plantar wart, the senile or seborrhoeic wart, and the moist or fig wart are all manifestations of a virus infection. Variot (1893) reported the first successful inoculation of a wart from a child to an adult, and the infectivity of warts has been established by similar experiments. Cuiffo (1907) showed

that the infective agent could be filtered, and his work was confirmed by others, the usual incubation period being one to eight months, probably depending upon the susceptibility of the individual. Filtrates from condylomata acuminata were also found to be infective. Immunity to the virus has been demonstrated, and its spontaneous development probably accounts for the sudden disappearance of lesions. Acidophilic bodies in the cytoplasm and basophilic ones in the nucleus of affected cells have been described as inclusion bodies. Histologically there is evidence of active proliferation of cells in the Malpighian layer, resulting in the formation of a surface projection and in elongation and widening of the interpapillary processes, with thickening of the stratum corneum. The amount of cellular infiltration and inflammatory reaction varies widely, and is most marked in the case of moist warts. It is probable that the clinical varieties enumerated depend upon the following variable factors:

1. The reproductive activity of the germinal layer.
2. The degree of acanthosis.
3. The degree of corneous hypertrophy.
4. External influences such as pressure, humidity, and friction.

CONCLUSION

I am aware that there are many omissions in this brief paper, and I have not mentioned the effects of physical and chemical agents upon viruses, nor have I discussed general problems of immunity. With regard to the latter it is perhaps worthy of remark that there is no real difference between viruses and bacteria. In other words, the immunity which follows recovery from virus infections is just as variable between diseases as that following bacterial infections.

To conclude, I would like to associate myself with Goodpasture when he deplores the abuse of the group of virus diseases as a repository for all sorts of nondescript and ill-defined conditions of unknown aetiology and indefinite pathology. There are a number of common dermatological conditions the origins of which are completely obscure, and naturally the viruses are suspect. However, since Pasteur's suggestion more than fifty years ago that some diseases might be due to ultra-microscopic organisms, there is no originality of thought in incriminating a virus without supporting evidence.

I am very happy to acknowledge my indebtedness to the London Hospital for the research facilities and the financial assistance its Research Fund Committee has so generously afforded me. I have been working on certain aspects of virus diseases under the direction of Dr. S. P. Bedson in the Freedom Research Laboratory of the London Hospital since November, 1930, and my acquaintance with these problems and my few contributions to the solution of some of them are alike due to much instruction and expert help from Dr. Bedson. I record these facts because they account entirely for my present part in this discussion, and for these reasons I regard the implied distinction as something impersonal.

In composing this paper I have drawn largely from the volume on virus diseases produced by the Medical Research Council and also from the excellent paper by Goodpasture on cellular inclusions and the aetiology of virus diseases. The numerous references given in these two sources are omitted from the list below.

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NASAL GRANULOMATA*

BY

PATRICK DEMPSEY, F.R.C.S.I.

SURGEON FOR DISEASES OF THE THROAT, NOSE, AND EAR, MATER MISERICORDIAE HOSPITAL, DUBLIN

Tumours mainly composed of granulation tissue may occur in any region of the body. They are not commonly met with in the nasal cavities, but certain varieties, when present, are of great interest to the rhinologist. From the point of view of histology their general structure is always broadly the same, though certain differences in detail may be present, which will depend on the aetiology of the tumours. According to Baum¹ all granulomata present "collections of rapidly growing blood vessels whose walls are formed by a single layer of epithelium supported by a stroma of young connective tissue containing many cells." In addition, however, the growth may present a specific or infective organism, which will definitely decide the nature of the tumour.

For the purpose of this discussion I shall first describe granulomata which show no specific organism to either histological or bacteriological examination. This class, which in structure corresponds most closely to pure granulation tissue, may be divided into two groups—simple and malignant.

SIMPLE GRANULOMA

Tumours of the first, or "simple," group may be met with in any part of the body; when occurring in closed cavities such as the abdomen or thorax they may grow to a huge size and closely resemble malignant growths in their behaviour and appearance. Prima² reports five such cases, three in the abdominal cavity, one in the thorax, and one on the back; owing, however, either to their enormous size or to their position complete removal was impossible, and treatment had to be confined to partial excision and packing. Histological examination showed these growths to be what he termed "chronic inflammatory granulomata," and it is of much interest that in each case the growth completely disappeared as a result of the operative intervention. Very extensive simple granulomata are not met with in the nasal cavities, for the reason probably that they produce symptoms which draw attention to their presence at an early date. When occurring they are usually due to trauma or the presence of a foreign body.

In the first instance they are most often post-operative, while in the second any of the more common varieties of foreign body may, as a result of inflammatory changes, become surrounded with granulation tissue to such an extent as to form a true tumour. Pearlman and Pilot³ report such a case, caused by strands of gauze which had remained in one side of the nose for a period of two years. They point out that granulomata due to foreign bodies often resemble polypoid growths, and have a distinct inclination to myxomatous changes. Giant cells with an enormous number of nuclei are usually found in the neighbourhood of the irritant. The diagnosis and treatment of such growths are not usually difficult.

MALIGNANT GRANULOMA

In the year 1896 McBride⁴ published a case of "rapid destruction of the nose and face in a young man of 28." It started as a pustule on the inside of the ala nasi, following a scratch from a finger-nail. The disease manifested itself as a steadily progressive phagedaenic ulceration, which resisted anti-syphilitic treatment and caused the death of the patient some nine months later. Histological

* Read in opening a discussion in the Section of Oto-rhinolaryngology at the Annual Meeting of the British Medical Association, Dublin, 1933.