

disease of the same kind. In the cases he has seen, he has thought that we had an explanation in the anatomic asymmetry so frequently found in the body. We may have asymmetry of the optic nerve. We do not often have perfect symmetry. All have probably observed that in the vessels of the retina we find a certain condition of thickening of the arterioles of one eye and not a corresponding condition in the other. We know that we may have atheromatous conditions, or arteriosclerosis, affecting some parts of the body and not others. Why should it not be so in the eye? The condition may exist in one radial vessel and not the other. The same explanation may apply in these cases, particularly in some of the cases of unioocular neuro-retinitis. Whether it has any bearing on the ultimate prognosis he did not know.

DR. GEORGE E. DE SCHWEINITZ, Philadelphia, referred to unilateral optic neuritis with a swelling of at least two diopters. These cases, which have been referred to so extensively in the literature, are not at all uncommon. They are conveniently classified into four groups: 1. Unilateral optic neuritis due to brain tumor and other intracranial causes. 2. Unilateral optic neuritis due to certain well-known infections—the so-called unilateral forms of infectious optic neuritis of Uthoff's classification. 3. Unilateral optic neuritis due to local causes, for example, diseases in the neighborhood of the optic foramen or the contiguous sinuses. 4. Unilateral optic neuritis due to conditions associated with the vascular supply, for example, arteriosclerosis and endophlebitis. There are certain types of unilateral retrobulbar neuritis which may precede or follow facial palsy, and there is a similarity of anatomic surroundings of the optic foramen and the Fallopian canal as referred to in Green's paper on this subject. Dr. de Schweinitz agreed with Dr. Wilder's explanation which determines for anatomic reasons a unilateral instead of a bilateral neuritis and agreed that it is not a disease entity, but a local manifestation.

DR. MELVILLE BLACK, Denver, called attention to the value of the estimation of blood pressure in these cases. It has been found that where the tension is high its reduction by proper medication will do much toward bringing about recovery from the condition. It seemed that the universal use of iodid of potassium might have been due largely to its effect on the blood tension.

DR. A. A. HUBBELL, Buffalo, agreed with Dr. Wilder and Dr. de Schweinitz. He thought Dr. Herron had applied cases that are not in this category. He had taken into consideration the diseases of the contiguous sinuses and the results of arteriosclerosis, and thought that arteriosclerosis is perhaps one of the best explanations we have for most of these cases. As to Dr. Kipp's suggestion, it might apply in some cases, but he had not felt that a choroiditis had any relation to this condition.

THE RELATION OF NERVE IMPULSE TO CUTANEOUS INFLAMMATION.*

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Of the many unsolved problems in the pathogenesis of skin diseases there is one which, by reason of the broad applicability of the points involved, is of pre-eminent importance, namely, the relation of the nervous system to cutaneous inflammation. To illustrate the diversity of opinion and general confusion which obtains on this subject a few instances may be cited. There is a condition called by the French *névrodermite*; it is regarded by them as a distinct disease entity of nervous origin, but by American dermatologists the pathogenesis given is not accepted and, therefore, the condition is scarcely recognized. The adherents of the Vienna school speak of *neurotische* or *reflectorische Entzündung* or *Dermatitis*, thereby conceding that an inflammatory lesion may have a nervous cause. Turning to authorities in our own

language, a striking example of obscurity with respect to nerve relations in pathology is to be found in the textbook of a prominent author.¹ He devotes one short paragraph to the pathology of herpes progenitalis as follows:

"The presumption is in favor of the disease being due to a reflex irritation of the neighboring sympathetic ganglia through irritation of the sensory nerves of the part."

Far from being a clear-cut and complete elucidation of the pathology of the disease in question, this meager statement really throws no light on the subject, and coming, as it does, from an eminent authority its very deficiency in this respect makes it a confession of general lack of understanding of nervous relations in cutaneous inflammations.

These three citations: the *névrodermite* of the French, the *reflectorische Dermatitis* of the Vienna school, and the instance of vaguely expressed pathology of herpes, as understood by a great dermatologist, suggest the propriety of an inquiry along certain lines of pathogenesis in which the nervous system is a prominent factor. This inquiry may be introduced with a consideration of the Vienna idea. It is observed that the skin of an individual suffering with an acute localized dermatitis is often subject to a sudden outburst of a similar type elsewhere without an apparent external cause. These secondary appearances are regarded as reflex in origin, the explanation being that, in the absence of other causative factors, the nervous system acts as the effective intermediary agent in the spread of the disease from the primary area.

Analyzing this conception, the use of the term reflex is first to be considered. If its application be in a general sense only, without reference to any pathogenic relationship, its use, however convenient, is not to be commended, since the word reflex has a definite significance in medical parlance; if not used in conformity with this significance, it becomes at once misleading. On the other hand, if the term is intended to express a distinct etiologic fact, to show in a concise word a definite pathogenic relation, then its use postulates a certain proposition, the proof of which may properly be demanded, though perhaps not easily given.

By the expression dermatitis we understand, in a broad sense, an affection of the skin characterized by the clinical manifestations of inflammation. The term reflex as understood in medicine defines a physiologic complex, of which certain nerve structures and nerve impulses constitute the necessary elements. This complex in detail is as follows: An impulse passes along an afferent (sensory) nerve to a center whence it is reflected along an efferent (motor) nerve to a peripheral part, causing eventually some organ to perform its function. In the light of these definitions a reflex dermatitis may be said to be an inflammation of the skin the result of reflex nerve action; or, more strictly, of efferent nerve impulse, since that portion of the reflex act comprising the afferent or sensory impulse ends with the receiving center, and, irrespective of the nature of the stimulus producing it, is incapable of changing the fixed character of the efferent or motor impulse. From these considerations we are able to formulate the broader proposition, namely, that the pathogenic process called inflammation can be initiated through the medium of motor-nerve impulse alone.

This is a postulate which underlies the *névrodermite*

* Read in the Section on Cutaneous Medicine and Surgery of the American Medical Association at the Fifty-seventh Annual Session, June, 1906.

1. Crocker: Diseases of the Skin, third edition.

of Brocq and Jacquet.² Its presence may be traced in a very appreciable portion of dermatologic thought today, because it lends itself so readily to the support of an obscure pathogenesis, a fact well illustrated in the quoted paragraph on herpes. It is a postulate which calls for proof. Its use and abuse will not diminish so long as its validity as a premise is accepted. But that validity is not so easily established as casual thought would expect; it is, therefore, in the interest of scientific accuracy in dermatology that the question be made a subject of discussion.

The problem, then, is this: Can the process of inflammation be produced by nerve impulse alone? Has a motor impulse, having its source in the conversion at a receiving center of a sensory impulse from the periphery, the power of creating the inflammation complex? If these questions be answered in the negative, another arises: What additional elements are necessary to bridge the gap between the factor nerve impulse, sensory and motor, and the result inflammation?

Clinically, inflammation is recognized by the so-called classical symptoms—*rubor, calor, tumor* and *dolor*. These constitute the surface manifestations of a complex series of changes taking place within the tissues, in which the blood and its constituents, the blood vessels, and the fixed tissue elements all participate. The various steps in the process, approximately in the order of their development, may be described as follows: There is first a dilatation of the blood vessels; this is succeeded by a slowing of the blood current, with margination of the leucocytes; next occurs a passing outward of the white blood corpuscles and the fluid elements of the blood, with a varying number of erythrocytes, through the vessel walls into the surrounding tissue, thus forming an exudate; lastly, proliferative changes occur in the fixed tissue of the part.

A question here suggests itself: What is the essential element in inflammation? Or expressed in another form: Which one of the steps above enumerated must necessarily be present in order that the condition may be termed correctly inflammation? The answer must take into consideration the purpose of the process. Though regarded as a manifestation of disease, it is in itself unquestionably a conservative measure, having for its purpose, first, the removal from the organism of irritants which threaten the safety of the whole or its component cells, and, second, the repair of any damage that may have resulted. Such removal may necessitate actual destruction of the irritant by phagocytosis, its dilution or neutralization by exudate, or its encapsulation by connective tissue; repair is accomplished by proliferative changes in the tissue which has suffered injury. The process of inflammation fulfills these requirements. The comparative value of the changes may be studied in avascular structures.³ If the epithelium of the center of the cornea be damaged to a very slight degree, degenerative changes occur in the corneal tissue in the immediate neighborhood, but repair takes place without accumulation of leucocytes. If the injury be greater, repair is preceded by a massing about the lesion of leucocytes drawn, not from the circumcorneal blood vessels, which remain unaffected, but from the free wandering cells of the tissue. If, however, the injury done be severe, the vessels nearest the lesion dilate, diapedesis of leucocytes takes place, and fluid accumulates in the tissue. These findings would seem to indicate that in

the work of repair and defense the impulse to proliferation ranks first and the migration of leucocytes second; vascular changes are subservient to the latter. It must be admitted, however, that authorities differ in their conception of inflammation. Metchnikoff⁴ holds that it is the response of the organism to external irritation; thus, he would regard the process which followed the first and second instances of corneal injury cited above as true inflammation. Heinz,⁵ on the other hand, considers that vascular changes are necessary and would reject these instances as not inflammatory. While Metchnikoff's conception has more in it to commend itself, it is immaterial which of the two is correct, inasmuch as we are concerned with vascular tissues. It is significant that the migration of leucocytes and fixed tissue proliferation are common to both conceptions.

To determine the exact part taken by nervous impulse in inflammation, a further analysis of the stages given must be made.

I. DILATATION OF THE BLOOD VESSELS.

The calibration of those vessels which are supplied with muscular coats is known to be under the control of the vasomotor nerves. These are of two kinds: vasoconstrictors and vasodilator. Stimulation of the former results in vessel constriction; paralysis of the former or stimulation of the latter leads to vessel dilatation. The principal vasomotor center has been located by method of spinal-cord section in the floor of the fourth ventricle; subsidiary centers are present in the cord, in the sympathetic ganglia and on the vessel walls. The constrictor nerves pass through the lateral sympathetic ganglia to their terminations in the vessel walls; the dilators have their relay stations in the great ganglionic plexus of the thoracic, abdominal and pelvic cavities, whence they are distributed to the vessels. The innervation of those blood channels not provided with muscular coats, i. e., the capillaries, is not so clear. It was formerly believed that they were not under nervous control, but more recently it has been demonstrated⁶ that contractile cells are present in their walls, and that their lumen can be changed by stimulation applied directly or through the medium of the nerves. We are justified, therefore, in assuming that all vessels are under vasomotor influence. Such being the case, reflex action becomes a very important agent in the production of vessel dilatation in inflammation. Two other factors are to be mentioned as contributing to hyperemia: the loss of vessel tone due to direct paralysis of the muscular elements, and the diminution of extravascular tension before the development of large exudate. Both of these actions result from the local presence of toxins.

II. SLOWING OF THE BLOOD STREAM AND MARGINATION OF THE LEUCOCYTES.

Cohnheim,⁷ the discoverer of diapedesis and one of the earliest investigators of the phenomena of inflammation, observed that at first an acceleration of blood flow occurred, followed later by retardation. The arterial pressure and the vascular endothelium remaining unaltered, increase in the cross section of the vessel should result in acceleration of current; this, however, is soon neutralized by the action of other factors. Retardation has been explained in various ways: by increase of fibrin in

2. *La Pratique Dermatologique*, vol. 11.

3. Adam: *Allbutt's System of Medicine*, vol. 1.

4. Metchnikoff: *Comparative Pathology of Inflammation*.

5. Heinz: *Handb. d. exp. Path. u. Pharm.*, vol. 1, part 1.

6. Steinach and Kahn: *Arch. f. d. ges. Physiol.*, Bonn, xcvii, 105-133.

7. Cohnheim: *Vorlesungen über allgemeine Pathologie*, 2 Aufl., vol. 1.

the blood and by actual deposition of fibrin in the capillaries, by an attraction exercised on the blood by the surrounding tissue, which under the stimulus to hypertrophy requires more nutritive material, and by change in the endothelium of the vessel walls in the direction of greater viscosity. These theories are not easy of demonstration; that some sort of alteration occurs in the endothelium may be inferred from the subsequent act of diapedesis and secretion of fluid (since it is probable that the endothelium possesses a secretory function⁸). A change resulting from local toxic action must also be admitted. It can not be asserted positively that any alteration from these possible causes necessarily increases cell viscosity.

The margination of leucocytes is explicable, in part at least, by the law of hydrodynamics that the lighter bodies carried in a current seek the slower portions of the latter. The white corpuscles, of less specific gravity than the red, would drift to the periphery of the blood stream where the greatest retardation would occur. A second factor is to be found in chemotaxis, the physiologic property by virtue of which leucocytes are attracted or repelled by other substances. This action is exerted through the vessel wall and is due to the presence of an extravascular toxic agent. Leucocytic migration is independent of direct nerve influence.

III. DIAPEDESIS.

The leucocytes pass outward through the vessel walls as the result of several factors, the most vital of which are: first, the inherent property of certain white corpuscles of ameboid movements, and, second, the reaction of the leucocytes to the chemotactic influence of an extravascular irritant. To these may be added: the *vis a tergo* of the blood stream and the change in the cells of the vessel walls; both of these factors are necessary for the passing outward of the red corpuscles. The alterations in the vessel tissue comprise a thinning of the intercellular cement substance and a widening of the stomata marking the points of contact of several cells. Through these stomata, serum, leucocytes and red corpuscles may be forced by pressure alone; the attenuation of the intercellular substance and the altered consistency of the endothelium probably facilitate the migratory act of the leucocytes. The fluid portion of the blood reaches the exterior of the vessels through the stomata, as already mentioned, by the physical act of osmosis and probably by secretory action of the endothelium. Local toxic influences may favor osmosis by producing alteration in the cells of the vessel walls and by disturbing the isotonic relation between vessel content and perivascular fluids. Any secretory power possessed by the endothelia must be under direct motor nerve control.

IV. PROLIFERATION OF FIXED TISSUE ELEMENTS.

The replacement of destroyed tissue is accomplished by proliferation of the fixed cells of the part. The stimulus to this activity is to be found in the increased nutrition of the portion involved, and in that innate property of cells which causes them to multiply when there is a demand for cellular increase.

V. SUMMARY OF NERVE INFLUENCES.

In summing up the influence which the nerves are thus shown to have in the evolutionary stages of inflammation it must be borne clearly in mind that we are now concerned with those impulses which occupy the distal portion of the reflex arc only; that is, those which are

motor in nature. From what has been said we are warranted in affirming:

1. The dilatation of the blood vessels is very largely the result of direct nerve action.

2. The slowing of the blood stream and margination of the leucocytes is related to direct nerve action only so far as a secretory impulse to the vessel endothelium changes their physical properties; that is, increases their adhesiveness.

3. Diapedesis of leucocytes is in no way dependent on direct nerve action; it is favored by conditions to the development of which nerve action has contributed. The pouring out of fluid from the vessels is probably due, in part at least, to direct nerve action.

4. Proliferation of fixed tissue elements is not the result of direct nerve action.

From this summary we may conclude that motor nerve impulse *per se* does not suffice to produce all the phenomena of inflammation.

VI. INFLUENCE OF SENSORY NERVES.

The question arises: What part in the production of inflammation is contributed by the sensory nerves, the proximal arm of the reflex arc? The function of a sensory nerve in this connection can be nothing other than to transmit to a center an impulse received at its peripheral termination. That impulse can be influenced by the nature of the irritant which produces it only as regards intensity, and it can impart to the motor impulse at the reflex center no other quality than that of intensity. The sensory impulse, therefore, while a necessary part of the reflex arc, influences the process of inflammation only as it prompts a mild or an energetic motor action beyond the receiving center. Combining this conclusion with the one previously made, we have the answer to our first question: The phenomena of inflammation can not be produced by reflex action alone.

VII. FACTOR SUPPLEMENTING NERVE INFLUENCE.

From what has been said it is patent that some factor must operate to supplement nerve influence in the pathogenesis of inflammation. This factor must furnish an effective cause for the development of those steps in the complex which are not the result of combined sensory and motor nerve stimulation. Of these steps the most important is the migration of leucocytes, and, as this migration is dependent on chemotaxis plus the ameboid properties of the cells themselves, the factor necessary must embody the further requirement of chemotaxis; that is, the power of attracting leucocytes. This embodiment is to be found in the presence locally of an irritant.

If we seek to define more specifically the nature of the irritation thus required, we will find that all types may be classified, according to source, under four headings, namely, chemical, mechanical, thermal, and actinic. If now we consider the exact manner in which the various forms of irritation accomplish their work as provocators of inflammation, we must admit that the first, chemical irritation, includes them all. It is a mooted question whether a substance acting in a purely mechanical way induces inflammation because of the difficulty of eliminating a coincident bacterial infection. It must be accepted, however, that the products developed from the degeneration and destruction of protoplasm are capable of acting as chemical irritants, and that in mechanical injury, even of slight degree, by a perfectly sterile agent, these products appear *in situ* with power to incite inflammation. The same statement holds with respect to

⁸ S. Söhler: Jour. Experim. Med., vol. 5, p. 493.

the action of thermal and acutic agencies: the cellular degeneration and destruction which ensue result in the formation locally of substances, derivatives of protoplasm, which are inimical to the welfare of the unaffected tissue; hence inflammation occurs.

Given an area of skin within which a chemical irritant acts and we have all the necessary elements for the development of a dermatitis; there is a stimulation of sensory nerves, reflex response in vessel dilatation and cellular secretion, migration of leucocytes to the site of irritation, development of an exudate, and, lastly, repair of tissue destroyed. We find in chemical irritation, therefore, the answer to the second question: It is the factor needed to induce and to supplement nerve action in the production of inflammation.

With respect to the pathogenesis of the various types of herpetic disease it may be said that the theory of the development of toxins at the site of lesion as the result of cellular disintegration has not been given the attention it merits. Granting that degenerative changes have been found in the spinal ganglia and in nerve trunks at considerable distance from the herpetic eruption: these can not directly produce the latter by conducting, as it were the pathologic condition inflammation from one part of a nerve to its terminations, leaving the intervening section of the nerve trunk intact. The more rational explanation is that these changes in nerve ganglia and trunk modify in some manner the normal trophic impulses, thereby leading to necrotic or necrobiotic alteration in the part innervated where, as suggested by Blaschko,⁹ the products of disintegrating protoplasm alone suffice, without the help of secondary infection, to exert a local toxic action and to develop an inflammatory lesion.

SUMMARY.

To recapitulate:

1. The idea that nerve impulse alone can initiate inflammation is widespread in dermatology and forms the basis of the explanation of the pathogenesis in several conditions.

2. Reflex action is the form of nerve influence most frequently set forth as the originator of inflammation.

3. A reflex requires for its production two kinds of nerve fiber, sensory and motor, a receiving center, and a stimulus applied at a sensory termination. The sensory impulse thus created is converted at the center into a motor impulse which, passing to the terminations of the motor fibers, causes the organ innervated to perform its function. Any nerve impulse to be directly effective in producing inflammation through reflex action must be motor in nature.

4. Inflammation is a complex which when complete presents the following stages in its development: Dilatation of the blood vessels, slowing of blood stream and margination of leucocytes, diapedesis of cellular and fluid constituents of the blood, with formation of an exudate, and proliferation of fixed tissue elements.

5. Authorities differ in their conception of inflammation. In the broadest view taken, tissue proliferation is always present, migration of leucocytes usually is found, and vascular changes may occur. In the most restricted view, vascular phenomena must be present; in other words, all the stages enumerated must be found. Tissue proliferation and leucocytic migration, therefore, are common to all conceptions of the process.

6. Of the stages mentioned, direct motor impulse can

produce: dilatation of the blood vessels and secretion of fluid by the endothelium. It is possible that it may influence indirectly the slowing of the blood stream, the margination of the leucocytes, and the readiness of passage of the latter through the vessel walls. Motor impulse has no direct relation to the migration of leucocytes and proliferative tissue changes, and hence is not sufficient to produce inflammation unaided and alone.

7. The factor necessary to supplement nerve action must embody the requirements of chemotaxis, the power of attracting leucocytes. This embodiment is found in external irritation.

8. The four sources of irritation, chemical, mechanical, thermal, and actinic, by analysis, may be narrowed to one, namely, chemical. In chemical irritation reside all the essentials for the production of the full inflammation complex; it can initiate the requisite nerve action and can supply those factors which are necessary in addition thereto for the complete development of the process.

9. The products arising from the degeneration or destruction of protoplasm, whether from trauma, perversion of trophic nerve influence, or disturbance of cellular nutrition, may be toxic to living cells, and so furnish the chemical irritation requisite for the initiation of inflammation. This is probably the *modus operandi* in the various forms of herpes.

10. Finally, a purely reflex dermatitis is an impossibility, for the reason that every inflammatory skin lesion, because of the nature of the pathologic process involved, must have in its etiology the factor, local toxic irritation.

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PERSONAL EXPERIENCE IN PREVENTING SPREAD OF YELLOW FEVER.

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The control of epidemics of yellow fever has resolved itself into a very simple method, that of adopting measures based on the doctrine of the transmission of yellow fever by means of the *stegomyia* mosquito alone.

During the past summer a number of instances occurred in which an epidemic was controlled long before cold weather set in, but was not entirely eradicated. To entirely eradicate the disease from a community requires a prolonged campaign on the same lines and often waits for the aid of winter weather so inimical to the life of the mosquito.

It was my province to advise authorities in fever-stricken communities as to the best methods to be adopted in order to prevent an epidemic. In this it was always advisable to enlist the co-operation of the public, and for this purpose lectures were given explaining the method of spread of this disease by means of the *stegomyia* and the measures necessary to prevent its spread.

Probably the most serious task was to convince the people that the *stegomyia* mosquito was the only means by which yellow fever is spread. It was recognized that in order to be successful in carrying out the measures to be adopted an educational campaign must be instituted. The convincing experiments of Surgeon Walter Reed and his colleagues were explained and personal observations regarding the spread added much interest to the subject and gave added confidence.

9. Blaschko: Mrazek's Handb. d. Hautkrankh., vol. 1, art.: Herpes.