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ALLERGY AND THE NERVOUS SYSTEM

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## FOREWORD

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ALLERGY AND THE NERVOUS SYSTEM

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The role of the nervous system in allergic reactions has always been a subject of lively interest to investigators. Back in 1907 A. M. Bezredka suggested that the brain is the main reacting substratum in anaphylaxis in guinea pigs, which he proposed to call the anaphylactic shock reaction.

Development of the idea of nervism in our country (I. M. Sechenov, I. P. Pavlov) contributed to the subsequent detailed study of allergic reactions with various research techniques. The appearance of local allergic reactions on the skin, in muscles and other tissues following a greater or lesser degree of denervation has been fully investigated (D. N. Vyropayev, 1940; Yu. M. Lazovskiy and M. M. Kogan, 1939; Ye. V. Kolpakov, 1940). A large group of pathophysiologists used various pathophysiological methods to investigate the action of allergens as irritants of the nervous system (P. F. Zdrodovskiy, 1950; A. Ya. Alymov, A. D. Ado, 1952; A. N. Gordiyenko, 1953; L. M. Tshimova, 1954, and others).

Along with the accumulation of new data on the role of the nervous system in allergic reactions, attempts were made to formulate theories on allergic phenomena in connection with nervism. Two lines of thought may be distinguished. One (A. D. Speranskiy and his successors) was to the effect that the nervous system functions as an apparatus capable of reproducing an allergic condition in the organism without the participation of an allergen as a causative factor in the process. The other view (A. D. Ado, A. N. Gordiyenko, and others) emphasized, on the basis of detailed investigations, allergens as irritants of the nervous system, with attempts made to determine the way they act on its various parts.

An example of the first view is the work of A. A. Kanarevskaya (1937). In her experiments injury to the hypothalamus of dogs heightened their sensitivity to horse serum. Allergy against the background of these ideas was a variety of unusual "nervous dystrophy". Further extension of the ideas logically led to the need of denying the very existence of allergic reactions as specific reactions. There were even suggestions that the term "allergy" itself should be eliminated from the usage of theoretical and practical medicine. These ideas had peculiar repercussions in the clinic where allergic theories of the pathogenesis of many diseases (rheumatism, bronchial asthma, dermatosis, etc.) were contrasted with "neurogenic" theories. To some extent this approach fits in with the thinking of those investigators who regarded allergy as a constitutional reaction of the organism elicited by no concrete factors (Gebner, Rossle, and others). The effect was a temporary slackening of interest in allergy on the part of some physicians.

However, later more painstaking studies of the immunology and pathological physiology of allergic reactions clearly revealed the inconsistency in the above-mentioned view of allergy with respect to the ideas of nervism and I. P. Pavlov's theories. The extensive research of Soviet pathologicophysiology (N. N. Sirotinin, A. D. Ado, A. N. Gordiyenko, and others) on the phylogenesis of allergic reactions and on allergens as irritants of different parts of the nervous system showed that the nervous system together with other tissues is an area in which an allergen reacts with an antibody and that the products of this reaction are responsible for changing the reactivity of the nervous system in allergy. This trend in investigation of the role of the nervous system in allergic reactions is most fruitful. It should be emphasized that it originated and developed in our country alone and that the significance of the contribution of Soviet scientists was acknowledged by the Third International Congress on Allergy held in Paris in 1958.

The mechanism of allergic reactions consists of at least three stages: (1) immunological - reaction of the antigen with the antibody, (2) pathologicocochemical - release of biologically active products of allergic alteration of tissues, and (3) pathologicophysiological, during which stage the pathogenic action of the antigen and the products of its reaction with the antibody on various tissues - effectors - takes place. The nervous system is tissue the extent of whose involvement has now been shown for each of the above-mentioned stages in the development of allergic reactions.

The nervous system may be the place where antigens act and cause sensitization. Moreover, nervous tissue may itself be a source of allergens in the organism after various injurious allergens act on it. Antibodies may be elaborated (Ferrocci, 1935, and others) in nervous tissue, for example, in the brain. Finally, the allergic reaction of antigens with antibodies may well take place in this tissue.

The literature now abounds in data illustrating these forms of nervous system involvement in the mechanism of the initial or immunological stage in the development of allergic reaction. In this short article we can refer only to the most important of these reports.

A. M. Bezredka (1907) sensitized guinea pigs to horse serum, injecting it into the dura mater and into brain tissue. Cappelato (1938) sensitized the brain of guinea pigs. Alexander and Campbell (1937) observed allergic inflammation in the brain of sensitized guinea pigs after injecting them with challenge doses of horse serum. Repeated injections of an antigen into the brain of rabbits (Davidoff, Seegal and Seegal, 1936; G. Kh. Bykovskaya and M. B. Eydinova, 1935) and of dogs (Davidov and Kopelov, 1931) produced local changes of varying degree of severity depending on the duration of hypersensitization of the animal and number of sensitizing antigen injections. Davidoff and Kopeloff made similar observations in the case of monkeys. In A. D. Ado's experiments (1940) subdural sensitization of dogs and rabbits proved less effective than subcutaneous sensitization.

The role of nervous tissue as an auto- or homoallergen looms large in modern neurological and immunological literature. The development of allergic encephalitis, pathogenesis of multiple sclerosis, mechanism of complications in anti-rabies inoculations, and other lesions of the central nervous system are connected with the appearance in nervous tissue of autoallergens and their subsequent reaction with antibodies in the brain of man and animals. The most significant morphological expression of such changes in nervous tissue is demyelination. Similar encephalopathy has been noted in guinea pigs (Freund, Shtayng, and Zalin, 1947), rabbits (Morrison, 1947), dogs (Jervis, Burkhart, and Koprowsky, 1949), mice (Olitzky and Yager 1949), rats (Limfont and Kroyent, 1943) cats (Patterson and Brand, 1957).

Attempts have been made to induce experimental encephalomyelitis in various ways. V. K. Khoroshko (1912) immunized rabbits with emulsions of rabbit brain and obtained general and local allergic reactions. However, attempts to produce allergic encephalomyelitis in rabbits, guinea pigs, and monkeys by injecting emulsions or extracts of brain tissue into the brain did not in general yield positive results. For example, Stuart and Krikorian observed demyelination symptoms in only 23 out of 300 experimental rabbits. Much better results were obtained when experimental encephalomyelitis was induced by injecting emulsions of homologous brain with "conductors" (according to Freund). These last are a mixture of killed tuberculous bacteria with liquid paraffin and lanolin. Under these conditions Kabat, Wolf, and Bezer obtained infiltrations in 18 out of 19 monkeys after they were immunized with emulsions of brain tissue from monkeys and other animals (rabbits, chicks, etc.). The use of Freund's conductor enabled Jills and Kobrowsky to induce encephalomyelitis in 24 out of 30 guinea pigs 14 to 18 days after a single injection of an emulsion of guinea pig or rabbit brain tissue. Olitzky produced allergic encephalitis in white mice the same way. Lee and Olitzky also showed that sensitivity of mice to homologous brain tissues (with a stimulator) increases sharply after they are injected with whooping cough vaccine.

According to Morgan (1947), Kabat, Wolf, and Bezer (1952), and Loyzdan (1949), a challenge dose also induced allergic neuritis in monkeys, rabbits, and mice sensitized to homologous brain. It has been established that encephalogenic antigen is localized chiefly in the white matter of the brain (Morgan, 1947; Condie and Good, 1958) and is a protein lipid complex (Olitzky and others). Of special interest here is the research on the antigenic properties of brain tissues injured beforehand in various ways. Schwentker and Rivers (1935) observed that an autolysed brain or brain infected with vaccine virus possesses considerable sensitizing properties and is more likely to cause the formation of antibodies than a non-injured rabbit brain. Burky (1934), Frick (1950), Schwentker and Rivers (1935) reported on the increased antigenic properties of the brain after it is acted on by pig serumal proteins or vaccine virus. A. Kh. Kanchurin (1959) observed a marked increase in the allergenic properties of the brain of a rabbit infected with fixed rabies virus.

All these data indicate that the nervous system is tissue that can be sensitized by different allergens entering the organism from the external environment (exoallergens) and

that bacterial toxins, viruses, and other injurious agents can create secondarily in nervous tissue allergens of the type of autoantigens or complex antigens, which can also sensitize the organism and induce allergic reactions with the corresponding antibodies. Nervous tissue is not only the object on which allergens act, but also the source of their formation in the organism through the effect of different injurious agents reacting to it.

We know that the process of sensitizing any tissue is accompanied by the elaboration of antibodies. The question of whether brain tissue can elaborate antibodies has been answered in the affirmative by most of the investigators. They have based their conclusion on comparative studies of the effectiveness of immunizing animals in the brain and other tissues (subcutaneously, intravenously, etc) and on analyses of the antibody content of cerebrospinal fluid.

It has been established from several separate investigations that immunization in the brain is much more effective than other paths of immunization. This was shown in experiments on immunization to diphtheria anatoxin (A. V. Ponomarev, 1930), tetanus anatoxin (A. V. Ponomarev and V. A. Perrotti, 1935; O. I. Nikolayeva, 1940; D. G. Manolov, 1941), bacteria of the intestinal typhoid group (G. A. Pavlov, 1935). G. Kh. Gil'manova of our laboratory demonstrated that the maximum titer of hyaluronidase in rabbits following intracerebral injection of a culture of  $\beta$ -hemolytic streptococcus was higher than after intravenous injection. This difference was particularly marked during the spring. Immunization in the brain is associated with a relatively large antibody content in the cerebrospinal fluid, a factor regarded by the above-mentioned investigators as a proof of the local "cerebral" origin of these antibodies. Most of them also believe that antibodies are not elaborated by the nerve cells as such, but by the mesoglia (D. A. Shamburov, 1943; P. F. Zdrovskiy, 1950). It is a fair assumption that the effectiveness of intracerebral immunization is also due to the non-specific stimulating influence of this action on the nervous system with subsequent activation of the reticuloendothelial and lymphatic systems of the entire organism through the neurotrophic effect of the brain irritated by immunization (A. D. Ado, 1952). We must add that brain tissues can obtain antibodies from the blood by their passage through the encephalitic barriers (K. I. Matveyev and S. K. Sokolov, 1946; T. I. Bulatova, 1951; Kafka, 1953; Petronelle, 1955; and others).

Thus, brain tissue is susceptible to the sensitizing action of antigens. In addition, it is a substance wherein sensitizing antigens can be formed again under the influence of various injuries and where the reaction of antigens combining with antibodies can take place, i.e., where the immunological phase of the allergic reaction can develop.

The pathological chemical stage of allergic reactions of the nervous system has been the object of extensive research almost since the first formulation of the concept of allergy (Dale, 1911, and others). In theory, the question is whether allergic reactions of the central, somatic, and autonomic nervous system are the result of the primary and direct action of a specific allergen on nerve cells or whether these changes are a response to the action of irritants (histamine, acetylcholine, sympoathin, etc.) arising from the allergic reactions of other tissues structurally connected with nerve cells in the brain, ganglia or trunks (glial elements in the brain, connective tissue elements of nerve stems, "special cells", chemoreceptors of the blood vessels, etc.). There is as yet no definitive answer. Our research (1943) on the binding of horse serum proteins by the organs of sensitized guinea pigs showed that at certain periods of sensitization (24th to 26th day) the amount of horse protein bound by brain and spleen tissues is equal. At earlier periods of sensitization brain tissue binds the antigen much more weakly than does spleen tissue. Thus, brain tissue under suitable conditions of sensitization increases its capacity to bind a specific antigen with the same proportion of glial and nerve cells in its composition. However, all these data do not at the same time exclude the secondary effects of the above-mentioned irritants, which it was impossible to eliminate because of the way the experiments were set up.

The experiments of T. A. Alekseyeva and A. A. Podkolzin indicate that a specific antigen acts directly on the nerve cells. In these experiments the antigen was brought to the tissues of the superior sympathetic ganglion with a perfusate according to A. V. Kibyakov's method. Horse serum proteins act here as an agent inhibiting both excitability and the transmission of excitation in the synapses of the superior cervical ganglion when stimulated either by electrical current or chemical (acetylcholine, etc.). There is also a distinct decrease in liability of the ganglion tissue as a result of electrical stimulation.



However, there is no doubt that the nervous system in all its parts is the object of action by many secondary, biologically active products formed both in itself and in other tissues following allergic reactions. Among the most important of these products, besides histamine, are acetylcholine and sympathin produced in tissues having cholinergic (sympathetic ganglia, heart, intestines, etc.), or sympathetic (third eyelid of cats) innervation, respectively, or, as often happens, mixed innervation. Recently there have been indications that serotonin too is an irritant formed in brain tissue in anaphylaxis (Page, 1954; Ma Bao-li, 1959, and others). Rocha and Silva (1955) mention 12 biologically active products that take part, in the opinion of various investigators, in allergic reactions and serve as irritants of the nervous system in allergy. These include adenosine, kallikrein, heparin, bradikinin, the slowly acting Feilberg factor, etc.

Many investigators have concentrated on the role of histamine in functional disorders of the nervous system in allergy. Dragstedt (1941, Rocha and Silva (1955), Inderbitzin (1957) and others believe that histamine released in connective tissue (mast and other cells) inhibits the activity of cholinesterase and releases acetylcholine with its shift from a bound to a free state. The acetylcholine thus accumulated serves as the next link in the development of an allergic reaction and excites the cholinergic innervation apparatus (Hansen, 1957, and others). There is also an opposing view according to which allergic alteration of tissue results at first in the release of acetylcholine, which secondarily causes the release of histamine in the tissues and its shift from a bound to a free state (Wittich, 1944).

The relation of histamine to acetylcholine in allergic reactions of the heart, intestines, and uterus was once the object of special investigations of our own (A. D. Ado, 1952). We observed that the discharge of acetylcholine into the perfusate washing the isolated heart of a guinea pig sensitized to horse serum under the influence of a challenge dose of antigen was not followed by the liberation of histamine in amounts measurable by biological methods of titration (T. B. Tolpegin). Similar data were obtained on an isolated intestine by M. I. Undritsov (1939) and on an isolated uterus by I. V. Danilov (1949). We are still continuing this research (L. M. Ishimova). In agreement with the recent work of Shield (1958), we have shown that anaphylactic contracture of an isolated segment of guinea pig intestine develops fully in Tyrode's medium lacking calcium

ions. Shield pointed out that under these conditions the release of histamine is completely inhibited by the challenging action of the antigen. The biologically active product thus found is apparently acetylcholine.

The histamine hypothesis of allergic reactions is now being criticized from various aspects. It has been established that histamine is not involved in the development of allergic reactions of the slow type (Lecompte, 1956), in drug allergies, etc. We advanced a hypothesis (1946-1958) on the polyergic mechanism of allergic reactions whereby the antigen in an allergic reaction releases from the tissues that biologically active agent or agents which are released in a particular structure when it is subjected to physiologically adequate stimuli. According to this point of view, an allergic reaction of the cholinergic innervation apparatus is accompanied by the release of acetylcholine, an allergic reaction of the sympathergic innervation apparatus by the release of sympathin; the "histaminergic" nerves in an allergic alteration release histamine just as mast cells, endothelium of capillaries, and other histaminergic structures do. The intimate mechanism of the pathological chemical stage of nervous tissue allergic reactions is now the focus of attention of pathologicophysiologicals and requires further study.

The third or pathologicophysiological stage in the development of nervous system allergic reactions is closely connected with the second, and both stages apparently penetrate each other. At one time we defined the third stage (1944) as the stage of allergic alteration of nervous tissue. We have now accumulated an adequate amount of experimental material on the various functional indications of allergic alteration in all parts of the nervous system. A single injection of horse serum induces marked phase changes in the higher nervous activity of dogs (O. D. Gaske, 1953). Previously elaborated conditioned reflexes become weak, differentiation slackens, the latent period lengthens, and it is difficult to produce new conditioned reflexes. Anaphylactic shock is accompanied by severe inhibition of all conditioned reflexes and diffuse cortical inhibition. L. Ye. Khozak (1950) using L. A. Kotlyarevskiy's method obtained similar data. A. Kh. Kanchurin (1953) observed phase changes in the higher nervous activity of rabbits using the conditioned motor method. D. A. Brusilovskaya (1954) made similar observations while investigating vascular reflexes. Anaphylactic shock is expressed electroencephalographically by diminished electrical activity of the cortex, the appearance of slow waves and beta-waves (M. I. Rafiki, 1957).

Allergic alteration of subcortical formations is expressed by pronounced impairment of locomotion and coordination of muscular movements.

Several papers indicate involvement of the mid-brain area and hypothalamus in the development of anaphylactic shock. Data have been obtained on the action of serumal antigens on the midbrain of frogs (L. M. Rakhmatullin, 1946) and medulla oblongata of rabbits (L. G. Terekhova, 1947). According to Jacquelin's data (1955) on the desensitizing effect of hypothalamus irradiation, reactions of the diencephalic area are involved in allergic conditions. Hungarian scientists have shown that injury to the hypothalamus, tuber cinereum, or mammillary bodies prevent or weaken the course of anaphylactic shock in guinea pigs (Filipp, Szentivany, 1956; Szentivany and Szekely, 1956).

Clinical symptoms of disorders of the cerebral cortex and higher nervous activity include indications of allergy in the pathogenesis of certain forms of epilepsy, Jacksonian epilepsy, and transient lesions of the internal capsule. Thus, Walker (1954) found an allergic history in 14 out of 20 epileptic patients. There are data connecting epilepsy with migraine, asthma, and other allergic conditions (Hansen, 1958).

We must point out, however, that conclusions on the allergic nature of epilepsy are based more on gross analogies than on a precise pathogenetic analysis of this disease. We find more plausible assumptions concerning the allergic nature of certain disorders of the conduction pathways of the inner capsule where we have observed the development of a Quincke type acute angioneurotic edema and, therefore, the development of disturbances in the motor and sensory conduction pathways depending on the site of the edema in the capsule. Many specific neurological investigations include abundant illustrations of this type of disturbance. For example, Kennedy (1949) described a case of motor and sensory hemiplegia following a Quincke edema on the face and extremities. Hemiplegia occurred and disappeared four times during a single year, twice on the right side and twice on the left side. There have also been cases of allergic hemiplegia resulting from a food allergy to milk or meat, with accompanying hives, migraine, and asthmatic symptoms (Hansen, 1958).

Biddle and Krauss (1911) assumed involvement of the autonomic system in the pathogenesis of anaphylaxis. It was subsequently demonstrated that in protein sensitization the functional state both of the parasympathetic and sympathetic

portions of the autonomic nervous system changes. Cutting the vagus nerves in the neck somewhat weakens the course of anaphylactic shock in dogs and rabbits (A. D. Ado, 1940, and others). The injection of an antigen into a current of perfusion fluid in the superior cervical ganglion of cats sensitized to horse serum causes a decrease in lability and reduces excitability of the ganglion to electrical and chemical stimulation (T. A. Alekseyeva, 1959, and others). Among the clinical symptoms of serum sickness Ye. H. Korovayev (1949) was able to distinguish "autonomic" variants in the course of the disease in which dystonia of the autonomic nervous system, particularly in its parasympathetic part, is very clearly pronounced. A. A. Koltynin's idea on the vagus phase in the pathogenesis of infectious diseases has been newly confirmed by Korovayev's observations.

Finally, phase changes in the functional state have been observed in allergy in the nerve trunks, nerve endings, and nerve cells of the autonomic nervous system. Gay and Sousard (1907), Yamanuchi (1909), Kling (1913), Stowald, Sherwood, and Buduri (1931) and others noted increased irritability to a faradic current of the trunks of the sciatic, median, or vagus nerves in rabbits and dogs when sensitized to horse protein. After a challenge dose of the antigen (wetting) irritability of the nerve trunks diminished. Chronaximetric measurements of nerve trunks made by Marbe (1933), P. S. Kovbas (1940), L. L. Vasil'yev and D. A. Lapitskiy (1945), M. I. Rafiki (1950), and others also revealed phase changes (reduction - prolongation of chronaxie) during the period of sensitization and after a challenge dose of the antigen. Injury to the peripheral nerves after the injection of foreign sera occurs according to the type of serum neuritis, radiculitis or polyradiculoneuritis. The disease sets in between the 5th and 14th day after injection of the serum and develops over a long period of time (weeks and months) accompanied by paresis, hypesthesia, and even atrophy of the corresponding muscular groups, e.g., area of the scapula, shoulder girdle ( $C_5-C_8$ ), etc. Sometimes there is degenerative atrophy of the muscles of the hands and fingers, which is followed by edema of the perineural fissures of the nerve trunks of the "serous inflammation" type (Banivort, 1948; Mumme, 1950, and others). Similar forms of allergic polyneuritis also occur as complications ensuing from inoculations of intestinal vaccines (typhus, paratyphus, dysentery), infectious diseases (diphtheria), administration of drugs (salvarsan, etc.), plant pollen, etc.

The possibility of sensitizing sensory nerve endings to foreign protein was demonstrated by A. D. Ado and Yerzin (1938) on the chemo- and mechanoreceptors of the carotid sinus. Experiments were performed on dogs 13 to 17 days after they were sensitized to horse serum. The carotid sinus was isolated according to Moiseyev's method or was perfused through the vertebral artery feeding the glomus caroticus. The injection of the serum - antigen into the sinus isolated from blood circulation caused a severe hypotensive vasomotor reflex, acceleration and deepening of respiratory movements (the so-called "sinus shock"). Denervation of the sinus completely halted the appearance of these reflexes following action of the antigen on its receptor apparatus. The sensitivity of the receptors of the sensitized carotid sinus to mechanical and to some chemical stimuli (acetylcholine, nicotine, etc.) after action of the antigen is markedly depressed. Sensitivity of the carotid sinus is restored 30 to 90 minutes after the anaphylactic reaction.

Chernikov (1940) and A. N. Gordiyenko (1941) confirmed the experiments of Ado and Yerzin. Similar forms of allergic reactions were shown by Yerzin (1940) for the interoreceptors of the spleen and by A. D. Ado and Smirnov (1943) for the interoreceptors of the suprarenal glands.

Finally, in considering the allergic alteration of nervous tissue we must also keep in mind the various side effects on its function when blood circulation is impaired. Thus, impairment of cerebral blood circulation is an important link in the pathogenesis of migraine, a typical allergic condition. Hansen (1958) distinguishes four types of cerebral blood circulatory disorders underlying migraine: (1) vascular spasm (arterioles) and cerebral ischemia; (2) dilation of the capillaries and brain edema; (3) hypersecretion of fluid; (4) Quincke's edema of the meninges. Numerous investigations have established the connection between the appearance of migraine and other allergic diseases (bronchial asthma, urticaria, Quincke's edema, etc.). They cite as allergens food (chocolate, oranges), drugs (pyramidon, etc.), pollen, and other agents.

Thus, a change in the activity of the nervous system as a basic regulator of the organism is observed in all the classical allergic reactions and diseases of man. These include anaphylactic shock, serum sickness, bronchial asthma, Quincke's angioneurotic edema, etc. Functional changes in the central and autonomic nervous systems under these conditions can be both primary and secondary reactions, as

mentioned above. There are also several diseases of the central and peripheral nervous systems in which the main source of the illness is various forms of local allergic reactions occurring as allergic inflammation. These diseases include allergic encephalitis, encephalomyelitis, polyradiculoneuritis, etc. Migraine occupies a prominent place among them. Finally, some authors assume involvement of the allergic factor in the pathogenesis of multiple sclerosis, epilepsy, and even schizophrenia.

We must emphasize the fact that an allergic reaction anywhere in the nervous system is much more significant than if it developed in other tissues since a state of stimulation or dysfunction in any part of the nervous system affects in some degree the organism as a whole. Arthus' phenomenon in the area of the inner capsule or in the brain stem disturbs an animal's movements and functions of the cranial nerves depending on the site of a particular allergic inflammation. Allergic reactions of the autonomic nervous system are not only harmful in themselves, but they also disrupt the functions of the innervated organs. The result is attacks of bronchial asthma, allergic tachycardia, diarrhea and constipation, impaired tonus of the arterioles and, consequently, fluctuations in arterial pressure.

It is not inappropriate here to stress again the absurdity of contrasting the allergic mechanisms involved in dysfunctions of the above-mentioned organs with the "neurogenic" mechanisms. An allergen (from the external environment or formed in actual nervous tissue) causes the production of antibodies in the organism and its sensitization. The reaction of an antigen with an antibody in the central or autonomic nervous system impairs its functions and, consequently, those of the organ or system innervated by it. In other words, the "allergic mechanism" of a disease passes directly into the "neurogenic" mechanism. Both mechanisms may simply represent two successively developing links in the pathogenesis of a disease. Moreover, the allergic factor is frequently the initial link and, therefore, the etiologic factor. The so-called neurogenic factor is secondary and arises after sensitization of the tissues and subsequent development there of an allergic reaction that causes a great variety of changes in its functional condition.

A study of the mechanism of allergic reactions in terms of the ideas of nervism is particularly promising at the present time when investigations are apparently being drawn to studies of the properties of connective tissue (collagenosis and other allergic conditions) because far from excluding one another these investigations are actually complementary.

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