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PATHOLOGIC PHYSIOLOGY OF THE INFECTIOUS PROCESS

[Following is a translation of passages from the Russian-language book Voprosy Patologicheskoy Fiziologii Infektsionnogo Protsessa, (Problems of the Pathologic Physiology of the Infectious Process), Moscow, 1962.]

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THE ACTION OF DIPHTHERIA TOXIN ON THE CENTRAL NERVOUS REGULATION OF RESPIRATION (CONCLUSIONS)

(1) In the mechanism of disturbances of respiration during experimental diphtheria toxisicity, disturbances of the cholinergic mechanism of synaptic transmission in the respiratory center is of great importance.

(2) As a result of disturbances of the central regulation of respiration in diphtheria toxisicity, there are changes in the frequency and amplitude of the respiratory movements, disturbances of the respiratory reflexes (Hering-Breuer reflex and the respiratory reflex to stimulation of the sciatic nerve).

(3) Recording of action potentials from the peripheral end of the vagus nerve did not exert a substantial influence of diphtheria toxin on the stretch receptors of the lungs.

(4) Diphtheria toxin elicits, in rats and in cats, disturbances of respiratory movements which are enhanced by the administration of small doses of eserine into the fourth ventricle.

DISTURBANCES OF NERVOUS REGULATION OF RESPIRATION UNDER THE INFLUENCE OF THE TOXIC COMPONENTS OF PERTUSSIS BACILLI

(1) The toxin of the pertussis bacilus, in contrast to diphtheria toxin, causes an increase in the reflex

stimulability of the inspiratory portion of the respiratory center with subsequent intensification of the stimulability of the expiratory center.

(2) It may be suggested that the toxin of the pertussis bacillus directly effects the respiratory center, causing disorders in regulation of respiration.

ELECTROPHYSIOLOGIC STUDIES OF THE ACTION OF SERUM PROTEINS AND CERTAIN BACTERIAL TOXINS ON THE RECEPTORS OF SKELETAL MUSCLES

(1) Equine and bovine sera, diphtheria and tetinus toxins, complete typhoid fever antigens injected into the blood vessels of the gastrocnemius muscle (of cats and of rabbits) cause negligible changes in the background pulses of sensory nerves of these muscles.

(2) The injection of the above-mentioned antigens into the vessels of the muscles of sensitized animals is accompanied by a marked acceleration of the biocurrents of the sensory nerve.

(3) Under the conditions of our experiments, we did not notice any particular specific pulsation in the sensory nerves of muscles which would characterize the effect of a definite type of antigen on the muscle receptors.

ELECTROPHYSIOLOGIC STUDIES OF THE FUNCTIONAL STATE OF THE MUSCLE RECEPTORS IN LOCAL TETANUS

(1) Spontaneous pulsations of the muscle fibers of a "tetanic" extremity is intensified as compared with a control extremity. After transection of the anterior roots, the electrical activity of the fibers of the extremity which is poisoned with the toxin noticeably declines.

(2) The injection of the tetanus toxin into a preliminarily de-efferented extremity is not accompanied by the development of local tetanus. The electrical activity of the fibers in such a case is distinguished by a lower level

of activity of the fibers of the control extremity.

(3) The same result is observed under the conditions of combined poisoning of an animal first with the toxin of botulism, and then by the induction of paralysis with the tetanus toxin.

(4) The muscle fibers of the extremity infected with the tetanus toxin shows a more intense series of pulses in response to stretching the muscle with a weight than do the fibers of the control extremity. After transection of the anterior roots, which contain gamma fibers, there is an almost identical reaction of the muscle fibers of the "tetanic" and the control extremities.

(5) Changes in the functional state of the muscle fibers in local tetanus depends not on a direct effect of the toxin on the receptors but rather are connected, it would seem, with its fixation in the corresponding cells in the spinal cord. It is possible that these are the gamma-motor neurons, or perhaps with other nerve structures which are functionally connected with the gamma-motor neurons, which participate directly in the regulation of the tone of the muscle fibers.

ON THE PROBLEM OF THE MODE OF ACTION OF TETANUS TOXIN ON THE SPINAL CENTERS

(1) The development of local tetanus is accompanied by a considerable intensification of the polysynaptic reflex discharges on the side of the injection of toxin. In this case, during the first two to three days of the disease, there are no substantial differences in the magnitude of the monosynaptic responses to the "tetanic" and the control sides.

(2) Along with an enhancement in the polysynaptic reflexes, there is a disappearance of the different types of synaptic inhibition of motor neurons of muscles of the "tetanic" extremity.

(3) The changes described in the character of the reflex activity of the spinal cord, which accompany the development of local tetanus on the first day after the injection of the toxin, are similar to those which are seen upon injection of tetanus toxin into the nerve trunk or directly into the spinal cord (Brooks, Curtis, and Eccles, 1957).

(4) By the fourth to fifth days, and sometimes even on the third day after infection of the toxin, the "tetanic" extremity shows a marked reduction in the magnitude of the maximal mono-synaptic reflexes, even to the extent of complete disappearance of them. At the same time, the poly-synaptic reflexes remain markedly enhanced.

(5) Upon testing the inhibition of the motor neurons of the extensor muscles with pulses from the afferent fibers of groups 2 and 3, in a number of cases on the side of injection of the toxin there is a replacement of the inhibitory effect by a facilitation of it.

(6) The action of tetanus toxin on the spinal centers is not limited to the suppression of the processes of central inhibition, but also consists in a weakening of the stimulatory influence on the motor neurons.

THE ACTION OF THE HERPES VIRUS ON THE FUNCTIONAL STATE OF THE SYMPATHETIC NERVOUS SYSTEM

(1) The virus of herpes strain L2, applied to a scarrified cornea of a rabbit's eye, causes the development of keratoconjuntivitis in this eye.

(2) In the injured cornea of the rabbit, the virus can be detected from the second to the eleventh days after infection.

(3) Upon application of the virus to the scarrified cornea of the rabbit's eye, the virus can be recovered from the superior cervical sympathetic ganglion of the ipsilateral side beginning with the fourth day after infection.

(4) Soon after infection, at a time when the virus cannot be recovered even from the superior cervical sympathetic ganglion, there is an increase in the functional mobility of the cells of the ganglion on the side of infection and a corresponding reduction in the threshhold strength of stimulation by three-fold as compared with the healthy side.

(5) Later following infection, when the virus can be recovered from the superior sympathetic ganglion, there is a reduction in the functional mobility of the ganglion cells on the infected side and an increase in the threshhold of stimulation by 2.6 fold as compared with contralateral side.

PATHOPHYSIOLOGIC STUDIES OF THE MECHANISM OF THE TOXIC EFFECT OF THE INFLUENZA VIRUS

(1) Electrophysiologic studies have shown that the normal allantoic liquid of a 13-day chick embryo does not modify the functional mobility of ganglion cells.

(2) An allantoic culture of the influenza virus of the Shklyaver strain in hemagglutination titers of 1:320 to 1:1280 exerts a toxic effect on ganglion cells which takes the form of a reduction in the functional mobility and a decline in the sensitivity to acetylcholine.

(3) Allantoic cultures of the influenza virus type A of the Shklyaver strain in low hemagglutination titers (1:80 to 1:160) stimulate the cells of the sympathetic ganglion, by increasing their functional mobility.

(4) In animals which are actively immunized to the influenza virus, the latter does not exert any toxic effect. The action of the influenza virus on the cells of the sympathetic ganglion are immunologically specific. In cats immunized with the influenza virus type A, the toxic effect of the virus type B is manifest to the same degree as in healthy animals.

(5) Ideas are developed in this work concerning the

importance of the data obtained for our understanding of certain aspects of the pathogenesis and immunity of influenza infection.

ON THE MECHANISM OF CHANGES IN THE PRESSOR CAROTID SINUS REFLEX IN ANAPHYLAXIS

(1) Against the background of anaphylactic shock, there is a complete disappearance of the carotid sinus pressor reflex.

(2) In the pressor zone of the reticular zone of the brain stem, during the course of anaphylactic shock, a state of inhibition develops which is evidenced by a disappearance of the pressor effect upon stimulation of this zone and a preservation of the pressor effect upon stimulation of the preganglionic trunk of the splanchnic nerve.

(3) The injection of aminazin into a sensitized animal stabilizes the level of the blood pressure with respect to the subsequent injection of the antigen, and prevents a fatal outcome from the anaphylactic shock.

THE PROBLEM OF THE MECHANISM OF DEVELOPMENT OF TOLERANCE TO THE PYROGENIC EFFECT OF CERTAIN BACTERIAL ANTIGENS

(1) The development of an antipyrogenic tolerance is related to a certain extent to the participation of pathophysiologic mechanisms of immunity.

(2) On the basis of the pathophysiologic mechanisms of antipyrogenic tolerance lie the changes in the functional state of the heat regulating center, obviously involving an inhibition of it.

(3) The antipyrogenic tolerance to the antigen may be reversed in the process of developing a conditioned reflex hyperthermic reaction.

ON THE MECHANISM OF DIFFERENT PHASES IN THE ANAPHYLACTIC CONTRACTION OF SMOOTH MUSCLES OF THE SMALL INTESTINE

(1) The isolated intestine of guinea pigs and white rats is more sensitive to acetylcholine than to histamine.

(2) The anaphylactic contraction of the intestine in sensitized rats and guinea pigs takes the form of a biphasic reaction: an initial rapid part -- the peak phase, and a subsequent slow portion -- the plateau phase.

(3) Histamine is not an intermediate link in the mechanism of the first phase, since diprazin does not inhibit the development of it.

(4) In the mechanism of the first phase of the anaphylactic contraction of the small intestine, stimulation of the cholinergic intramural apparatus is of great importance. This is proved by the fact that atropine eliminates, while eserine enhances this phase.

(5) The first phase of the anaphylactic reaction of the isolated intestine -- the peak phase -- is eliminated by the action of the ganglionic-blocking substances.

ON THE CHANGES IN THE REACTIVITY OF THE ORGANISM UNDER THE INFLUENCE OF THE TOXIC COMPONENTS OF THE PERTUSSIS BACILLI.

(1) Experimental pertussis toxicity is accompanied by a heightening of the general sensitivity of animals not only to histamine but also to acetylcholine and carbocholine.

(2) Under the influence of the toxic components of the pertussis bacillis, there is an increase in the sensitivity of the smooth muscle of the trachea and bronchi to acetylcholine and to carbocholine.

THE INFLUENCE OF SINGLE SENSITIZATION TO CONDITIONED REFLEX ACTIVITY IN DOGS

(1) Single sensitization with horse serum with dogs of the strong type does not cause prolonged and substantial changes in higher nervous activity.

(2) In dogs of the weak type of higher nervous activity, following sensitization there is a disturbance in the differential inhibition. The strength of the stimulatory process is noticeably increased.

(3) A non-specific stimulus in the form of injection of physiologic saline solution causes changes in the higher nervous activity which are similar to the changes observed upon single sensitization.

ON THE CAUSES OF THE CHANGES IN THE REACTION OF THE CARDIOVASCULAR SYSTEM OF RABBITS INFECTED WITH B. TYPHIMURIUM TO SYMPATHOMIMETIC SUBSTANCES

(1) In rabbits infected with B. typhimurium, there is a reduction in the pressor reaction of the blood pressure not only to adrenalin but also to ephedrine.

(2) Upon injection of solutions of adrenalin, the constriction of the vessels of the ears in sick rabbits was more pronounced than in the control rabbits. Hence, it may be suggested that the lesser increase in the blood pressure in sick rabbits upon injection of sympathomimetic amines is not a consequence of the reduction in the sensitivity of the adrenoreactive systems.

(3) One of the causes of the increased sensitivity of the ardenoreactive systems is, it would seem, a reduction in the content of adrenalin in the blood, since frequently, against a background of atropine, a greater pressor reaction to adrenalin corresponds to a smaller concentration of adrenalin in the blood.

(4) There is a definite relationship between the content of adrenalin and the pressor reaction to ephedrine. Apparently, the reduction of the concentration of adrenalin is one of the causes of the lesser increase in pressure upon injection of ephedrine.

ON THE CONTENT OF ADENOSINE TRIPHOSPHORIC ACID, CREATINE PHOSPHATE, AND MINERAL PHOSPHORUS IN THE BLOOD, BRAIN, AND SKELETAL MUSCLES OF WHITE RATS DURING DIPHTHERIA TOXISICITY

(1) In the cardiac muscle and in the brain of white rats, adenosine polyphosphoric compounds are present in smaller amounts than in the skeletal muscles.

(2) Experimental diphtheria toxisicity in white rats is accompanied by a negligible increase in creatine phosphate in the cardiac muscle and in the brain by a more noticeable increase of it in the skeletal muscles.

(3) In the skeletal muscles, a reduction in the content may be noted regardless of the degree of manifestation of the diphtheria toxisicity, whereas in the heart, such a reduction is noted only in the presence of a severe degree of toxisicity.

(4) Mild diphtheria toxisicity in white rats is accompanied by a reduction of mineral phosphorus in the heart, brain, and skeletal muscles, whereas a more severe toxisicity is accompanied by an increase of it only in the heart and in the brain.

(5) Disturbances of phosphorus metabolism in diphtheria toxisicity occur primarily in the skeletal muscles, and subsequently in the heart and brain.

(6) The position regarding the resistance of white rats to diphtheria toxin has been confirmed essentially by our experimental data, through studies of phosphorus metabolism.

ON THE CHANGES IN THE COURSE OF THE FEBRILE REACTION DURING THE USE OF CORTISONE

(1) Cortisone inhibits the development of the febrile reaction caused by the streptococcal vaccine. With prolonged daily injection of cortisone, it gradually loses its antipyrogenic properties and the febrile reaction again emerges.

(2) During the process of prolonged administration of cortisone, the heat-regulating centers are first inhibited, and then begin to escape from this inhibitory influence, which serves as a basic demonstration of the development of the febrile reaction in the presence of pyrogenic factors in the organism.

CHANGES IN THE RESISTANCE OF WHITE RATS TO THE TOXIC EFFECT OF VACCINE UNDER THE INFLUENCE OF ADRENALECTOMY AND THE ADMINISTRATION OF CERTAIN HORMONES

(1) The bilateral removal of the adrenal glands or the injection of insulin is accompanied by a marked reduction in the resistance of the rats to the toxic effects of vaccine made from the Gertner bacillus.

(2) The administration of cortisone completely, and of thyroid hormone only partially, restores the resistance to the toxic effect of vaccine, which has been diminished by adrenalectomy.

(3) Cortisone (in the dose used) does not reduce the resistance of normal animals to the toxic action of vaccine.

ON THE MECHANISM OF THE NEUROENDOCRINE INFLUENCES ON THE RESISTANCE OF WHITE RATS TO DIPHTHERIA TOXIN

(1) The removal of the pituitary gland is accompanied by a reduction in the resistance of white rats to diphtheria toxin.

(2) ACTH, administered to rats in which the pituitary has been removed, restores their resistance to diphtheria toxin.

(3) Disruption of higher nervous activity alters the reaction of animals in the direction of enhancing their sensitivity to diphtheria toxin.

(4) Disruption of higher nervous activity does not

exert any dilatarious influence on the resistance of rats to the diphtheria toxin under conditions of absence of the pituitary.

(5) Upon administration of ACTH, the resistance of neurotic rats to diphtheria toxin is increased.

(6) The pituitary, it seems, participates in the realization of the influence of disruption of higher nervous activity on the resistance of white rats to diphtheria toxin.

ON THE PARTICIPATION OF THE HYPOTHALAMUS IN THE DEVELOPMENT OF ANAPHYLACTOID SHOCK IN WHITE RATS

(1) Upon inflicting damage upon the ventromedial nuclei of the mid-hypothalamus, there is atrophy of the adrenal glands which appears by the 15th day and reaches its greatest extent at later times following operation (35th to 40th day).

(2) On the 7th and 15th days after operation, changes in the sensitivity of white rats to intravenous injection of egg albumin cannot be demonstrated.

(3) By the 35th to 40th days after operation, there is a reduction in the value of the DL50 of egg albumin by three-fold as compared with the control animals.

THE ROLE OF THE ADRENAL-PITUITARY SYSTEM IN THE DEVELOPMENT OF ANAPHYLAXIS IN WHITE RATS

(1) Anaphylactic shock in white rats may be produced by sensitizing them to foreign serum admixed with vaseline.

(2) Adrenalectomy reduces the resistance of rats to anaphylaxis. Cortisone increases their resistance to anaphylaxis whereas DOCA and adrenalin proved to be ineffective in this respect. The removal of the pituitary gland did not change the sensitivity of rats to the first injection of foreign protein, but substantially changed their susceptibility to sensitization. ACTH increases the resistance of rats from

which the pituitary has been removed almost to the level of the resistance of non-sensitized animals. Cortisone is less effective in this regard than ACTH. Adrenalin shows no influence.

(3) The permeability of the skin capillaries in rats sensitized with horse serum in vaseline is increased. Removal of the pituitary or the administration of ACTH to the operated animals is not reflected in the state of permeability of the skin capillaries.

(4) There is no parallelism between the anaphylactic reaction in vitro and the general reaction of the organism. The isolated intestine of rats sensitized to foreign serum in vaseline does not show any pronounced anaphylactic contraction. Removal of the pituitary or of the adrenal glands heightens the sensitivity of the small intestine to foreign serum and to histamine both in sensitized and in non-sensitized rats.

(5) The intensity of anaphylactic shock does not depend on the degree of accumulation of precipitins in the blood. The titer of precipitins in the blood of sensitized rats is low. Adrenalectomy or the administration of cortisone exerts no marked influence on the titer of precipitins. Removal of the pituitary reduces the titer of precipitins, whereas injection of ACTH increases it slightly.

(6) The role of the adrenal-pituitary system in anaphylaxis consists in its non-specific protective and adaptive function; in the realization of this function, an important link is the cortex of the adrenal glands.

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