# THE ANTAGONISTIC ACTION OF THE VAGUS AND SYMPATHETIC DIVISIONS OF THE AUTONOMIC NERVOUS SYSTEM IN PULMONARY TUBERCULOSIS

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# THE ANTAGONISTIC ACTION OF THE VAGUS AND SYMPATHETIC DIVISIONS OF THE AUTONOMIC NERVOUS SYSTEM IN PULMONARY TUBERCULOSIS.

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FOR a number of years I have interested myself in the study of reflex action as it affects the individual suffering from inflammation of the pulmonary parenchyma, particularly tuberculosis. This study has been difficult because of the fact that its very foundation is enveloped in mystery. In offering an explanation of the various phenomena noted, we are compelled to reason from effect to cause in a great many instances, because physiology has not yet made the paths of all the reflexes clear.

This study lies largely within the field of the autonomic nervous system, a field which is particularly characterized by our lack of knowledge, but one which offers great encouragement for future investigations.

The tuberculous patient cannot be understood clinically if we look upon him only as one afflicted with an infection of the pulmonary parenchyma, no matter how small the lesion. We must endeavor to know how the inflammation in the lung affects other organs which are supplied by the same system of nerves or which stand in such a relationship that they may be influenced reflexly; and we must study him as a human being suffering from a chronic disease which produces a chronic toxemia and one which is accompanied by a varied emotional state, both of which conditions exert a powerful influence upon the sympathetic nervous system. Realizing fully the difficulty of the task before me I shall endeavor to suggest some of the symptoms and conditions which arise from the irritation of the two great divisions of the autonomic system, the vagus and the sympathetic, and show the antagonistic action which is constantly going on.

I have been greatly stimulated in this study by the splendid work of Eppinger and Hesz on Vagotonia ("Die Vagotonie," Sammlung. Klinischer Abhandlungen, von Noorden. Heft 9 u. 10, 1910) which has recently come into my hands, and those valuable and suggestive monographs by Cannon ("Bodily Changes in Pain, Hunger, Fear and Rage," Appleton, 1915) on the effect of emotions upon the human organism, and the studies of Beidl ("Innere Sekretion," Urban and Schwartzenberg, Wien, 1910) on the internal secretions.

The autonomic nervous system supplies impulses to structures which are not controlled by the will. These are the organs which are supplied by smooth muscles, such as the stomach, intestines, blood vessels, ducts of glands, skin and secreting glands; also certain organs possessing striated muscle fibres, such as the heart, the beginning and terminal portions of the alimentary canal, and the generative organs.

This system is characterized by the fact that under no circumstances do organs or parts receive innervation directly from a neuron whose cell bodies lie in the brain or spinal cord. Ganglia are interposed between the nerve cells in the central nervous system and the part innervated which act most prob-

ably by modifying impulses. In these ganglia are cell bodies belonging to neurons which have postganglionic fibres which go to supply the viscera.

The cerebrospinal nervous system, on the other hand, is controlled by the will. Its action is quick and definite. There are no ganglia interposed along the path of the nerve to modify the impulses which originate in the brain, but they are carried directly from cell bodies in the brain and cord to the muscles involved, and immediate action results.

The autonomic system consists of three divisions, the cranial, the thoracicolumbar or sympathetic, and the sacral, as shown in Fig. 1 taken from Cannon. No connecting neurons for the autonomic system are given off from those portions of the cord which send out nerves to the fore and hind limbs.

Some writers divide the autonomic system into two divisions, and classify the cranial, bulbar and sacral divisions together as the vagus system, and the thoracic and upper lumbar as the sympathetic system.

The fibres of the sympathetic all pass through the ganglionated cord, while those which come from the cranial, bulbar and sacral portions of the cord do not.

The cranial fibres pass for the most part within the trunk of the nervus oculomotorius (III cranial), are interrupted in the ciliary ganglion, whence they furnish constrictor impulses to the sphincter of the iris.

The bulbar portion passes through the nervus facialis (VII cranial) and nervus glossopharyngeus (IX cranial) to the salivary glands and blood vessels of the mouth. Stimulation causes increased salivary flow in the one case and constriction of the vessels of the mouth in the other.

The most important branch of the autonomic coming from the bulbar portion of the cord is the nervus vagus (X cranial) which is the chief source of nerve supply for the internal viscera. It supplies the heart, bronchial tree, esophagus, stomach, intestines, pancreas, and liver.

The sacral branch is the nervus pelvicus. It innervates the descending colon, sigmoid, anus, bladder and generative organs.

The sympathetic fibres pass from the spinal canal in the thoracic and upper lumbar regions. They pass out and form the ganglionated cord and from this are widely distributed throughout the entire body. Many structures are innervated by both the vagus and the sympathetic systems, and wherever this double innervation is found, the action of the two is antagonistic; as in the eye, where the vagus contracts the pupil, the sympathetic dilates it; or in the heart—where the vagus slows, the sympathetic accelerates.

The cranial and sacral divisions of the autonomic system have a more direct action than the sympathetic because the fibres coming from the cranial and sacral divisions run more directly to the organs innervated than do those of the sympathetic. Thus, the fibres of the vagus supplying the heart and gastrointestinal tract do not enter ganglia until they reach the substance of the organs, while the sympathetic fibres pass through several ganglia each of which complicates and modifies their action. Consequently, stimulation of the cranial, bulbar, and sacral fibres of the autonomic system may cause a resultant action in some individual organ, while stimulation of the sympathetic fibres causes a widespread effect involving several or many organs. This affords us a physio-

logical explanation for the general widespread character of sympathetic impulses.

The following table shows the antagonistic action between the vagus and sympathetic systems in the principal structures concerned in our study:

| Action of the Sympathetics When Stimulated. | Organ | Action of the Autonomic When Stimulated. |
|---|---|---|
| I-II thoracic ..... | dilates pupil | |
| | contracts pupil ..... | III N. |
| I-III thoracic ..... | stimulates orbital muscle | |
| | stimulates m. ciliaris ..... | III N. |
| II-IV thoracic .... | inhibits salivary secretion | |
| | stimulates salivary secretion..... | Chorda tympani |
| II-IV thoracic .... | contracts vessels of skin of head and vessels of brain | |
| | dilates vessels of brain..... | X N. |
| | contracts vessels of cheek..... | IX N. |
| *II Th.-IV L..... | contracts intestinal vessels | |
| I-IV lumbar ..... | contracts genital vessels | |
| | dilates genital vessels..... | N. pelvicus |
| II Th.-IV L..... | stimulates sweat glands | |
| IV-VII Th. ..... | stimulates hair muscles of face and head | |
| I-V Th. ..... | accelerates heart contractions | |
| | slows heart contractions..... | N. X |
| II-IV Th. ..... | relaxes oesophagus | |
| | contracts oesophagus ..... | N. X |
| II Th.-IV L. ..... | relaxes cardia | |
| | contracts cardia ..... | N. X |
| II Th.-IV L. ..... | diminishes gastric tonus | |
| | increases gastric tonus..... | N. X |
| II Th.-IV L. ..... | inhibits gastric peristalsis | |
| | increases gastric peristalsis..... | N. X |
| II Th.-IV L. ..... | diminishes gastric secretion | |
| | increases gastric secretion ..... | N. X |
| II Th.-IV L. ..... | inhibits motility of small intestine | |
| | stimulates motility of small intestine.... | N. X |
| II Th.-IV L. ..... | inhibits (?) pancreas secretion | |
| | stimulates pancreas secretion..... | N. X |
| I-IV L. ..... | relaxes contraction of colon | |
| | stimulates contraction of colon..... | N. pelvicus |
| I-IV L. ..... | relaxes sphincter ani | |
| | stimulates sphincter ani..... | N. pelvicus |
| | stimulates liver secretion ..... | N. X |
| II Th.-IV L. ..... | contracts and dilates vessels of upper and lower extremities. | |

*Th.—thoracic. L. Lumbar.

The vagus system takes part in many reflex acts. The sympathetic also carries afferent impulses, when its end fibres in any organ are irritated, which result in reflex action; and, besides, the system as a whole, is influenced greatly by toxic conditions and by emotional states such as fear, anxiety, discouragement and disappointment.

In pulmonary tuberculosis it can readily be seen that we have a most complex study. There is primarily an inflammation of tissue which irritates filaments belonging to one of the chief branches of the vagus system. Resulting from this, afferent impulses are sent to the cell bodies in the central nervous system and are there transmitted to other cells and through them to fibres which pass out through other branches of the vagus system to produce increased vagus tone in the fibres affected. This increased vagus tone may be distributed more or less generally through the different branches of the vagus system or it may be selective in that it affects certain branches more than others.

Along with the vagus stimulation resulting in increase in vagus tonus, there is a stimulation of the sympathetics, which results in a reflex increase in sympathetic tonus in practically the same organs. Whether sympathetic or vagus tonus shall predominate depends on the conditions present. Cannon has demonstrated the effect of fear, rage and pain on the organism. In tuberculosis we have a central stimulation of sympathetics by the toxins and an exaggerated emotional state, as a result of the disease which also acts as a stimulant upon the sympathetics. Allied to fear and rage are malaise and depressive nervous states which accompany the tuberculous toxemia and which, acting through the sympathetics, have a general antagonistic action to vagus impulses wherever met.

In this connection it is interesting to note how closely the emotional states and toxemias (in this case tuberculous toxemia) are allied in their symptomatology and end effects. The individual in a state of great emotion, shows dilatation of the pupil, pallor, feels his hairs rise on end, suffers from dryness of the mouth, rapid pulse, a stoppage of digestion and other similar symptoms which are characteristic of sympathetic irritation. The toxemia which accompanies tuberculosis, the same as all other toxemias, produces general sympathetic stimulation. The nervous condition resulting is characterized by malaise, anxiety, discouragement, fear and general depression; and these, in turn, cause the same chain of symptoms, only not so pronounced, as a rule, as those which follow violent emotion. Such patients, however, during the periods of marked toxemia, suffer from pallor, rapid pulse, dry mouth, coated tongue, disturbed appetite, slowness of digestion and stasis of intestinal contents. During slight toxemia these symptoms may not be noticed or they may be very slight in character. The symptom-complex of toxemia is an expression of general discharge through the sympathetic nervous system, and is practically the same, though different in degree, no matter what the nature of the toxemia.

The action of the sympathetic on the sacral division is also evident in toxemia as shown in the inhibition of the sexual desire. It is not at all impossible that the increased desire which so often marks periods of improvement in tuberculosis is evidence of increased sacral tonus, and an overbalancing of the equilibrium normally maintained between the sacral and the sympathetic. Inasmuch as these changes in this division of the autonomic system are not so im-

portant in symptomatology as those in the vagus system we shall not discuss them further at this time.

The above symptoms are not constantly present. Variability characterizes the symptoms produced by nervous stimulation in early tuberculosis. This is due to the fact that several important and antagonistic influences are operative at the same time; and also to the fact that the tuberculous inflammation in the lung goes through cycles of greater and lesser activity, producing varying degrees of stimulation; and, further, to the fact that the relative vagus and sympathetic tonus differs in different individuals.

The nerve endings of both the vagus and sympathetic systems are irritated by the pulmonary inflammation; and through their respective fibres afferent impulses are sent centralwards, which result in reflex stimulation of other branches of their respective systems or of nerves with which they communicate, going out to supply such other organs as the eye, heart and gastrointestinal tract. Sometimes the stimulation is greater in the vagus system; at other times in the sympathetic. As a rule, however, except during the periods of increased toxemia, which I shall discuss later, my observation leads me to believe that the vagus tonus is greater than the sympathetic tonus in the majority of patients suffering from early tuberculosis. This seems to be true in nearly all except those of the distinctly asthenic type. This is shown on the part of the heart and particularly on the part of the gastrointestinal tract, as described later.

In estimating the relative tonus of the vagus and sympathetic systems it is necessary to bear in mind that increased tonus might show in one division of nerves and not in all; and that this increased tonus in particular divisions might not be constant. This variability is due to the fact that there are many factors causing the stimulation and that some of these have selective action for certain structures. This is not only evident in the reflexes, but also in the internal secretions which affect the two systems. It is also evident from the fact that the tuberculous patient may have increased or decreased tonus in either the vagus or sympathetic systems from causes other than those which operate as a result of the pulmonary infection. From the antagonistic action of the vagus and sympathetic systems the function of many organs is rendered unstable. The heart particularly in early and nonactive tuberculosis while at rest, is often slower than normal; but on exertion or during periods of emotion at once becomes more rapid than normal and settles down to the normal much slower than it should. The appetite, while disturbed during acute toxic states and during conditions which favor increased absorption of toxins, such as overexertion, or during periods of anxiety and discouragement, is often normal and even sharper than normal when the patient is put at rest in the open air under favorable circumstances which offer him hope of cure. The same is true of the gastric and intestinal disturbances. Hyperacidity and hypermotility are the rule in early tuberculosis, when toxemia is relieved. The intestinal tract also shows the same increased tonus. The vagus system, the one which conserves the healthful action of the important internal organs, overcomes its antagonist in early tuberculosis for the most of the time and thus offers the patient an increased opportunity for restoration to health.

During the waves of increased activity in the tuberculous focus, however,

and when the patient is causing increased absorption of toxins by overexertion and other faulty habits, likewise during periods of discouragement and mental depression, which are not uncommon, the excessive stimulation of the sympathetic system produced by both reflex action, and the toxemia and emotional states, overcomes the increased vagus tonus and causes symptoms which are characteristic of sympathetic irritation, such as rapid heart, decreased appetite, hypochlorhydria, deficient gastric motility and alteration in the secretion and motility of the intestinal tract. Whether this is wholly a direct action upon the sympathetic system or partly a general disturbance of internal secretions is not clear, but the effect is that of a general discharge through the sympathetic system.

The extent to which the sympathetic tonus can be relieved is a factor in prognosis. As the disease increases in virulence and activity, the vagus tonus gradually yields to the supremacy of the sympathetic.

Aside from the antagonistic action of these two systems it seems well established that antagonistic fibres are at times supplied to organs by the same system.

In health a state of equilibrium is maintained in the various organs as a result of the antagonistic action of these two systems. In any disease which affects either by stimulation or by setting aside the normal nerve tonus of any important branch or group of fibres of either or both of these systems, there is a consequent disturbance of equilibrium which results in a pathological state.

This is evident in the production of nausea through eye strain, or the slowing of the heart in abdominal lesions which affect the depressor fibres of the vagus. So it is evident in pulmonary inflammation.

Aside from the direct stimulation of the nerves by inflammatory processes we must recognize the influence of substances of a chemical nature which act either upon terminal filaments or nerve centers. The primary action of the toxins is a direct stimulation. The secondary action may be a totally different one and depend on certain secretions (hormones) which are set free as a result of the primary toxic influence, such as occurs when adrenalin is set free by certain emotional states or gastric secretion is stimulated by the small or taste of savory food.

It is more and more believed as we study deeper into the problems of physiology, that the harmonious and dysharmonious action of cells and special groups of cells is increased not only by direct nerve stimulation, but also by internal secretions which, coming from some distant gland, act as hormones or messengers calling forth normal harmonious action when the parts are in a normal state, and abnormal action when the parts are abnormal. Such action is on the organ itself and not on the nerve supplying it.

This is evident in case of the thyroid, suprarenals, pituitary body, testicles and ovary; and probably just as true in the case of such other organs as the kidney, liver, spleen, pancreas and even such secreting glands as those in the gastrointestinal tract. A dysfunction of one gland may be followed by a disturbance in others because of a failure of the normal secretion of that gland to course in the blood and produce its relative stimulation of other glands. The stimulation of these glands which results in the production of such hormones is at least partially under direct nerve control; and, in this manner, the stim-

ulation of a nerve supplying a given organ may not only affect that particular organ, but one widely separated from it through the internal secretion which is affected by such stimulation.

No doubt future study will clarify this subject very much by the discovery of the true relationship which exists between many of the internal secretions and the structures controlled by them. An important beginning has been made in this direction in the discovery of the fact that the secretion of adrenin is stimulated by the same conditions (emotional states) which stimulate the sympathetic nervous system (Cannon), and that when this substance is thrown out into the circulation, it finds its way to the various structures controlled by the sympathetic nervous system and exerts for the most part, the same antagonistic action against the vagus as the sympathetic itself. This may partly explain the action of toxemia as well as a central stimulation of the sympathetic neurons. There are doubtless other organs which produce hormones antagonistic to sympathetic action; in fact, the observation that dogs whose pancreas are removed have an overstimulation of the adrenal system indicates that such a hormone is produced in the pancreas.

Let us now proceed to apply these principles to pulmonary tuberculosis and the explanation of such phenomena as are caused by the disturbed balance in the vagus and sympathetic systems.

In tuberculosis we must conceive of a condition in which both the vagus and sympathetic systems are simultaneously stimulated, but one in which either one or the other usually yields with a resultant disturbed equilibrium.

*Pupil.* At least fifty per cent of tuberculous patients show a dilated pupil on the side of involvement during the time that the inflammation is acute; and it is probable that a much larger per cent would show it if observation could be made continuously. This indicates that the action of the sympathetic overcomes that of the vagus. This dilator effect is due to irritation of the fibres from the Ist and IInd thoracic segments of the cord. Artificial stimulation of these fibres causes the same dilator effect. Aside from the pupilary effect, the equilibrium of the ciliary body and orbital muscle is disturbed. I am led to believe, that, aside from the dilatation of the pupil, there is a serious disturbance in the muscle balance resulting from the antagonistic action of the vagus and sympathetic which causes a disturbance of accommodation. It is surprising to see how many patients complain of headache, if they continue to use their eyes for reading, knitting, or sewing, as they have been accustomed to do prior to their illness. They also seem to show an increased and abnormal sensitiveness to bright light; and I often find it necessary to suggest that the bed be so placed that the light will not shine directly in the eyes. Change of eye glasses is made necessary more often than prior to illness even in early and chronic cases which are only slightly active. This is usually explained as being due to the lowered physical state; but may not this altered muscle balance be the cause?

*Hectic flush.* The vasoconstrictor fibres of the cervical sympathetics take their origin from the upper thoracic roots, particularly from the IId, IIId and IVth, and supply the vessels of the face and head. Hectic flush is present, for the most part, only during periods of acute toxemia, and comes on only after a considerable amount of tissue is involved. It is confined to the side affected,

the same as is noted in the reflex dilatations of the pupil. This of itself suggests that reflex action is at least the localizing factor, although the toxic action may also be required to overcome the constrictor effect.

*Heart.* In the heart, in tuberculosis, we have so many conditions present which influence the pulse rate that it is impossible to accurately ascribe to the vagus and sympathetic systems the part which each plays. Impulses are carried through both systems, because both are more or less constantly irritated.

As a result of this double source of impulses, the one through the vagus tending to slow the heart, the other through the sympathetic, attempting to quicken its action, there is a marked disturbance in equilibrium. This shows early in the disease before such conditions as loss of pulmonary tissue, heart strain, and degenerative changes can be considered. The heart beat may be normal, or only slightly faster than normal, while the patient is at rest; but unduly rapid on exertion. Rapidity is also increased during states of toxemia and during periods of depression.

This characteristic relative slowness of the heart beat while at rest is sometimes noticed even during periods of temperature in advanced tuberculosis. When compared with the pulse rate accompanying the same degree of temperature in other diseases it is often lower. This is most probably a result of an inhibitory reflex through the vagus, the impulse coming from the irritation in the lung. When the intestinal tract is affected with tuberculosis, then another division of the great vagus system is stimulated and we often see this inhibitory action accentuated, with a still greater departure in pulse rate from that which would be expected with the degree of temperature present. If an unusual slowing of the pulse occurs in the course of pulmonary tuberculosis coincident with an elevation of one or two degrees in the temperature curve, reflex vagus irritation should be considered as a probable cause and a complicating intestinal tuberculosis be suspected.

Irritation of other branches of the vagus will also cause inhibitory action upon the heart. Thus pressing upon the eyeball and irritating the nasal mucous membrane will both cause slowing of the heart; so does intracranial pressure as shown at times in tumors and conditions accompanied by fluid.

Opposing this inhibitory action through the vagus, we have acceleration through the sympathetic, either by direct stimulation, or through toxins or through the various emotional states which affect the patient. Often the sympathetic irritation gains the upper hand and a markedly rapid pulse results.

*Gastrointestinal tract.* The antagonistic action of the vagus and sympathetic on the different portions of the intestinal tract is extremely interesting; and our understanding of this action will aid greatly in forming an accurate clinical conception of the digestive capabilities of the tuberculous patient.

Early in tuberculosis the toxemia present is neither constant nor of a high degree as mentioned above, and its action upon the sympathetic is negligible as compared with that present in the more advanced cases. From the very first, however, vagus stimulation seems to be important. This is shown in the larynx, in hoarseness due to interference with the innervation, and also in the irritation which produces cough. It is likewise marked in the intestinal tract, as I shall now describe.

*Increased salivary flow.* This is present at times in tuberculous patients, though by no means constant. This could be due to reflex stimulation of the salivary glands through the vagus branch which courses with the chorda tympani. The dry mouth and coated tongue are almost always present during the periods of toxemia, and, at times, when this has passed away. This is an expression of increased sympathetic action.

*Coated Tongue.* A dry coating of the tongue is often noticed during periods of temperature in cases where toxemia is a factor. The drying effect on the secretions through the sympathetics must be thought of as an etiological factor. The fact that this is nearly always accompanied by a diminution of appetite and deficiency in gastric and intestinal efficiency makes the cause the more probable, for these other conditions are likewise due to deficient vagus tonus or increased sympathetic tonus.

*Stomach.* The disturbance on the part of the stomach in early tuberculosis, except during periods of acute toxemia and periods of depression are those which belong to the class of so-called nervous dyspepsias. The form which seems most common is a slight hyperacidity. This may be brought about by a reflex through the vagus, the impulse coming from the inflamed pulmonary parenchyma. The digestive powers are, if anything, above par. This may be a reason why the tuberculous patient at these times is able to care for such large amounts of food. Associated with the increased secretion there is also an increased motility and at times, a spastic constipation. This increased vagus tonus sometimes shows itself in a feeling which approaches nausea. These conditions, however, are not continuous. They alternate with decreased vagus tonus as mentioned above. This increased vagus tonus can be relieved by the administration of atropin, and following its administration hyperacidity and hypermotility often disappear. There are several factors which come in to cause sympathetic stimulation and inhibition of vagus action, notably reflex irritation, the toxemia and the depressed nervous state which is so common and which is characterized by mental depression, anxiety, discouragement and fear. These emotional states come and go all through the disease. They are sometimes dependent upon and sometimes independent of toxemia.

*Intestines.* A similar condition obtains in the intestinal tract where we have states of increased vagus tonus, causing increased secretion and increased motility, and abnormal sympathetic irritation inhibiting this and interfering with secretion and peristaltic action. Spastic constipation as a result of increased vagus tonus is common in early tuberculosis, while the atonic type is the rule later. Definite effects of each system are not so easy to point out in the intestinal tract because of the preponderance of stasis and constipation, which are regularly found in general life and which affect so many of those who are afflicted with tuberculosis prior to the time when the disease becomes manifest. We can say, however, that, as a rule, digestion becomes impaired and stasis and constipation become more pronounced as the disease advances and toxemia and the various depressive emotional states become more marked.

Thus, it would seem that early tuberculosis is largely a condition in which increased vagus tonus predominates over sympathetic stimulation, and advanced

tuberculosis a condition in which sympathetic irritation seems to be greater than the vagus tonus.

In offering this analysis of nervous action in tuberculosis, I realize fully that it is impossible to always point out the direct relationship between cause and effect; because we are dealing with a disease which produces dysfunction on the part of many organs and which results in a multitude of conditions which might produce symptoms similar to those which could be explained at one time by irritation of the sympathetics, at another by irritation of the vagus. It can be seen, however, that these two systems are to be taken into account, and that, as long as inflammation in the lung exists, so long are impulses carried to various organs through these two systems, which, acting antagonistically, disturb the normal equilibrium, which is so necessary to normal function.