The sympathetic nervous system in disease / by W. Langdon Brown.

THE SYMPATHETIC NERVOUS SYSTEM IN DISEASE

LANGDON BROWN

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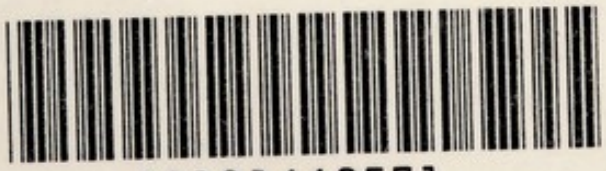

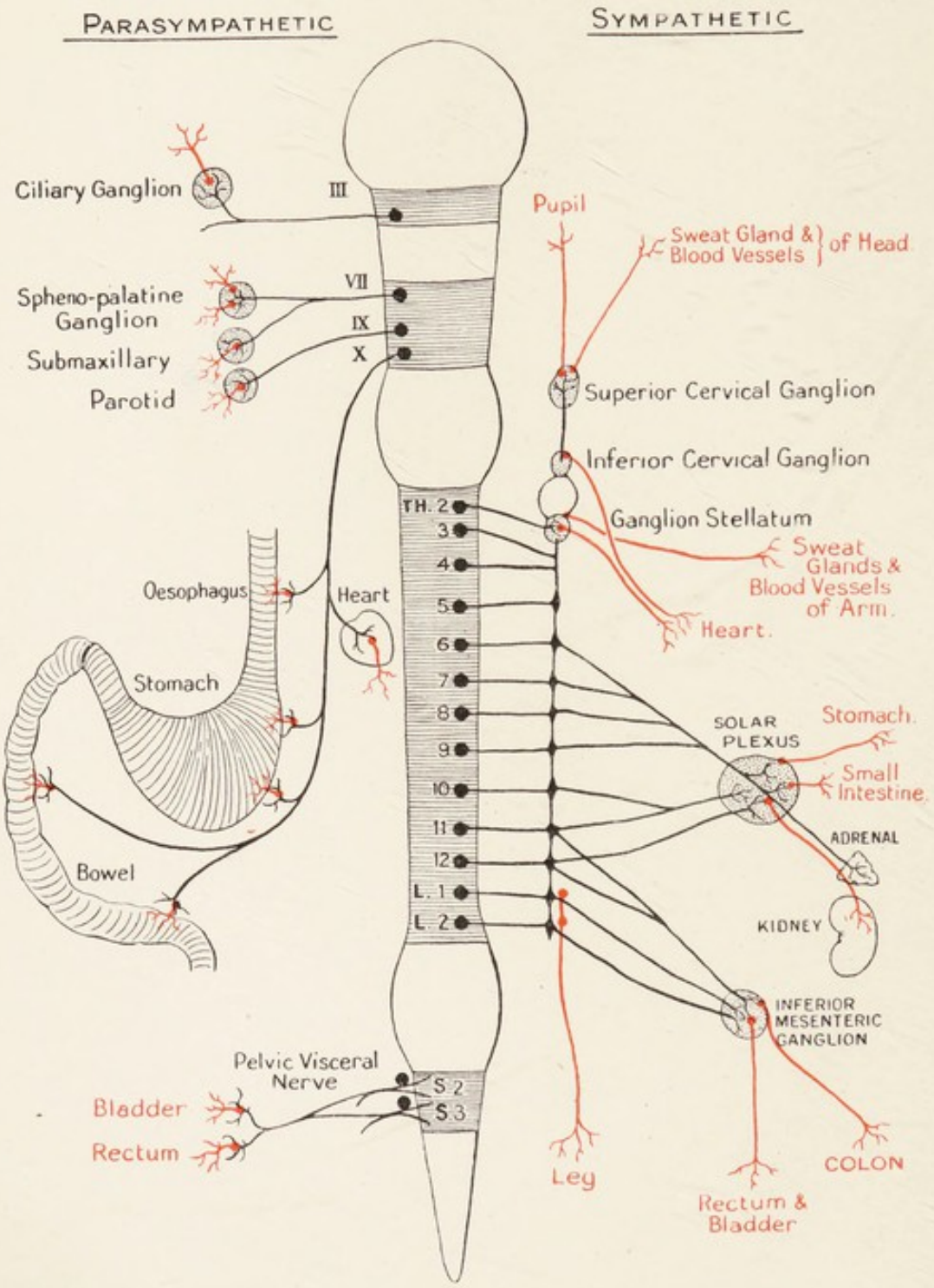

FIG. 1.—Scheme of the general arrangement of the Autonomic Nervous System, the distribution of the Sympathetic and Para-sympathetic portions being contrasted on the two sides of the diagram. Pre-ganglionic (connector) fibres in black, post-ganglionic (excitor) fibres in red.

THE SYMPATHETIC NERVOUS SYSTEM IN DISEASE

BY

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PREFACE

THIS book is based upon the Croonian Lectures delivered before the Royal College of Physicians of London in 1918. The kindly interest displayed in different quarters in those lectures emboldened me to hope that they might prove of service in an expanded and rearranged form. I find some justification for that hope now that a second edition has been called for, and have taken the opportunity to incorporate some new material, while thoroughly revising the whole.

I have not attempted to give a detailed account of the anatomy of the autonomic or vegetative nervous system. Several excellent accounts are already in existence, but the mass of detail necessarily involved tends to give the general practitioner an exaggerated idea of its complexity. I have aimed rather to emphasize its main plan. This is simple, and its comprehension aids in the elucidation of many clinical problems.

Nor have I attempted to describe in detail the reaction of the autonomic system to disease. Rather, I have chosen to illustrate its relations to a few large groups of disease—such as affections of the endocrine glands, of the digestive and circulatory systems, and glycosuria.

The close interaction of the endocrine glands with the sympathetic nervous system on the one hand, and with the reproductive organs on the other, is a fact of paramount importance in the understanding of the emotional response of the sympathetic nervous system, and of the influence of emotion on structure.

Just as the effects of psychic conflicts, shocks, and strains may show themselves not only at the highest level of the

nervous system as obsessions, but also at the sensori-motor level as contractures, palsies, tremors, and altered sensations, so they may reveal themselves in the still lower, autonomic level of the nervous system. I have referred but briefly to such topics, contenting myself with collecting some of the physiological and clinical data on which conclusions must be based if we are not to be lost in a maze of speculation. But I hope these data may serve as a contribution to that study of the unconscious mind which I am convinced will make rapid progress in the next few years. To this end the observation of war neuroses, alike in the soldier and the civilian, has already contributed much.

It is my pleasing duty to express my sincere thanks to the President and Censors of the Royal College of Physicians for honouring me with the invitation to deliver the Croonian Lectures. I must also express my indebtedness to the Editor of the *Lancet* for permission to republish those parts of this book which have already appeared in its columns.

W. Langdon Brown.

31, Cavendish Square, W.1.
December 1922.

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THE SYMPATHETIC NERVOUS SYSTEM IN DISEASE

CHAPTER I

THE PLAN OF THE AUTONOMIC NERVOUS SYSTEM

Although more than thirty years have passed since Gaskell first published his work on the Visceral Nervous System, it is only quite recently that the clinical bearings of his generalizations have been appreciated, chiefly owing to the writings of Cannon, and of Crile in America. In the same way it took a quarter of a century for his work on the heart to find its clinical application. Gaskell was essentially a pioneer in both fields, striking out entirely new paths. His was one of the greatest minds that have ever adorned British physiology, and he wrought better than he knew. Interested only in elucidating the main facts, without troubling himself as to their practical bearing, we are realizing to-day how much we are beholden to him for the explanation of many clinical phenomena, some of which it has required the shock, the stimulation, and the exhaustion of a great war to enforce upon our notice. To read an account of the sympathetic nervous system before Gaskell is like reading a description of the circulation before Harvey. Just as even the course of the blood was in doubt till Harvey elucidated it, so even the direction of the impulses in the sympathetic chain was uncertain till Gaskell made it clear. But in both of these great works there are essential gaps. Harvey did not know of the existence of the capillaries, and

Gaskell left many points still in doubt as to the course and distribution of the sympathetic impulses. Our gratitude to Gaskell must not blind us to our indebtedness to Langley, whose beautiful and accurate researches on this subject are of paramount importance. The elucidation of the plan of the sympathetic nervous system is almost entirely due to these two men, and remains one of the greatest achievements of the Cambridge School of Physiology.

Gaskell first showed that the nerve fibres which flowed from the spinal cord into the sympathetic chain were of a smaller calibre than the nerves to the skeletal muscles. Adopting this as a standard, he was able to show that there were fibres with visceral functions in the cranial and the sacral nerves (see figs. 2 and 3). Such fibres subserve the functions of organic life, and are not under the control of the will. Various names have been suggested to include all such visceral fibres. The term "autonomic nervous system," introduced by Langley, has, perhaps, met with the most general acceptance.[1] It will, therefore, be convenient to classify the whole of the visceral or involuntary nervous system thus (see fig.1) :

AUTONOMIC NERVOUS SYSTEM

1. Sympathetic (thoracico-lumbar outflow).
2. Para-sympathetic :
   - (*a*) Cranial outflow :
     - (i) From the mid-brain.
     - (ii) From the medulla.
   - (*b*) Sacral outflow.

These groups of sympathetic and para-sympathetic fibres are separated by the cervical and lumbar enlargements of

[1] In view of the two senses in which "autonomic" has been employed, the name "vegetative nervous system" has been suggested and is widely used in America. But vegetative is hardly an appropriate term for the violent reactions typical of this system.

the cord, which are devoted to the innervation of the somatic muscles of the limbs. So much have these areas become specialized for this purpose, that the limbs have to obtain their visceral fibres from the part of the cord which lies between them.

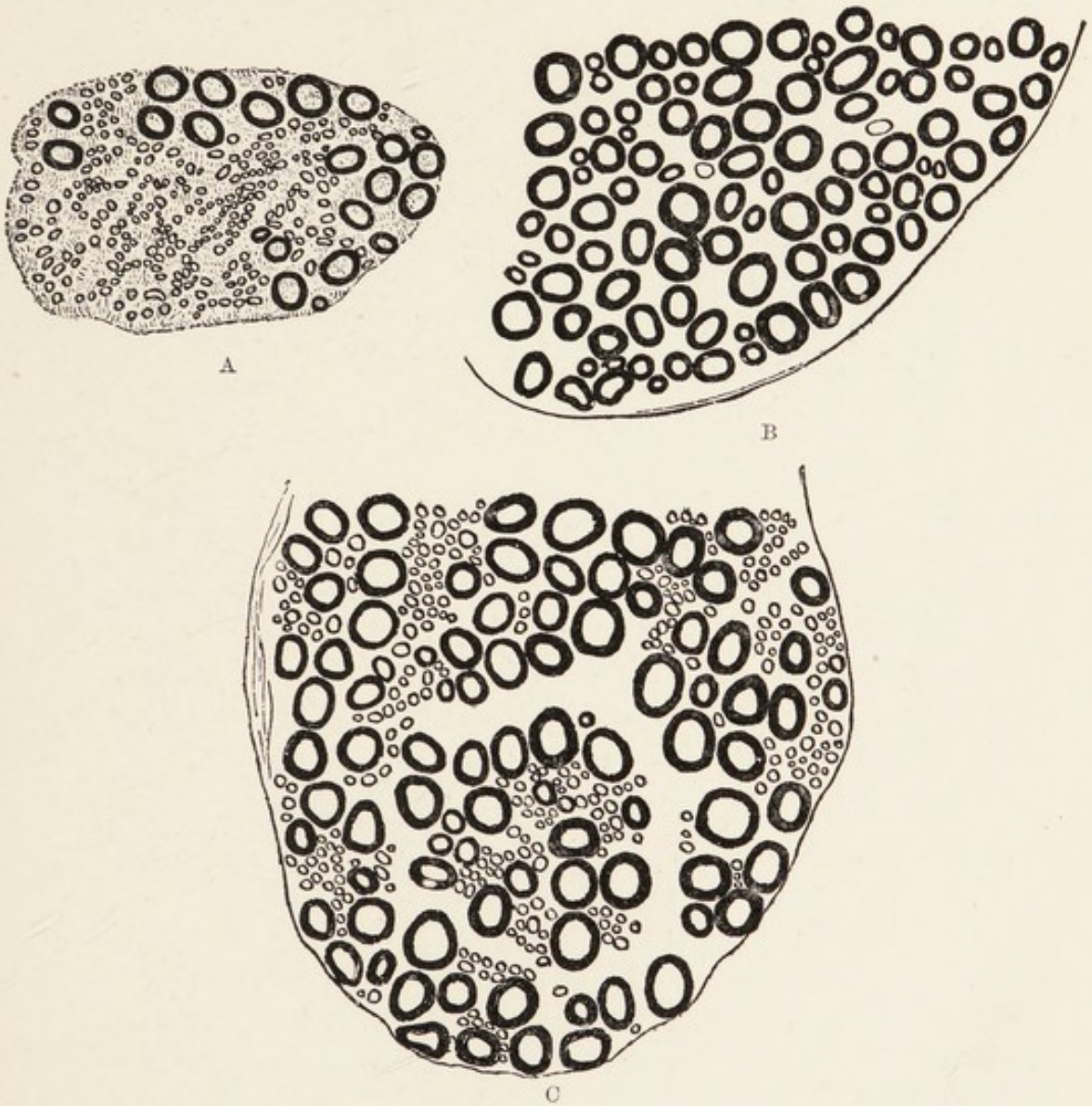

FIG. 2.—Sections across parts of the roots of various nerves of the dog, to show the variations in size of their constituent fibres (Gaskell).

A—from one of the upper roots of the spinal accessory.
B—from the first cervical anterior root.
C—from the second thoracic anterior root.

The small calibre of the fibres with visceral functions is clearly shown in A and C. Such fibres are absent in B.

The essential parts concerned in a reflex action are the receptor and excitor elements. The former consists

of an afferent fibre with its nerve cell, and an afferent root ending in the cord against another neuron. The receptor elements in the autonomic reflex will be considered later.

On the efferent side is the excitor element, consisting of the nerve cell in the anterior horn of the spinal cord,

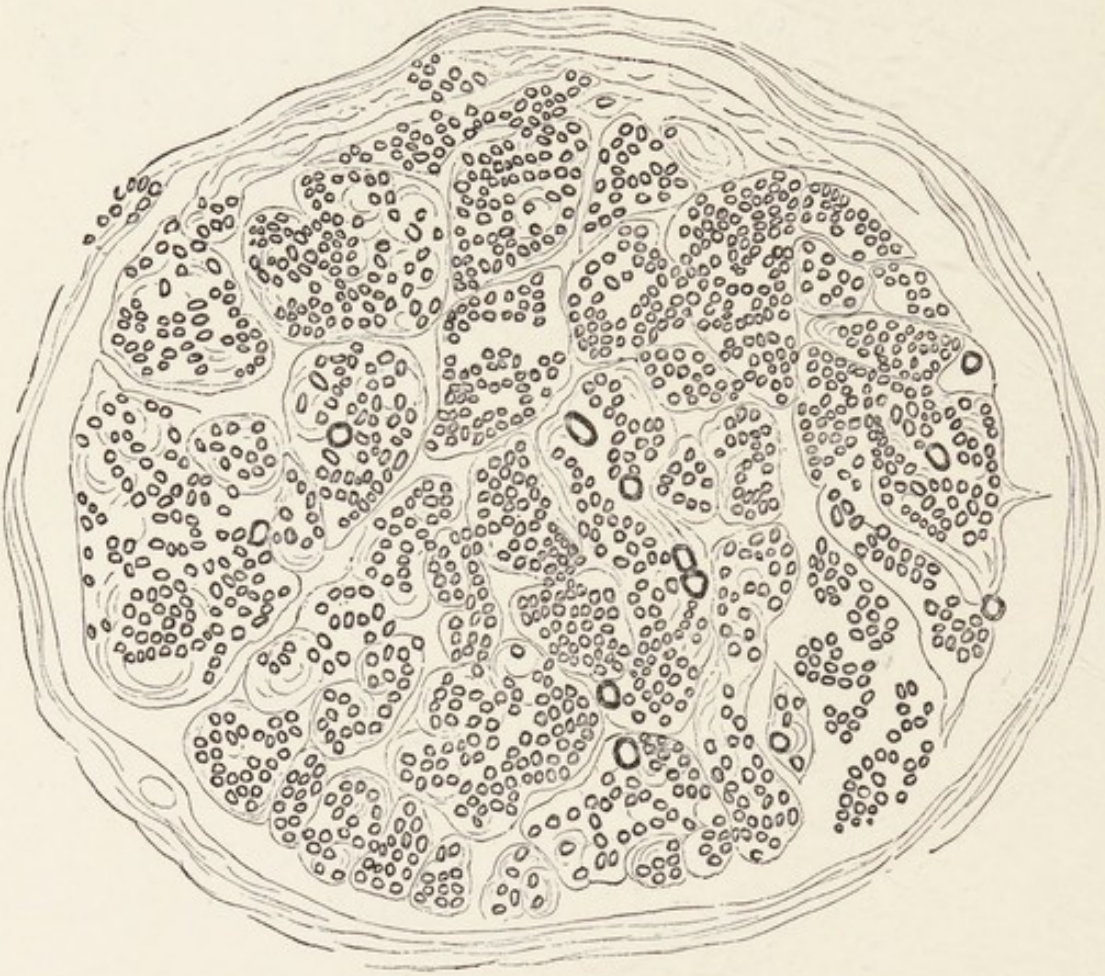

FIG. 3.—Section of a white ramus communicans from the dog (Gaskell). The section is drawn to the same scale as those shown in fig. 2. It shows that the small fibres pass into the ramus communicans, together with a very few large fibres, which latter are held to be afferent in function.

with its axon distributed to the muscle. Now, certainly in most cases, probably in all, the receptor element does not connect directly with the excitor, but there is an intermediate neuron, bringing the two into relationship. For this, Gaskell suggested the name "connector element."

The connectors need not simply associate receptors and excitors of somatic nerves in the same level of the cord: they may run up and down in longitudinal tracts, bringing neurons of different levels into relationship. Now, in the autonomic system, the outflow of small medullated fibres represents the connector element, while a cell in the

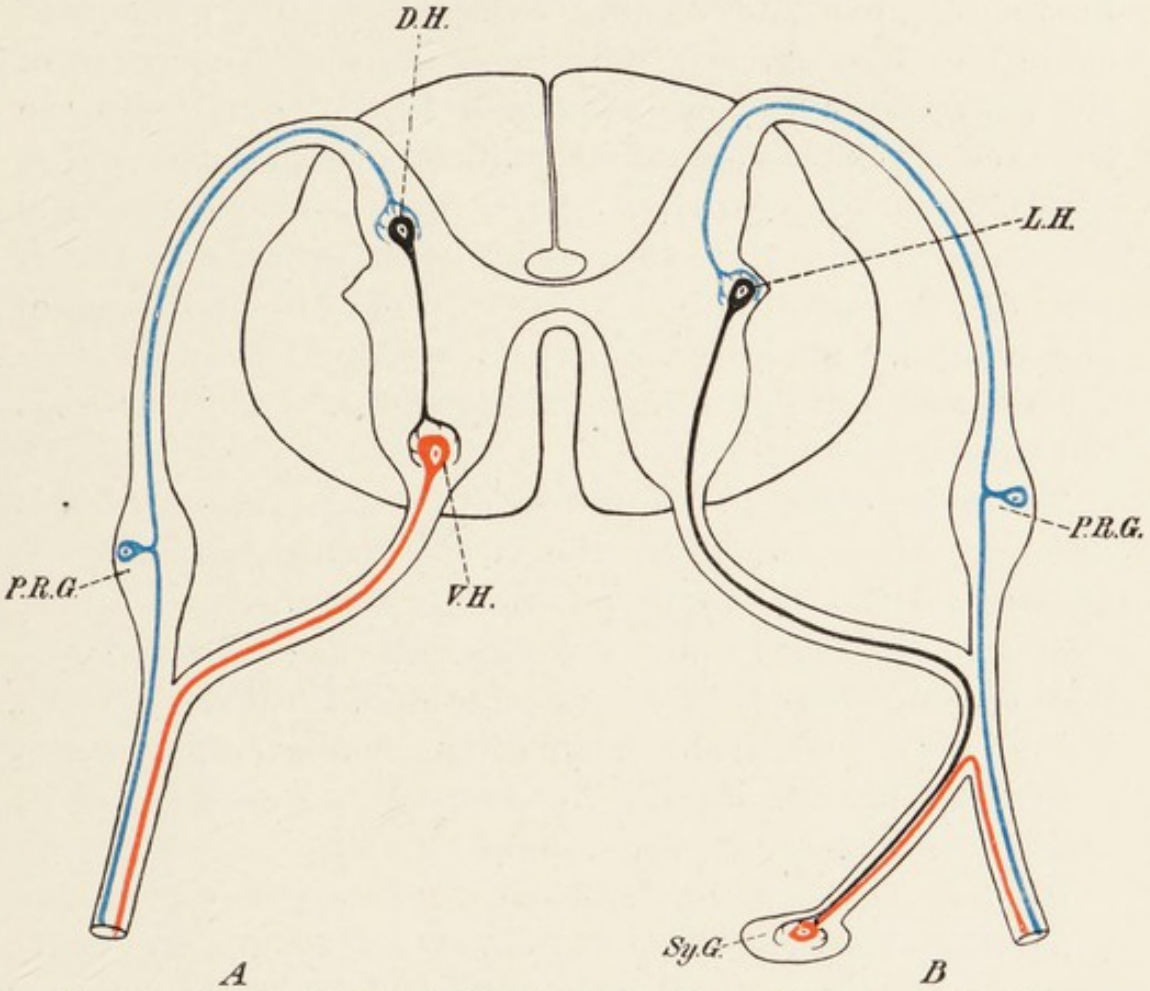

FIG. 4.—On the left-hand side the paths of an ordinary spinal reflex are shown; on the right the paths of a sympathetic reflex. It will be seen that the white ramus communicans in the latter corresponds to a fibre in the former which remains entirely intraspinal. The afferent fibres and cells are blue, the connector fibres and cells black, the excitor fibres and cells red. (After Gaskell.) *D.H.*, posterior horn cell; *L.H.*, lateral horn cell; *V.H.*, anterior horn cell; *P.R.G.*, posterior root ganglion; *Sy. G.*, sympathetic ganglion.

sympathetic ganglion, with its axon, represents the excitor element. For, as Langley showed by his nicotine method, every one of these small medullated fibres ends round cells in one or more sympathetic ganglia, whence

a new non-medullated fibre passes to its ultimate destination. Hence there is a connector pre-ganglionic medullated fibre, and an excitor post-ganglionic non-medullated fibre. Just as the connector element of somatic nerves may run longitudinally in the spinal cord, so the connector element of visceral nerves may run longitudinally in the sympathetic chain. Just as, in the process of evolution, the receptor cells have been withdrawn from the periphery into close proximity to the spinal cord, so the excitor cells of visceral elements have migrated from the cord into outlying ganglia. As Bayliss puts it: "Whereas the somatic nerves are formed by *axons* growing out from cells in the central nervous system, the autonomic system is formed by chains of *cells* growing out from the same system and forming axons subsequently." Fig. 4 brings out this contrast clearly.

When we come to inquire what is the purpose of this different arrangement in the two systems, we find the answer in the different functions performed by them. The somatic nerves are for localized accurate reflexes, the visceral nerves are for widespread diffuse effects. The secret of the arrangement of the sympathetic nervous system is its adaptation to produce, as easily and as speedily as possible, generalized effects.

Briefly to recall the anatomical arrangement of the sympathetic nervous system, there are two nerve cords along the entire ventral surface of the vertebral column, from the atlas to the coccyx, where they converge and unite in the single unpaired coccygeal ganglion. The cervical part of each cord has three ganglia: superior, middle, and inferior. The thoracic portion has eleven or twelve, the first two or three of which are fused into a single stellate ganglion, while the lumbar and sacral portions possess four or five ganglia. These thoracic and lumbar ganglia constitute the vertebral or *lateral* ganglia. In addition to being joined together by the sympathetic chain, they are united to the neighbouring spinal nerves by

white and grey rami communicantes, and they send out branches that either run directly to the peripheral organs or to more outlying ganglia. These last branches often enter into large plexuses, such as the solar plexus. The vagus also enters into such plexus formation. These more outlying ganglia are termed *collateral*. There are also smaller groups of cells situated more peripherally along the course of the different nerve trunks before these enter the visceral organs, or even after they have so entered, such as the plexuses of Auerbach and Meissner in the intestines. These ganglia of the third order are called *terminal* ganglia.

We must consider next, more precisely, how the sympathetic outflow reaches its destination (see fig. 5). The fine medullated pre-ganglionic connector fibre springs from a cell in the lateral horn: it passes out in the anterior root, which it leaves by a white ramus communicans (*r.a.*) to enter the sympathetic chain. It ends by forming synapses round cells in the lateral (*G.vert.*) collateral (*G.sol.*) or terminal (*p.G.*) ganglia. In this way a single connector fibre may stimulate a number of cells. From these cells start the non-medullated post-ganglionic excitor fibres, which pass to their destination mainly along blood-vessels to the deeper parts and along spinal nerves to the more superficial parts, being distributed to the latter by the grey rami communicantes (*r.g.*). This plan allows a wide radiation of sympathetic impulses, as was well shown by Langley in the case of the sympathetic fibres which erect hairs, the pilo-motor fibres. On stimulating a single grey ramus, the hairs will only erect over a single segmental area, but on stimulating a white ramus, erection occurs over a number of areas, usually five or six. The sympathetic ganglia, therefore, act as distributing-stations. Although every sympathetic impulse has one cell station outside the cord, no impulse passes through more than one such station: the excitor fibre runs straight to its destination. The term "made

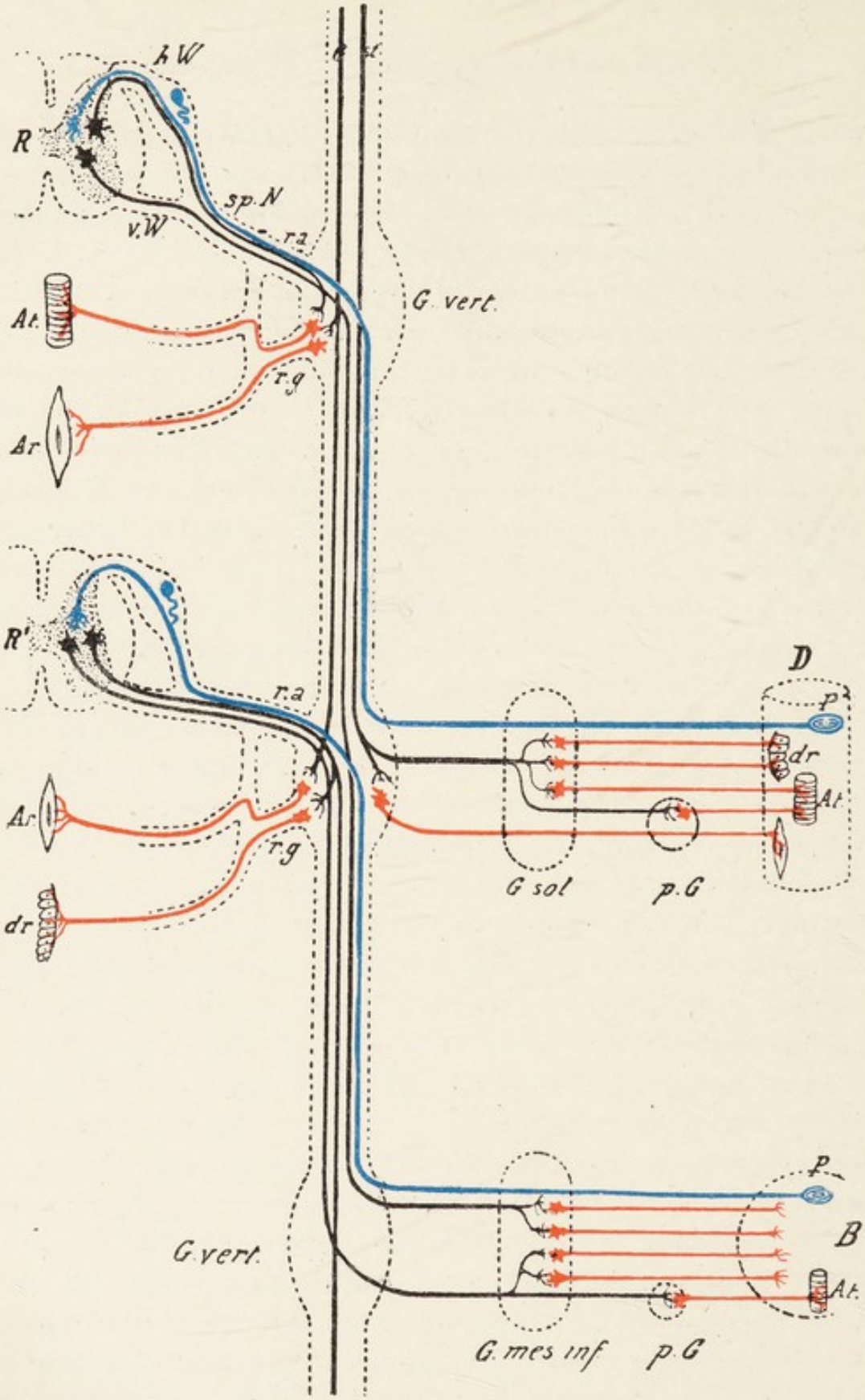

FIG. 5.—Diagram of the nervous elements which make up the sympathetic or splanchnic system (Baglioni).

R.R., spinal cord; *h.W.*, dorsal root; *v.W.*, ventral root; *sp.N.*, spinal nerve; *r.a.*, white ramus communicans; *r.g.*, grey ramus communicans; *G.st.*, lateral chain; *G.vert.*, ganglia of lateral chain (vertebral ganglia); *G.sol.*, solar ganglion; *p.G.*, peripheral ganglia (terminal); *G.mes.inf.*, inferior mesenteric ganglion; D, intestine; *B*, bladder. The left side of the figure shows the peripheral cutaneous system (*At.*, arterial walls; *Ar.*, erector muscles of hairs; *dr.*, gland cells). The right gives the peripheral splanchnic system (*Ar.*, arterial walls; *dr.* gland cells; *p.* Pacinian corpuscles). The afferent paths and cells are blue; the efferent pre-ganglionic, black; the efferent post-ganglionic paths and cells, red.

up spinal nerve" has been applied to the nerve which has shed its connector fibres and has received its quota of post-ganglionic excitor fibres. This make-up really amounts to a resegmentation of the peripheral impulses. In this way all parts of the body can be supplied with sympathetic fibres, although the original outflow is confined to the area between the limb plexuses.

There is no evidence that the lateral and collateral ganglia act as centres for reflex action. Their function appears to be confined to that of distributing-stations, as described above, allowing of a wide spread of the

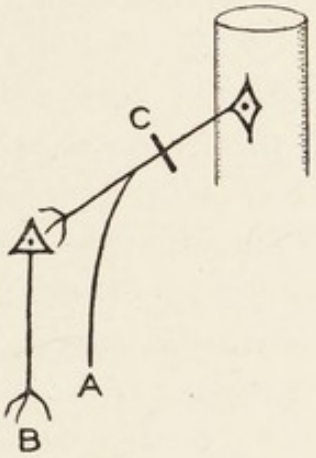

FIG. 6.
Axon reflex (Langley).

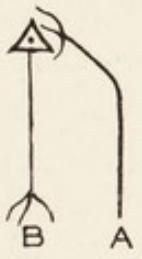

FIG. 7.
True peripheral reflex.

sympathetic impulse. Langley and Anderson showed that all observations to the contrary failed to take account of the possibility of "axon reflexes." Thus on stimulating at A in fig. 6 in a central direction, if a response occurs at B, it is possible that it is due to an overflow through a pre-ganglionic branch of fibre A stimulating the cell which governs B. In that case, if the nerve is cut at C and time is given for degeneration to occur, stimulation at A would be ineffective. This has actually proved to be the case, so that a true reflex as figured in fig. 7 can be excluded. With regard to the possible action of terminal ganglia as centres

of reflex action, direct experimental demonstration is wellnigh impossible, but indirect evidence is less conclusive against such a possibility. As shown in the chapter on Digestive Diseases, Bayliss and Starling regard the plexus of Auerbach in the intestine as the centre for the reflex act of peristalsis. Without invoking such an action on the part of the terminal ganglia, it would also be difficult to understand the results obtained in 1896 by Goltz and Ewald, who gradually removed the spinal cord of dogs, and yet maintained the animals in a good state of health for many months.

When we consider the results of sympathetic stimulation, we see that they all serve to activate the body for a struggle, and to increase its powers of defence. The pupil dilates to increase perception of light: the heart beats more quickly and more forcibly to supply the muscles with blood: the blood-vessels in the visceral area constrict, raising the blood-pressure and driving the blood from the digestive area, whose functions are simultaneously inhibited, into the skeletal and cardiac muscles, the lungs and the brain. The sweat glands are stimulated to cool the body heated by its excessive muscular effort, and the hairs are erected, in many animals, to render them more alarming. As Crile says: "The mechanisms for self-defence which we now possess were developed in the course of vast periods of time, through innumerable intermediate stages, from those possessed by the lowest forms of life. One would suppose, therefore, that we must now be in possession of mechanisms which still discharge energy on adequate stimulation, but which are not suited to our present needs." The pilo-motor fibres are an example of this, for, however useful the erection of hairs may be to a cat confronted by a dog, the "goose-skin" experienced by man under emotional stress can serve no useful purpose. Some emotional responses, like some of our bodily structures, are vestigial remains.

On turning to the para-sympathetic, we find that there are certain features of general resemblance between it and the sympathetic, with special differences correlated to the functions subserved. They both control functions of organic life and act apart from the will. They both arise from corresponding groups of cells, with pre-ganglionic elements composed of small medullated connector fibres, and conform to the rule that no efferent autonomic impulse runs from the central nervous system to muscle or gland without having a nerve cell on its course. The post-ganglionic fibres do not, in any case, run to other nerve cells of the system, but are distributed direct to the peripheral tissues, branching as they go. But the para-sympathetic fibres have their cell station close to their destination, so that the effects produced through the post-ganglionic portion are more localized and less widely spread. The cranial portion of the para-sympathetic sends fibres in the third nerve via the ciliary ganglion to constrict the pupil: in the seventh nerve through the chorda tympani via Langley's and the sublingual ganglion to the submaxillary and sublingual glands: and in the ninth nerve through Jacobson's nerve via the otic ganglion to the parotid gland, both these being secretory in function. But the main cranial para-sympathetic nerve is the vagus, which is distributed to the heart and to the alimentary canal, with its outgrowths—*i.e.*, lungs, liver, gall-bladder, and pancreas. The cell stations for the cardiac fibres are in the heart itself, and those for the alimentary tract are found in Auerbach's plexus. While motor and secretory to the alimentary tract and its outgrowths, it is inhibitory to the heart (see fig. 1).

Gaskell was able to show, both by the positive variation in the demarcation current of an injured heart and by the improved conductivity of cardiac muscle which follows vagus stimulation, that its inhibitory action may be looked upon as anabolic. The display of kinetic energy is replaced by the storage of potential energy.

And Cannon has extended this by pointing out that the functions of the cranial visceral fibres may all be regarded as anabolic. He says: "A glance at these various functions of the cranial division reveals at once that they serve for bodily conservation: by narrowing the pupil they shield the retina from excessive light, by slowing the heart-rate they give the cardiac muscle longer periods for rest and invigoration: and by providing for the flow of saliva and gastric juice, and by supplying the muscular tone necessary for contraction of the alimentary canal, they prove fundamentally essential to the processes of proper digestion and absorption, by which energy-yielding material is taken into the body and stored. To the cranial division of the visceral nerves, therefore, belongs the quiet service of building up reserves and fortifying the body against times of need and stress."

The sacral division of the para-sympathetic consists of the pelvic visceral nerve. It may be regarded, mainly, as a mechanism for emptying. "Like the cranial division, the sacral is engaged in internal service to the body, in the performance of acts leading immediately to greater comfort" (Cannon).

The next generalization that we owe to Gaskell is, that when the sympathetic and para-sympathetic are distributed to the same structure, the effects are antagonistic. The main functions of the sympathetic and para-sympathetic and their essential antagonism are given in Table I, modified from Langley. Thus the sympathetic dilates the pupil, and the para-sympathetic contracts it: the sympathetic accelerates the heart, while the para-sympathetic slows it: the sympathetic inhibits the movements of the stomach and bowels, while the para-sympathetic increases them: the sympathetic contracts the exit from the bladder, while the para-sympathetic relaxes it.

TABLE I

Effects of stimulating the mid-brain, bulbar and sacral para-sympathetic fibres.	Contrasted effects of stimulating the corresponding sympathetic nerves.
MID-BRAIN	
Contraction of iris.	Contraction of dilator of iris.
Contraction of ciliary muscle.	Contraction of unstriated orbital muscle. Contraction of arteries of eye.
BULBAR	
Inhibition of heart, and of vessels of mucous membranes of head.	Acceleration of heart and contraction of blood-vessels in mucous membranes of head.
	Inhibitory effects on smooth musculature of œsophagus.
Motor and inhibitory effects on smooth musculature of œsophagus and cardiac half of stomach.	Inhibitory effects on smooth musculature of gut from pyloric half of stomach to descending colon. Motor effects on sphincters of these regions.
Motor effects on smooth musculature of rest of gut down to descending colon.	
Motor effects on muscles of trachea and bronchi.	Inhibitory effects on muscles of trachea and bronchi.
Secretion of gastric glands and pancreas.	Inhibition of gastric glands and pancreas. Contraction of vessels of gut from œsophagus to descending colon. Contraction of vessels of bronchi. Contraction of vessels of abdominal viscera.
	Contraction of musculature of spleen, ureters, and internal generative organs. Contraction of smooth muscles and arteries of skin. Secretion of cutaneous glands.
SACRAL	
Inhibition of arteries of rectum, anus, and external generative organs.	Contraction of arteries of rectum, anus, and external generative organs.
Contraction of smooth musculature of descending colon, and rectum.	Inhibition of smooth musculature of descending colon, and rectum.
Inhibition of smooth muscles of anus.	Contraction of anus.
Contraction of bladder.	Inhibition and contraction of bladder.
Inhibition (? contraction) of urethra.	Contraction (? inhibition) of urethra.
Inhibition of muscles of external generative organs.	Contraction of muscles of external generative organs.

In pain, fear, rage and any intense excitement the sympathetic neurons are brought rapidly into play, and the action of the cranial division of the para-sympathetic is inhibited. In other words, the anabolic activities of the body are in abeyance, and the katabolic activities go on unchecked. Potential energy is converted into kinetic, and reserves are freely spent. This is comprehensible now that we see these katabolic activities are defensive in origin and aided the primitive animal in its struggle with its antagonist: and that complex organism the State, when at war, like the individuals of which it is composed, inhibits its anabolic activities, spends its reserves, and brings into play every katabolic activity which can aid it in its struggle for victory.

The Receptor Channels of the Sympathetic Nervous System

Although the bulbar and sacral autonomic nerve trunks apparently receive afferent fibres from all the organs to which they send efferent fibres, this is not the case with the sympathetic, which receives none from the body walls or limbs, nor from the head where it overlaps the bulbar autonomic. It receives relatively few from the region where it overlaps the sacral autonomic.

In the thoracic and abdominal viscera most of the afferent fibres, which on electrical stimulation give rise to pain, pass by the sympathetic and not by the vagus. Afferent fibres can be traced in the sympathetic from the Pacinian corpuscles in the cat's mesentery (see fig. 5, p. 8). They pass along the same spinal nerves as the efferent fibres, but there is no evidence of their being subdivided into pre- and post-ganglionic portions. There is no satisfactory evidence of the existence of non-medullated afferent fibres, and the medullated ones are large, not small like the efferent fibres (see fig. 3). They appear to have their trophic centres in the posterior

root ganglia, after passing by the white rami communicantes from the sympathetic chain.

The special features of the afferent nerves to the viscera may be briefly summarized as follows (Langley):

(1) The healthy viscera give rise to little or no sensation when cut. This is probably due to the comparatively small number of sensory fibres running to a given area. In pathological conditions, however, cutting may be painful, and strong contraction may give rise to intense pain.

(2) The localization of pain is very imperfect.

(3) In pathological conditions the viscera readily give rise to pain and tenderness in the body wall.

Each of these points calls for further consideration. Under normal conditions we are not clearly conscious of our internal organs, whereas the specific sensations aroused by the action of the outer world on the afferent nerves of our skin and special sense organs are the source from which our consciousness is developed. But, although secretory processes and the movements of the gut do not usually pass the threshold of consciousness, our internal sensations send impressions to the brain which affect and colour our individuality, and we become aware of any great change in them. Hence they may play a part in producing melancholia and hypochondriasis on the negative side, or a sense of well-being on the positive side. But the threshold of consciousness is not fixed or invariable. It may alter considerably in individuals who are specially predisposed or trained. Thus the neurotic learns to speak of his internal sensations with an intimate knowledge to which the normal man is a stranger. This is said also to be the case in some persons while in the hypnotic state.

Usually if our internal sensations are intense enough to affect consciousness they excite pain. As Luciani puts it: "The deep organs innervated by the sympathetic normally feel little pain, but they have a very high

latent sensibility which may become apparent under abnormal conditions, particularly in inflammation." It is difficult to imagine that this pain is conveyed by special nerves, which may never be called into action throughout the life of an individual or the history of a race. It is far more probable that, as Foster says, "the constant smouldering embers of common sensibility may be at any moment fanned into the flame of pain." Thus any sensation, whether of internal or external origin, if it becomes sufficiently intense, becomes painful.

Lennander believes, on clinical grounds, that all the pains produced in the abdominal cavity must be referred to the parts (and in particular the parietal peritoneum) innervated by the lumbar and sacral somatic nerves. When viscera are diseased they remain insensitive, but transmit the irritation to the sensitive parietal peritoneum, either by exaggerated peristalsis, abnormal distension, traction, or irritative chemical products. Similarly he refers intrathoracic pains to the pleura and pericardium, and intracranial pains to the dura mater.

But though serous membranes are probably an important source of visceral pain, they are not the only ones. Hurst, whose work on the Sensibility of the Alimentary Canal should be consulted for fuller details, points out that, in coming to the conclusion that the viscera are insensitive, Lennander did not take into consideration the fact that an adequate stimulus must be applied. The stimuli he used were cutting, pinching, and pricking, none of which occur under natural conditions. Tension on the fibres of the muscular coat of the alimentary canal is the stimulus which it naturally has to encounter, and this stimulus proves adequate to elicit pain.

The scantiness of the afferent fibres in the viscera and their defective power of localizing internal sensations have an important bearing on *referred pain*. Head pointed out that, when a painful stimulus is applied to a part of low sensibility in close central connection with a part of much

greater sensiblity, the pain is referred to the latter rather than to the former, where, however, the stimulus actually arose. To appreciate the clinical importance of this it is necessary to understand the distribution of cutaneous sensibility. The segmental arrangement of the primitive vertebrate still persists in the skin and muscles. Bolk calls the former *dermatomes*, the latter *myotomes*. Metamerism is more obvious in the former. Both have a ring-shaped distribution in the neck and trunk, but in the limbs the metameric arrangement has become obscured in a way which is only intelligible when we recall their development. When we remember that the limbs arise as buds which have their axes at right angles to the trunk, we can see that the higher segments will be distributed along the pre-axial or primitive upper side of the limb, while the lower segments are placed along the post-axial side. So that the lowest segments of all will be grouped around the coccyx and perineum, which represent the caudal region of the primitive vertebrate. The metamerism of such efferent sympathetic nerves as the pilomotor and vasomotor fibres to the skin corresponds with the dermatomes.

These dermatomes overlap one another to a certain extent; but in the central part of each, sensibility is still preserved when all overlapping is abolished by section of the neighbouring posterior roots (Winkler & van Rynberk, *Proc. Roy. Soc.*, 1901–2). The central portions of the dermatomes correspond with the zones of hyperæsthesia which Head found on the surface of the body in the presence of visceral disease. He explained them by saying that, when abnormal excitations from a diseased internal organ reach the cord by way of its afferent nerves, the excitability of the spinal segment becomes exaggerated, so that when another cutaneous excitation of low intensity reaches the same segment it provokes pain, whereas under normal conditions it would only arouse a sensation of contact. And he also was able to demon-

strate that the distribution of herpes zoster, which is due to an inflammation of one or more posterior root ganglia, corresponds to these zones of hyperæsthesia. Both are alike segmental. This fact that internal sensations have a cutaneous representation has provided us with a valuable method of localizing visceral disorders, as had previously been pointed out by Ross and by Sir James Mackenzie. A pin is drawn lightly over the surface of the body, and at a certain point its contact becomes distinctly painful. By repeating the process in different directions a zone is mapped out. Knowledge of the corresponding viscera innervated by the same spinal segment enables us to locate the source of the internal pain.

In many diseases of the stomach, particularly ulcer, there is a zone corresponding to the tenth left thoracic segment, which includes the umbilicus. In duodenal ulcer the tenth right thoracic segment may be found hyperæsthetic ; in angina pectoris the axillary portion of the third and fourth left thoracic ; in gall-stones the ninth right thoracic ; in appendix troubles the twelfth right thoracic. These are the ones that I have found particularly helpful in practice. Such zones may not correspond with the local tenderness elicited by pressure, which depends upon deep sensibility in the inflamed structure. Thus in gastric ulcer the epigastric tenderness is distinctly higher than the zone of hyperæsthesia. This tenderness, as Hurst showed, is located by the brain according to the average position of the part in which it originates, and the localization is accordingly most accurate in those viscera which are most fixed.

The Action of Drugs on the Autonomic Nervous System

The action of drugs on the autonomic nervous system is of interest and importance because they have assisted

in the analysis of its constituent parts, and because this response to pharmacological action has recently been adopted as the criterion of anatomical origin. Some consideration of pharmacological data may help towards comprehending the plan of the autonomic nervous system,

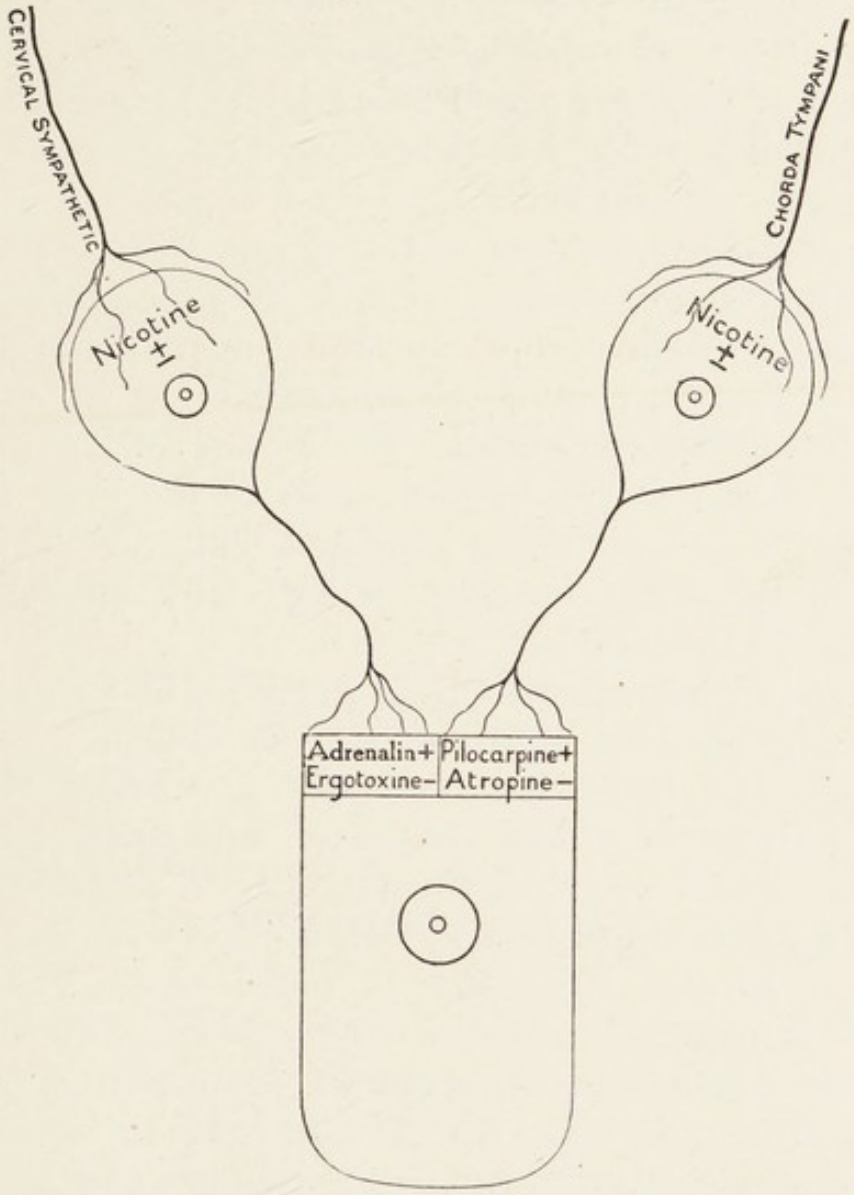

Fig. 8.—Diagram of double nerve-supply to salivary gland, to illustrate points at which different drugs act (Dale).

while indicating the pitfalls which beset the use of this method.

Drugs acting Centrally.—Certain drugs act centrally, others peripherally. Thus Timme gives *picrotoxin* as a central excitant and the *toxin of botulism* as a central

depressant of the para-sympathetic, while he classes *cocaine*, *atropine* and *caffeine* as central stimulants of the sympathetic, and *morphine* as a depressant. In horses, cows, and cats, however, morphine causes sympathetic central excitation, producing, for example, all the phenomena of fright in cats. But the peripheral effects of drugs on the autonomic nervous system are of more importance than the central.

Drugs acting on the Pre-ganglionic Terminals.—Thus Langley showed that *nicotine* first stimulated and then paralysed the pre-ganglionic synapses. Both these actions are more marked in the sympathetic than in the para-sympathetic nervous system. Some of these effects are masked by the primarily stimulating action of nicotine on the adrenals, leading to an outpouring of adrenalin with its usual consequent production of sympathetic effects. For this reason the action of the drug is more clean-cut if it is painted on the ganglion cell. These and other drug effects are clearly indicated in the above diagram by Dale (fig. 8).

Drugs acting on the Post-ganglionic Sympathetic Endings.—The action of *adrenalin* is detailed in the next chapter. It suffices here to say that it produces the same effect as that of stimulating the sympathetic nerves to the part concerned though the pilomotor muscles are but slightly affected, while the sweat glands are hardly influenced at all. *Ergotoxine* in sufficient doses paralyses all the sympathetic nerve-endings which are motor or augmentor in action, while those connected with inhibitor action are unaffected. By the combined use of adrenalin and ergotoxine, therefore, the inhibitory actions of the sympathetic are revealed and isolated.

Drugs acting on the Post-ganglionic Para-sympathetic Endings.—Just as adrenalin stimulates sympathetic effects, *pilocarpine* stimulates para-sympathetic effects. Its actions have been summarised by Dale as follows: Acceleration of all glandular secretions, except those which appear not to be under nervous control—viz.,

the bile, the milk, and the urine; contraction of the plain muscle of the eyeball, of the bronchioles, of the whole alimentary tract, the bladder and the uterus; inhibition of the heart-beat, giving way, if the dose be large, to secondary paralysis of the vagus mechanism, with acceleration of the beat; certain secondary effects attributable to accelerated output of adrenalin, among which is glycosuria. There is a leucocytosis, which, according to Harvey, is a lymphocytosis, attributable to contraction of the plain-muscle coats of the spleen and lymph glands. Now, it will be noted that, while the majority of these effects can be attributed to para-sympathetic stimulation, others cannot. Thus pilocarpine has a marked effect on the sweat glands, which have a sympathetic supply. It has a similar effect on the uterus to the sympathetic, while the contraction of the spleen and of the nictitating membrane of the eye are both sympathetic effects.

Muscarine has a closely similar action to pilocarpine, but its effects on involuntary muscle are relatively greater, and those on secretory glands less marked. Its most conspicuous effect is inhibition of the heart by stimulation of vagus nerve-endings. Chemically it is related to cholin, and it is interesting to note that recent work has found in *acetyl-cholin* the most discriminating of all the stimulants to para-sympathetic terminals.

Physostigmine is another drug which stimulates para-sympathetic endings. It acts most intensely on the ciliary muscle, and in general its effect is more marked on involuntary muscle than on secreting glands; like pilocarpine, it can act on the uterine muscle and on vaso-constrictor muscles which have no para-sympathetic nerve-supply.

Atropine is antagonistic to all this group of para-sympathetic stimulants, but its action is not so overwhelmingly potent against physostigmine as against pilocarpine or muscarine. It is easy to diminish an atropine paralysis by physostigmine, and to check or paralyse the stimulating

effect of pilocarpine by atropine. Atropine diminishes secretions in general, and entirely arrests most when given in adequate doses. Those which escape its effect are those which are not under nervous control or only partly so. This paralysing effect of atropine is as marked on sweat glands as the stimulating effect of pilocarpine. The sweat nerves, therefore, show a pharmacotropic affinity with the para-sympathetic, although they belong morphologically to the sympathetic. But considering the selective action of drugs on certain structures—*e.g.*, on muscles as compared with glands—this fact cannot override morphological considerations as Eppinger and Hess have allowed it to do in their hypothesis of vagotonia. Atropine can readily paralyse the inhibitory effect of the vagus on the heart. It only acts on the unstriped muscle of the œsophagus, leaving the striped muscle unaffected. It has little effect in paralysing vaso-dilators, or on the muscles of the stomach, bowels, and bladder.

All these actions are summarized in fig. 8; the + sign representing stimulation, the — sign paralysis.

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CHAPTER II

THE SYMPATHETIC NERVOUS SYSTEM IN RELATION TO THE ENDOCRINE GLANDS

It is both interesting and suggestive to note that an important group of endocrine glands—the adrenals, the thyroid, and the pituitary—have three features in common ; the secretion of each is stimulated by the sympathetic, they all lower carbohydrate tolerance, and they all act and react with the reproductive organs.

As Starling pointed out, the development of a nervous system is a comparatively late event in evolution ; the stimuli to which the most primitive forms of life respond are chemical. Thus a plasmodium turns away from boiled water and creeps towards an infusion of dead leaves, a process we call chemiotaxis. As soon as we pass from the protozoa to the metazoa, the continuity of the species depends not on simple fission, but on special germ cells. And as differentiation proceeds the chemical stimulants, or hormones of the body, become concentrated and specialised in certain ductless glands. The close association between reproductive and endocrine glands is thus based deep in evolution. The development of a nervous system enables response to be much more rapid than can be achieved by simple chemical reaction. Now, clearly the first purpose for which rapid response would become most vital is that of self-preservation. As I showed in the first chapter, the sympathetic nervous system is specially adapted for rapid and widespread reaction in the struggle for existence. It is only to be expected that this newer

express route would be evolved in connection with the more primitive mechanism, so that as both endocrine glands and the sympathetic nervous system became specialised they remained associated. This association is reciprocal—as not only does the sympathetic nervous system stimulate the secretion of these ductless glands, but their secretion increases in turn the sympathetic response. Thus the sympathetic nervous system, the endocrine glands, and the gonads form a basic tripod entrusted with the duty both of the preservation of the individual and the continuity of the species. Their relationship is shown in disease as well as in health, and is reflected in many of the neuroses and psychoses.

The Adrenals

I will deal with the adrenals first, since their association with the sympathetic is the closest of all. They are the one exception to the rule that connector fibres are not distributed direct to a muscle or a gland, since the adrenal nerves are pre-ganglionic. And, to use a phrase often erroneously employed with tiresome reiteration, this is really an exception which proves the rule. For the chromaffin cells of the adrenal medulla are nervous in origin, and important results follow from this apparent exception. Phylogenetically, embryologically, and functionally, the adrenals and the sympathetic are in the closest association. The chromaffin cells appear to originate in the central nervous system, and in the segmented worms they remain there. When, in evolution, the sympathetic cells emigrate from the central nervous system into outlying ganglia, they are accompanied by the chromaffin cells. "In the lowest vertebrate (Ammocœtes) . . . masses of them are still found close against the cells of the posterior root ganglia. . . . As we pass from the lowest to the highest vertebrates, the sympa-

thetic cells become more numerous and the chromaffin cells diminish in number, until at last in the mammalia the sympathetic system is fully developed, and the chromaffin system reduced to the cells found in the medulla of the adrenals. The evidence of embryology and comparative anatomy thus points strongly to the conclusion that the sympathetic nervous system arose from nerve cells containing adrenalin . . . and that when these cells left the central nervous system to become peripheral, they left not as single cells, but as two separate cells, one of which contained all the adrenalin and formed the chromaffin system, and the other the nerve cells of the sympathetic system of the vertebrate" (Gaskell). This throws a flood of light on the meaning of the adrenals. It explains why in them alone the connector fibres end, and prepares us for Langley's generalization that the effect of adrenalin on any part is the same as the stimulation of its sympathetic nerve. For the chromaffin cell represents the excitor element.

In the adrenals we have a most interesting example of the correlation of nervous and chemical stimuli previously referred to. With the development of the sympathetic system the chromaffin cells are reduced in extent and concentrated in position. The sympathetic, as the defensive mechanism of the body, pre-eminently needs the power of rapid response, but the chemical stimulant is still retained. The sympathetic excites a secretion of adrenalin, and adrenalin increases the sensitiveness of the response to the sympathetic. Just as we have *vasa vasorum* and *nervi nervorum*, so we may look upon the relationship of adrenalin to the sympathetic as that of *excitor excitorum*.

Many observers have found an increased amount of adrenalin in the circulation after stimulation of the splanchnic nerves. Elliott showed that if one adrenal is isolated by cutting its splanchnic supply, and the other is stimulated, either electrically or emotionally, adrenalin

remains in the isolated gland, but is diminished in the other. The proof, therefore, appears complete that stimulation increases the output of adrenalin. This emptying of the adrenalin reservoirs occurs not only in direct stimulation of the splanchnics and in strong emotions, but also in trauma and acute infections. The wide differences between the various effective stimuli is in itself suggestive. This mobilization of adrenalin serves a useful purpose in that it lowers the threshold to sympathetic stimuli which, by acceleration and augmentation of the heart-beat, raising blood-pressure, altering the distribution of blood, causing sweating, dilating the pupils, and inhibiting digestive activities, aid in defence. But adrenalin appears to have other actions, also obviously advantageous, for it increases the blood-sugar, hastens the clotting of blood, and diminishes muscular fatigue. When Blum, in 1901, found that injection of adrenalin would produce glycosuria it was regarded as a toxic action ; it was not suspected that this was a pathological exaggeration of a valuable physiological function. Noel Paton and Drummond showed that this glycosuria was associated with hyperglycæmia. I shall discuss the production of this hyperglycæmia in more detail in my chapter on Glycosuria. Here it suffices to point out its defensive value. Muscle in action can consume three and a half times as much sugar as resting muscle. Schumberg found that the ability of his muscles to do work, as tested by the ergograph, was greater if he drank a sugar solution than if he drank an equally sweet solution of dulcite. As he did not know which solution was given him, the influence of suggestion was eliminated. The increased blood-sugar must, therefore, be an advantageous preparation for the muscular efforts necessary in the impending conflict, and it is provided by the sympathetic without calling upon the digestive powers of the body, which are then in abeyance. In so far as the excess of blood-sugar overflows into the urine, it is wasted, but

probably, in general, physiological stimulation does not reach this level. That it occasionally does so was shown by Cannon and Fiske, who found that, out of twenty-five members of a Harvard University football squad, twelve had glycosuria immediately after the final and most exciting contest of the season. It is noteworthy that five of these men were substitutes not called upon to enter the game. "Emotion moves us," says Sherrington; "hence the name." But when, under conditions of modern life, emotion is dissociated from the movement it should evoke under more natural conditions, the preparations made for that movement are wasted. It is, therefore, not surprising to find temporary glycosuria more commonly in intense pain and emotional excitement than after strenuous exertion. This is only one example of that dissociation of sympathetic stimulation from the action to which it should be preparatory. I think this principle explains some of the phenomena of disease, and renders intelligible the fact that worry is more injurious than work. Crile quotes the saying, "When stocks go down in New York, diabetes goes up."

Next as to the influence of adrenalin in hastening the clotting of blood. Vosburgh and Richards were the first to claim this influence, but it has been denied by Wiggers. Cannon and Gray investigated this point more carefully in 1914, and concluded that adrenalin usually definitely hastens coagulation. For some time it has been known that exclusion of the liver from the circulation greatly lengthens coagulation time: the liver appears to furnish continuously to the blood a factor in clotting which is as continuously destroyed in the body. They suggested that adrenalin may stimulate the liver to discharge this in greater abundance. With Mendenhall, Cannon found that, though stimulation of the splanchnic normally hastened clotting, this did not occur in the absence of the adrenals. To avoid the depressing effect of total excision, they made use of Elliott's observation that in the cat the

splanchnic innervation of the adrenals is uncrossed. One adrenal was removed, and it was found that stimulation of the corresponding splanchnic did not hasten clotting, while stimulation on the intact side did. They also found that central stimulation, which would cause pain in the conscious state, increased the speed of clotting in the anæsthetized animal, and that clotting occurred more quickly in the enraged animal. According to Grabfield (*American Journal of Physiology*, 1917, vol. xlii, p. 46) adrenalin acts by increasing the amount of prothrombin in the circulating blood. The conservative value of this sympathetic-adrenalin effect in diminishing loss of blood in a conflict is self-evident.

Lastly among these actions of adrenalin comes its influence on fatigue. In Oliver and Schafer's original paper on adrenal extract, they stated that it improved the height and duration of voluntary muscular contraction in the frog. This seemed to explain the profound atony of the skeletal muscle in Addison's disease, which is not only a familiar clinical observation, but was demonstrated more precisely by Lombard with the ergograph, by the rapid development of the fatigue curve in patients suffering from this disease. I was, therefore, perplexed by the statement of later observers that adrenalin did not act on structures which had never been innervated by the sympathetic. Some observations certainly suggest a sympathetic influence on the tone of striped muscle, but they are by no means conclusive. In consequence of this statement, it has usually been assumed that the muscular atony of Addison's disease was due to the low blood-pressure, and consequent poor supply of blood to the muscles. To a certain extent this is true, for Grüber showed that increased blood-pressure was able to restore normal irritability to fatigued muscle, even when the adrenals had been removed. That this low pressure is partly responsible is easily intelligible, for a good circulation is required to remove those metabolites which are

such a powerful factor in inducing fatigue. But Oliver and Schafer's observation was made on excised muscle, where such an explanation would not apply. It is interesting, therefore, that Grüber found that, although adrenalin did not increase the irritability of normal muscle, it promptly lowered the threshold stimulus necessary for fatigued muscle, even when a rise of blood-pressure was prevented. The restoration of a fatigued muscle, which is effected by resting for an hour, is accomplished by adrenalin in five minutes.

Cannon, in summing up the results of this interesting series of researches, says: "Thus [adrenalin] plays an essential rôle in calling forth stored carbohydrate . . . flooding the blood with sugar: it helps in distributing the blood to the heart, lungs, central nervous system, and limbs, while taking it away from the inhibited organs of the abdomen. It quickly abolishes the effects of muscular fatigue, and it renders the blood more rapidly coagulable. These remarkable facts are, furthermore, associated with some of the most primitive experiences in the life of higher organisms, experiences common to all, both man and beast, the elementary experiences of pain, fear, and rage, that come suddenly in critical emergencies. . . . The most significant feature of these bodily reactions . . . is that they are of the nature of reflexes, they are not willed movements; indeed, they are often distressingly beyond the control of the will." Now, one of the features of a reflex is its purposive character. The reflex of a skeletal muscle is not voluntary, but it is purposive, and by its means, for example, our eyes are protected from foreign bodies, and we recover our balance before we are conscious that we have slipped. Just so these emotional reflexes are purposive and defensive, but, as I have already said, they were evolved under conditions which differed from those now existing, so that the reaction sometimes becomes inappropriate. If we seek for an explanation of the similarity of the sympathetic response to fear, pain,

rage, and other strong emotions, we may find it given admirably by Darwin in his " Expression of the Emotions in Man and Animals " : " In the agony of pain, almost every muscle is brought into strong action . . . for great pain urges all animals, and has urged them during endless generations, to make the most various and diversified efforts to escape from the cause of suffering. . . . A man or animal driven through terror to desperation is endowed with wonderful strength, and is notoriously dangerous to the highest degree." And again : " Men through numberless generations have endeavoured to escape from their enemies or danger by headlong flight or by violently struggling with them, and such great exertions will have caused the heart to beat rapidly, the breathing to be hurried, the chest to heave, and the nostrils to be dilated. As these exertions have often been prolonged to the last extremity, the final result will have been utter prostration, pallor, perspiration, trembling of all muscles or their complete relaxation. And now, whenever the emotion of fear is strongly felt, though it may not lead to any exertion, the same results tend to reappear, through the force of inheritance and association." Crile illustrates this by a modern instance and a modern simile : " And now, though sitting at his desk in command of the complicated machinery of civilization, when he fears a business catastrophe his fear is manifested in the terms of his ancestral physical battle in the struggle for existence. He cannot fear intellectually, he cannot fear dispassionately : he fears with all his organs, and the same organs are stimulated and inhibited as if it were a physical battle with teeth and claws. . . . Nature has the one means of response to fear, and, whatever its cause, the phenomena are always the same, always physical." " Under modern conditions of life, neither fight nor flight is *de rigueur*. The individual under the stimulation of fear may be likened to an automobile with the clutch thrown out, but whose engine is racing at full speed. The petrol

is being consumed, the machinery is being worn, but the machine as a whole does not move, though the powers of its engine may cause it to tremble."

McDougall gives us another reason for this similarity of response of the sympathetic to different emotions when he points out how all instinctive impulses, when met with opposition, give rise to, or are complicated by, the combative instinct directed against the source of opposition. The dog threatened with the loss of the bone he is eating, the conflict of the males for the possession of a mate, the maternal instinct converted into the anger of combat against an attempt to injure her young, are examples which will occur to the mind at once. There is, indeed, as Cannon says, obvious reason why the visceral changes in fear and rage should not be different, but rather why they should be alike : these emotions accompany organic preparations for action.

But we can extend this idea and explain thereby some of the responses of the body to asphyxia, infections, and shock. To take asphyxia first, why should deep emotion be accompanied by deep respirations ? As emotion is a preparation for movement, we can understand that deep respirations are needed to lower the alveolar content of CO_2 in anticipation of the augmented discharge of CO_2 into the blood which these movements will produce. Sympathetic-adrenalin action also relaxes the bronchial muscles, as is seen when adrenalin is given for asthma, and this facilitates respiratory exchange. But if the emotional response to exertion is inadequate, the exertion itself augments the response, for imperfect oxidation means that lactic acid is produced, which is a further stimulant to the respiratory centre, and hence there is a still greater increase in the respiratory rhythm. If this is still inadequate, the onset of asphyxia still further increases the output of adrenalin, and shows the characteristic sympathetic effects by raising the blood-pressure, exciting sweating and dilatation of the pupils, increasing

the blood-sugar, and relaxing the bronchial muscles. If the response to all this is adequate, respiratory distress abates, and the man gets his "second wind." But if oxidation is still insufficient, the next step is still defensive in character, though a desperate one. The powers of offence are paralysed, while the vital mechanisms are stimulated still further. For, as Crile points out, acidity, when carried too far, inhibits the functions of the cerebral cortex, while stimulating those of the medulla. This antithetic reaction to increased hydrogen-ion concentration is an adaptation to prevent an animal from killing itself by over-exertion, for the mechanisms for initiating a discharge of energy are in the higher centres, while the essential part of the mechanisms for the neutralization of acid metabolites, the centres governing circulation and respiration, are in the medulla. Clinical equivalents which will readily occur to the mind are the air-hunger in the acidosis which precedes diabetic coma, and the "asthma," also due to acidosis, which may anticipate uræmic coma. It is clear that the onset of asphyxia is drawing on the final reserves, bringing exhaustion in its train: so that, in its final stages, we see a reversal of many of the effects above described. There is then complete muscular relaxation, the respiration is slow, the blood-pressure, after showing Traube-Hering oscillations, falls, and the heart fails. Asphyxia, through striking at a vital process, may show us the whole series of events of sympathetic-adrenalin excitation and exhaustion within the compass of a few minutes. But we must beware of too facile an interpretation of these facts, and avoid forcing them too far into the general picture. There is, for instance, another factor to which I have referred which may be of importance, the rapid development of acidosis.

The same caution is needed in the interpretation of traumatic shock. Unfortunately, during the war there was opportunity of observing traumatic shock on a large

scale, but, fortunately, the opportunity was seized. I shall deal with these researches in my chapter on the Circulatory System. For the present I want to call attention to the fact that, although the body may respond to trauma in the same way as to emotion, as Crile urged, shock may be fully developed before sympathetic-adrenalin exhaustion can have come on. Thus the amount of adrenalin (Bedford and Jackson) and of sugar (Cannon) may still be high in the blood when shock is profound.

With the reservation, then, that the development fo shock is a more complicated matter than mere sympathetic-adrenalin stimulation succeeded by exhaustion, we can still agree with Crile that, as fear is born in innumerable injuries in the course of evolution, the initial response to trauma and to fear is likely to be similar. Sherrington showed that the shock-producing receptors or noci-ceptors, as he termed them, were most developed in certain regions of the body which, as Crile observes, have been exposed to injury through long periods of time. The abdomen and chest stand first in their facility for causing the discharge of nervous energy—*i.e.*, they stand first in shock production. Then follow the extremities, the neck and the back. In this connection it is interesting to note the instinctive effort of an animal to get at the ventral surface of its antagonist, and also that tearing, crushing injuries cause a much greater response than the clean cut of a knife, for these were the injuries to which primæval man was most subjected.

A further interesting point, in confirmation of these views, is that animals with some natural means of protection have few noci-ceptors, show little fear, and suffer but slightly from shock. For instance, the turtle, the porcupine and the skunk all feel fairly safe, though for different reasons. " It seems more than a coincidence that proneness to fear, distribution of noci-ceptors, and susceptibility to shock go hand-in-hand " (Crile).

The reaction to infection, similarly, shows in the

quickened pulse, the initial shivering, the subsequent sweating, the inhibited digestive processes, and in the increased katabolism necessitated by fever, the resemblance in the behaviour of the body towards the seen and the unseen antagonist. And Crile extended these superficial points of resemblance when he demonstrated the increased adrenalin content of the blood which followed the injection of the toxins of *Bacillus coli communis*, streptococci and staphylococci, and even of foreign proteins. Cramer has demonstrated increased secretory activity of the adrenals in fever of bacterial origin, heat-stroke, and after injection of a drug like T.H.N., which excites hyperpyrexia. Elliott and Tuckett had previously found a marked reduction of chromaffin substances in the adrenals in fatal cases of diphtheria, so that here the excessive secretion is certainly followed by exhaustion. I suggest that in more prolonged infections exhaustion predominates in the fatal issue ; in the more acute, shock will be the most important factor.

And I may sum up this part of my subject by saying that, as the sympathetic normally acts as a whole and according to a pattern evolved by the most vital necessities, all critical stresses evoke a response on the same general plan. But the body is too complicated a mechanism to break down in only one way, and the initial response will be differentiated and graded to meet varying strains. In this way we may appreciate the importance of the co-operation of the adrenals and the sympathetic without overstating it.

It is only fair to state that Stewart and Rogoff, in a series of papers, have opposed the whole theory of the emergency action of adrenalin. In order to prevent the complication arising from the development of pressor substances in shed blood, they collected the adrenalin in a pocket of the inferior vena cava made by tying the vessel above and below the point of entry of the adrenal veins. On releasing the upper

ligature, the entrance of adrenalin into the general circulation was judged by the resulting dilatation of the pupil and by its effect on segments of uterine and intestinal muscle. The spontaneous discharge of adrenalin into the circulation of cats was found to range within rather narrow limits, and its percentage in the blood to vary inversely with the rate of blood-flow. The excision of one adrenal and denervation of the other were compatible with the maintenance of normal health, but appeared to stop the discharge of adrenalin completely for as long as five weeks after the operation, although massaging the remaining gland led to renewal of its flow. Peripheral stimulation of the splanchnics always increased the secretion of adrenalin, and they located the centre controlling this secretion in the upper three thoracic segments. As they found that the section of one splanchnic diminishes the discharge of adrenalin by one-half without causing any material fall of blood-pressure, they concluded that adrenalin was not an important factor in maintaining this pressure. They were unable to find any increased secretion in asphyxia or ether anæsthesia, or on central stimulation of sensory nerves. They did not think that the emptying of the adrenals when morphia is administered to cats had anything to do with the associated fright, as Elliott urged, since this occurs in dogs when there are no signs of fright. "Morphia fright" can also be elicited in a cat with one adrenal removed and the other denervated, where no emptying of the gland occurs. When a dog frightens a cat (each with one adrenal nerve-supply cut), the amount of adrenalin on both sides remains about the same in each animal, although both show intense excitement. Marked depletion of adrenalin occurred in the innervated glands of animals dying from various infections, in striking contrast to the effect seen when the glands were denervated. They found hyperglycæmia in asphyxia or anæsthesia when no adrenalin was being secreted, because one gland

was excised and the other denervated, and that while so-called " emotional " hyperglycæmia is not a constant, or even a common, phenomenon in cats, in any case it does not depend upon increased adrenalin output. They concluded that sugar mobilization is not mediated through the reaction to adrenalin. Their results, therefore, point to a steady secretion of adrenalin solely under nervous action controlled from a spinal centre, which is not specially brought into play by emotional stresses and physical strains, and do not support the idea of its being essential to the organism. These conclusions are so diametrically opposed to the results of others that it is best simply to state them, merely adding that Cannon's recent work seems to answer many of them.

The Thyroid Gland

The thyroid gland, like the adrenal, can be thrown into increased activity by the sympathetic, and in turn increases the response to the sympathetic. McCarrison, whose work has aroused so much interest in the subject, says: " The thyroid gland is to the human body what the draught is to the fire." We may, therefore, expect that when the defensive mechanisms are called upon, all the bodily activities have to be quickened and the fire must be kept burning brightly, the thyroid gland must be brought into play. This is true whether the defensive mechanism is directed against an external foe when muscular energy is demanded, or against bacterial invasion when the gland helps to produce a febrile reaction. It develops as a ventral outgrowth from the pharynx, between the first and second branchial clefts. It sometimes retains, in the thyroglossal duct, vestigial remains of its old connection with the alimentary tract, and it is probably due to this primitive course of the secretion that it, in contradistinction to other hormones, is so easily absorbed when given by the mouth. Like other out-

growths of the alimentary tract, it has both a sympathetic and para-sympathetic nerve-supply, the former being derived from the superior cervical ganglion, the latter reaching it through the superior and inferior laryngeal branches of the vagus. In a gland which has so profoundly an accelerating katabolic action we should expect to find that the sympathetic supply carried the chief secretory nerves. That this is so was proved by Cannon, who joined the central end of the phrenic to the peripheral end of the cervical sympathetic nerve on one side in the cat, so that the gland was stimulated with every breath. This resulted in tachycardia, increased excitability, loose motions, exophthalmos on the side of the operation, a great increase in metabolism, and in some cases in an increased size of the adrenals.

The fresh secretion of the gland is quite fluid, or only slightly gelatinous, and it is in this form that it reaches the circulation. The colloid in the vesicles may be looked upon as a reserve of iodine for the body. In the resting stage the vesicles are distended with colloid, and their lining cells are flattened. In the active stage there is little colloid, and the cells are cuboidal, or even columnar. The resting stage can be produced by giving iodine or iodine-containing foods. The discharge of colloid can be effected by a meat diet which is poor in iodine (Chalmers Watson). According to the recent observations of Kendall, the active constituent of the secretion is an indole compound of iodine, called thyroxin. In view of the intestinal disturbances so common in Graves' disease, it is a suggestive fact that indole is a putrefactive decomposition product of the tryptophane in the protein molecule.

This emergency ration is drawn upon at puberty, marriage, and pregnancy, while the gland shows retrogressive changes at the climacteric. The close functional association between the thyroid gland and reproduction has long been known, and makes specially interesting Gaskell's observation on the even closer structural asso-

ciation between the thyroid and the uterus of the vertebrate ancestor. McCarrison has also laid special stress on the demand made on the thyroid by infections and intoxications, while Crile has emphasised the influence of the emotions in the same direction. Sometimes this process goes beyond the limits of physiological demands, so that pathological changes ensue. The frequency of some degree of parenchymatous goitre in anæmic girls at puberty is recognized. At Queen Charlotte's Hospital 50 per cent. of pregnant women were noted to have slight enlargement, and it was specially noteworthy in primiparæ. In my experience tonsillar sepsis is a potent factor in thyroid enlargement. McCarrison has called attention to the part played by intestinal toxæmia in this direction, and has succeeded in inducing such enlargement by fæcal flora. His conclusions as to the genesis and course of thyroid enlargements (apart from neoplasms) are as follows :

(1) They are all due to psychic, nutritional or toxic factors, acting singly, or more commonly in combination.

(2) In all, the pathological process is essentially the same : greater or less degrees of hyperplasia, followed by greater or less degrees of fibrosis and atrophy.

(3) In all, there is an alteration in the quantity and quality of the thyroid secretion poured into the blood-stream.

In exophthalmic goitre we have the continued action of some excitant which admits of no period of rest, so that the gland is soon emptied of its colloid reserves, while the secreting structures undergo compensatory hypertrophy. The heightened excitability of the sympathetic nervous system is shown in the exophthalmos, the rapid pulse, the sweating, and the diminished secretion of gastric juice. As with adrenal stimulation, we find raised blood-sugar, a tendency to glycosuria and to pigmentation of the skin. The stimulation of the whole of the emotional apparatus

is so obvious that the aspect has been well compared to a state of continuous fear, as seen in the staring eyes, the downward curve of the mouth, and the tremors. There is a remarkable lowering of the brain thresholds to stimuli of all kinds. According to Crile, the responses to emotional, infective, and nociceptor stimulation are all equally exaggerated, and he describes similar changes in the brain cells produced by Graves' disease, fear, shock, and exhaustion. The continuous action of the sympathetic appears to lead to degenerative changes in the superior cervical ganglion also: for Wilson found hyperpigmentation, chromatolysis, atrophy and fibrosis in all of the thirty-one cases he examined. Probably the overstimulation leads to an anticipation of those degenerative changes found by Hale White in this ganglion in later life.

As McCarrison says, the ideal conditions for the development of exophthalmic goitre are provided when all, or at any rate more than one, of the three factors, nutritional, psychic, and infectious, are at work, and Crile observes: "I have never known a case of Graves' disease to be caused by success or happiness alone, or by hard physical labour unattended by psychic strain, or to be the result of energy voluntarily discharged." I have been struck, for instance, by the frequency of hyperthyroidism following the air-raids on London, and others have commented on this to me as the result of their own experience. Beebe noted this also in America, among the recruits under training, and observes that after the Kishineff massacres in Russia and after the San Francisco earthquake the same thing occurred. In my opinion a psychic factor of matrimonial origin is specially liable to induce the condition. The excitability of the nervous system in the subjects of Graves' disease is further shown by the liability of diabetes, neuroses, and psychoses to occur in the family. All this is in agreement with views expressed more than twenty years ago by Ord and Hector Mackenzie, who

said: "The thyroid condition is at any rate not the primary cause of the disease. We conclude that the disease depends on a derangement of the emotional nervous system, together with an altered perverted condition of the thyroid gland, which serves to keep up many of the characteristic symptoms." We can, however, express it with a little more exactitude now that we appreciate the fact that the emotional response is the phylogenetic expression of a defensive response, and that the thyroid is one of the defensive mechanisms of the body. In fact, we have here an example of a vicious circle: the sympathetic stimulating the thyroid, and the thyroid increasing the sympathetic response. I would urge, in passing, that it is the establishment of a vicious circle which is the most important agent in nullifying the *vis medicatrix naturæ*.

That this continuous unrest of the thyroid is followed by its exhaustion is not surprising, and it is well recognized that a condition resembling myxœdema may supervene. More curious are the cases where the thyroid enlargement subsides, but the other signs of sympathetic stimulation continue, the tremors, the tachycardia, the nervousness, and the wasting, of which I have had several interesting examples. The opinion has been expressed that in all cases of Graves' disease the adrenals are also involved, but even without that assumption such manifestations can be explained as due to the continuance of sympathetic stimulation when the thyroid is approaching exhaustion, or acquiring a higher threshold of response.

If the thyroid secretion is mainly katabolic, it may be asked why Graves' disease is so much commoner in women than in men, since one regards male metabolism as being the more katabolic. Perhaps we may find a reason when we note that in women the disease is almost confined to the child-bearing period. Now, thyroid secretion, although accelerating katabolism in adults, has a marked effect on growth. Thus Gudenach caused tadpoles to reach the stage of metamorphosis in eighteen days by thyroid

feeding, instead of requiring the usual ten to twelve weeks. McCarrison found that during fœtal life the developing thyroid is peculiarly susceptible to influences which damage the mother's thyroid. The thyroid does not attain to full functional activity until some months after birth. Meanwhile the maternal thyroid continues in a state of heightened activity, which gives thyroid juice to the milk. I have recently seen a recurrence of myxœdema during lactation in two young women who had sufficiently recovered under treatment to bear a healthy child. In chlorosis—another disease restricted to the child-bearing period—the essential feature is a pathological exaggeration of the normal heaping-up of nutritive material in the blood for the next generation. In the same way, the greater responsiveness of the female thyroid to nutritional, psychic or toxic strain may be a pathological exaggeration of a mechanism designed for the benefit of the next generation. The liability of women to myxœdema about the time of the climacteric is capable of a similar interpretation. In men, neither Graves' disease nor myxœdema shows a striking age-incidence. Another suggestion has been made that as the thyroid represents the Palæostracan uterus, it will naturally be more active in females. Indeed it has been urged that even men with hyperthyroidism have a tendency to femininism.

The view here put forward should give pause to enthusiastic operators on the thyroid gland for Graves' disease, and also suggests caution in advocating the milder procedure of applying X-rays to the gland. For we may thereby merely remove the outward and visible result of the toxic, nutritional or psychic strain, while leaving the cause untouched. Furthermore, we may be precipitating the final exhaustion of the gland which is so apt to ensue. The utility of both these procedures is limited to breaking the vicious circle between the sympathetic stimulation of the thyroid, and the lowering of the threshold to sympathetic effects by thyroid secretion. Within these

limits the utility may however be considerable. Incidentally I can confirm McCarrison's observation on the striking benefit often resulting from the administration of 5 grains of quinine hydrobromide three times a day, especially when reinforced by small doses of mercury. It has encouraged me to try the drug in other diseases associated with the sympathetic nervous system, though not, so far, with the same degree of success.

The Pituitary Body

Like the adrenal gland the pituitary body has a partly glandular, partly nervous origin. Like the thyroid gland, the glandular portion arises in connection with the alimentary tract. Its association with the sympathetic nervous system is chiefly displayed in certain cases of glycosuria, and in that special type of polyuria known as diabetes insipidus.

It is clear, from reading various accounts of diabetes insipidus, that several different conditions have been thus described.

I should exclude from this category the type described by Meyer in 1905. He regarded diabetes insipidus as due to a *primary defect in the kidneys*, the patient being incapable of secreting urine of normal concentration, so that he requires a much greater quantity of water to remove the normal products of metabolism. He found that in this type 20 grammes of sodium chloride would cause a marked diuresis, but not in the other types, where the kidneys, being sound, could respond by temporarily increasing the concentration of the urine. In this renal type of the disease the excretion of the ingested salt may take a considerable time—often days. It will be noted that there is a resemblance between this condition and interstitial nephritis, in which the power of secreting concentrated urine and salt is also distinctly reduced,

while the minute trace of albumin is hardly recognizable in such a large amount of fluid. Indeed, in some post-mortem records of cases classified as diabetes insipidus it is by no means clear that the patient had not really suffered from chronic interstitial nephritis. Saundby has stated that in diabetes insipidus the cause of death may be the gradual destruction of kidney substance, producing uræmia. He was evidently describing an example of this renal incapacity. Observations on the blood-pressure are badly needed. If this proves to be distinctly raised, it provides an additional point of resemblance to interstitial nephritis. Meyer has introduced an interesting test for recognizing this condition. Theocin-sodium acetate increases the permeability of the kidney, and when this permeability is reduced for solids, the drug, by facilitating their excretion, does away with the necessity for further dilution of the urine. Hence, though it ordinarily acts as a diuretic, here it merely raises the concentration of the urine without increasing the amount of fluid. Applying this test in a case of syphilitic origin, I found that 2 grains of theocin-sodium-acetate twice a day raised the excretion of water from 5,600 to 8,000 c.c., showing that there was here no renal incapacity. It follows that restriction of the ingested fluids is a futile and cruel procedure in this type. The patient must excrete a dilute fluid, and if fluid is not given to him he must obtain it from his own tissues. He loses weight, and the output of nitrogen rises, showing that the deprivation of water is producing tissue breakdown. This increased excretion of nitrogen in turn demands more excretion of water. The appetite and the general health will soon suffer, while the distress from thirst becomes extreme. But I am not yet satisfied that even in this type the pituitary is entirely normal. In the syndrome of infantilism with interstitial nephritis and recrudescent rickets described by Morley Fletcher, the pituitary may be enlarged and the condition approximates to this renal type of diabetes insipidus. I would urge,

however, that this type should not be classed as diabetes insipidus—it is essentially a form of chronic interstitial nephritis. Rabinowitch has shown that in ordinary diabetes insipidus, unlike chronic interstitial nephritis, the power of concentration at any rate for nitrogen is quite good, which accords with the distinction I have drawn here.

(1) A *syphilitic meningitis* at the base of the brain is responsible for a large proportion of the cases. Futcher laid emphasis on the frequency with which this is the cause of diabetes insipidus in children. It is therefore imperative that in every case the Wassermann reaction should be tried before treatment is undertaken. I have obtained a strongly positive reaction in a boy of thirteen with diabetes insipidus who certainly presented no other stigmata of congenital syphilis. The following is an instance of this type in an adult which came under my observation. A woman at the age of forty married for the second time. Two years later she suddenly began to pass twenty-five pints of urine a day. The Wassermann reaction was strongly positive. She improved on anti-syphilitic treatment and valerian, but two years later the reaction was still strongly positive, although the quantity of urine had fallen to nine pints. The thirst and polyuria were certainly better when she had valerian as well as mercury and iodide. A curious feature of this case was the way her tissues remained fat and flabby throughout. She showed none of that desiccation so often seen in this disease.

The fact that the nearer the meningitis is to the inter-peduncular space, the more apt it is to excite diabetes insipidus, suggests, in the light of the next type, that irritation of the pituitary is the mechanism by which this specific form also is produced.

(2) Gross *disease of the pituitary body* is responsible for another group of cases.

In 1912 Frank recorded the case of a bullet wound

involving the posterior fossa which produced diabetes insipidus, and from an analysis of the literature urged strongly the pituitary factor in this disease. Fractures at the base of the skull may induce prolonged polyuria following a transient glycosuria, and the association of pituitary tumours with diabetes insipidus has been recognised since 1882. The occurrence of primary optic atrophy, bi-temporal hemianopsia, and some form of ophthalmoplegia, is not unknown in diabetes insipidus, and would point strongly to pressure in the region of the pituitary fossa. In 1898 Bousfield recorded three consecutive cases of diabetes insipidus with primary optic atrophy. Out of eighty-five cases of bi-temporal hemianopsia collected by Frank, eighteen had diabetes insipidus. Kennaway and Mottram point out that no record is to be found of any case of diabetes insipidus in which abnormality of the pituitary was excluded by post-mortem examination, whereas in a considerable number of cases the disease has been associated with a lesion of the posterior lobe of the gland. According to Bailey and Bremer it is not so much the posterior lobe of the pituitary which is at fault, but the nervous tissues of the hypothalamus. This they regard as an important head ganglion of the visceral nervous system, thus relating the disease even more directly with the sympathetic. A striking case of Cushing's deserves more particular mention. A woman aged forty was admitted with a history of headaches, vomiting, and drowsiness, followed by loss of vision, which had progressed to almost complete blindness, and convulsive seizures with an olfactory aura. Her Wassermann reaction was negative and the blood-pressure 110 mm. X-ray examination showed that the outlines of the pituitary fossa were completely obliterated. Such light as could be perceived was on the nasal halves of the visual field. The pupils were dilated, reacting but sluggishly to bright light, and that better when thrown from the nasal sides. There was bilateral primary optic

atrophy and complete anosmia. Tolerance for levulose was raised to 200 grammes. Sellar decompression by the trans-sphenoidal root revealed the anterior lobe of the pituitary body flattened, presumably by a tumour behind it. This operation was followed by persistent polyuria reaching twelve litres a day. Her thirst was unquenchable, and a jar of water had to be kept at the head of the bed with a tube attached to it which she sucked almost continuously. Restriction of the liquid intake caused too much distress to justify its continuance. Tests showed that the functional activity of the kidneys for the excretion of solids was unimpaired. A right subtemporal decompression was next undertaken, with ultimate relief of the headaches and polyuria, though the olfactory aura, convulsions, blindness and drowsiness remained.

(3) But there is a type remaining which shows no evidence of syphilitic meningitis, pituitary disease, or renal incapacity. The polyuria is sometimes regarded as secondary to *polydipsia*. The following two cases illustrate this.

(*a*) A young man came under my observation who had had polyuria varying from 5,300–9,000 c.c. a day since the age of seventeen. The Wassermann reaction was negative. X-rays showed nothing abnormal in the pituitary fossa, and theocin-sodium acetate did not produce diuresis or diminution in the urine. Glycosuria produced by the injection of phloridzin appeared and disappeared normally. Sodium chloride was readily excreted, as shown by the fact that, his output having been determined for several days on as low a salt intake as 3 grammes, 20 grammes were given in one dose, and 21 grammes were excreted in the following twenty-four hours, showing that only 2 grammes of the total amount had not been eliminated. Restriction of the intake of fluid produced a diminution in the output, and valerian had a definite effect in diminishing thirst. Under treatment he still passes about 3,500 c.c. of urine a day.

(*b*) In 1908 a girl aged eighteen, who had been much distressed by the death of her sister, began to suffer much from thirst, and was found to be passing 16½ pints of urine a day. She has attended St. Bartholomew's Hospital both as an out- and in-patient ever since. During the earlier part of the time she was under the care of Dr. Morley Fletcher, and during the latter part under mine. I am indebted to Dr. Morley Fletcher for permission to embody his observations with mine. Her intake of liquid generally exceeded the output. Thus on ten consecutive days the average intake was 219 ounces and the output 176 ounces. On a saltless diet the average intake of five consecutive days was 174, the output 146 ounces. Thus deprivation of salt lowered the intake by 45 ounces and the output by only 30, suggesting that salt acted by increasing thirst rather than by calling for greater dilution of the urine. Indeed, tests showed salt to be eliminated normally, so that it was not a case of renal incapacity. The Wassermann reaction was negative, and a skiagram showed a normal pituitary fossa. She responds well to valerian in large doses.

Whereas in the syphilitic group I have noted that the amount of urine exceeded the liquid drunk, in this last group the two either balanced or the liquid imbibed exceeded the amount of urine. Buttersack believes the latter condition points to a primary polydipsia, and notes that in such cases there is a normal secretion of sweat. Ralfe advises that, if the liquids ingested and excreted approximately balance, the amount of fluid drunk should be reduced by two pints. If this is followed by a fall in the liquid excreted, the fluid drunk is reduced by another pint every three days, but as soon as there is any more reduction in diuresis the intake should not be restricted any further. It should be noted that this method was originally suggested for diabetes insipidus in general, but from the foregoing considerations it will be clear that it is only likely to meet with success in cases secondary

to polydipsia. But even in this type it will not be found possible to diminish the urinary excretion to a normal level. A point will be reached at which further restriction of the intake will lead to great distress without a fall in the output. It cannot be, then, merely the result of a perverted thirst, for in that case, if the patient were prevented from gratifying that thirst, the diuresis would fall even though at the cost of much discomfort. I can confirm the general belief in the benefit derived from the free administration of valerian in this type. I cannot regard valerian merely as the remnant of a bygone superstition, as does Ernest Jones, who says ("Papers on Psycho-Analysis," p. 14):

"For a great many centuries asafœtida and valerian were administered on the grounds that hysteria was due to the wandering of the uterus about the body, and that evil-smelling drugs tended to drive it down to its proper position and thus cure the complaint. Although these assumptions have not been upheld by experience, nevertheless at the present day most cases of hysteria are still treated by these drugs. Evidently the operating influence that leads to their administration is the blind response to a prevailing tradition, the origin of which is largely forgotten. But the necessity of teachers of neurology to provide reasons to students for their treatment has led to the explanation being invented that the drugs act as 'antispasmodics'—whatever that may mean—and they are often given in the following refined form: One of the constituents of valerian—valerianic acid—is given the name of 'active principle,' and is administered, usually as the zinc salt, sugar-coated so as to disguise its unpleasant taste. Some modern authorities, aware of the origin of the treatment, have even remarked how curious it is that the ancients, in spite of their false views about hysteria, should have discovered a valuable line of treatment and yet given such an absurd explanation of its action."

At the risk of being labelled a " rationalizer " of effete superstitions, I venture to assert that I have never regarded the exhibition of valerian as a punitive measure. In fact, when patients need valerian they frequently do not appear to dislike it. The older observers often empirically determined the usefulness of a drug without understanding its mode of action—of this quinine is an historical example. The fall in the output of urine when valerian is given to a case of diabetes insipidus is a point which can be determined by direct observation. Even in the syphilitic type valerian should be combined with anti-syphilitic treatment. I have noted in the syphilitic type that valerian would cause the output which previously exceeded the intake to fall below it. Such observations make it unlikely that the first and third types I have described are completely separate. I have shown that the first type probably acts by damaging the pituitary ; that the second, *ipso facto*, does so ; that in the condition described by Meyer the pituitary cannot be exonerated, and it is naturally tempting to assume that even in this third type there is nervous disturbance of the pituitary when we know that the same drug can help, and when nervous ties between the medulla and the pituitary by the curiously indirect course provided by the sympathetic have been shown to exist by Cushing, Weed and Jacobson. On such an hypothesis the influence of shock and emotion in invoking this form of diabetes insipidus would afford an explanation of nervous and hysterical polyuria as due to a transient emotional disturbance passing along the same channel. At the present time it seems to me that a structural or nervous interference with the posterior lobe of the pituitary affords the most plausible explanation of diabetes insipidus. The benefit sometimes derived both in diabetes mellitus and insipidus from the administration of codeine is a further suggestive and interesting point.

We have next to consider whether diabetes insipidus

is associated with increased or diminished action of the posterior lobe. The diuretic effect of pituitrin described by Schafer and Magnus in 1901 has been proved by later observers to be quite transitory. Indeed, most of the earlier experiments must be discarded because allowance was not made for the complications introduced by anæsthetics. It has now been repeatedly shown that when pituitrin is injected into the normal animal it has a definitely inhibitory effect on diuresis. This effect has also been demonstrated in the normal man and in patients with diabetes insipidus (e.g. by Christie and Stewart, Kennaway and Mottram, Otto May, Poulton). In the case of a boy suffering from diabetes insipidus studied by Graham and myself we found that whereas 0.5 c.c. of pituitrin had no effect on diuresis, 1 c.c. would check it for 16 hours.

An interesting case was related to me by Dr. C. H. Miller. A young officer was admitted under his care for diabetes insipidus following some pyrexial attack at Salonika. He passed about 590 ounces of urine a day and drank a corresponding amount of fluid. The Wassermann reaction was negative, and there were no signs of pituitary tumour. Dr. Miller noted a thrombotic condition of the saphenous vein over the internal malleolus which he had found more commonly in typhoid and para-typhoid fevers than in other conditions. The vein was hard, rigid and solid like a tendon, the same condition extending back along the branch communicating with the deep veins among the calf muscles. He therefore had a stool examined, with the result that para-typhoid B. organisms were found in pure culture. He concluded that diabetes insipidus had been started by para-typhoid fever, the patient now being in the carrier stage of the disease. He tried the effect of pituitary extract, and found that great improvement followed immediately. The urine fell to 200 ounces, the skin became moist and the thirst much less. After a few injections pallor and faintness were produced, so

they were suspended, but a week later another injection had a similarly good result. The urine decreased from 580 to 200 ounces, the patient had no thirst, and his night's rest was undisturbed. Dr. Miller's suggestion is that there was a partial interference with pituitary function as a result of para-typhoid fever.

It is clear that pituitrin does not exert its antidiuretic effect through the vasomotor system since it is equally effective on the denervated kidney (Bailey and Bremer). Priestley's experiments, in which pituitrin delayed the onset of diuresis by 4 to 6 hours, during which the ingested water was stored up in the tissues, while dyes could still be excreted in a concentrated form, point to some direct action on the renal tissues. I agree with Rabinowitch in regarding diabetes insipidus as due to the lack of some internal secretion which normally regulates and moderates diuresis by acting on the cells of the kidney, and I should look upon pituitrin as that secretion. Its output may be diminished either by structural or toxic damage to the pituitary, and probably by sympathetic inhibition. In this connection it is interesting to note that Cow found the diuretic effect of water absorbed from the bowel to be greater than if it were injected intravenously. Does something absorbed from the bowel with the water also diminish the secretion of pituitrin;—a converse to the pro-secretin of the pancreas? Finally it may be observed that on the current theory of urinary excretion, the action of pituitrin would be to promote reabsorption of water by the renal tubules, so that urine would become more concentrated. In its absence reabsorption fails and a very dilute urine results.

To sum up the relations between this group of endocrine glands and the sympathetic nervous system, we may say that the secretion of all three tends to raise blood-sugar and lower carbohydrate tolerance; the adrenals co-operate with the sympathetic in every way, so that the injection of adrenalin imitates the effect of stimu-

lating the sympathetic nerves; the thyroid aids all the katabolic activities of the sympathetic; while the pituitary plays a large part in controlling the excretion of urine. The secretion of the first two is not only excited through the sympathetic, but in turn increases the response of other structures to such stimulation; this reciprocation has not been observed in the case of the pituitary.

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CHAPTER III

THE SYMPATHETIC NERVOUS SYSTEM IN RELATION TO GLYCOSURIA

CONSIDERATION of the influence of the sympathetic and the endocrine glands on glycosuria follows naturally from my previous topics. I also propose to discuss the question of the relationship of the blood-sugar to glycosuria. I do not suggest that this will solve all the problems of diabetes. There is much of truth in Abderhalden's remark that "Up to the present, the most prominent symptom, that of glycosuria, has dominated the entire investigation of problems concerning diabetes, and it is very probable that this is the reason why the disease is, as a whole, so little understood." I have long felt that it is a mistake to look upon the disease merely as a disturbance of carbohydrate metabolism because that part of the disease was first recognized. More than two centuries elapsed between Willis's recognition of sugar in the urine and Gerhardt's discovery of the ferric chloride reaction in severe diabetes. It took some years after that before the significance of this reaction in relation to fat metabolism was realized. Still later came the recognition of the disturbed protein metabolism in diabetes, and now we are finding out that the metabolism of the inorganic salts is perverted as well. We must look upon diabetes as a disease of metabolism as a whole, though it is probable that the history of our knowledge of diabetes repeats itself in each patient, the carbohydrate disturbance preceding the others.

The centre of interest, as far as sugar metabolism is concerned, has shifted of recent years from the urine to the blood. Improved methods, such as that of Bang, allowing the blood-sugar to be estimated in a single drop, have greatly simplified observations on this point. The normal percentage of sugar in the blood plasma during fasting may be taken as 0.1 per cent., and this is, approximately, maintained through prolonged starvation, almost up to death. Graham (*Journal of Physiology*, vol. l, p. 283) showed that 100 grammes of dextrose would produce a sudden rise in the blood-sugar within ten minutes, usually reaching its maximum in twenty minutes, and returning to its original level in one to one and a half hours. The determination of the curve of the sugar in the blood at intervals after a dose of dextrose is the only way to obtain information as to the real condition of affairs. The level which the blood-sugar has to reach before it appears in the urine shows considerable variation in different individuals. As Graham put it, some have a high and others a low leak-point. I should prefer the term "threshold" to "leak-point," as the former has a well-recognized connotation in physiology. In diabetes, hyperglycæmia will persist long after the glycosuria has been controlled, and may remain at a figure such as 0.25 per cent., which in an ordinary individual would inevitably excite glycosuria, as if the kidneys had acquired a raised threshold for sugar. On the other hand there may be glycosuria with hypoglycæmia, which recalls the experimental condition of phloridzin glycosuria. On this analogy, such cases have been called renal glycosuria, though it is by no means clear that such a term is correct.

Renal Glycosuria and Diabetes Innocens

The first case of the kind described by Klemperer in 1896 had renal disease, but renal lesions may lead either to increased or diminished permeability of the kidney to

sugar. It is probable that many of the remedies, such as uranium, which have been employed to diminish glycosuria really do so by damaging the kidney. Nephritis of this type may be accompanied by hyperglycæmia. On the other hand, toxæmic kidney and some forms of nephritis may be associated with glycosuria and hypoglycæmia, and to such cases the term renal glycosuria might fairly be applied. Thus, I remember sending into Sir Wilmot Herringham's wards an elderly man with chronic interstitial nephritis, glycosuria, and marked retinal changes. The blood-sugar was found to be definitely subnormal, and the retinal changes were regarded by the experts as typically those of nephritis.

But quite apart from obvious renal disease, there is a condition of hypoglycæmia with glycosuria. It was defined thus by Sir Archibald Garrod in 1912, in his Lettsomian Lectures: "Persistent slight glycosuria in which small quantities of sugar are continually present in the urine, in which variations of diet have little or no effect on the output of glucose, and in some of which the quantity of sugar in the blood has been shown to be rather diminished than increased." To these may be added the fact that of ingested sugar only 1 per cent. to 2 per cent. is excreted. The following is an example: A schoolmaster, aged thirty-five years, was sent to me because sugar was found in his urine just before he was going to be operated upon for varicose veins. He felt quite well, except that ever since he was twelve he had had occasional fainting attacks. The amount of sugar in the urine varied between 1 per cent. and 2 per cent. On a restricted diet he lost flesh, but the sugar in his urine was unaffected. There was no sign of disease of any ductless glands. Dr. Mackenzie Wallis estimated the blood-sugar, and found it was as low as 0.062 per cent. Salamon, in 1914, gave the name of "diabetes innocens" to the condition, and found that the level of the blood-sugar was not affected by 100 grammes of dextrose.

Graham has recently described another variety of diabetes innocens (*Quarterly Journal of Medicine*, vol. x, 1917, p. 245). The amount of sugar excreted is higher, 20 to 50 grammes in the day, and the percentage may be as high as 5, instead of only 1 to 2. The effect of a dose of sugar is also greater, as from 7 per cent. to 17 per cent. of it is excreted, instead of 1 per cent. to 2 per cent. Lastly, although sugar is excreted when its level in the blood is normal, and the response of the blood to a dose of sugar is no greater than that of a normal individual, more sugar is excreted when the blood-sugar rises at all. But, though the condition occurs in young people, it is, apparently, non-progressive. In the pure diabetes innocens of Salamon the only lesion is a lowering of the threshold for sugar. But in Graham's type this is combined with a diminished carbohydrate tolerance. The distinction between these two types has also been made by C. V. Bailey in America. I saw a case of this kind in a lieutenant of the Royal Navy, aged twenty. Sugar was found in the urine when he was in hospital for dysentery and a gunshot wound. Dr. Geoffrey Evans, who sent him to me, reported that a slight reduction in the carbohydrate intake had no effect on the sugar excretion, which amounted to 10 to 15 grammes a day. On withdrawal of all carbohydrate, the urine was free from sugar. But on adding 2 ozs. of bread or potato to the diet, a small amount of sugar at once reappeared. He was passing 12 grammes a day on a very slightly restricted diet when I saw him. I put him on a diet containing 104 grammes of carbohydrate, and of these only 4 grammes appeared in the urine. At no time did he have any symptoms referable to his glycosuria. He was not wasting, and felt quite well. Unfortunately, it was not possible, in this case, to get an estimation of the blood-sugar. An interesting and important point was that his father had a temporary glycosuria when twenty-eight, which cleared up entirely. Of the eighteen cases referred to in Graham's paper, the

familial element was shown by seven cases, belonging to three families, and three other cases had parents or brothers or sisters similarly affected.

I also saw a good example of this type in a woman who has been known to pass sugar for thirty years, yet her blood-sugar is subnormal. The case has been fully reported by Parkes Weber.

But it is not safe to assume, from a single observation showing hypoglycæmia, that the case is non-progressive. It is necessary to observe the response of the blood to a dose of dextrose before reaching this conclusion. Early cases of true diabetes may certainly show hypoglycæmia when fasting. I have seen several cases of this kind approximated clinically to ordinary diabetes, and one of them developed a severe and ultimately fatal form of the disease.

The renal and innocent types call for no treatment. Such patients probably cannot be kept free from sugar by the strictest diet, though the general health will suffer in the attempt to do so.

Allen's Conception of Diabetes

Allen's conception of diabetes is a definite entity sharply contrasted with all other forms of glycosuria. The interest aroused by the practical results of Allen's method of treatment has overshadowed his theoretical conceptions based on experiments. Yet these are important in themselves, and necessary to the appreciation of his therapeutic conclusions. He boldly defines diabetes mellitus as the condition resulting from the reduction of what he calls pancreatic amboceptor below the requirements of normal metabolism. He bases this mainly on the antidiuretic effect of parenterally administered dextrose, and his paradoxical law of its assimilation in the non-diabetic, even though glycosuric, organism as opposed to the diabetic. In diabetes, he maintains, dextrose takes on

a new and uniform behaviour, while other sugars behave as in the normal organism. Dextrose is then a diuretic, however given—intravenously, orally, subcutaneously, or intraperitoneally. In the non-diabetic, dextrose is a diuretic when given intravenously, unless in a small enough dose to permit prompt combination with something else, in which case the quantity of urine will be diminished, as Pavy and Godden showed. It is an anti-diuretic when given in any other way. Give sugar to a diabetic, and the typical result, along with hyperglycæmia, is polyuria and glycosuria, representing a considerable quantity of sugar. Give sugar to a non-diabetic sufficient to cause the same hyperglycæmia as in the diabetic, and the result is an insignificant excretion of sugar with oliguria. Increase the dosage, so as to increase the hyperglycæmia, and thus attempt to cause an excretion of sugar by the non-diabetic equal to that of the diabetic, and the result will be increased oliguria, and, in the most extreme cases, albuminuria or anuria. Give the sugar intravenously in large doses: the non-diabetic shows no more injury than does the diabetic, he excretes sugar actively, with polyuria. Sugar in diabetes therefore acts as a typical crystalloid. In the non-diabetic it behaves as a typical colloid, except when given intravenously, when it acts like a crystalloid, just as in diabetes. It should be noted that Allen does not take the alteration of the threshold of the kidney for sugar into consideration. No doubt this is because his work was done on animals, recently rendered diabetic by excision of a sufficient amount of pancreas. It would not be correct to say that the normal individual only passes a small amount of sugar with a degree of hyperglycæmia which would lead to the output of a large quantity of sugar in the diabetic. On the contrary a chronic diabetic may have hyperglycæmia to a degree which would inevitably lead to glycosuria in the normal subject, and yet pass no sugar because his threshold for sugar has been raised as a compensatory

measure. This illustrates the fallacies underlying the application of animal experiments to clinical medicine.

Allen states his paradoxical law as follows: "If, with a given dose, any utilization of a carbohydrate occurs at all, an increase of the dose causes the utilization of a larger quantity." And he illustrates it thus: "Give the sugar by any route; increase the quantity at pleasure; it is possible by sufficient dosage to kill the animal, but it is not possible to cause more than a fraction of the whole to be excreted in the urine. . . . In the non-diabetic the limit of assimilation is only apparent—in the diabetic it is real. This furnishes a distinction between diabetes and every other form of glycosuria." The fact that some sugar appears in the urine does not imply, apparently, that no more can be utilized, but merely that the method of utilization cannot be brought quickly enough into play to prevent some escape. When we say, therefore, that the tolerance for dextrose is 150 to 200 grammes as a single dose, we only mean that above this point a small fraction of the ingested sugar escapes before it can be dealt with. We can therefore understand why, in the normal individual, glycosuria *ex amylo* cannot occur. The time occupied in its digestion and absorption prevents the escape of any of the sugar into the urine. This accords with Naunyn's dictum that anyone who passes sugar after free ingestion of starch is virtually a diabetic. Anything which increases the rate of carbohydrate digestion and assimilation increases glycosuria. If there is any lowered carbohydrate tolerance, the more slowly carbohydrate is presented to the tissues the better. This probably accounts for the rectal utilization of sugar in diabetes (Foulkes), and explains why malted foods increase glycosuria more than ordinary starch in such circumstances. It is better to express this apparent limit of sugar tolerance as a fraction of the body weight. It is usually given as 2.5 grammes per kilo (*i.e.*, $\frac{1}{4}$ per cent.) of the body weight. Allen puts it as 2 to 4 grammes per kilo when given by

the mouth, and 1 to 1.5 grammes per kilo when given subcutaneously. This is a lower level of tolerance than that found in most animals, and it is still lower in infants, reaching the adult level at the age of ten.

The limit of tolerance for different sugars varies, but apparently no sugar (unless intravenously injected) circulates in an absolutely free state in the non-diabetic organism. We know that when disaccharides are injected intravenously, they are quantitatively excreted, the body being, apparently, unable to deal with them unless and until they are broken down into monosaccharides. The normal organism shows towards parenteral lactose that entire inability to utilize it which the " totally " diabetic organism shows towards dextrose.

In what form, then, do monosaccharides circulate in the blood ? Some years ago, Pavy adapted Ehrlich's side-chain theory to explain this. He maintained that there was no such thing as impermeability of the kidney to sugar. Where a molecule of water would go, a dissolved molecule of sugar, not so very much larger, must be able to follow. He regarded the internal secretion of the pancreas as providing an amboceptor which linked the dextrose molecule on to larger colloidal molecules. Though all of Pavy's views on diabetes have been by no means generally accepted, this idea is steadily gaining ground.

Pancreatic Diabetes

It will, therefore, be convenient to discuss, first, the glycosuria which depends on a frank pancreatic lesion, and then to compare it with other forms. It is unnecessary to detail Minkowski's classical experiments on dogs, which showed that extirpation of sufficient pancreatic tissue caused glycosuria, and that removal of a less amount lowered carbohydrate tolerance. If sufficient glandular tissue were left, it could still exert its control, even if its

connection with the duodenum were severed. Sandmeyer made the further interesting observation that the pancreatic remainder tended to atrophy, so that in time a secondary diabetes followed when the remnant was originally only just large enough to check immediate glycosuria. In repeating Minkowski's experiments, Allen found, as opposed to various uncertain and discrepant results, that severe diabetes regularly occurred when the remnant was only one-tenth of the gland, and frequently when it was larger. The dog thus provides an admirable subject for observations on experimental diabetes.

The position of the pancreas in the portal circulation would make it a favourable source for the sugar amboceptor, for as the sugar streams up the portal vein on the way to the liver, it must meet the internal secretion entering by the pancreatic vein. Hédon's experiments on cross-circulation show the importance of the amboceptor entering the blood at this point. He found that if he passed the carotid blood from a diabetic animal through the normal pancreas into the jugular vein, there was no effect on the glycosuria, but if blood from the splenic artery of a diabetic animal were passed through the normal pancreas and returned by way of the splenic vein, the glycosuria fell to a very low figure, and remained there for several hours. He had previously shown that the intravenous injection of serum from the pancreaticoduodenal vein of a normal dog had no influence on the glycosuria of a depancreatized dog unless it was slowly injected into the mesenteric vein, so as to enter the portal circulation directly. Then the glycosuria diminished almost to zero, and remained low for several hours. That is to say, the blood had to be passed through the portal area for the sugar to be attached to the protein. Yet there can be very little amboceptor in the blood at any given moment, since intravenous injection of sugar is the quickest and surest way of inducing glycosuria. As sugar enters into combination when introduced orally,

subcutaneously, and intraperitoneally, the only factor common to the three is the capillary endothelial wall. Allen believes that this is the site of combination, and that the stock of amboceptor is, presumably, replenished from the small supply constantly carried by the blood. He suggests that a similar process provides for the assimilation of sugar by the tissue cell. Sugar approaching a cell probably encounters a denser stratum of amboceptor, and thus is firmly retained, being built up into the colloid protoplasm through increasingly firm colloid combinations. Knowlton and Starling's experiments on perfusion through the dog's heart seem to show the influence of this pancreatic amboceptor in promoting the utilization of sugar by the heart muscle. Their results may be expressed in tabular form:

On perfusing the heart of a—	With blood from a—	Sugar consumption—
Diabetic	Diabetic	Is diminished or absent.
Normal	Diabetic	Is diminished.
Diabetic	Normal	Occurs.
Diabetic	Diabetic + boiled pancreatic extract	Occurs.

Here normal blood, or diabetic blood enriched with pancreatic amboceptor, enabled the heart muscle of a diabetic animal to utilize sugar. Clarke has extended these observations, with interesting results. He finds that when a fluid containing dextrose is perfused through a pancreas, its dextrorotatory power diminishes, while its reducing power remains unaltered. Presumably, then, it is converted into some combination which is easily broken up in the process of reduction estimation. When this fluid is circulated through a living heart, the dextrose still further disappears from the circulation. Even without this pancreatic factor, the normal heart can utilize either dextrose or levulose. But on the addition of pancreatic perfusate there is an immediate and rapid utilization of dextrose, in preference to the levulose. This

explains several things. In the first place, it points to the dextrose entering into some combination as the result of circulating through the pancreas. It also shows that, when there is pancreatic insufficiency, the body can still burn dextrose and levulose to a certain extent. It further explains why the diabetic can utilize levulose, though only to quite a small extent.

Whether the pancreas as a whole supplies the internal secretion, or whether its cell islets alone are responsible, has been much disputed, but opinion is tending to the latter view. Both acini and islets may be formed from the ducts at any stage of existence. But whether fully-formed acini can be converted into islets, or vice versa, is more doubtful. Dale found, by exhausting the gland with repeated secretin injections, he could apparently greatly increase the amount of islet tissue, and regarded the islets not as independent structures, but as formed by changes in the arrangement and properties of ordinary secreting cells. In that case it would be improbable that they had special functions. But most observers believe that he confused exhausted shrunken acinar cells with islets. Bensley denies that such mutual transformations are seen in the normal pancreas, though admitting the unproved possibility under some conditions. He describes an intricate arrangement of tubules by which the great majority of islets stand in permanent relation with the ducts. This and the wide tortuous capillaries or sinusoids with which they are supplied, together with the different position of the islets in different animals, all suggest that they are permanent structural elements in the gland. Nichols, Helmholtz and Cecil have all recorded tumours of the pancreas apparently composed solely of islet tissue. This has been interpreted in favour of the independence of islet and acinar tissue, but it seems to me that it might equally well be explained as due to degenerative changes in the malignant cells, to which they are known to be prone. But, on the whole, the evi-

dence may be regarded as against the view that normally the cell of one type is transformed into the other type.

After all, this does not prove where the internal secretion is formed. In the liver we do not find certain bile-producing cells and other glycogenic cells, but all the cells seem equally concerned in the internal and external secretions. Noel Paton found that, although cell islets are well developed in the duck, the pancreas plays no important part in regulating its sugar metabolism, for excision of the gland does not cause glycosuria.

The point has more than an academic interest. If it could be shown that in all cases of diabetes there were changes in the cell islets, an important step would have been taken towards establishing the view that the disease always has a pancreatic origin. Opie strongly supports this view. He claims that the more selective the influence of a lesion upon the islets, the more likely is it to cause glycosuria. Thus, interstitial pancreatitis may be interlobular or interacinar. The latter soon affects the islets, which lie deep within the lobules, whereas the former has to be far advanced for the islets to become involved. Corresponding to this, he finds the interacinar form is much more frequently associated with glycosuria than is the interlobular. Hyaline degeneration, too, which he describes as particularly liable to affect islets, he believes to be specially apt to produce glycosuria. Allen is not prepared to go so far as this. He agrees that experiments on the pancreas show that whether glycosuria follows or not depends on whether the islet tissue is, or is not, degenerated. But he admits that these changes may be absent in the spontaneous disease : " The average diabetic has almost as good a pancreas as normal," is his conclusion. If we adopt his view that pancreatic and spontaneous diabetes differ from all other forms of glycosuria in that dextrose now acts as a crystalloid owing to loss of the pancreatic amboceptor, while admitting the structures which form that amboceptor may be intact in

spontaneous diabetes, we are forced to conclude that they cease to act owing to some nervous action or inhibition. Whether right or wrong, this view has paved the way to an important advance in therapeutics, for he bases the *rationale* of the fasting method of treatment on an antagonism between the internal and external secretions of the pancreas.

Various observers have noted that if diabetics are fed with pancreas there is an increase of glycosuria. But Reach showed that any raw meat had a similar effect. Indeed, it would appear, from Cohnheim's and Klees' experiments, that all foods (except fats) which excite pancreatic external secretion increase glycosuria. On the other hand, Allen found that relief from the duty of external secretion appeared to permit of a more continuous production of internal secretion. In the experimental disease, Allen found that conditions which regularly produce severe diabetes when the pancreatic duct is patent regularly fail to do so when the duct is tied at the primary operation. Also that sometimes a secondary ligation may check glycosuria which has already begun. There is, then, a sort of antagonism between internal and external secretion. Treatment by alimentary rest means that the lessened work thrown on the external secretion helps to restore the internal secretion. I think, therefore, that the practical benefits of the fasting treatment may be regarded as supporting the pancreatic origin of spontaneous diabetes.

Clinically, an organic lesion of the pancreas produces other effects besides glycosuria. Defective external secretion is indicated in the fæces by (*a*) the presence of undigested muscle nuclei after a meat meal ; (*b*) the presence of starch grains after unboiled starch has been given ; (*c*) and the presence of excess of neutral fat. Of these, the last is the most striking. The intestinal fermentation of carbohydrate may lead to oxaluria (Cammidge). Observations on the amount of diastase in the urine will aid

in the recognition of pancreatic lesions. Its presence has been regarded as due to amylopsin reabsorbed from the pancreas into the blood-stream. Cammidge however regards it as originating in the liver, its output into the blood being regulated by the internal secretion of the pancreas. When this secretion is inadequate the output of diastase by the liver is unchecked for a time, though ultimately it falls off because the liver does not manufacture as much. On either hypothesis, a gross rise in the amount of urinary diastase would indicate damage to the pancreas.

Normally there are some 10 to 30 units per cent. of diastase in the urine. In acute diseases of the pancreas this may be increased to 300 units or more—in one case of mine it reached 1,000—while in chronic diseases figures of 64 to 128 are more usual. The Wolgemuth technique has been followed in my cases (see Corbett, *Quarterly Journal of Medicine*, 1913, vol. vi, p. 351).

The dilatation of the pupil within twenty minutes to one hour after instillation of two separate drops of liquor adrenalin. hydrochlor., with an interval of five minutes between them, is considered by Loewi to be another sign pointing to insufficiency of the pancreas. He noted this occurred in depancreatized animals, and referred it to a loss of balance between the antagonistic internal secretions of the adrenal and pancreas. The internal secretions of these glands are certainly antagonistic in their effects on sugar metabolism, and Pemberton and Sweet have shown that even the external secretion of the pancreas is antagonised by the adrenals. This test is also positive in hyperthyroidism because the adrenal action is then reinforced at the expense of the pancreas (see Polyglandular hypothesis).

Disintegration of pancreatic substance may result in the appearance of a pentose-like body in the urine, probably derived from the pancreatic nucleo-protein. Cammidge's reaction appears to depend on this substance.

But I note a diminishing tendency to rely on this reaction. Symptoms of pressure on the bile duct and of irritation of the solar plexus may also accur. Hyperchlorhydria may result from deficient secretion of alkaline pancreatic juice, and then pyloric spasm will be excited.

Of all these signs, I have come to rely most on the excess of neutral fat in the stools, and of diastase in the urine. Mackenzie Wallis calls the diastase test, glycosuria, and Loewi's reaction the tripod on which the evidence of a pancreatic lesion mainly rests. If creatorrhœa and steatorrhœa are also present the diagnosis is practically assured.

Now, it sometimes happens that a case of diabetes may start with pancreatic symptoms, which subside while the glycosuria progresses. Thus, if the case was not seen in its early stages, its pancreatic origin might be missed. As an example of this I may quote the following case :

A lady, aged thirty-one, was sent to me in April 1915, with the history that in January of that year she had had a "chill," followed by severe digestive symptoms. For five days she vomited everything, and rectal feeding was resorted to. After this she was seized with insatiable thirst, and sugar was found in the urine. On dieting and codeine the glycosuria soon cleared up. But she relaxed her diet rather quickly, and sugar returned, at first intermittently and then continuously, later with diacetic acid. When I first saw her, the blood-sugar was 0.299 per cent., and her diastase 50 units. Taken in conjunction with the history, this points strongly to an attack of pancreatitis. She was dieted on the basis of determining her sugar tolerance and keeping within this. For most forms of carbohydrate this was only 30 grammes a day. At the same time she was given aspirin and hexamine, as these antiseptics are known to be excreted by the pancreatic ducts. Gradually she improved, the diacetic acid went, and then the sugar. She gained weight rapidly,

and kept free from sugar and diacetic acid until November 1915, and although under treatment this improvement was maintained for a time, she ultimately went downhill, and died in 1917. This was the more disappointing, since examination in January 1916 had shown that the pancreatic diastase had returned to the normal level, 25 units. The blood-sugar, however, remained above normal, 0.209 per cent. In the later stages of this case there would have been no reason to have suspected a pancreatic origin.

In the following case the recovery of carbohydrate tolerance preceded the return of the urinary diastase to normal. A man, aged thirty-one, had been refused for life assurance two years previously on account of glycosuria amounting to 6 per cent. to 7 per cent. He suffered from thirst and polyuria, and was losing flesh. He had been put on to a diet which affected the sugar very little. He then put himself on the Salisbury treatment for six weeks, and greatly reduced the sugar by that, but lost flesh and did not feel well. After that, however, the sugar continued to diminish, and when I saw him there was no sugar, even to Nylander's test. More important, the blood-sugar was below normal, 0.06 per cent. As, however, the diastase in the urine was high—50 units—I presumed that the case originated from a pancreatic lesion. I gave him a test diet of 100 grammes of carbohydrate, on which no sugar came through. I then gave him 200 grammes of carbohydrate in the day, still without any glycosuria resulting. Evidently he had a marked, though temporary, glycosuria, apparently depending on a pancreatic lesion.

Temporary pancreatitis need, of course, produce no glycosuria. The following case illustrates this:

A man who had been an engineer in India for sixteen years, began, in 1913 when 37, to suffer from dyspepsia, with what he described as a dull sickening feeling in the epigastrium, which became almost continuous. There

were, also, irregular pains in the right side, under the ribs. He had hunger pain. In April 1916 he noticed that he was losing weight, and he was advised to eat more fat. In October 1916 he noticed that he began to pass white firm lumps in the fæces, rather angular, almost facetted. He brought some of these lumps for examination, and they were found to consist of a fat with a melting-point of 47° C., and a little cholesterol. Dr. Hurtley, who kindly made the analysis for me, was of opinion that this fat was due to the patient eating margarine, but that a normal person would naturally be expected to be able to absorb such a fat. In 1918, however, not only was he passing no such fat, but Dr. Hurtley found that the total percentage of fat and fatty acids in the dry fæces was 13·4 —*i.e.*, well within the normal limits. Further interesting points were, that the diastase units amounted to 128, and that there was a reducing substance in the urine which was not dextrose, but, in Dr. Hurtley's opinion, was a pentose obtained from nucleo-protein. He regarded this as probably the same substance as that responsible for Cammidge's reaction. It will be noted that the stools are now normal, but that the pancreatic diastase is still raised, and the presence of this unusual reducing substance suggested that pancreatic disintegration was proceeding. Such a case is liable to develop the Sandmeyer type of diabetes later on. I am glad to be able to add, however, that some time afterwards the patient appeared quite well, and there were no signs of pancreatic disintegration proceeding.

Of pancreatitis causing frank and obvious disturbance of both external and internal secretions I need not give examples. My point is to show that the evidence of the pancreatic origin of a case of glycosuria may be slight and temporary.

Yet when an ordinary case of diabetes reaches post-mortem, and shows, as many do, a histologically normal pancreas, we are not justified in assuming that it belongs

to the above group. In ordinary diabetes the diastase is not raised ; indeed, it is generally low. This might be due to mere chronicity of the pancreatic lesion, for the raised diastase output is not permanent in such lesions. But all the other signs of pancreatic disease may have been negative throughout. If we are to claim that all diabetes is pancreatic in origin, as Allen does, it is necessary to assume, with him, that some nervous action is involved. He believes such an action would be of central rather than peripheral origin, irritative rather than paralytic, and, presumably, affects the gland through the sympathetic. Now, we do not regard the pancreas as being specially sensitive to sympathetic control. Indeed, its external secretion seems to be chiefly dependent on chemical stimuli. The other glands which influence carbohydrate metabolism are far more sensitive to sympathetic stimulation, and this is where the polyglandular doctrine would help to explain things. But before discussing this hypothesis, it will be well to consider certain other endocrine glycosurias.

Pituitary Glycosuria

Oversecretion by the pituitary gland always lowers the tolerance for sugar, and may excite a frank glycosuria. It appears to be the pars intermedia which is responsible for this. I will give two examples of glycosuria of pituitary origin :

A lady, aged sixty-three years, was sent to me with the history that four weeks before her sight had failed, and she noticed a " spot " in her right visual field. Sugar was found in the urine, and the defective eyesight had been referred to this. In the past history the only significant thing was that for the last year she had suffered from pains in the neck and shoulders. I found that the urine contained only 0.5 per cent. of sugar, and no diacetic acid.

It hardly seemed likely that such a mild degree of glycosuria was responsible for her failing sight, particularly as there were no retinal changes. There was a great contraction of the field of vision in the left eye; on the nasal side there was only macular vision, while the temporal side showed considerable reduction. Central vision was fairly good. In the right eye central vision was very defective, but there was not nearly so much reduction of the field of vision, such as it was only affected the nasal half. Now bitemporal hemianopia is the usual visual defect in acromegaly, but in view of the glycosuria with binasal hemianopia, I was not surprised that an X-ray examination of the skull showed a definite enlargement of the pituitary fossa, and a shadow, differing in intensity from that of the surroundings, could be seen invading the base of the brain. The Wassermann reaction was negative. Her glycosuria soon cleared up with moderate dietetic restrictions, and there was some improvement in vision on administration of potassium iodide. The pituitary growth must have been quiescent, as she was no worse four years after its recognition. The complaint of pain shooting down the neck into the shoulders is, I think, commonly made by sufferers from a pituitary growth. The combination of this with glycosuria and a marked alteration of visual fields should lead us to suspect the pituitary body. Optic atrophy and interference with the third or sixth nerve may occur, but retinal hæmorrhages or white patches, such as are seen in ordinary diabetes, are not likely. A central scotoma for red and green may be met with in diabetics if they are smokers, even though moderate in the use of tobacco. The ophthalmoplegia which occurs in ordinary diabetes is due to neuritis of the third cranial nerve, and generally clears up with dieting. The ocular signs in pituitary glycosuria are therefore usually quite distinct from the ocular complications of diabetes.

A woman, aged forty-two, was sent to me at St. Bartho-

lomew's Hospital by Dr. Williamson from the Gynæcological Department because she complained of pruritus vulvæ, and sugar was found in the urine. There was no diacetic acid. Her general aspect suggested acromegaly, and this was supported by the growth of hair on her cheeks and the raised blood-pressure (170 mm.). This was confirmed by an X-ray examination, which showed the pituitary fossa to be enlarged. I commented on the fact that she had amenorrhœa, which is not common in hyperpituitarism. The reason for this soon became obvious: she was pregnant, and she subsequently developed hydramnios. The sugar at first yielded to dietetic restrictions, but as the pregnancy progressed it became less amenable. The occurrence of hydramnios is interesting, as it is a common complication of pregnancy in true diabetes. Yet pregnancy is not very likely to occur in diabetics of forty-two. Ultimately she was successfully delivered of a living child, after which she remained free from sugar on ordinary diet. This case is of exceptional interest, because it shows features common to pituitary glycosuria and true diabetes. The conclusion would appear to be that her pregnancy stimulated a pituitary already tending to be too active, and it was only during this extra stimulation that carbohydrate tolerance was lowered sufficiently to excite glycosuria.

That the sympathetic nervous system can produce glycosuria through stimulation of the pituitary was clearly shown by Weed, Cushing, and Jacobson. We know that the main glycosuric effect of Bernard's puncture of the fourth ventricle is due to irritation thereby of the splanchnic nerve-supply to the adrenals; but part, at any rate, may be attributed to the pituitary, for after section of the spinal cord at a level above the origin of the splanchnic nerves, puncture will still excite glycosuria if glycogen is present in the liver. It evidently acts through the superior cervical ganglion, as direct stimulation of this structure will excite glycosuria after exclu-

sion of all possible downward impulses to the abdominal viscera by section or by paralysing all preganglionic endings by means of nicotine. On the other hand, if the posterior lobe of the pituitary with the pars intermedia has been previously removed, stimulation of the superior cervical ganglion has no effect. The fact that nicotine does not abolish such glycosuria shows that the immediate stimulus to its occurrence must be chemical. Post-ganglionic nerve-endings in the pituitary must excite the formation of some hormone which induces glycosuria, for a nervous reflex would be cut out by nicotine. But, equally clearly, outpouring of that hormone is effected by sympathetic stimulation, just as the thyroid secretion can be excited through the sympathetic.

Thyroid Glycosuria

Thyroid extract is known to excite glycosuria. I have noted this particularly when quite small doses have been given with the object of improving the circulation, as in cases of cerebral thrombosis. In Graves' disease there is hyperglycæmia with a lowered tolerance for sugar and sometimes frank glycosuria, while in myxœdema there is an extraordinary increase in sugar tolerance, which may be reduced by the administration of thyroid extract. I have been struck with the frequency of glycosuria during the retrocedent stage of Graves' disease. It is usually amenable to treatment. Since there is generally hyperglycæmia during the active stage of the disease, even though there is no glycosuria, it would appear that the threshold of the kidney is then raised. As the disease quiets down the threshold appears to fall sooner than the hyperglycæmia. The following more serious cases of glycosuria I regard as of thyroid origin :

A girl with Graves' disease was unfortunately treated

with thyroid extract, which exaggerated her symptoms, and well-marked glycosuria followed. Her blood-sugar when I saw her was .308%. Under treatment the sugar cleared up, but she died suddenly some months later apparently from ventricular fibrillation.

A girl of eighteen who had much cause for anxiety developed Graves' disease. She was living in a district where goitre was prevalent. Under X-ray treatment the swelling of the thyroid diminished, but eighteen months after the onset of the disease she suffered from thirst polyuria and pruritus vulvæ. Glycosuria was found, together with a high grade of hyperglycæmia. Under treatment she established a carbohydrate tolerance of 62 grammes.

A lady, aged thirty-three years, was sent to me with the history that in September 1913, when six months pregnant, she was troubled with pruritus vulvæ, and large quantities of sugar were found in her urine. On a rigid diet, the sugar gradually disappeared. At the same time the thyroid was noticed to be enlarged; the eyes had always been rather prominent. She sometimes had palpitation, and it was found that she occasionally dropped a beat. She kept free from sugar until September 1914, when, being again pregnant, she took some drug with the object of inducing a miscarriage. She succeeded in this, whether because of the drug or not I cannot say. Unfortunately for her, sugar promptly reappeared in her urine, and has been present, on and off, ever since. Moreover, her cardiac symptoms increased, and in June 1915 a mitral systolic murmur appeared. It was rasping in character, and clearly organic in nature. She was also troubled with attacks of diarrhœa. The combination of enlarged thyroid, tachycardia, valvular disease, glycosuria and diarrhœa can be explained by Graves' disease, and, as far as I can see, by nothing else. Other thyroid enlargements are not associated with endocarditis and diarrhœa, so that, although there were not ocular signs or tremors, I considered this to be a case of hyperthyroidism

in which sugar tolerance was lowered out of proportion to the other signs. The fact that it first came on during pregnancy supports this idea, for the glycosuria, as distinct from the lactosuria, of pregnancy is most probably due to the well-known stimulating influence that pregnancy exerts on the thyroid or pituitary. The blood-pressure in this case was only 110 mm., which is against the pituitary being involved.

Adrenal Glycosuria

Although there is experimental evidence that glycosuria can be excited by excess of adrenalin, there is very little clinical evidence of a definite adrenal diabetes. Emotional temporary glycosuria is, naturally, regarded as due to excessive adrenal stimulation through the sympathetic, and cases of slight and temporary glycosuria in soldiers suffering from shell-shock are probably of this class. It seems likely that some of the cases of glycosuria in later life, accompanied by raised blood-pressure, are of this nature, for we have seen that strain increases the secretion of the adrenals into the blood stream, and the two most obvious results of that excess would be raised blood-pressure and hyperglycæmia. But at present we have no conclusive evidence that such cases are due to overaction of the adrenals. As I have already pointed out, the main effect of the diabetic puncture is produced through the adrenals (McLeod), and both the effect of puncture and of adrenal glycosuria appear to be limited by the amount of glycogen present in the liver. When this has been mobilized, glycosuria ceases.

The Polyglandular Hypothesis

Previous to Allen's work, no proof had been attempted that pancreatic and spontaneous diabetes resembled one

another and differed radically from all other forms of glycosuria. The inconstancy of pancreatic lesions and the knowledge that other glands could influence carbohydrate tolerance made the hypothesis of a functional loss of balance between these glands attractive to many.

The hypothesis of a co-operation of the thyroid, pituitary, and adrenals in an antagonism towards the pancreatic internal secretion, which was put forward by Eppinger, Falta and Rudinger, can be summarized in the accompanying diagram (page 78).

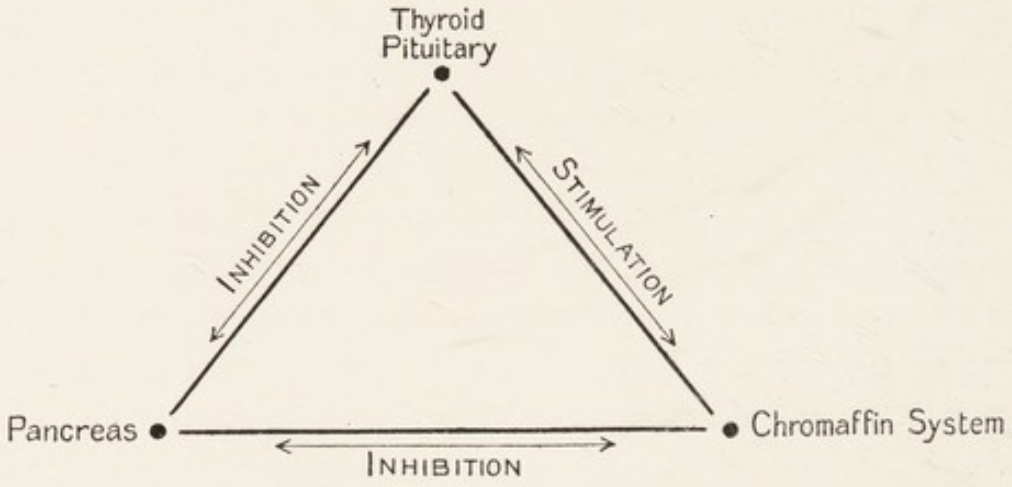
A difficulty in this hypothesis is that, despite all the advances in our methods of investigating diseases of the ductless glands, we have not been able to detect such diseases in the majority of our diabetic patients.

If one endocrine gland were diseased we could understand how a loss of balance may be brought about, comparable to the loss of the balance between muscles. When one group is paralysed, the opponents show a contracture, due to unopposed contraction. But such signs of endocrine gland disease are lacking in ordinary diabetes, even if carefully looked for.

Again, when glycosuria occurs as a complication of a ductless gland disease, it seldom attains the serious proportions seen in diabetes.

For Allen, however, the pituitary, thyroid and adrenal merely produce a toxic glycosuria which is quite distinct from diabetes. He criticizes the polyglandular doctrine so severely that the experiments on which these criticisms are based call for consideration in some detail. I cannot help feeling that his criticisms, and the deductions he makes from his experiments, are not marked by the same unbiassed judgment that characterizes most of his other work. To investigate the influence of the thyroid on carbohydrate tolerance, he injected animals with a solution of dextrose, observed the glycosuria produced, and then removed seven-eighths of the thyroid, repeated the injection of dextrose, and compared the glycosuria that

followed. In the case of the dog, whereas 2 grammes of sugar appeared before, only 0.12 gramme appeared after —*i.e.*, the glycosuria was only 6 per cent. of its former amount: yet he considers this experiment tells against the influence of the thyroid on carbohydrate metabolism. In the case of the cat, he states that dextrose tolerance after removal of seven-eighths of the thyroid gland, "though high, was not beyond the limit of variation which may be shown by a normal cat." Unfortunately, he gives no protocols for this experiment. He concludes that "the assimilative power for dextrose is not percep-



tibly altered by the removal of such fractions of thyroid tissue as were found in the case of the pancreas to alter the assimilation in an extreme degree." Still, I should have thought that a reduction of a glycosuria to 6 per cent. of its former figure might fairly rank as a "perceptible alteration." Next, he removed seven-eighths of the thyroid and eleven-twelfths of the adrenals of a cat, and gave a subcutaneous injection of dextrose, which, though raising the blood-sugar to 0.452 per cent., caused only slight glycosuria. Yet he thinks that an increased ability to utilize dextrose was not demonstrable. Here, again, I should have thought his own experiment told against his conclusion.

In the next experiment he gave a cat thyroid extract,

while adrenalin and sugar were injected. There was a much more marked glycosuria than when thyroid and sugar were given without adrenalin. Moreover, while he injected 6·6 grammes of sugar the animal excreted 7·97 grammes. He admits that the amount excreted was in excess of that injected, as would happen in true diabetes, but he lays stress on the fact that the sugar still showed anti-diuretic action, and was, therefore, behaving as a colloid. He did not attempt to demonstrate his dextrose paradox, but contents himself with the remark that "it could undoubtedly have been demonstrated."

He then tried the effect of thyroid feeding on the carbohydrate tolerance of a cat. Before, the tolerance for injected sugar was 4 grammes per kilo, afterwards it was only 1·25 grammes per kilo, for sugar given *by the mouth*, and there was then moderate glycosuria. The anti-diuretic effect was still present, but it seems to me that he conclusively demonstrated a marked reduction of sugar tolerance as the result of thyroid feeding. Subsequent experiments on the same animal confirmed the lowered sugar tolerance.

Next, to a dog with four-fifths to five-sixths of its pancreas removed, in which the sugar tolerance was low, thyroid was given, and glycosuria with polyuria resulted. He explains away this result by saying that, owing to greatly increased drinking, diminution of urine was absent. But, surely, a more reasonable view would be that here, as in ordinary diabetes, the drinking was due to thirst excited by hyperglycæmia. It is a gratuitous assumption to regard the animal's thirst as the exciting cause of the polyuria.

Then he removed the adrenals from a diabetic dog, and found an immediate reduction of glycosuria. On one day no sugar was excreted. He urges that the animal was just as diabetic, but that it had merely suffered an additional, fatal injury, and was worse off than before. But no one claims that regulation of carbohydrate meta-

bolism is the sole function of these glands. And, of course, the animals suffer as to these other functions when the glands are ablated. But it does appear to me that Allen's own experiments may be quoted as supporting the polyglandular theory in so far as the adrenals and thyroid act in a contrary sense to the pancreas on carbohydrate metabolism, and that it is rather special pleading to explain away his own results in the way he does.

As against Allen's observations, we may quote the experiment of Cushing, Weed, and Jacobson, who found in animals that had acquired a high sugar tolerance after extirpation of the posterior lobe of the pituitary, subsequent extirpation of the pancreas did not cause glycosuria. We may conclude that underaction of the pancreas, or overaction of the adrenals, thyroid or pituitary can all lead to glycosuria. How is such a loss of balance supposed to be brought about if, as I have shown, there is no evidence of disease in any one? I should like to call attention to the way in which this loss of balance could be brought about through the sympathetic. The following general statements may be said to have gone beyond the stage of hypothesis to that of established fact:

(1) Sympathetic stimulation increases blood-sugar as a defensive measure.

(2) Sympathetic stimulation causes increased secretion of adrenals, thyroid, and pituitary.

(3) Vagus stimulation excites secretion of the pancreas, and on the generalization of the opposing actions of the para-sympathetic and sympathetic it would appear probable that sympathetic stimulation inhibits the secretion of the pancreas. The antagonism between its internal and external secretions does not mean an antagonistic nervous supply: it means a diversion of nervous energy from one channel to another.

(4) The general effect of sympathetic stimulation is katabolic, and mobilization of blood-sugar is a preparation for katabolic action.

(5) Therefore the sympathetic, both by increasing the secretion of glands which diminish carbohydrate tolerance and by inhibiting the gland which increases carbohydrate tolerance, would raise blood-sugar above the leak-point, and glycosuria would result.

I suggest that the failure of the carbohydrate of the food to be assimilated, owing to defective action of the internal pancreatic secretion, would produce far more profound disturbance of metabolism than the increased action of glands which simply increase the sugar mobilization, because the action of the latter would be limited to that on the stored carbohydrate in the body, which does not reach a large amount. This accords with the fact that pituitary and thyroid glycosuria are more amenable than the glycosuria dependent on frank pancreatic disease. It would also explain why spontaneous diabetes resembles pancreatic diabetes so much more closely than the glycosuria originating from any other endocrine gland, and yet why, as Allen says, the diabetic may have as good a pancreas as anyone else, and although, as I have said, all other signs of pancreatic inadequacy are lacking. I suggest as the most reasonable classification of persistent glycosuria:

(1) *Organic origin*, with structural changes in the endocrine glands leading to (*a*) overaction of adrenal, thyroid, pituitary, or (*b*) underaction of pancreas.

(2) *Sympathetic origin*, with no evidence of structural changes in any endocrine gland, but producing a functional (*a*) overaction of adrenals, thyroid, pituitary, and (*b*) underaction of pancreas.

My object is to show by a process of exclusion that no theory of diabetes is adequate which leaves the sympathetic nervous system out of account. This is not a new idea, though I hope I have given some additional reasons for believing it. Futcher, in his account of diabetes in Osler and McCrae's "System of Medicine," gives it as his opinion that functional disturbance of the

autonomic system is responsible for some cases. Its association with neuropathic family history, with Graves' disease, with excitement, shock, and bereavement, has been recognized for many years. The influence of heredity and race is equally explicable on such a view. The special liability of the Jewish race, one of the most emotional of all, is a point in the same direction. If Graves' disease is " a state of continuous fear," diabetes is a state of continuous mobilization of blood-sugar, and either of these may be due to dissociated action of the sympathetic nervous system.

If there is organic disease of the endocrine glands our present methods of examination can reveal it. If such signs are lacking we are thrown back on a functional disturbance of one of the endocrine glands which control metabolism or on a loss of balance between them, either of which conditions must be due to nervous stimuli. And it is in the sympathetic that we find the one nervous control common to them all.

Finally, we may inquire whether the improved treatment of diabetes by alimentary rest is explicable in terms of this theory. Emphatically I think it is. Sympathetic irritation means increased katabolism and diminished anabolism, while diabetes is characterized by a wasteful metabolism. Now, the quickest way to compel metabolism to be economical is to cut off supplies. As soon as no food protein is taken, the nitrogenous output falls. Yet the old method of treatment, by greatly increasing the amount of protein in the food, threw fuel into the flames, since excess of protein quickens all metabolic processes. During the war the normal individual found he could balance his metabolism at a much lower level than he previously thought possible. The diabetic has to be taught the same lesson. As long as he can balance at a level where the caloric value of his food is adequate to maintain life and a fair display of energy the outlook is good, but if he cannot acquire a balance until the intake

is reduced below this level the outlook is bad. But the treatment does not attack the underlying cause, and carbohydrate tolerance may continue to fall despite it. Nevertheless it represents a great advance in therapeutics.

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CHAPTER IV

THE SYMPATHETIC NERVOUS SYSTEM AND DISEASES OF DIGESTION

THE object of digestion is to reduce the food molecules into a form capable of passing through a membrane. For this purpose two processes are brought into play—chemical and mechanical. Juices containing active chemical substances are poured on to the food while these are aided by the mechanical processes of mastication, deglutition, and peristalsis, by which every particle of food is brought into contact first with the active juices, and then with the absorbing membrane.

THE INNERVATION OF THE ALIMENTARY TRACT

The dominant nervous agent in all this is the para-sympathetic, both on the secretory and motor sides. An outstanding fact is the way the vagus controls the digestive processes right down to the point at which the sacral division of the para-sympathetic takes charge. This is explicable in terms of Gaskell's theory. Although his main conception of the autonomic nervous system was laid down in 1885, he continued for thirty years to extend his views in accordance with the progress of our knowledge, as is shown by his book on "The Involuntary Nervous System," the proofs of which he had nearly completed at the time of his death in 1915. His conception of the origin of the vertebrates was confirmed in many particulars by researches made by others subsequent to the publication of his original hypothesis. But, coincidently with this, his conception was modified in such a

way as to remove many of the objections to it previously expressed by morphologists. Briefly it is as follows: The central nervous system of the invertebrates formed the central nervous system of the vertebrates by growing round and enclosing the alimentary canal of the former, which persists as the ventricles of the brain and the central canal of the cord. So that a new alimentary canal had to be formed for the vertebrate from structures already existing in the invertebrate ancestor. He regarded the new alimentary canal as formed by the fusion of a number of branchial appendages, the striated muscles of which are supplied by the facial, glosso-pharyngeal and vagus nerves. At first the chamber so formed extended right up to a similar chamber—also formed, possibly, by appendages at the anal end of the body—and opened into that chamber. So that originally, as at present in the arthropods, the double segmentation due to appendages and trunk muscles existed throughout the whole length of the animal. As new body segments were formed by which greater mobility was gained, there would not be a corresponding formation of new appendages of the invertebrate type, but the new-formed gut would simply lengthen and its muscles would be supplied by those nerves already formed. Hence the distribution of the vagus right up to the point at which the pelvic visceral nerve takes control. On the other hand, the limbs of the vertebrate are a new outgrowth from the longitudinal muscles of the body, which outgrowth must carry its investments of skin with it. Hence the absence of visceral fibres from the new part of the cord corresponding to this, and hence, also, the drawing out into the sweat glands, hair follicles and blood-vessels of the limbs of the sympathetic fibres which always supply these structures. Hence, again, the reason for the segmental skin areas being arranged preaxially and postaxially, and not circularly as they are around the trunk. This phylogenetic theory is necessary to the comprehension of the absence of a segmental arrangement of the

muscles of the alimentary canal, and of the meeting within it of such widely separated anatomical units as nerves of bulbar and sacral origin.

Further, the para-sympathetic and sympathetic are antagonistic in their action throughout the alimentary tract. The para-sympathetic produces those sensations of hunger which lead to food being taken. It starts, and to some extent maintains, the secretion of the active chemical juices that digest the food. It causes the peristaltic waves in the œsophagus ; it plays an important part in gastric peristalsis ; it maintains the tone which is necessary for the pendulum movements and peristaltic waves in the bowel, and it can increase them when required. It also controls the final evacuation of the fæcal residue. It is anabolic, for it is responsible for the digestion and assimilation of the food molecules which are the ultimate source of the bodily energy.

It leads to the taking in of food by exciting a feeling of hunger. It is generally agreed that the pangs of hunger are caused by contractions of the stomach and other parts of the alimentary canal. This was suggested by Weber in 1846, and again by Hurst in his Goulstonian Lectures in 1911. Boldireff, in 1905, proved the existence of rhythmical contractions of the alimentary canal under such conditions, and Washburn was able to show that these contractions coincided with the sensations of hunger by accustoming himself to tolerate a balloon in the stomach attached by a rubber tube to a recording apparatus. He signalled when the hunger pang was experienced, and it was found that this occurred just as a rhythmic contraction was reaching its maximum. Under certain conditions there is an abnormal sensation of hunger to which the name of bulimia has been given. Abnormal hunger may be experienced with pituitary tumours and tapeworm, but this falls into a different category. Violent impulses of hunger may also occur as an aura in epileptics. Apart from such conditions it is regarded as a neurosis

due to overaction of the vagus, a view which is supported by the known effect of the vagus on gastric motility.

The chorda tympani and the auriculo-temporal have long been known to contain the secretory fibres to the salivary glands. Pawlow's masterly experiments have proved the importance of the vagus in the secretion of gastric juice, and the influence of appetite and the sense of taste in exciting the secretory action of the vagus, when the subject is really hungry. From this point on chemical mechanisms begin to assume greater importance as secretory stimulants. The secretion of gastric juice, begun by the vagus, is carried on by the action of gastric secretin formed in the pyloric glands (Edkins). The secretion of pancreatic juice is due, mainly, to the formation of secretin in the duodenal mucosa by the action of the hydrochloric acid in the gastric juice on the prosecretin stored there (Bayliss and Starling). But even here nervous mechanisms are not altogether in abeyance. In 1911, Cathcart obtained pancreatic secretion in animals by vagus stimulation, while Bennett and Dodds have shown that the introduction of atropine into the duodenum will check pancreatic secretion. Clayton-Greene has also recorded a case which seems to point to nervous control. During pylorectomy for malignant disease of the stomach a pancreatic fistula was accidentally formed. A few seconds after food was swallowed, pancreatic juice began to appear, and this occurred even when the food had only been seen, and not swallowed. Nervous mechanisms are distinguished from chemical by their speed, and here the reaction was very rapid. However, we may assert that, although the para-sympathetic initiates digestive secretions, as food passes along the alimentary canal the nervous factor becomes less important, and the chemical factor more important. Corresponding to this, we find that the antagonistic action of the sympathetic on secretion is more clearly demonstrable in the inhibition of salivary secretion than of gastric or pancreatic. This inhibitory

action is well seen in the dry mouth of fear, which is the physiological basis for the old Indian "rice ordeal," in which persons suspected of crime were given consecrated rice to chew. The man who spat it out dry was adjudged guilty, for the fear of detection had stopped salivary secretion. There can be little doubt that the sympathetic has a corresponding inhibitory action on gastric secretion. Cannon clearly showed this by the cessation of secretion in frightened or enraged animals. Domestic strife is a fertile cause of dyspepsia, and the inhibitory effect on digestion of emotional stimulation of the sympathetic is proverbial: "Better is a dish of herbs where love is, than a stalled ox and hatred therewith."

On turning to the mechanical factors, we see that from the moment the food bolus passes between the pillars of the fauces to the time that its residue reaches the rectum, it has escaped from the control of the voluntary nervous system, and is directed by the autonomic nervous system. We may regard this part of its course as divisible into three main districts: (1) The pharynx, œsophagus, and cardiac half of the stomach, where probably both motor and inhibitory nerves are supplied by the vagus (bulbar division of para-sympathetic). (2) The pyloric half of the stomach and the small intestine, supplied with motor fibres by the vagus and inhibitory nerves by the sympathetic through the solar plexus. (3) The colon and rectum, supplied with motor fibres by the pelvic visceral nerve (sacral division of para-sympathetic) and inhibitory nerves by the sympathetic through the inferior mesenteric ganglion. To these we must add, in accordance with Elliott's law of the innervation of a hollow viscus, "when the quiet lodgment of contents is facilitated by the presence of sympathetic inhibitory nerves to the body of the viscus, there will also be sympathetic motor nerves to the sphincter closing the exit." Such motor nerves obviously reinforce the general inhibitory effect of the sympathetic

on the alimentary canal. These rules for the innervation of the alimentary canal apply also to such outgrowths from it as the gall-bladder and its ducts.

At the moment the constrictors of the pharynx are drawn over the food bolus, voluntary control over the movements of the alimentary canal is lost. The parasympathetic takes over control, and a slow peristaltic wave, started by the vagus, passes along the œsophagus. In the swallowing of liquids, however, there is no need for peristaltic waves, the œsophagus remaining dilated and passive. The passage of fluid to the stomach takes four to eight seconds, half of which time is occupied in passing through the cardiac sphincter. Solids require the aid of peristalsis, and take eight to eighteen seconds if well lubricated, but a dry bolus may remain above the cardia for many minutes (Hurst). When the food enters the stomach, active peristaltic waves are soon seen sweeping towards the pyloric sphincter about three times a minute, gaining force as they go. The absence of peristaltic waves at the cardiac end enables salivary digestion of carbohydrate to continue while gastric digestion is proceeding at the pyloric end. This affords a rationale for the custom of taking carbohydrate at the end of a meal. As the stomach empties, it is pulled up until the pyloric orifice becomes the lowest part, which assists the completion of the process. In duodenal ulcer it is noteworthy that this pulling up of the stomach can be observed from the very beginning. Long after the fundus returns to its fasting condition the pyloric portion contains food, and shows those vigorous waves of contraction which form the gastric mill. The semi-digested food is thus kept in close contact with the glands in which the stimulant to gastric secretion is elaborated, and thereby contributes to its own digestion. It is probable that the much greater frequency of lesions at the pyloric, as compared with the cardiac end, is due to injuries incidental to its greater activity. When the food

passes into the small intestine, movements of two kinds are observed: (1) Pendulum or segmentation movements, which travel at the rate of 2 to 5 cm. a second, and depend on muscle tone. They cannot move the contents along, but serve to mix them thoroughly by forming a number of alternately constricted and dilated areas, each of which is divided exactly into two by the next movement. (2) Peristaltic movements, a powerful wave of constriction following immediately on a wave of dilatation, so that the contents are always being driven from a contracted into a dilated area. According to Bayliss and Starling, these waves depend on an intrinsic nervous mechanism of the bowel, the plexus of Auerbach. If this is true, it is the only example of a true local nervous reflex, and Gaskell gives reasons for caution in accepting this conclusion as yet. There is no doubt that the extrinsic nerves affect these waves, the vagus increasing, and the splanchnic inhibiting them. As regards the large intestine, this can be divided into three portions, which do not correspond exactly to the anatomical divisions: (1) The proximal part, characterized by the presence of anti-peristaltic waves; (2) an intermediate part, conforming to the type of movement seen in the small intestine; and (3) a distal portion, the rectum, where the central nervous system again assumes control. Disturbances are most likely to occur in this part, because the call for the discharge of its contents can be voluntarily suppressed. "Anti-peristalsis" is hardly a correct description, for really a rhythmical series of reversed segmentation movements occur, depending largely on the degree of tension present. They churn the residue of the food and delay its onward progress. This necessitates a true muscular sphincter at the ileocæcal valve to prevent regurgitation into the ileum, and the development of a cæcum is a natural consequence. In the rabbit and herbivora in general, where the cæcum is long, anti-peristalsis is the only mechanism by which it can be filled. In such

animals the emptying of the cæcum is therefore never complete.

Keith has provided us with a new conception of the movements of the alimentary tract. He divides the alimentary canal up into a number of neuro-muscular sections, each section being cut off from its neighbour by a sphincter which effectively blocks the passage of contraction waves, and prevents them spreading from one section into the next. As in the heart, probably each section is provided with a special centre or " pace-maker," where the impulse arises that starts the rhythm of that section. Four of these centres are actually known. He has likened the alimentary tract to a railroad, divided into block sections, each provided with its signalman and telephonic apparatus. The signalman of one section refuses to accept any further traffic until his section is clear; all the sections are closely correlated; if one is blocked, the others, too, become automatically blocked.

He divides the sections as follows: (1) The pharyngeal section, ending in a sphincter at the upper end of the œsophagus. (2) The cardiac sphincter marks the end of the œsophageal section, and just beyond it lies some nodal tissue which acts as the pace-maker for the movements of the stomach. (3) The gastric section ends at the pylorus, but the pace-maker for the duodenal section is not reached until just above the entrance of the bile duct. This fact is interesting in view of the close functional and pathological relations between the stomach and the acid area of the duodenum. (4) The duodeno-jejunal junction is marked by another sphincter, with its special nerve-supply. There are three peritoneal bands lying to the right of the duodeno-jejunal flexure, each containing a branch of the vagus and splanchnic fibres, the first going to this and the others to the next two sphincters. (5) The ileocæcal valve is really provided with a long sphincter immediately above it, as shown some years ago by Elliott and Barclay Smith. This is

supplied by the second branch. (6) There is a sphincter with the third of these special nerve-supplies in that part of the transverse colon which lies below the pylorus. This marks the end of the part of the colon in which anti-peristaltic waves may occur (see fig. 9). (7) At the junction of the pelvic colon with the rectum is another sphincter. This corresponds with the point at which the intestinal contents are held up in a normal person. As soon as the fæces pass beyond this point the defæcation

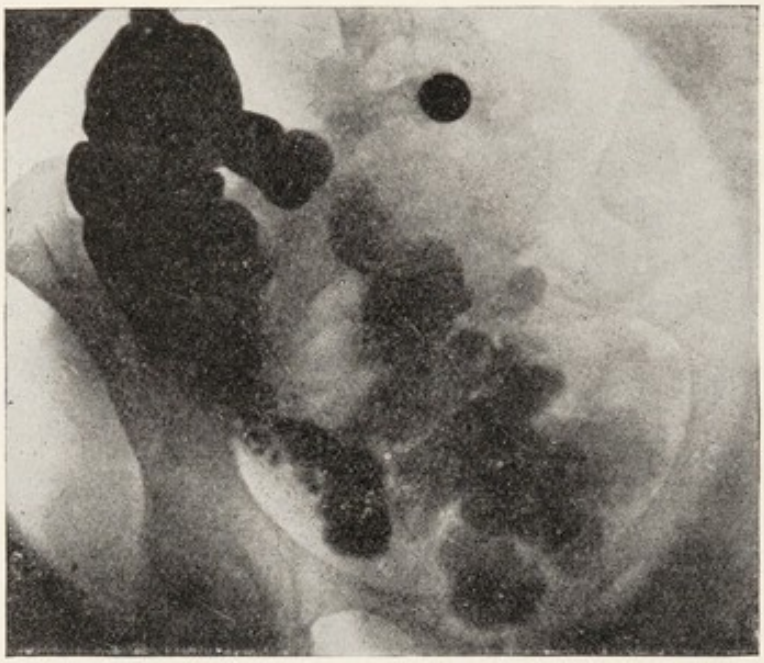

FIG. 9.—Skiagram showing " Sphincter " in the Transverse Colon (Dr. W. H. Overend).

reflex should be excited, though, if this is neglected, the rectum may become unduly tolerant of the presence of fæces, with resulting atony of the rectum, as in one common and troublesome type of constipation. (8) Finally, the alimentary tract is closed by the anal sphincters. This conception of the alimentary tract explains, as we shall see, many of the observed disturbances of the mechanical side of digestion. An irritable focus in any section disturbs the onward progress of the food, by causing a spasm of the sphincter immediately above, and often indirectly of sphincters some segments higher up.

We can express the motor disturbances of the alimentary tract under the heads of irregular and exaggerated contractions, tonic spasms, and atony. Irregular and exaggerated contractions are due to irritation of the para-sympathetic, and, when in the vagal area, produce colic, when in the pelvic area, tenesmus. Tonic spasm and atony are both due to sympathetic irritation, which may express itself in excess of normal movements—spasms due to constriction of sphincters, or in defect—as atony—due to inhibition of normal movements, as seen in atonic dilatation of the stomach and in intestinal stasis.

Œsophageal and Gastric Spasm

With this general preface we can proceed to discuss certain motor and secretory disturbances of digestion, more especially those associated with the sympathetic nervous system. The œsophagus appears to differ from the rest of the alimentary tract in that both motor and inhibitory supply are para-sympathetic in origin. I have been quite conscious of the existence of Keith's first sphincter in passing the œsophagoscope. In a case of new growth near the cardiac orifice, a tight ring of constriction was encountered at this point, yet at the subsequent post-mortem there was nothing to be found there. Globus hystericus is considered to be spasm of the œsophagus in its lowest degree : an actual point of constriction may pass up and down in a kind of peristaltic wave. I recently saw an extreme condition, apparently, of this kind in a discharged soldier. He stated he was unable to swallow more than half a tablespoonful of the bismuth emulsion, and X-rays showed a general spasm of the whole of the upper part of the œsophagus, yet no organic disease was found, and he must have been able to swallow some food, for he increased in weight. On re-examination, he was told he would have to continue his attempts to swallow the bismuth until some reached the stomach.

The next mouthful passed easily and quickly the whole length of the œsophagus. One must be cautious, however, about considering œsophageal spasm as purely functional, as it is so frequently excited by organic disease. Thus it is well recognized that the obstruction in new growth of the œsophagus is largely due to the associated spasm. I saw a good example of this in a man of sixty-three, who had dysphagia, anorexia, and wasting. I suspected malignant disease of the stomach, but X-rays merely showed a spasm at the lower end of the œsophagus, and the test meal showed 0.12 per cent. HCl, an amount which might be thought much too high to be compatible with malignant disease of the stomach. Yet a little later, when X-rays were repeated, there was distinct irregularity of outline in the upper part of the stomach, and soon an obvious mass was palpable there. Occult blood was present at every examination of the stools, and the course of the disease and its fatal issue accorded with the diagnosis. My point is that the œsophageal spasm was the earliest objective evidence of organic disease in this case.

Much interest has been taken in so-called "cardiospasm," in which the cardiac sphincter remains obstinately closed, with consequent dilatation of the œsophagus above. Brown Kelly showed that on passing an œsophagoscope, rhythmical opening and closing of the cardiac sphincter can be seen. In cases of so-called cardiospasm, when the tube came into contact with the parts at the level of the diaphragm, these movements ceased, and the parts remained closed until the tube was withdrawn a little. Hyperæsthesia at this point is, therefore, a potent factor in producing the condition, which may explain why it is often aggravated by excessive gastric acidity.

Hurst has pointed out that this "cardiospasm" is not an active spasm of the cardiac sphincter, but a failure of that sphincter to relax. He therefore suggested the term *achalazia* as a more accurate description. This is not

merely a distinction without a difference, for he showed that a mercury tube could find its way into the stomach by its own weight. But I think we may conclude that this failure to relax is often produced by just the conditions which excite true spasm in other parts of the alimentary tract, for, as he says, it is often associated with organic disease lower down. In one very severe, and ultimately fatal, case of mine, an organic hour-glass contraction was found in the stomach as well. Keith's comparison with the block system therefore applies. It may be that this peculiar reaction of the cardiac sphincter is related to its single innervation by the vagus, and the absence of sympathetic supply.

The spasm so commonly observed with X-rays over an active gastric ulcer must also sometimes be due to the vagus, as it occurs in parts to which the sympathetic only supplies inhibitory fibres. One can hardly doubt that such spasm is as definitely protective in its inception as the spasm of the muscles round an inflamed joint, and the rigidity of the abdominal muscles over an inflamed appendix. What is not, perhaps, so fully recognized is the spasmodic element in many forms of dyspepsia, where the spasm, though protective in nature, is probably a large factor in causing the pain. I may refer particularly to those forms of dyspepsia which are accompanied by hyperchlorhydria.

What constitutes hyperchlorhydria ? In its strict sense it means that if we give a test breakfast of fifteen ounces of tea without sugar or milk, and two slices of dry toast, and then withdraw the contents at the end of an hour, the total acidity exceeds the normal 0.2 per cent. HCl. But this might arise in one of two ways : either there is oversecretion of hydrochloric acid, or there is a delay in the escape of the gastric contents, which by prolonged stimulation of the pyloric glands, where gastric secretin is formed, may enhance acidity. In other words, pyloric spasm may produce hyperchlorhydria. And I would

suggest that this spasm may be a considerable element in the pain. The work of Bennett and Ryle, on fractional test meals, though necessitating revision of our views in many particulars, helps to support this contention, since they found that in hyperchlorhydria the stomach empties more slowly than normal. Hurst has shown that the introduction of an amount of acid into the stomach, far exceeding that ever met with in gastric ulcer, may cause no pain at all. We must look, therefore, to something else to explain the pain. Take the case of duodenal ulcer: there is no more characteristic feature of this disease than the temporary relief of pain afforded by the taking of food. One might have supposed that this was due to closure of the pylorus shutting food off from the inflamed area. But what do we find on X-ray examination? The stomach is hypertonic, and the contents are propelled into the duodenum with unusual speed, the so-called "duodenal rush," so that just at the time the patient is free from pain, food is passing over the ulcer. But though the stomach begins to empty quickly, subsequent examination may show that emptying has not been completed in the normal time; that pyloric spasm has supervened, and, as we know, it is at this later stage that pain returns. The occurrence of peristaltic waves against a closed pylorus would produce tension, which is known to cause pain in a hollow viscus.

Reflex Dyspepsia

For some years controversy raged over the question of hyperchlorhydria. By some it was regarded merely as a functional disorder of the stomach, while the extreme other position was expressed by Moynihan when he said that hyperchlorhydria was merely duodenal ulcer masquerading in the medical wards. The truth—as usual—lies between these extremes. We recognize to-day that duodenal ulcer is only one of the causes of hyperchlorhydria. I think that the position is well expressed by

Craven Moore, who calls hyperchlorhydria "reflex dyspepsia." He says: "The gastric functions may be disordered reflexly by a lesion situated more or less remote from the stomach itself. The two essential factors in the production of this condition are the existence of such a lesion and an increased susceptibility of the reflex nervous mechanism. These may vary indirectly. Thus, some lesions, as a duodenal ulcer, may assert their existence through a nervous mechanism little more susceptible than the normal, while others, as some ileocæcal lesions, may remain latent until the susceptibility becomes greatly exaggerated. There is little doubt that many such cases were formerly classed as nervous dyspepsia. The chief lesions are, duodenal ulcer, cholecystitis, chronic appendicular lesions, ileal kinks, chronic ileocæcal inflammations, cæcal and colonic stagnations, diseases of the generative organs in females, mobility of the kidneys, diseases of the central nervous system."

Sir Frederick Taylor, some years ago, aptly said, in speaking of diseases of the spleen, that the spleen was more sinned against than sinning. To a less degree this is true of the stomach. It is, of course, a site of primary new growth; but, apart from this, it is resistant to disease unless it is injured by eating or drinking—particularly drinking—unsuitable things, or by swallowed pus from the mouth, or by circulating toxins. In many cases of dyspepsia it is not at fault at all, it is worried by some irritable focus elsewhere. It seems unnecessary to labour the point that when gastric symptoms are strikingly intermittent, the irritable focus is, presumably, outside the stomach. A more or less regularly recurrent lesion in the stomach is rather difficult to conceive. Yet what physician has not seen a case of tabes in which gastro-jejunostomy has been performed for gastric crises? On consideration, it must be clear that if a patient at times can eat freely and fearlessly of any ordinary food, and at other times rejects everything and anything, or is in pain

whatever he takes, it is unlikely that the stomach itself is really at fault. Such intermittent attacks, if at all violent in character, in my experience point most frequently to the gall-bladder or the appendix as the site of the irritable focus, and it is in just such positions that a variation in the degree of reflex irritation may most easily occur. It is still frequently stated in the textbooks that gall-stones may remain for years in the gall-bladder without producing symptoms. This is, generally, only true if we add the limiting clause " symptoms referable to the gall-bladder," for on inquiry it will almost always be found that such patients have had repeated attacks of so-called acid dyspepsia. A slight increase in the associated cholecystitis, a small alteration in the position of the stone, and a violent reflex irritation of the stomach is set up, with pyloric spasm.

Murphy and Cannon found, after high intestinal section and suture, that for about six hours after recovery from the anæsthesia the pylorus remained tightly closed. There is a remarkable agreement between the period of delay in the discharge of gastric contents and the time required for the primary cementing of the intestinal wound. This is clearly protective, and helps to explain the spasm and the consequent hyperchlorhydria of reflex dyspepsia. It is a pathological extension of Elliott's law of the hollow viscus. Thus we see that the same condition which inhibits movements in the affected segment leads to spasm of the associated sphincter. And, from Keith's conception of the alimentary canal, we can understand that this spasm need not be confined to the associated sphincter, but may affect those higher up. Hence the occurrence of hyperchlorhydria from quite small irritations of the bowel in persons in whom nervous reflexes are exaggerated.

But I think we may fairly assert that the nearer the lesion is to the pylorus, the more likely are reflex symptoms to occur, however stable the nervous system. Thus

anyone with a duodenal ulcer will almost certainly respond with marked symptoms of reflex dyspepsia, and the same is generally true of gall-stones. With pancreatitis there is not only the reflex disturbance set up by the inflamed organ, but the hyperchlorhydria due to inadequate neutralization of the gastric juice in consequence of diminished pancreatic secretion. The terrible pain of pancreatic hæmorrhage is, no doubt, mainly due to the great tension produced, but the widespread sympathetic inhibition which accompanies it is proved by the way in which it produces symptoms of intestinal obstruction.

Tyrell Gray and Pirrie have published interesting observations on hypertrophic stenosis of the pylorus in infants which are in harmony with the conception of pyloric spasm here put forward. Sympathetic irritation could cause not only this spasm but the pancreatic inadequacy which usually goes with it. They point out that hyperadrenalism might lead to both, which is intelligible in view of the known antagonism between the adrenals and the pancreas.

Pancreatitis as a Cause of Enteralgia

I do not think the part played by the pancreas in producing severe abdominal pain is sufficiently realized, especially when the pancreatic lesion is chronic. More precise methods of examination, such as the combined use of X-rays, test meal, and examination of the stools for occult blood, reinforced by estimation of the urinary diastase, have certainly removed many cases from the category of gastric neuroses and enteralgia to that of organic disease. Clifford Allbutt, in the first edition of his "System of Medicine" (vol. iii, p. 481), writes thus concerning enteralgia: "The most terrible of all neuralgias . . . it is usually a piercing, agonizing and prostrating pain, leading soon to symptoms of the incipient collapse which is at hand in all abdominal neuralgias." This description

was recalled to my mind when, some years ago, I was examining a man with a prolonged history of such attacks. On palpating the abdomen I touched a spot in the epigastrium which started a train of violent symptoms. He jumped as if stabbed, raised himself in bed, and then began a series of convulsive movements. His pupils dilated, and his face assumed an almost maniacal expression. The paroxysm lasted for about two minutes, and gradually passed off. He sank back exhausted, and appeared to lose consciousness. Instantly I recalled witnessing a somewhat similar seizure in a patient Sir Archibald Garrod had asked me to see in the hospital two years previously. The patient was a Belgian refugee, aged thirty-two. In his case the convulsion was tonic rather than clonic. He lay writhing in bed in the attitude of opisthotonos ; the hands clenched and holding the bedclothes, the face flushed and then becoming dusky, the eyes rolling upwards. The patient appeared semiconscious, and made no response to questions. Several people who witnessed the attacks thought they were purely functional, but one point of interest and importance was strongly against this view ; the urinary diastase was raised to 100 units, which pointed to a pancreatic lesion. Some time after the patient had a severe melæna, and the diagnosis was made of a duodenal ulcer burrowing into the pancreas. Mr. Waring performed a short-circuit, but the man collapsed. The post-mortem showed a large ragged ulcer in the duodenum, with the pancreas forming its floor. Remembering this case, I had my patient's fæces tested for occult blood. The reaction was strongly positive, and remained so at the end of six weeks. The urinary diastase was also estimated, and found to be definitely raised. I therefore felt the provisional diagnosis of duodenal ulcer involving the pancreas to be justified. He was put on a Lenhartz diet, and improved greatly. The paroxysms ceased altogether. But an X-ray examination showed duodenal rush and an altered duodenal

cap, and the occult blood test continued to be positive. I accordingly asked Mr. Wilson to operate, and he found an ulcer on the duodenal side of the pylorus with firm adhesions to the pancreas. He performed a short-circuit, and the man has apparently made a complete recovery. He has no pain or tenderness on pressure, and he put on weight very quickly. Soon after this a third case came under my observation. The patient was aged thirty-five, and was seen in his fourth attack, the first having occurred thirteen years before, the next three years before, the third six months before; so that, though few, they were increasing in frequency. The attack took the form of sudden abdominal pain, vomiting, collapse, and brief unconsciousness. X-ray examination showed hypertonicity of the stomach, a distorted pyloric end to the stomach, a rapid beginning of the emptying of the stomach, but a delayed completion. There was also marked spasm of the terminal coil of the ileum, and delay in the onward progress through the colon. The urinary diastase was 128 units, but the occult blood test was negative. Corresponding, then, to the infrequency of the attacks, it would appear that the ulcer is not in an active bleeding condition. His last attack was in October 1917.

In a fourth case of the same kind that I saw, the character of the attacks pointed to duodenal ulcer involving the pancreas. X-rays showed hypertonicity of the stomach and duodenal rush. Examination of the fæces showed the presence of occult blood. The pancreatic diastase test, on the other hand, showed only 16 units—a normal figure. I therefore concluded that the clinical diagnosis of involvement of the pancreas was not correct. However, he subsequently died from septic infarcts in the spleen, and post-mortem showed a large ragged duodenal ulcer, the floor of which was partly condensed fibrous tissue and partly pancreas, which was in a condition of advanced interstitial inflammation. Indeed, it was surprising that there was no glycosuria with such advanced

disease, but this may explain the failure of the diastase test to confirm the diagnosis, since with chronic and advanced lesions the urinary diastase falls again.

These cases have impressed on my mind the fact that intermittent attacks of very violent abdominal pain, tending to rapid collapse, with intervals of apparently normal health, should lead one to suspect chronic ulceration near the pylorus on its duodenal aspect, involving the pancreas.

Travelling down the bowel, the next irritable focus for severe but intermittent attacks of acid dyspepsia and pain is Meckel's diverticulum. In 1917 I had under my care, in the First London General Hospital, a soldier who had repeated attacks which resembled appendix dyspepsia in many respects, and yet were not quite similar. Colonel Waring explored, at my request, and found a Meckel's diverticulum, which he removed, with complete cessation of the attacks. Colonel Sir D'Arcy Power tells me he has had several such cases.

Appendix Dyspepsia

The next site of origin of these reflex attacks is the appendix. Appendix dyspepsia has attracted much attention of recent years, and demands careful consideration. The account I shall give of it is based on my own cases, which may lead to its differing from the generally received descriptions.

There is often a history of "gastritis" or "gastric fever" in early life, which I believe represents the original attack of appendicitis. The patient is usually constipated and suffers from flatulence, but there are intervals between the attacks when digestion is almost normal. There are times when the symptoms chiefly consist of hyperchlorhydria—pain two or three hours after food, pyrosis, flatulence, and temporary relief of pain on taking more food. At intervals there are severe attacks when all food causes pain and there is much vomiting.

On examination the tongue is found to be furred, there is cutaneous hyperæsthesia to the touch of a pin, and tenderness on pressure over the right iliac fossa with perhaps resistance on deeper palpation and on rectal examination. A characteristic point is that palpation in the right iliac fossa causes discomfort in the epigastrium. When examined with bismuth and the X-rays the stomach begins to empty quickly, but usually has not completed emptying in four hours. There is delay in the passage of the bismuth along the cæcum, and as the bismuth passes there may be a break in the column, so that while the rest may be seen in the transverse colon, or even in the rectum, there is still some left in the cæcum. The appendix does not fill regularly. The test meal may show hyperchlorhydria, but quite as frequently does not, and generally the degree of hyperchlorhydria is less than the symptoms would lead one to expect. The more the symptoms resemble those of hyperchlorhydria while the test meal does not, the more likely, in my experience, is the appendix to be responsible.

I believe the explanation of this discrepancy between the symptoms and the test meal is that the hyperchlorhydria is due in these cases simply to pyloric spasm, and not to oversecretion. Generally speaking, this spasm has not come on at the end of the first hour, the time at which the test meal is withdrawn. There seems to be sympathetic inhibition of the peristaltic waves in the cæcal region, owing to the proximity of the irritated appendix. This on Keith's theory establishes a block high up in the alimentary canal with resulting pyloric spasm which, when severe, causes marked gastric symptoms.

It is generally recognized that the structural change in the appendix may be quite slight. In several of my cases showing all the signs and symptoms of appendix dyspepsia operation only revealed an appendix thickened by old inflammation on its terminal inch, yet its removal stopped the occurrence of attacks. Unfortunately this is

not always the case, and I think that then the condition of the appendix is only part of a more general inflammatory change in the colon, for it is quite clear that colitis may cause hyperchlorhydria, though the attacks do not then show the marked intermittence typical of appendix dyspepsia.

Less commonly appendix dyspepsia may be associated with spasmodic hour-glass constriction of the stomach, as in the following case :

A woman, aged thirty-six, suffered from vomiting sometimes at once after food, sometimes an hour later. The chief thing discovered on examination was a tender swelling to the outer side of the appendix. X-rays showed that the movements and position of the stomach were natural. As she improved so rapidly under ordinary medical treatment, it was decided not to have the appendix explored at that time. Some months after there was a return of symptoms, and X-ray examinations on three separate occasions showed an hour-glass constriction. The test meal showed the active hydrochloric acid to be only 0.14 per cent. Sigmoidoscopic examination showed nothing abnormal, and repeated examinations for blood in the stools were negative. Sir Gordon Watson explored, and at the operation there was an interesting demonstration of the appearance of the hour-glass stomach. On the stomach being explored one saw a constriction in the middle which passed off as she got more deeply under the anæsthetic. The region of the appendix was explored, and the appendix itself was found to be swollen and bent upon itself and its tip adherent to the cæcum. It was removed, and the patient made an uninterrupted recovery. Subsequently, however, she developed a gastric ulcer.

It is hardly surprising in these circumstances that appendix dyspepsia is so frequently mistaken for gastric ulcer, since it may apparently produce conditions which ultimately lead to it.

Hyperchlorhydria from Diverticulitis

Even when the irritable focus is far removed from the stomach, the reflex hyperchlorhydria may be marked. Thus a clergyman of forty-three consulted me on account of hyperchlorhydria of twenty years' duration. His bowels had always given him trouble, and of recent years he had noticed that after they had acted he felt that they had not emptied completely, and the desire for defæcation remained.

Examination of the rectum showed it to be empty, but palpation over the descending colon revealed a distinct resistance which persisted after repeated enemata. It was not possible to pass a sigmoidoscope high enough to reach the point of resistance. I concluded that the resistance could not be due to new growth, in view of the prolonged history and entire absence of wasting, but that it was more probably due to pericolitis sinistra, or diverticulitis, as it is commonly called.

Sir Gordon Watson operated and found that this was the case. The affected segment of the bowel was removed, and although there was considerable difficulty in closing the resulting colostomy, the attacks of hyperchlorhydria ceased. Some years later they recurred, and a further area of diverticulitis was found by X-rays, and confirmed at operation by Mr. Lockhart Mummery.

The general conclusion as to hyperchlorhydria, then, is that it is usually due to some reflex cause—an irritable focus somewhere lower down in the alimentary canal, and that the high acidity of the test meal need not mean oversecretion, but retention of the gastric contents due to pyloric spasm. The more excitable the nervous system, the lower is the threshold stimulus required to initiate symptoms. Inhibition of segments of the alimentary canal and stimulation of the sphincters, both due to the sympathetic, play a large part in the production of this type.

A simple hyperchlorhydria due to oversecretion and presumably associated with overaction of the vagus, though not so common, undoubtedly exists. When the stomach empties in less than its usual time, and yet the test meal shows high acidity, there must be both increased secretion and increased motility; both of these effects would be produced through the vagus. If, in addition, X-rays reveal no lesion lower down in the bowel, and examination of the stools shows no occult blood, we are justified in placing a case in this category. It is not difficult, therefore, to distinguish between the vagal and sympathetic type of hyperchlorhydria.

Atonic Dilatation of the Stomach

Just as the sympathetic may cause spasm of a sphincter, so it may produce inhibition in a segment of the alimentary canal which will naturally lead to dilatation of that segment. This leads me to consider what is usually termed atonic dilatation of the stomach. It is much more common than usually supposed, and it may explain many cases of chronic indigestion. The chief symptom is not acute pain, though in one case I found an acutely tender spot over the stomach. The patient will generally complain of a sense of depression and indefinable misery after food. He may also complain of fermentation and a sour taste. Hurst pointed out that such patients usually complain of feeling full up as soon as they start eating—due to the fact that the dilated stomach cannot relax further as a normal stomach does when food is ingested, so that the intragastric pressure rises. He further pointed out that precisely the same symptom is complained of by patients with the opposite condition of fibrosis of the stomach, because here again the stomach is incapable of relaxation. A diminished secretion of gastric juice is what one would expect, but the condition is compatible with an entirely normal test meal, as I have repeatedly found. Occasion-

ally I have even seen hyperchlorhydria with well-marked atonic dilatation. The condition can be recognised at once with the X-rays. The broad, flat-topped, inert meniscus of bismuth is most characteristic, and may persist for eight hours or more. There is one fallacy, as Sir Archibald Reid pointed out to me. An obstructive dilatation is ordinarily associated with powerful peristaltic waves, but a point may be reached where the stomach muscles, as it were, give up the struggle and remain toneless and quiescent. In view of the violent peristalsis which may be seen with an enormous degree of dilatation, this may sound improbable, but not all stomachs are capable of maintaining such waves when the pylorus is obstructed, and I have had the opportunity of seeing atony follow in a case of obstructive dilatation where operation was refused. Subsequently operation was consented to, and obstruction was found. This is more apt to occur when obstruction takes place in old and debilitated subjects, but not only in such circumstances. It is comparable to the dilatation of the heart which follows hypertrophy.

Within a few weeks I saw two cases, one of simple ulcer at the pylorus and one of malignant disease there. In both the stomach was dilated and atonic. Both of these were in elderly patients who had had severe pain, and no doubt this may play a part in exciting sympathetic inhibition. But such cases should not encourage us to advise short-circuiting when atonic dilatation is found unless there is evidence of obstruction also, for there is a general agreement that gastro-jejunostomy in simple atonic dilatation has disastrous results.

The conventional statement is that atonic dilatation is a sequel of chronic gastritis. This may be so sometimes, but when the test meal shows a normal or even increased secretion, gastritis cannot be responsible. The symptoms may, as in several of my cases, date from some enfeebling illness, particularly typhoid. If an acute infection can

produce acute dilatation of the stomach, presumably a less severe, but more prolonged, toxæmia can lead to chronic dilatation. Certainly some of my cases have apparently so originated. I have noted the marked effects of fatigue in aggravating the symptoms, and recent observations by Kast explain this. He found that in such persons the evacuating power of the stomach and intestines was directly affected by physical or mental effort. But I am convinced that sympathetic inhibition alone may play an important part in producing such atony.

A man, aged about thirty, was admitted under my care at St. Bartholomew's Hospital in 1914, with a history of pain and flatulence half an hour after food for the previous twelve months. For the last two months the pain had not occurred till four or five hours after food. On examination there was a well-marked succussion splash, and X-rays showed great dilatation and atony of the stomach, with the greater curvature down to the pubes. Yet the test meal showed a total acidity of 0·29 per cent., the physiologically active hydrochloric acid being as high as 0·27 per cent. He was treated by lavage with marked improvement. In 1916 he had some acute abdominal attack, for which he was admitted to the West London Hospital and immediately operated on. The position of the incision showed that the stomach was suspected as the site of trouble, but a gangrenous appendix was found and removed. I subsequently had an opportunity of re-examining him. There was no atony or dilatation of the stomach to X-rays, and the test meal showed only 0·195 per cent. of acidity—*i.e.*, a normal amount. Here a controlling appendix would appear to have been responsible both for hyperchlorhydria and atonic dilatation. This leads me to conclude that, when atonic dilatation is combined with hyperchlorhydria, an irritative focus causing reflex dyspepsia and sympathetic inhibition should be looked for. A curious example of anxiety alone apparently acting as a cause of atonic dilatation is as follows :

A young man, who was very nervous at the idea of being called up for military service, consulted me about his health, and I found on X-raying him that he was suffering from atonic dilatation of the stomach. He obtained exemption, and when I re-examined him by the X-rays some three months later there was no sign of atony. Subsequently, when the question of his military category again came under review, there was a return of the atonic dilatation. Such a condition cannot be simulated; it must be, in my opinion, the direct result of a sympathetic inhibition from emotional causes. Since then I have had many cases of this sort, and they are not uncommon in anxiety neuroses. As Hurst has urged, the description of "atonic" is not really applicable to a condition due to active inhibition. The muscular tone is found to be good as soon as the inhibition is removed.

Another muscular condition which may be confused with atonic dilatation, and which may interfere with the evacuation of the gastric contents, is gastroptosis. It is possible also for them to coexist. Here too I have been struck by the frequency with which gastric secretion may remain not merely normal (which might perhaps be expected), but actually increased. I must conclude that it is due to reflex irritation from the bowel, which, being also dropped, is liable to various disturbances. Many of the symptoms referred to movable kidney are due to the associated visceroptosis, and it is important to realize that some of the symptoms noted when the stomach is dropped are due to the dropped bowel. Just as a patient's general health has an important bearing on the symptoms of an atonically dilated stomach, so it may cause a gastroptosis previously existent to assert itself. It is clear that gastroptosis must often have existed for years before producing symptoms. Some intercurrent disease may be responsible for exciting symptoms. Symptoms which do not appear till after childbirth or operative removal of pelvic viscera can be easily understood. The X-ray

appearances naturally differ entirely from those of atonic dilatation. Instead of the horizontal increase in the stomach shadow, we see a vertical increase. Though the symptoms of gastric discomfort are somewhat similar, the patient with gastroptosis, if questioned, will often have noted that upwardly-directed pressure on the abdomen relieves the discomfort to some extent. In such a case an abdominal support will probably afford marked and immediate relief. One patient told me that as soon as she put on the support she was able to ride a bicycle again, which she had been unable to do for two years. Another said that life seemed a different thing, and that her miserable feelings were relieved at once. But this is exceptional, and both these patients had expressed themselves as conscious of a feeling of dropping. Most patients are not conscious of this, although X-rays may show marked gastroptosis. They will probably require time to become habituated to the support before they express themselves as relieved. It is clear that the support merely acts, as Hurst suggested, by raising the general intra-abdominal pressure, for X-rays will show that the position of the stomach usually remains unaltered.

Visceroptosis will also be benefited by such a support, and this brings me to a brief reference to intestinal stasis. Sir Arbuthnot Lane's work has naturally aroused much interest in this subject. The very enthusiasm with which he has advocated his views has perhaps tended to arouse opposition. Still, we must admit that he has described a clinical condition which can be recognized. The patient, usually a woman, has a loose and inelastic skin, which becomes pigmented. The breasts show chronic mastitis, often undergoing cystic degeneration. The appetite is poor and the breath offensive; there is flatulence, constipation, attacks of nausea and vomiting, and frequently abdominal pain with points tender to pressure. Depression and lack of energy, both physical and mental, characterize the state. The circulation is

impaired, the hands and feet are cold, clammy, and often livid. Progressive emaciation, headache, backache, muscular pains and aching joints are not uncommon. As is well known, Lane attributes the condition to the adoption of the upright position by human beings, which has resulted in the dropping of the viscera.

The three principal results of this visceroptosis are, according to Lane: (1) The formation of conservative adhesions along the lines of resistance to downward displacement. (2) The consequent production of "kinks" along the course of the gastro-intestinal tract, leading to (3) stasis, with delayed digestion, constipation, and auto-intoxication. Many more remote effects have been assigned to this cause which, starting with diminished resistance to tuberculous infection, threaten to extend until every ailment and lesion are thus explained, tempting us to wonder why four-legged animals are ever ill at all. But we may note the ingenious way in which the theory is made to account for many diseases of the alimentary tract and its annexes. The mechanical retention of stomach contents would cause them to become more acid from continued secretion, which may be a factor in erosion and ulceration of the gastric mucosa. The mucous membrane of the "kinked" duodenum becomes congested and then ulcerated. Ascending infections of ducts can occur more readily when, as the result of stasis, bacteria normally confined to the large intestine ascend into the ileum, and so gall-stones and pancreatitis are explained. Lane also holds that adhesions round the appendix are more frequently the cause than the result of appendicitis. Mucous colitis is referred to similar causes, and carcinoma of the intestines is held to result from irritation due to material passing along the various "kinks" and flexures.

Such sweeping conclusions have naturally aroused opposition. It must be remembered that Cannon found that peristalsis was able to drive on the contents of the bowel past sharp "kinks," and in tuberculous peritonitis

or malignant disease of the intestines " kinks " are formed which in many cases produce neither constipation nor stasis. Waugh's views on the importance of a dropped ascending colon as a cause of many digestive troubles are also worthy of consideration. Without committing myself to their acceptance in full, I may say I have been struck with the frequency of dyspepsia of right-sided origin, and with the co-existence of more than one lesion on that side, such as appendix trouble combined with cholecystitis or with duodenal ulcer.

It is noteworthy that the position of most of Lane's " kinks " corresponds to those of Keith's " sphincters," and it is at least possible that many of the appearances are produced by muscular contractions of these sphincters as much as by mechanical kinks. Such sphincteral spasms would be produced through the sympathetic, and general sympathetic stimulation would produce not only spasm of the sphincters, but inhibition of normal peristalsis in the segments between them. Under such conditions increased intestinal putrefaction and fermentation must result.

This would account for a condition, which on the mechanical view must be congenital, not producing the effects until some debilitating illness or psychical shock occurs. Tyrell Gray and Pirrie have shown how stasis from sympathetic irritation would tend to increase visceroptosis, which in its turn would produce more drag on the sympathetic nerves in the mesentery, thus setting up a vicious circle. I have several times thought I could trace the onset of symptoms attributed to intestinal stasis to a bereavement and other psychical causes. With the removal of the cause, or the healing effect of time on the grief, the condition has appeared to clear up. Some of the worst cases occur in women who have no employment and no object in life. The acquisition of a definite rationale for existence, whether a happy marriage, an absorbing profession, or even a political agitation, may

have the most remarkable effect on the symptoms of visceroptosis. This is the type of case also where the auto-suggestion of Christian Science often achieves extraordinary results, results which surprise and may annoy the practitioner who does not sufficiently allow for the influence of the mind upon the body. And it does seem to me that this undoubted influence of the mind on the body can be most readily explained by the action of the sympathetic nervous system, since through it depressing and disagreeable emotions inhibit the processes of digestive secretion and absorption while stimulating katabolism elsewhere. Thus the reserves of the body are spent, while the restoration of its energy and tone is prevented.

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CHAPTER V

THE SYMPATHETIC NERVOUS SYSTEM IN DISEASES OF THE CIRCULATORY SYSTEM

The adaptability of the circulation to the needs of the body is based on the vaso-motor system, which regulates both the general blood-pressure and the local blood-supply. These functions are carried out by the vaso-motor centre in the medulla, aided by secondary centres in the cord. The *receptor* channels for the vaso-motor reflexes are of two kinds :

(*a*) *Pressor*, calling for a rise of blood-pressure. All sensory nerves are pressor in their action, causing the vaso-motor centre to throw out increased constrictor impulses, particularly to the splanchnic area. This tends to produce a rise of pressure in all painful conditions.

(*b*) *Depressor*, producing a fall of blood-pressure by causing the vaso-motor centre to relax the normal tone of the splanchnic area, which thereby becomes flushed with blood. The only pure depressor nerve is the depressor branch of the vagus. It provides a way of escape for the heart when labouring against too high a blood-pressure. But depressor fibres may also be demonstrated in sensory nerves, since on regeneration after section they recover before the pressors, and on cooling they retain their function longer. Stimulation of the mucous membrane of the rectum and vagina may also produce a depressor effect, especially under light anæsthesia.

The *effector* channels are also of two kinds :

(*a*) *Constrictor*.—These are much the most numerous, and are confined to the sympathetic. The connector element is

comparatively short, the cell station generally being in the first sympathetic ganglion which is reached. Here the new post-ganglionic fibre starts, and is distributed along the spinal nerves to the more superficial structures, and along the blood-vessels to the deeper. This is the method of distribution whatever the part of the body to be supplied.

(*b*) *Dilator.*—These are not nearly so numerous. The muscular coats of the blood-vessels being always partly contracted, it is possible for dilatation to be produced by inhibition of a constrictor. Pure dilator nerves will, therefore, only be found where there is a special need for marked and rapid dilatation, such as the chorda tympani to the submaxillary gland, the auriculo-temporal to the parotid gland, and the pelvic visceral nerve springing from the second and third sacrals. It will be noted that all these belong to the para-sympathetic system and, therefore, have their ganglionic stations close to their destinations. The existence of dilator fibres in mixed nerve trunks has been proved by taking advantage of the fact that constrictors degenerate more quickly after section and are more readily affected by cooling than dilators, whereas dilator fibres are more easily stimulated by slow, rhythmically-repeated shocks. Dilator nerves to the limbs have appeared in a new aspect, since Bayliss has shown that they seem to be in every way identical with the sensory nerves. Under experimental conditions, at any rate, these fibres are able to carry "anti-dromic" impulses. That is to say, the same fibre is able to convey sensory impulses towards the brain and dilator impulses towards the periphery. In this way the blood-supply is simultaneously increased at the point where the painful impulse is *received* and where it is *perceived*, thus facilitating the appropriate reaction in each case.

Bruce (*Review of Neurology and Psychiatry*, vol. x, p. 471) explains the eruption of herpes zoster by these observations. The posterior root ganglion is inflamed,

and thereby sends at the same time painful impulses into the spinal cord, and antidromic vaso-dilator impulses to the peripheral area of skin supplied by the same ganglion. If the sensory terminals are paralysed with a local anæsthetic, vaso-dilatation does not occur. He regards the process as similar to Langley's "axon-reflex." The eruption is looked upon as the direct consequence of the vaso-dilatation.

At first sight it is not a little surprising that the organs composing the "tripod" of life—the brain, the lungs, and the heart—either lack or are very scantily supplied by vaso-motor nerves. Yet on consideration it will be clear, as I pointed out in 1908, that it is just because they are so important that they cannot be subservient, for the vaso-motor system can override the local requirements for the general needs. The efferent path in a reflex arc is open to impulses coming from many quarters, although the afferent channel is reserved for impulses coming from the particular organ it supplies. The organs composing the "tripod" of life cannot allow themselves to be subordinated in this way. This may cause them in disease to override the interests of the general economy for their own advantage, though it is merely an example of the survival of the fittest, the most vital organs being protected at all costs. We may consider some of the results of this exemption of the "tripod" of brain, lungs and heart from the operation of the vaso-motor system.

Brain

The quantity of blood plus cerebro-spinal fluid in the cranium is a constant, since the brain substance is incompressible and enclosed in a rigid box. The first effect of a rise of arterial pressure will be to express the cerebro-spinal fluid from the cranium, and then to compress the cerebral sinuses until the pressure in them rises to that

which the brain substance exerts against them. Thus the conditions approximate to those obtaining in a system of rigid tubes. Now, the medulla must keep up its supply of arterial blood at all costs, since it contains the centres that are essential to life. If the blood supplied be too rich in carbon dioxide, the respiratory centre is excited to increase the respiratory rhythm; if the quantity of blood be not adequate, the slightest degree of cerebral anæmia excites the vaso-motor centre to contract the vessels in the great splanchnic pool, and thus to force more blood up to the head. The blood-supply to any part may be increased in two ways—by local vaso-dilatation, or by vaso-constriction elsewhere. In a rigid box a local relaxation of muscular tone would not be effective, for it might easily be overridden by the intracranial pressure. Forcing the blood in by a general rise of blood-pressure would be a much more powerful mechanism. Thus it is we find that the blood-supply to the brain is mainly controlled by means of the splanchnic area, which, in its turn, is controlled by the vaso-motor centre within the cranium.

So that, although vaso-motor nerves have been found by Morison and by Gulland in the cerebral vessels, they must play an entirely subsidiary part, since all the vaso-motor effects ordinarily observed can be adequately explained without reference to them. That they do not function actively is further shown by their slight contraction when perfused by adrenalin.

To avoid cerebral anæmia, the general blood-pressure must be kept at a point above the intracranial pressure, as was shown by Cushing, who varied the intracranial pressure in animals by introducing normal saline solution into the cranial cavity from a pressure bottle. The general blood-pressure was observed simultaneously by a tracing taken from the femoral artery. Until the intracranial pressure exceeded the blood-pressure, nothing more than a slight quickening of pulse and respiration occurred, and

even this could be avoided if the fluid did not interfere with the sensitive dura. But when that point was reached, the blood-pressure was raised at once until it again exceeded the intracranial pressure. This was repeated with each increase of intracranial pressure until the blood-pressure was forced to a level considerably over 200 mm. of mercury. Then the vaso-motor centre began to show signs of giving way. The splanchnic area could be seen to contract every time the brain was compressed, and to dilate again as the pressure fell. If the vagi were divided before the compression was applied, the blood-pressure could be seen to correspond even more closely than before to the degree of intracranial tension, always remaining slightly higher. If both vagi and spinal cord were divided, a rise of intracranial pressure did not affect the blood-pressure at all, showing that the adjustment was produced by vaso-constriction in the rest of the body. This has a practical bearing on the treatment of cerebral hæmorrhage. If we reduce blood-pressure—*e.g.*, by venesection or amyl nitrite—to the point at which the reduction will be effective in checking the hæmorrhage, we are obviously in danger of reducing it to the point at which the medulla is starved (Leonard Williams). The absolute necessity of maintaining the blood-pressure at a higher level than the intracranial establishes a vicious circle, for the hæmorrhage produces a rise of pressure, and the rise of pressure increases the hæmorrhage. A rising blood-pressure in cerebral hæmorrhage is of very grave prognosis, as it shows the bleeding is still continuing. It may be asked how a cerebral hæmorrhage can ever be recovered from? The answer appears to be that the tentorium can shelter the medullary centres from some of the ill-effects of the high intracranial pressure existing above it. The rapidly fatal effect of even small pontine hæmorrhages supports the idea, for here no such shelter is possible.

If intracranial pressure could be lowered directly, the

vaso-motor centre would allow the blood-pressure to fall, thus assisting the arrest of hæmorrhage and breaking the vicious circle.

It is true that lumbar puncture, which will diminish intracranial tension, is sometimes risky, for it leaves the arteries less supported, and therefore more liable to bleed. But since the blood-pressure will fall as soon as the intracranial pressure is reduced, it is also true that the necessity for such support is diminished. I prefer only to do it in grave cases where the blood-pressure continues to rise. Thus a man in whom I had diagnosed cerebral hæmorrhage had a blood-pressure rising from 165 to 210 mm. Lumbar puncture withdrew blood-stained cerebro-spinal fluid. The pressure fell at once to 175 mm., and then more gradually to 135 mm., while consciousness was soon regained.

Cushing's experiments also explain why we so frequently find more than one hæmorrhage into the brain substance, if the initial one be at all large. If looked for, small hæmorrhages into the pons will be found very commonly in cases of ordinary lenticulo-striate hæmorrhage. It was formerly difficult to decide whether they occurred simultaneously with, before, or after, the large hæmorrhage. It is now clear that the large hæmorrhage is responsible for driving up the general blood-pressure so much that diseased arteries in other parts of the brain are unable to withstand the strain.

Lungs

The absence of direct vaso-motor effects in the pulmonary vessels has an important bearing on the treatment of hæmoptysis. It must be remembered, however, that the lung receives blood from the systemic circulation also, through the bronchial arteries, which spring from the aorta. In the hæmoptysis of mitral stenosis the pulmonary vessels alone are involved; vaso-constrictors such as adrenalin will therefore do harm by forcing

blood from the systemic into the pulmonary vessels. But vaso-dilators such as the nitrites may do good, because they will relieve the engorged lung by drawing the blood into the dilated systemic vessels. In the hæmoptysis of phthisis, either pulmonary or bronchial vessels may be eroded, though the former, being more numerous, are more likely to be implicated. But even if we could be sure that a bronchial artery were the source of the hæmorrhage, styptic drugs would still be inadvisable, for any benefit derived from their local action would be outweighed by the general rise of pressure and by the pulmonary turgescence, which might cause other weak spots to rupture. Nitrites might still be useful, as the widespread dilatation would draw blood away from the lungs, and thus more than counterbalance the risks of reopening the bleeding-point. Also the lowered pressure would favour the sealing of this point by blood-clot. The same principles would therefore guide us, whichever set of vessels were involved. The success of adrenalin in relieving the asthmatic paroxysm is, at any rate in part, due to its constricting effect on the turgescent vessels in the bronchial mucosa.

Œdema of the lung can similarly be explained by the absence of vaso-constrictors from the pulmonary vessels. It is a terminal event; as Cohnheim said: "A man does not die because he gets œdema of the lung; he gets œdema of the lung because he is dying." It may also come on quite suddenly, particularly in patients with high pressure or aortic regurgitation. There is sudden dyspnœa and cyanosis, with much restlessness and distress. Then the patient begins to cough incessantly, and a quantity of fine froth, often blood-stained, may pour from both mouth and nose. Unless the condition can be speedily relieved, death will inevitably follow, and that swiftly.

Quite forcible heart sounds may be audible till near the end, but these are probably produced by the right heart. The usual explanation given is that the left heart

fails somewhat suddenly, and as there are no vaso-constrictors in the pulmonary vessels, the right heart forces blood into them, so that they become engorged and pour out serum into the alveoli until the patient's lung is literally drowned. Two interesting cases of acute œdema of the lungs I saw support this view. In one, a man with a fatty myocardium proved to have torn his chordæ tendineæ from his musculi papillares during a strong muscular effort; in the other a dissecting aneurism had occurred just above the aortic valves, almost blocking the lumen of the aorta. Both of these accidents would throw an immediate and desperate strain on the left ventricle, allowing of no time for adjustment to the burden.

Again, in aortic regurgitation sudden stoppage of the left ventricle is not uncommon, and it is with this lesion that acute œdema is perhaps most apt to occur. Venesection to 10 or 12 ounces appears to be the only treatment likely to be effective, which would relieve the overloaded right heart and the stagnant pulmonary circulation.

Heart

The reason for the absence of vaso-constrictors to the coronary arteries is readily understood. If a rise of general blood-pressure is produced by vaso-constriction, the heart is given more work to do, so that a better blood supply must be given to its muscle. If the coronaries shared in this vaso-constriction, their blood-supply would be diminished, but as they do not, the rise of pressure automatically forces more blood into them. If the heart has less work to do, the blood-pressure falls, and the coronaries receive less blood. In this way the supply to the heart muscle is made proportional to its requirements. The power of compensation is very great so long as the coronary arteries remain supple, but if they become atheromatous this means of regulation is frustrated and compensation easily breaks down. Note the way in

which acute dilatation of the heart is apt to follow on an attack of angina pectoris.

Starling's recent work on the heart has thrown a new light on the association of high blood-pressure with heart disease. It is often a surprise to find that, when the heart is failing and the pulse feeble, blood-pressure is quite high, perhaps 200 mm., or even more. The first explanation that occurs is that the heart is failing behind the high pressure, but if so, lowering the pressure should relieve the heart, which as a matter of fact it fails to do. The next explanation offered was that as the output of the heart diminishes, vaso-constriction must occur to diminish the size of the bed to be filled, and thus to spare the heart. This would account for pressure being maintained at its normal level, but not for its rising as the heart fails. But we now know that the strongest stimulus to a muscular contraction is the previous stretching. Hence the profound disturbance to cardiac rhythm resulting from pericardial effusion, for this interferes with diastolic filling, and therefore with the stretching of the cardiac muscle. Hence also the marked hypertrophy of the left ventricle in aortic regurgitation, where the ventricle is filled during diastole both from the auricle and from the aorta, and so is stimulated to increased work. In the same way we may regard the vaso-constriction produced through the sympathetic as an attempt, by raising blood-pressure, to stimulate the flagging heart, for the diastolic stretching will be increased thereby. But when the myocardium is diseased it fails to respond to a remedy which is at best a desperate one—the overstretched muscle fails to respond and dilatation increases.

Pope has calculated the enormous amount of work which the heart normally performs. If it only pumps $2\frac{1}{2}$ ounces of blood at each contraction (and it usually pumps more), this amounts to $7\frac{1}{2}$ tons of blood a day ; when the pressure is normal, this is equivalent to lifting a ton of blood 122 feet high. This gives us some idea of the great extra

work which is imposed on the heart if it has to lift the blood, not against a pressure of 120 mm., but say 180 or 200 mm.

And so it comes about that anything which leads to the maintenance of an unduly high pressure must use up the cardiac reserve. The rise of pressure so common in later life must thereby in itself shorten the remaining span of years. This does not mean that in vaso-dilator drugs is to be found the elixir of life. Quite the contrary, for we know that the rise of pressure is in itself a necessary and conservative measure, and that to lower pressure directly, without attacking the cause of its rise, is to invite disaster.

The height of the diastolic pressure is often of more importance than the systolic tension. It is far less subject to temporary variation, and it indicates more exactly the resistance which the heart has to overcome. A constant diastolic pressure of or above 100 mm. indicates hypertension according to Norris, regardless of whether the systolic pressure be 180 or 140 mm. Stone points out that taking the systolic pressure at 120 and the diastolic pressure at 80, the pulse pressure is 40, so that the amount of energy expended in maintaining the circulation in excess of that required to open the aortic valves is 50 per cent. of the diastolic pressure. Therefore, with a systolic pressure of 170 and a diastolic pressure of 100 mm., the pulse pressure would be 70 per cent. of the diastolic, and would represent an overload of 20 per cent. He finds that clinical symptoms do not appear until the overload exceeds 25 per cent., and that when it reaches 50 per cent. myocardial exhaustion may be precipitated by any sudden strain. That the vessel wall can hypertrophy to maintain the raised pressure is shown by the interesting observation of Fischer and Schmieden that the transplantation of sections of a vein into an artery by Carrel's method does not lead to a dilatation of the vein despite the greater pressure to which it is exposed in its new

position ; in fact, a thickening and decrease of its calibre result.

Hypertension

The belief that a rise of blood-pressure can occur before structural vascular lesions take place has been expressed by von Basch, by Huchard, and by Clifford Allbutt. Though not universally accepted, such a view is in accord with what we know of the general vaso-constrictor effect of sympathetic stimulation. It is supported by Norris's observation that " periods of arterial hypertension are often traceable to hygienic or dietetic variations ; they are very closely associated with psychic phenomena, which are generally by far the most potent factors for good or ill."

The discovery by Barger and Dale of diamine bodies resulting from putrefactive decomposition of proteins which have a pressor effect may explain how dietetic factors can produce hypertension. And I showed in the last chapter how sympathetic irritation will produce stasis in the bowel both by inhibiting adequate peristalsis and by exciting spasm of the several sphincters. Such stasis must increase putrefactive changes, and can thus play a part in raising blood-pressure.

But it would lead us too far afield to discuss all the causes of rise of blood-pressure. I only wish to indicate certain ways in which the sympathetic nervous system plays a part. And, incidentally, I would point out that we must not attribute too large a part to renal lesions in the *causation* of high pressure. For, as Janeway said, " Amyloid disease, which is *par excellence* a disease of the glomeruli in its pure form, is almost invariably without effect on the blood-pressure." It is true that Lee (*J. Amer. Med. Assoc.*, 1911, vol. lvii, p. 1179) found, in a series of post-mortem examinations on cases of hypertension, that all patients who had a pressure constantly or repeatedly above 200 mm. had some renal disease.

But post-mortems only show the terminal stage, and do not throw light on the inception of raised pressure.

Hypotension

And now I must briefly refer to the opposite condition—that of unduly low pressure, which is indeed more urgently dangerous than one which is too high. There is no chronic disease in which the blood-pressure is persistently so low as in Addison's disease. I have repeatedly observed a pressure as low as 80 mm. and even 65, though that was shortly before death. I have heard of a case with a pressure of 40 mm., though I should have thought this was inconsistent with the maintenance of life. Now that we appreciate the co-operation of the adrenals with the sympathetic, the symptoms of the disease become more easy to explain, and Wilks's view of the " unity of Addison's disease " receives fresh confirmation.

It is essentially due to the absence of adrenalin from the circulation. We can now reconcile the two views originally held as to its pathology—one ascribing it to fibro-caseous change in the suprarenals, the other to changes in the adjacent sympathetic. If the sympathetic cannot act in the absence of adrenalin, the cardinal symptoms of Addison's disease are explained. As the sympathetic supplies accelerator fibres to the heart, and constrictor fibres to the blood-vessels, their paralysis must result in profound cardio-vascular atony. The sympathetic also provides the stomach with inhibitory fibres ; their loss must lead to motor irritability of the stomach, and therefore to vomiting. This will be intensified because, the closure of the pyloric sphincter being under the control of the sympathetic, regurgitation into the stomach can now easily occur from the duodenum. The effect of adrenalin in maintaining the tone of voluntary muscle explains another factor in the profound asthenia. The pigmentation probably results from the relaxed condition of the blood-vessels, like that after poulticing

or exposure to light. The distribution of the pigmentation in the disease supports this view. Another hypothesis is that the pigmented areas contain a material which is compensatory for the deficient adrenalin.

Occasionally the gland is found to have been completely destroyed, and yet the signs of suprarenal inadequacy have not developed. Peyton suggests that the similar cells in connection with the sympathetic chain have assumed the function of the gland in such cases.

As typical of an acute condition associated with low pressure we may take shock.

Wound shock has been the subject of much investigation during the war, as its importance in swelling the death-roll indeed demanded. I will briefly summarise the conclusion reached by Bayliss in his Oliver-Sharpey Lectures, by Cowell in his Arris and Gale Lectures, in the various reports to the Medical Research Committee, and in the discussion at the Royal Society of Medicine.

Cowell generally noted hypertension in those unwounded soldiers subjected to stress or excitement. Temperament played a large part in producing this hypertension. He attributed it to the sympathetic-adrenalin stimulation, and thought that consequent exhaustion of this from prolonged excitement might prove a factor in the initiation of wound shock. Yet, as shown in Chapter II, shock may be fully developed before sympathetic-adrenalin exhaustion has come on. In trivial wounds, where the man becomes momentarily faint, hypotension does not exist long enough to be measured. In slight wounds the pressure is more often raised, presumably from sympathetic-adrenalin stimulation. As long ago as 1870 Goltz showed that a blow on the exposed mesentery of a suspended frog caused vagus arrest of the heart and loss of arterial tone, so that blood tended to accumulate by gravity in the splanchnic area. Pure "nervous shock" of this kind does not cause death in man, according to Cowell, unless there is some latent cardiac weakness;

primary shock is rarely seen apart from hæmorrhage. There is a reaction after the hypotension of primary shock, which is the most favourable time for operation. Then secondary wound shock develops after several hours in a large proportion of serious wounds, accompanied by a great fall of blood-pressure.

What is the cause of this secondary shock ?

Reduction of CO_2 in the blood owing to increased respirations (acapnia), adrenal exhaustion, vaso-motor paralysis, and cardiac failure have all been shown not to be primarily responsible. If neither the vaso-motor centre nor the heart is responsible, why is there a low arterial pressure in shock ? Apparently because of the diminished volume of blood in active circulation. But where is the lost blood in cases in which there has not been gross hæmorrhage ? It is not in the heart or lungs. It cannot be in the arteries, since if it were, with both a capable heart and an efficient vaso-motor centre, an adequate amount of blood would be accompanied by a normal height of arterial pressure.

We are left, then, with the alternatives of the veins and the capillaries. The former alternative has been widely accepted. " In shock," it is said, " the sufferer bleeds into his own abdominal veins." But surgeons of extensive experience at casualty clearing stations have testified that on opening the stomach they have not found any primary splanchnic congestion. Moreover, if this were the case, it should be possible promptly to remedy the condition by lowering the head, bandaging the limbs, and compressing the abdomen. Such methods, though sometimes helpful, do not give the results that would follow were venous stagnation the cause.

The capillaries alone remain. Cannon, Fraser, and Hooper have demonstrated in shock a concentration of the blood and a stagnation of the corpuscles in the capillaries in such widely separated parts as the ears, fingers and toes, and even in deeper parts, so that capillary blood

may contain eight instead of five million corpuscles per cubic millimetre. Moreover, it has been calculated that the capillary capacity is sufficient to contain the lost blood in shock and that the chances of its doing so are greater the more concentrated the loss of blood becomes.

Such concentration must seriously increase the viscosity of the blood, which is also increased by a fall of temperature. This rise of viscosity has been directly observed by Trevan. Now, a prompt and striking reaction to injury is profuse sweating, doubtless due to sympathetic stimulation. The fall of temperature thus produced will be accelerated if the clothing is soaked with rain. The temperature often falls below 95° F., and readings as low as 87° have been obtained. According to Cowell, shivering is rarely seen under these conditions, so that heat loss is not compensated for by heat production.

Capillary stagnation means diminished oxidation, with consequent production of intermediate acid metabolites. The H-ion concentration therefore rises in the capillaries and still more in the tissues.

As long ago as 1880 Gaskell showed that acids dilated peripheral vessels. To some extent this is compensated for by the stimulating influence of H-ion concentration on the vaso-motor centre.

Although this leads to contraction of the arterioles, it would not prevent accumulation of blood in the capillaries. The development of acidosis, moreover, acts unfavourably on cardiac contraction, and increases the viscosity of the blood by actually increasing the size of the already abundant corpuscles. When acidosis is once established, then, it would tend to continue the disturbances of the circulation which have been produced by other conditions. It is, however, merely secondary to the lowered blood-pressure and defective circulation.

This view of shock as due to stagnation was originally put forward by Malcolm in 1909, though he regarded the veins as the site of the lost blood. It met with great

opposition at the time, partly due, I venture to think, to lack of lucidity in its exposition. Mann expressed the same idea in 1915, declaring that in shock there is a loss of fluid at a point beyond vaso-motor control. As shock has been used to describe so many other conditions, such as shell-shock, Cannon has suggested the revival of the Hippocratic term "exæmia." For such is the condition of the shocked man who has not bled—he is "drained of blood" into his capillaries, and the consequent fall of blood-pressure has disorganized the motive forces of his circulation.

I think this is a fair summary of the conclusions from recent work. It is interesting as suggesting that shock occurs not through paralysis of, but in spite of, the action of the vaso-motor system. Clifford Allbutt, writing of heart failure in high blood-pressure, protested "against the accusation of these striving hearts of complicity in the arterial diseases. They are stout and faithful to the end, even in defeat." And so, now, we may similarly exonerate the vaso-motor system in the low pressure of shock.

Cuthbert Wallace made the interesting observation that operations involving injury to large masses of muscles are especially liable to cause shock. McNee found that excision of injured parts, or even preventing the return of blood from them by a tourniquet, was followed by a marked improvement, while massage of recently injured parts accelerated the fall of blood-pressure. This suggests that some disintegration product of muscular tissue may have a toxic effect.

Recent observations by Dale and Richards seem to show that histamine may be this substance. With Laidlaw, Dale had previously shown that after injection of histamine half the total blood-plasma might transude from the vessels within five minutes. With Richards, he then investigated why histamine, which is a general stimulant of plain muscle, and which always causes vaso-

constriction in artificial perfusion, should on injection into the living circulation induce severe shock with vaso-dilatation and a consequent great fall of blood-pressure. In the first place they found that this was especially pronounced after nerve section, even when time was allowed for complete degeneration to occur. There was a very close parallelism between this dilator effect of histamine and that of a minimal dose of adrenalin, which, as we have seen, produces vaso-constriction in ordinary doses.

In the next place they were able to imitate this dilator effect in a perfused surviving organ, if adrenalin and red corpuscles were added to the circulating fluid. They concluded that histamine relaxes the tone of vessels only when adequate oxygen-supply is assured. Now, arterial plain muscles can retain their responsiveness even after being kept for days in Ringer's solution. The capillaries, with their intimate relation to the oxygen-using tissues, are again indicated as the seat of action.

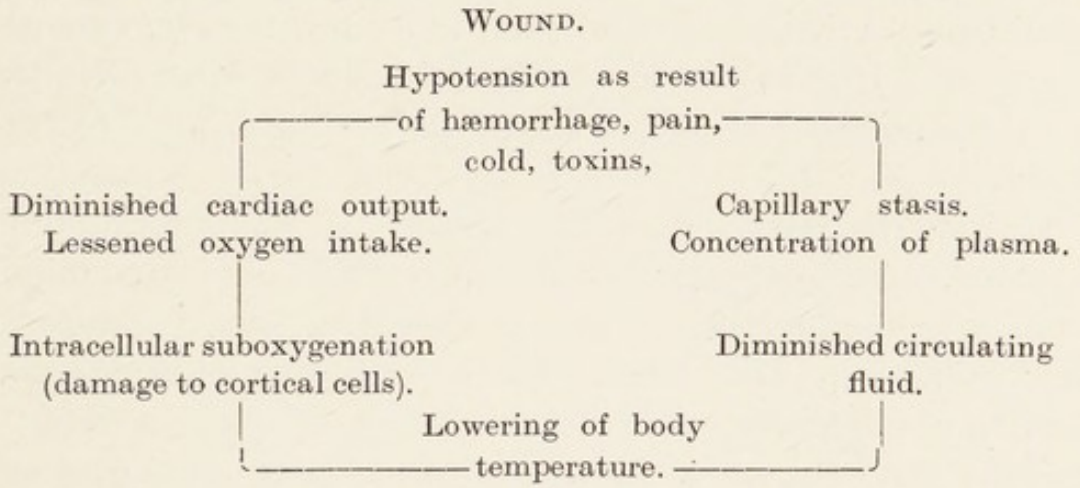
Finally, they cut off the branches of the superior mesenteric artery close to the intestinal wall, so as not to include any capillaries, and perfused them with histamine, adrenalin, and red corpuscles, and found that this mixture always caused vaso-constriction whatever the strength of the dose. Yet if they perfused it through the vessels of a loop of the bowel (which would necessarily include the capillaries) vaso-dilatation was produced. This seems direct evidence that the dilator action of histamine is a capillary effect. It confirms from another standpoint the exæmia theory of wound shock, and appears to necessitate a revision of the current theory according to which the effective peripheral resistance is in the arterioles, that in the capillaries being negligible.

Cowell has summarized the factors which predominate in the pathogenesis of wound shock thus :

(1) *Before the wound*—fatigue—exposure—lack of fluids —presence of excitement.

(2) *After the wound*—pain—hæmorrhage—cold—absorption of tissue or bacterial toxins.

And he has expressed the vicious circle which is established in shock in the following diagram :



The effects of shock may be permanent. If the maximum blood-pressure has remained at 60–70 mm. for 4–6 hours, the patient cannot as a rule be resuscitated even by transfusion of blood. Too much damage has been done to the finer cells from lack of tissue oxygen. Even if pure oxygen were breathed the plasma would only carry 2 per cent. more oxygen than normal. The only possible way of increasing the oxygenation of the body is to give more oxygen-carrying material in the shape of hæmoglobin by sufficiently early blood transfusion.

But it lies outside my topic to discuss the treatment of shock by intravenous injections, whether of solutions of gum-arabic or of blood. For it is clear that such methods act at a point beyond the sphere of influence of the sympathetic nervous system. But I cannot refrain from a quotation from Pepys' diary which brings the founder of the Croonian Lectures into close relation with present-day problems. Under the date of November 14th, 1666, he says : " Dr. Croone told me that at a meeting at Gresham College to-night, which, it seems, they now have every Wednesday again, there was a pretty experiment of the

blood of one dog let out, till he died, into the body of another on one side, while all his own run out on the other side. The first died upon the place, and the other very well and likely to do well. This did give occasion to many pretty wishes, as for the blood of a Quaker to be let into an Archbishop, and such like ; but, as Dr. Croone says, may, if it takes, be of mighty use to a man's health for the amending of bad blood by borrowing from a better body."

It may be asked how the theory of shock here put forward can explain the low pressure of profound toxæmia, as may be seen in the collapse of so-called " heart failure " in pneumonia. Dale makes the illuminating remark that capillary dilatation with transudation of plasma represents a generalization throughout the body of a process which, if locally limited, we should recognize as one of mild inflammation. Just so a bacterial toxin, causing inflammation when locally limited, would cause intense prostration and shock-like failure of the circulation if it spread rapidly through the system.

The futility of combating shock by employing drugs that act on the vaso-motor system is now a demonstrated fact. Digitalis, adrenalin, pituitrin, and barium salts alike fail to reach the point at which the failure occurs. Warmth and the maintenance of an adequate volume of circulating fluid comprehend in a phrase the best means we have at our disposal of treating shock when it has once developed.

The effect of all this work is to dethrone the vaso-motor system, and therefore the sympathetic, from the position of autocratic control of the circulation hitherto assigned to it in physiology and pathology. And in saying this I hope I make some amends to those who may think I have been inclined to exaggerate the rôle of the sympathetic nervous system in disease. But it does not exclude nervous action altogether, since recent observations by Krogh suggest that capillary dilatation and contraction

may be due to local axon reflexes which are probably conveyed along sensory nerves.

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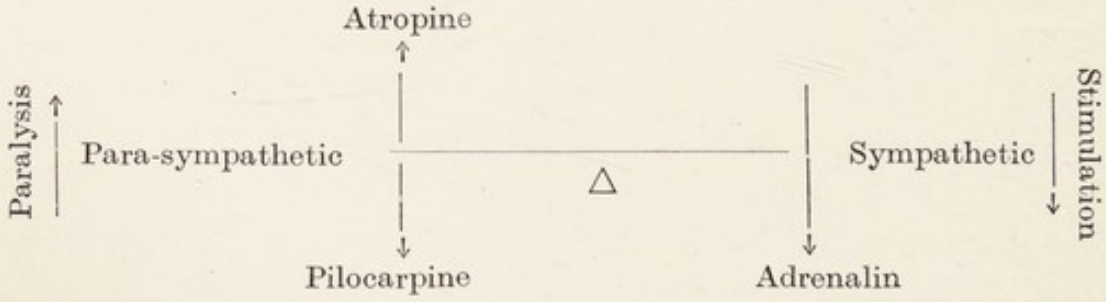
CHAPTER VI

ON VAGOTONIA

The fact that the two parts of the autonomic system by which the visceral functions are subserved are antagonistic in function has led Eppinger and Hess to formulate an interesting but at present inconclusive hypothesis. They suggest that there are types of individuals in whom the normal balance between the sympathetic and parasympathetic is disturbed in one or the other direction. The continuous action of the autonomic system produces a state of tone, since section of an autonomic nerve results in loss of tone in the part supplied. If the para-sympathetic is unduly irritable, a condition is produced to which they give the name of vagotonia; a similar condition of the sympathetic is held to constitute sympathicotonia.

Vagotonia may be absolute or relative; in the second case it is due to some deficiency in the antagonizing sympathetic or in the chromaffin system, as in Addison's disease. This idea of a loss of balance between the sympathetic and para-sympathetic is largely based on the effect of drugs upon them. It can be symbolized thus:



The balance may be tipped either by increasing the load at one end or diminishing it at the other. The sym-

pathetic system is stimulated by adrenalin, and thereby diminished action of the para-sympathetic is produced. The para-sympathetic is stimulated by pilocarpine, and thereby sympathetic action may be diminished. Atropine, on the other hand, paralyses the nerve endings of the para-sympathetic. In some conditions atropine and adrenalin are known to produce similar effects, the former by paralysing the para-sympathetic, the latter by stimulating its antagonist. Now, Eppinger and Hess find that the response of individuals to pilocarpine and atropine varies, and among the multitude of conditions loosely termed neuroses they identify a type that is very responsive to pilocarpine, and relatively insensitive to atropine. Such persons they regard as showing vagotonia; hence the sensitiveness to a drug which stimulates the vagus, while its exaggerated tone would render a paralysing drug less effective.

Now, if such a state could be distinctly recognized, a definite advance in the classification of visceral neuroses would have been made. The idea is an attractive one, and would form a natural corollary to some of the conditions which I have attributed to undue action of the sympathetic. The general idea therefore appeals to me, but I feel certain grave difficulties in accepting the hypothesis as at present formulated. One of the greatest of these difficulties relates to the sweat nerves.

Pilocarpine produces sweating, and anatomical evidence points to the sweat nerves being sympathetic in origin. They therefore assume that pharmacological evidence must be more decisive than anatomical, and postulate that the nerves of the sweat glands are para-sympathetic. This seems a quite unjustifiable assumption, which is made in order to force into one category all those actions which are stimulated by pilocarpine and inhibited by atropine.

An interesting part of the hypothesis is that concerned with eosinophilia. Neusser claimed that pilocarpine caused eosinophilia, while atropine leads to its disappearance.

Eosinophilia is therefore regarded as a stigma of vagotonia. Now, we associate eosinophilia particularly with asthma, skin diseases, and intestinal parasites. Increased vagus action would produce both spasm of the bronchial muscles and vaso-dilatation of the bronchial mucosa, both of which effects occur in asthma, and can be relieved either by atropine, which would diminish vagus action, or by adrenalin, which stimulates the antagonistic action of the sympathetic. Dermography of the dilator type and urticaria are considered typical of vagotonia, and associated with a liability to eosinophilic skin eruptions. This seems to me merely suggestive and far from conclusive. Intestinal parasites are presumably regarded as producing eosinophilia by exciting the vagus, which increases peristalsis and spasmodic intestinal contractions. The eosinophile cells in the mucous secretion of spastic constipation are adduced in support of this. I prefer J. H. Smith's hypothesis that as eosinophilia occurs in conditions of known toxic origin, many of them demonstrably anaphylactic, its clinical appearance should suggest a toxic factor which also stimulates the vagus. It is claimed that eosinophilia is lacking in sympathicotonia. Stimulation of the vagus, in addition to producing asthma, would produce respiratory arrhythmia, if the stimulus were centripetal, while peripheral stimulation would excite laryngeal spasm, bradycardia, increased gastric tonicity, and hyperchlorhydria. The influence of respiration and of swallowing in varying pulse frequency would be increased. The blood-pressure would tend to be low.

All these are claimed as signs of vagotonia. There would also be increased speed of passage through the small intestine, which it is asserted can be demonstrated by X-rays in vagotonia, while either diarrhœa might be excited thereby or constipation from a countervailing spastic condition of the large bowel. Increased irritability of the pelvic visceral nerve, another para-sympathetic structure, would cause tenesmus and stammering

bladder. A similar condition of other cranial para-sympathetic fibres would produce salivation, retraction of the upper eyelid, and spasm of ocular accommodation.

All these effects are said to be produced or increased by pilocarpine in vagotonics, while the normal antagonizing effect of atropine is diminished or but transitory.

But the symptoms attributed to vagotonia by no means end here, and some of them are not easily associated with increased vagal tone. That there should be a high sugar tolerance might be expected from the influence of the sympathetic in lowering this. Mild anginal attacks are described in vagotonics, and are attributed to a constriction of the coronary vessels. If this is so it is the only example of a vaso-constrictor having any other than a sympathetic origin. The benefit derived from vaso-dilators in angina is capable of a far simpler explanation—the diminution of the work of the heart by general peripheral dilatation. As shown in Chapter V, the coronary arteries appear to be exempt from the action of the vaso-motor system. Pressure over the distribution of the fifth nerve is said to slow the heart in vagotonics. This is comprehensible (although they do not suggest it) in terms of Gaskell's scheme of cranial metamerism, according to which the sensory division of the fifth represents afferent elements of the same segment as the vagus. The brow-ache produced by swallowing too cold an ice is due to the same fact. Œsophagospasm combined with an anæsthetic pharynx is described as typical of vagotonia, though the latter condition, which is common in hysteria, is not explained. Colic of the bile passages may certainly be produced through the vagus, but that such a degree of spasm may be excited as to cause jaundice (as they suggest) seems very improbable. It is further stated that the diaphragm may be low in vagotonia, to which lack of support of the heart certain cardiac neuroses are attributed; but since the diaphragm is innervated by the phrenics, this could not be due to a direct vagal effect.

Enteroptosis is regarded as a symptom of vagotonia, though, as we have seen, it is common in those who show sympathetic irritation. They explain it as due to lack of support by the muscles of the abdominal wall. This seems most improbable, since these muscles are not innervated by the vagus, while it is a familiar observation that marked enteroptosis may coexist with good abdominal walls. Nor is it easy to see why vagotonia should be associated with lymphatism, as they state, except that both lymphatism and increased vagal irritability are commonest in early life. Liability to anaphylactic shock and to infection, yet without great febrile response, is said to be a sign of vagotonia, which would accord with the conception of the sympathetic as a defensive mechanism. The case of Graves' disease offers difficulty to the exponents of this theory. There is strong evidence of sympathetic overaction in this disease, and the sweating, which is a usual feature, is easily explained thereby. But Eppinger and Hess regard sweating as a para-sympathetic phenomenon. This makes it all the more difficult for them to explain the tachycardia, since they admit that the cardiac accelerator nerves are sympathetic.

Of the ocular signs von Graefe's is regarded as due to the para-sympathetic, and Mœbius's to the sympathetic. They therefore have to describe two types of Graves' disease, one vagotonic, the other sympathicotonic. But they state that the differences are not constant, and that one type passes into the other. The only support to this view lies in the occasional occurrence of bradycardia in early cases of Graves' disease, which is not explicable on the ordinary view. Indeed, Graves' disease raises powerful objections to their entire hypothesis. Spasm of the pylorus is described as occurring in vagotonia, yet the pyloric sphincter is undoubtedly innervated by the sympathetic. Such spasm could therefore only be secondary to the hyperchlorhydria with which they find it to be associated.

Their explanation of the variability of symptoms in various diseases by the presence or absence of vagotonia is ingenious. When a gastric ulcer fails to excite hyperchlorhydria, spasm, and pain, the patient is said never to be a vagotonic; while in a vagotonic all these symptoms will be exaggerated. The same is said to be true of the absence or occurrence of gastric crises in tabes. They believe vagotonia may have general or simply local manifestations. The general vagotonic disposition is described thus. The appearance is that of a nervous invalid: actions are hasty and precipitous. The colour of the face is changeable, and the skin shows blotchy red areas on exposure. The hands are cyanotic. The skin is thick, sweating easily, and marked by acne. "Goose-skin" (which is produced through the sympathetic) is rare, pigmentation common. The lymph glands and tonsils tend to be large. The patient complains of some trivial symptoms, stomach or intestinal troubles, a fear of heart failure, and presents a generally neurasthenic state. They regard it as a form of constitutional inferiority, and believe that it will ultimately be traced to some disturbance of the internal secretions, suggesting that we should look to the pancreas for the hormone which exerts a continuously stimulating action upon the whole of the para-sympathetic, just as adrenalin acts upon the sympathetic. For treatment they rely mainly upon small and repeated injections of atropine, which they regard as unlikely to affect a vagotonic injuriously.

The whole conception is an interesting attempt to associate a certain nervous type with overactivity of some part or all of the para-sympathetic, either absolute or relative, the latter being due to sympathetic defect. At the same time I have tried to make clear what seem to me strong objections to the theory as at present formulated. Like many enthusiasts, Eppinger and Hess appear to me to have greatly overstated their case. Either the theory will have to be considerably modified, or many

things now regarded as matters of common knowledge will have to be proved erroneous.

They place much reliance on the action of drugs in establishing it, but the response of different individuals to drugs is notoriously variable. Dr. Geoffrey Evans, to whom I am indebted for valuable criticisms of this chapter, tells me, nevertheless, that the variations to drug actions could be foretold to some extent if the cases are previously grouped according as clinical indications of vagotonia are present or not. The theory therefore appears worthy of further investigation, for I feel that it contains a germ of truth, and that, stripped of some of its present excrescences, it would form a helpful antithesis to the conditions of sympathetic irritation described in the foregoing pages.

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CHAPTER VII

THE RESPONSES OF THE SYMPATHETIC NERVOUS SYSTEM

THERE are scarcely any data for the study of the morbid anatomy of the sympathetic nervous system. Until this lack is remedied, we must remain at a loss to explain many diseases in which this system shows derangement. A suggestive beginning has been made with pellagra. During the war, Boyd, Wilson, and Roaf studied this condition in Turkish prisoners and Armenian refugees, and confirmed the impression that it was one of the so-called " deficiency diseases," tracing it to a fall of the assimilated protein below 40 grammes a day, quite irrespective of the total caloric value of the diet. Now Mary Morse in 1917 found chronic degenerative changes in the vertebral, semilunar and enteric sympathetic ganglia (*Journal of Mental and Nervous Diseases*, vol. xlv, p. 1), and Roaf, who independently found similar changes, has suggested that the disease is mainly due to the influence of this protein defect on the sympathetic nervous system. Hopkins has pointed out the varying degree of vitamin defect necessary to produce symptoms in the so-called deficiency diseases, and believes that lack of vitamins is much more potent for ill when the endocrine glands are also inadequate in function. So here, again, the close association between the sympathetic and the endocrine glands is asserting itself in a new aspect. It can hardly be doubted that a systematic study of the morbid anatomy of the sympathetic nervous system would yield results comparable in value to those which have followed the study of the morbid anatomy and histology of the spinal cord. The discovery

of discharging and destroying lesions would explain symptoms of excessive and defective action respectively. Our knowledge of diseases of the sympathetic will have to pass through the same stages as our recognition of diseases of the central nervous system.

The first stage finds expression in a description based on symptoms, the second in an anatomical, the third in a pathological description. Thus "locomotor ataxy" represents the first stage, and "tabes dorsalis" the second stage towards the recognition of a parenchymatous syphilitic degeneration of the lower sensory neuron. In diseases of the sympathetic nervous system we cannot, as yet, pass beyond the second stage, and I am content if I have been able to group together certain symptoms of sympathetic origin, some of which may be due to a structural, others to a functional alteration.

The conception of the evolution of the nervous system in three levels was one of Hughlings Jackson's most illuminating generalizations. Jelliffe labels these the vegetative, the sensori-motor, and the psychic levels. The first and lowest corresponds to the autonomic nervous system. Our ties with the external world are obtained through the middle or sensori-motor level.

Thus the vascular and visceral musculature, innervated as they are from the lowest level, are of a more primitive type than the skeletal muscles. A peculiarity of their innervation on the efferent side is the much greater prominence of inhibitory nerves. These inhibitory nerves have been largely superseded in the skeletal muscles of the higher animals by a principle of superior economy and efficiency. As McDougall says (*Brain*, 1903, vol. xxvi, p. 153): "All those muscles of the visceral system which are supplied by special inhibitory nerves exhibit a considerable power of spontaneous activity, a power which is lacking in the skeletal muscles. . . . The lack of spontaneity in them and the corresponding absence of inhibitory nerves must be regarded as results of that

increasing integration of the whole organism, that increasing centralization of control in the brain, which is the most striking feature of the evolution of the higher types of animal. . . . That is to say, the activities of the skeletal muscles are brought into a more and more intimate relation with the environment through the sense organs and reflex nervous arcs, while the viscera remain comparatively independent of such control, retaining in great degree their power of spontaneous movement." In Herbert Spencer's phrase, "the cessation of automatic action and the dawn of volition are one and the same thing." Inhibition would appear also to connote a diversion rather than a stoppage of the stream of nervous energy, since, as McDougall shows, it is the complementary result of a process of increased excitation in some other part.

In the same way we can understand the peculiar features of the autonomic nervous system on the afferent side. Pain is purposive. External pains are correctly localized in order to allow of accurate response. But internal pains are not accurately localized, because this would not have any real advantage. Instead, a reaction of the sympathetic nervous system is excited, which is also purposive, having as its object the stimulation of the organism to react against attack. In the primitive state the most imperative need is to combat the attack of another animal. In the violent excitement of the resulting conflict, pain, having achieved its purpose, may cease to be felt. But internal pain also has the object, as we know, of calling attention to and of exciting a reaction to the attack of disease. The art of medicine is to come to the aid of that response by interpreting its meaning. As Cowell says, from the pain of the individual we learn lessons which we apply to the benefit of the community at large. The Utopian aim of medicine is that as far as possible there shall be no more pain. It is Utopian in that the more we fly from pain, the more sensitive we

become. With increasing civilization the threshold to pain and painful emotion becomes lowered and the resulting disabilities are exaggerated. The instinctive attempt to avoid pain and distress and the natural reaction to them may have curious and far-reaching effects, leading to many so-called psychoneuroses. The psychical level then directly influences the sensori-motor level, and produces functional paralyses or contractures and alterations of sensation. The psychoneuroses of war have impressed this upon us with fresh and added force. As Roussy and Lhermitte point out ("The Psychoneuroses of War," p. 28), the initial shock that the soldier experiences may excite distressing visceral disturbances, but he nevertheless has the energy to escape from danger, driven by the deeply-rooted instinct of self-preservation. "It is when removed to calmer surroundings, far away from danger, that the pyschoneuropathic condition comes to light, whether as a contracture, a tremor, or a convulsive fit." They go on to show that the next stage is the fixation of the emotional reaction, which tends to escape from conscious control and to reach the depths of the unconscious rapidly. It is only by a voluntary effort that he can recall the emotional origin of the condition. The instinct of self-preservation which restrains the emotional reaction at the time of the shock tends to persistence of the emotional attitude later. It is not a question of malingering—a conscious and deliberate act—but of an automatic, instinctive phenomenon, advantageous to the individual, but troublesome to the community. This brings the psychoneuroses of war into line with protective mimicry—also not a voluntary but an instinctive act.

It may be urged that such psychoneuroses are quite distinct from the present topic. But my object is to show that, just as a psychical impression may produce a disturbance at the highest level exciting an obsession, or at the second level exciting paralysis, contracture, or

anæsthesia, so it also may do so at the lowest level. The shell-shocked soldier may develop a contracture of his arm, the girl exposed to an air-raid may develop Graves' disease. The former is more obviously purposive, for it is developed nearer to the psychical level. Yet the latter also originates in the development of an exaggerated response of a defensive mechanism. And both in the protective mimicry of a psychoneurosis and in the disorder of metabolism produced through the sympathetic nervous system, the exciting cause may long have passed from the region of consciousness and have been forgotten. As Herbert Spencer urged years ago, nervous impulses tend to run along accustomed channels. Or, as Mott puts it (*Journal of Mental Science*, October 1902): "Currents which represent nervous energy are continually flowing in all directions in the central nervous system. They flow with the greatest readiness along systems of neurones which have by habit and use been most functionally correlated." The effect of training in promoting skill is to beat down, as it were, a broad pathway through the nervous network, a path of lowered resistance. And a profound or a prolonged emotion may have a similar effect. The evil effects of depressing emotions, of anxiety, fear, pain, and anger, receive an explanation when we see that through the sympathetic nervous system they can lead even to structural change. Designed as an intensive preparation for action or defence, the sympathetic response may be so dissociated, perverted, or prolonged as to produce through the thyroid gland Graves' disease with its dangers to life, through the pituitary body diabetes insipidus with its attendant discomforts, through the pancreas and other endocrine glands excessive mobilization of the blood-sugar, which is the first stage of the metabolic disorder that culminates in diabetes; it may disorganize digestion by exciting spasm and atony in stomach and bowels, and inhibiting the secretion of digestive juices; it may keep

blood-pressure at a level which is inappropriate for the task of the heart and the arteries. These effects are not necessarily distinct—thus, intestinal stasis from sympathetic inhibition causes poisons of putrefactive origin to be absorbed, which in their turn lead to vaso-constriction, and hence an unduly raised blood-pressure. Further work will doubtless add to the list.

My main thesis is that the stimulation of the sympathetic and of its coadjutors, the adrenals and thyroid, means the spending of reserves in the supreme struggle for survival. The quickening of all the vital processes may produce—for a time—a feeling of exaltation and well-being. This may be regarded as a physiological justification for Nietzsche's injunction to live dangerously. But exhaustion lies in wait if the struggle is unduly prolonged. A vicious circle is the pathological equivalent of a prolonged struggle. Next, under physiological conditions the sympathetic acts as a whole, while one of the phenomena of disease is dissociation. Sensory dissociation is seen, for instance, in tabes and syringomyelia. Sympathetic dissociation may play a part in diabetes and in disorders of digestion and circulation.

Evolved in a subconscious plane, the sympathetic nervous system remains for ever beyond the control of the will. Timme (*Journal of Nervous and Mental Diseases*, 1914, vol. xli, p. 259) quotes an instance which, while apparently contradicting this, proved on further inquiry to support it. This was the case of a man who could voluntarily dilate his pupils, who could cause the pilomotor muscles to raise the hairs on his arm, and who could at will produce the phenomenon of "goose-flesh" in various parts of his body. When closely questioned, he admitted that the effects were produced not immediately by his will, but always by the intermediation of some association called into being by him. Thus, when dilating his pupils he always imagined himself looking far into space, under which conditions the pupil does dilate.

For the goose-flesh effect he would picture to himself his arm plunged into ice-cold water, and the goose-flesh appeared. Various associations produce autonomic effects without our will, and it is reasonable to infer that, if we can recall these associations through our will, the same autonomic effects will be produced.

The higher centres of the brain show their influence on the lower chiefly in the direction of inhibition. The highest organism is the most self-controlled, but the sympathetic cannot be thus controlled. The will can only help in so far as " it can make our voluntary activities harmonize with our environment " (Timme). Though we may deaden the emotion, we cannot prevent the response to an emotion once evoked. To regulate this we must trust to reserves, inherited and maintained through generations of stable and equable ancestors. Herein national characteristics will tell in the future, as they have in the recent past, for just as character is revealed in the instinctive response which occurs more quickly than conscious thought, so the powers of tenacity and endurance may be foreshadowed in the original emotional response.

I hope, in conclusion, that I may have been able to make clear the influence of the mind and emotions upon the organic functions of the body, even though stated in terms of current physiology, and without reference to those psychological factors with which, indeed, I am not competent to deal.

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