

**On the pathology of ague & other intermitting disorders, and on the action of quinine as a remedy for them : being a dissertation preparatory to the degree of Doctor of Medicine in the University of Oxford / by Francis Willis.**

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**Publication/Creation**

[London] : Printed by Odell & Ives, 1864.

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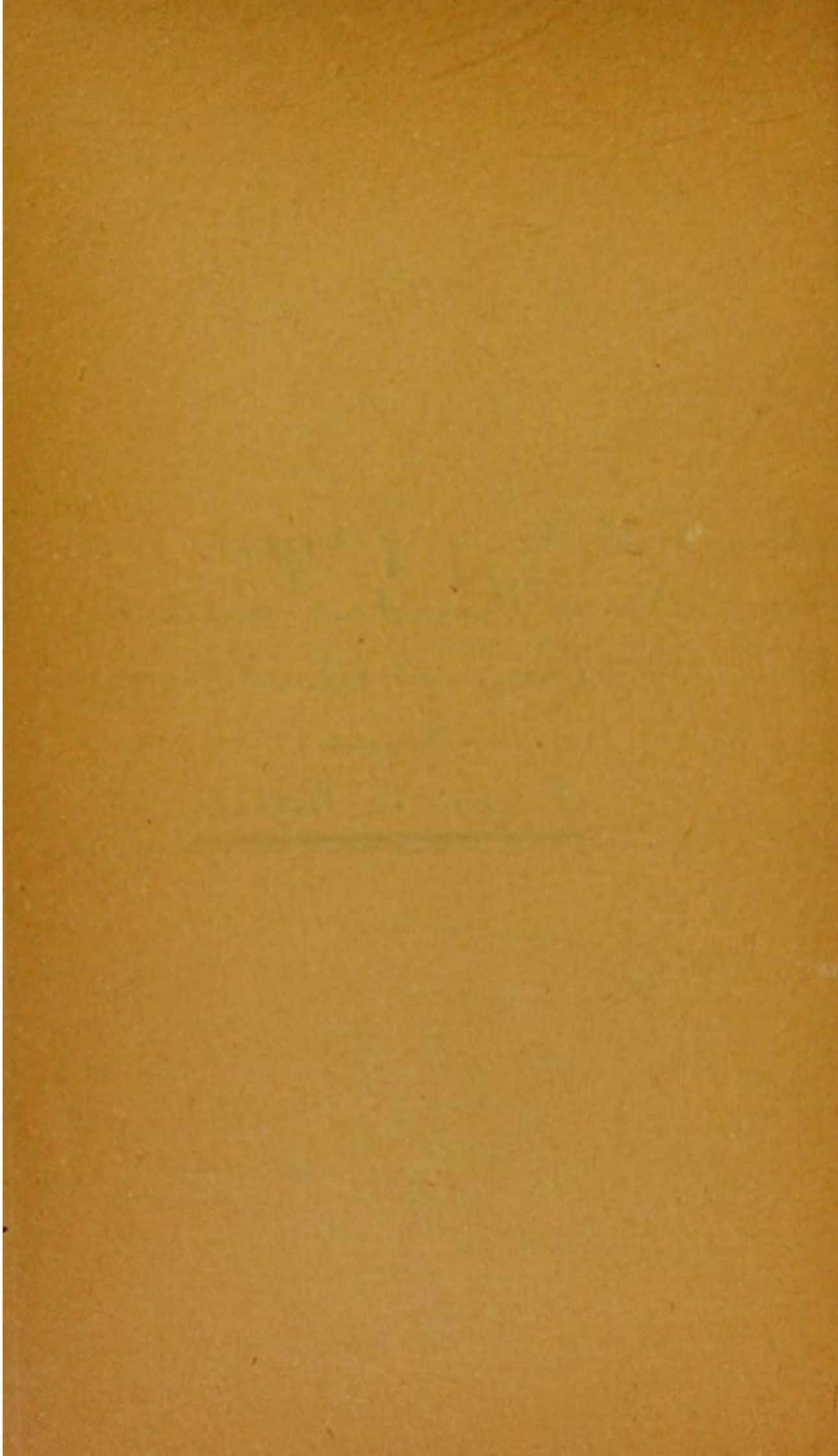
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On the Pathology of Ague and other  
Intermitting Disorders, and on the  
Action of Quinine as a Remedy.

— By —

Francis Willis

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ON THE PATHOLOGY OF  
**Ague & Other Intermitting Disorders,**  
AND ON THE ACTION OF  
QUININE AS A REMEDY FOR THEM;

BEING A

DISSERTATION PREPARATORY TO THE  
DEGREE OF DOCTOR IN MEDICINE IN THE UNIVERSITY OF OXFORD.

BY

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ASSISTANT PHYSICIAN, AND CURATOR OF THE PATHOLOGICAL MUSEUM,  
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"Singula hic veterum et recentiorum placita  
Recensere, in ordinem redigere, eorumque  
Rationes expendere esset opus nimii laboris  
Et tœdii; quare quid mihi, rem accurate  
Pensitanti, in mentem venerit, dubitans  
Proponam, aliorumque judicio submittam."

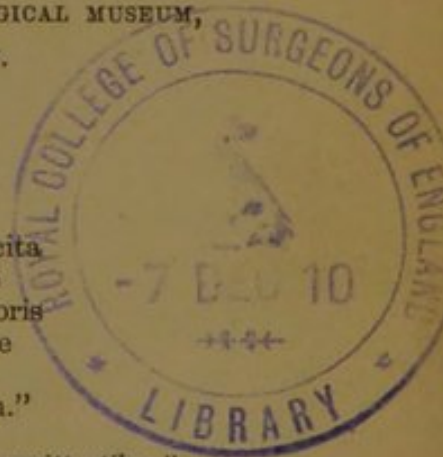
WILLIS, "*De Febris Intermittentibus*."

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JUNE, 1864.

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PRINTED BY ODELL & IVES, 18, PRINCES STREET, CAVENDISH SQUARE.





ON THE PATHOLOGY OF  
AGUE & OTHER INTERMITTING DISORDERS,  
AND ON THE ACTION OF  
QUININE AS A REMEDY FOR THEM.

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I propose in this essay not to discuss the multitudinous theories which have been proposed from time to time both by ancient and modern writers with regard to the pathology of intermitting diseases, a task which could scarcely be performed within the limits assigned to an academical thesis, but to proceed at once to bring forward some ideas which have occurred to me respecting the nature of these disorders, trusting that the obscurity which still prevails upon the subject will be considered to afford me a sufficient excuse for attempting to solve so difficult a problem. Before the discovery of the virtues of the Cinchona Bark Agues were called "*opprobria medicorum*,"\* and if the opprobrium is now in any way removed, it is so only in relation to the empirical practice of the art of medicine, for it confers no credit upon rational and scientific medicine that, in spite of a specific remedy having been in daily use for about two hundred years for the cure of Ague, no satisfactory explanation has yet been given either of the pathology of the disease, or of the mode of action of the remedy. But, as it is truly said that no one can pronounce absolutely upon the nature of anything without having first ascertained what it is not, there are grounds for hoping that, by continuing to propound and test hypotheses upon the subject,

\* Sydenham. Ep. I. Resp. § 17.



at last by the explosion of all false theories a true explanation of the phenomena may be arrived at ; and therefore, even if the views which I have now to propose are proved to be untenable, an advance may be made in the exhaustive process, and a step thus gained towards the discovery of the truth.

By the establishment of the efficacy of the Peruvian Bark as a remedy for Intermittent Fevers, a death blow was given to the humoral doctrines concerning them. Sydenham points this out very clearly. Speaking of "the habit of referring the different species of Intermittents to the different redundant humours in different parts of the body, and of directing the treatment towards the alteration and evacuation of them," he says, "that all this was an unfortunate attempt is shown in nothing better than in the success which attended the use of the bark itself ; by means of which we can at the present time, regardless of all humours and careless in the way of diet and regimen carry our point, simply by observing the proper method in the exhibition of the powder ; failing only when, without any necessity, we confine the patient to his bed during the time that he is taking it ; and even then, such is the power of the remedy that notwithstanding the inconvenience which is caused by the warmth of the bed in encouraging the fever, the recovery will generally take place in spite of the obstacles that should prevent it." \*

Sydenham does not offer any theory in the place of the humoral doctrines which he rejects, but Hoffmann advances a statement with regard to the action of the most efficacious remedies in general, which I shall try to show applies especially to the operation of Quinine. His words are "*Demum omnia eximie virtutis medicamenta, non tam in partes fluidas, earum crasin ac intemperiem corrigendo, quam potius in solidas et nervosas, earundem motus alterando, ac moderando, suam edunt operationem.*"† Hoffmann's teaching on this point is confirmed by that of the most distinguished physiologists of the present day.

That the most energetic drugs produce their effects by acting

\* Sydenham's Works, Syd. Soc. Trans. p. 162.

† Hoffmann. Medic. Rational. Systemic. Tom iii. § 1. chap. 4.



upon the tissues, and that different drugs act specially upon different tissues, is proved especially by the researches of Bernard. His experiments show that the several tissues of the body are physiologically and pathologically quite independent, that they have a life peculiar to themselves capable of being maintained under different physical conditions, and of being specifically acted upon by different agents. They prove for instance, that muscular tissue can support a degree of cold that would destroy the vitality of nerve tissue, and that nerve tissue can bear a degree of heat that would be fatal to muscular tissue; that a drug (Cyanide of Potassium) which is an energetic poison of muscular tissue does not affect the nerves, and that another (Curara) which poisons the motor nerves spares the muscles and leaves the sensitive nerves intact. The most complicated results can be traced to the action of a drug upon one single elementary tissue.

If a small animal such as a rabbit is inoculated with a drop of Curara poison, after four or five minutes it falls to the ground, all its muscles become relaxed, the urine escapes from the bladder, and it lies motionless and flaccid and to all appearance dead. You may pinch the limbs, but no movements either voluntary or reflex can be excited in them. The heart continues to act for a time, but the respiration has ceased, and complete death from asphyxia speedily ensues. All the functions of the body are arrested in a few minutes, and yet the poison acts only upon one single tissue of the body, the motor nerve tissue; all the other effects are entirely secondary to, and dependent upon, the paralysis of the motor nerves. The muscles are still capable of acting with their ordinary vigour, as may be proved by stimulating them directly by a galvanic current, but they lack the stimulus which should be conveyed to them by the motor nerves; hence the respiratory muscles cease to act and asphyxia ensues. But if by artificial respiration aeration of the blood can be maintained until the effect of the poison upon the motor nerves has passed off, the animal may recover, for, with the exception of temporary paralysis



of all its motor nerves, no injury has been inflicted upon it. Bichat's doctrine that death commences in one of the chief organs of the body, the brain, the heart, or the lungs, is superseded. The process that results in death commences really not in particular organs, but in particular tissues, and for a true insight into the action of disease and remedies we must study their primary effect upon the primary tissues.

With regard to the action of Quinine, and the pathology of Ague, I venture to advance the following propositions.

1. That all the effects of Quinine, as a tonic and an anti-periodic, may be referred ultimately to its action upon the sympathetic or vaso-motor nerve system.

2. That Ague is produced by paralysis of a certain portion of the vaso-motor nerve system; that portion which supplies the viscera of the body.

3. That Quinine cures Ague by curing the paralysis of the visceral sympathetic nerve.

One of the simplest morbid conditions in which we can study the action of Quinine is presented by that form of Conjunctivitis which arises in feeble or debilitated constitutions, and in which, when simply atonic, Quinine unmistakably controls the morbid vascularity of the eye. This form of Ophthalmia almost precisely resembles the hyperæmic condition of the eye which can be experimentally produced by dividing the sympathetic nerve in the neck, and thus paralyzing the vaso-motor nerves which regulate the calibre of its blood vessels, as is shown in the experiments of Brown Séquard. It is therefore not unreasonable to assume that in the atonic form of Conjunctivitis the injection of the vessels is due to a paralytic condition of their vaso-motor nerves; and that Quinine cures it by stimulating or otherwise restoring power to these nerves, and through them acting upon the small vessels, restoring their natural calibre. It is my object to show that the pathology of Ague can be explained in conformity with this hypothesis of the action of Quinine upon the sympathetic nerve.



In the endeavour to arrive at the ultimate pathology of any disease it is of course of the utmost importance to distinguish what is primary and essential from what is secondary and subordinate. The periodical paroxysm in Ague is so striking a symptom that it has tended to obscure the essential features of the disease.

The fit of an Ague, as Dr. Williams says, is the reaction of the vital powers against the influence of the poison.

The fit therefore is not part of the disease, as such, at all, but it is a healthy effort on the part of the system to recover from the morbid condition produced by the poison. In their most virulent form malarious fevers become continuous, the system becoming overpowered and incapable of healthy reaction.

To discover what is essential to the disease let us consider the first effect of the poison. "The first operation of the malarious poison," says Dr. Williams, "seems to be upon the quality and distribution of the blood; in the worst cases the liquid becomes speedily darker in colour and otherwise altered, and accumulates to an extraordinary amount in the internal organs, where it then suffers still further in consequence of its stagnation and want of purification by the ordinary processes of excretion."\* It must be almost impossible to determine by observation whether the primary change is in the quality of the blood or in its distribution, and I would suggest that the first change is probably in the distribution of the blood, and say, merely transposing Dr. Williams' words, the first effect of the malarious poison seems to be upon the distribution and quality of the blood, and attribute all the change of quality in the blood to the consequences of the irregularity in its distribution, whereby the processes of secretion and excretion are interfered with. If the first effect of the malarious poison is manifested by accumulation and stagnation of blood in the internal organs, and if this tendency to internal congestion can be removed by the operation of Quinine, then, upon the hypothesis that Quinine acts only upon the sympathetic system,

\* Dr. Williams' Principles of Medicine, p. 68.



we arrive at the conclusion that the internal stagnation is caused by a paralytic condition of that part of the vaso-motor nerve system which regulates the circulation through the visceral organs; and further, that malaria produces Ague by paralysing the visceral vaso-motor nerves.

That the Ague poison does act upon the sympathetic system is taught by several writers of the present day.

"The proximate cause of fever," says Sir Ranald Martin, "has been referred by various pathologists (German and British) to congestion round the central nervous ganglia with consequent alteration and diminution of the organic nervous influence, a perversion of innervation in short, together with a depravation of the blood through the entrance of a morbid cause the nature of which is unknown;"\* and further on he adds, "essentially and specially we have, in fact, a paresis of the great sympathetic and cerebro-spinal nerves with dilatation of the arteries, resulting in congestion and inflammations in those organs which derive their nerves from the sympathetic; and, in speaking of the treatment of the disorder, he says, "Quinine, the great febrifuge, justly administered acts purely as a nerve tonic to the cerebro-spinal and visceral sympathetic systems."† The special point which I wish to make out distinct from the views here stated is that the Ague poison produces all its effects through the abdominal sympathetic system alone, without affecting primarily the blood or even the cerebro-spinal system. For although the motor power of the sympathetic seems to be derived from the cerebro-spinal system, it appears nevertheless that it is only through the medium of the sympathetic ganglia that motor nervous influence is brought to bear upon the blood vessels, and it seems therefore not to be incorrect to attribute all alterations in the calibre and tone of vessels to some variation in the action of the sympathetic system.

Death from Ague being of such rare occurrence in England I must have recourse to observations made in other countries for

\* Martin's Influence of Tropical Climates, Sec. Ed., p. 318.

† Ibid, p. 340.



an account of the pathological appearances seen in post-mortem examination of fatal cases. A summary of these, as observed in India, is given by Sir R. Martin. "After death," he says, "the results of congestion or of inflammatory action are manifested in the peritonæum, stomach, liver, and bowels in the one case, while the membranes, the cavities, or the substance of the brain suffer injury in the other case."\* The only definite appearance of a morbid character mentioned by Sir R. Martin as seen within the cranial cavity is that of effused serum; and the occasional occurrence of this within the cranium would naturally be expected to result from cerebral congestion produced by the paroxysms, especially if there was any tendency to cerebral affection previously. The essential morbid changes seem to be those in the abdominal viscera. "These lesions," continues Sir R. Martin, "will be found in the stomach duodenum and mesocolon principally, and they are generally of a congestive or inflammatory nature, as evidenced by a turgid or dirty red condition of the inner surfaces, and by interstitial effusions; in very severe or protracted cases the results of congestions or of inflammatory actions, as redness, ecchymosis, or even ulceration, will extend to the mucous surfaces of the small and large intestines, while the liver, spleen, omentum, and mesentery exhibit various degrees of vascular engorgement."† It appears, therefore, that it is only in very severe cases that there is evidence of inflammation and ulceration in the abdominal organs, but that the ordinary condition is one of dirty red congestion and ecchymosis; and the localities in which this state of congestion is found accord in a remarkable manner with the distribution of the abdominal sympathetic nerve. A glance at the arrangement of the vascular system and of the sympathetic nerve in relation to the abdominal viscera shows this very clearly. At the very point where all the principal arterial trunks are given off to the several abdominal viscera we find a concentration as it were of the sympathetic nervous system in the solar plexus, offsets from which accompany the various vessels in their distribution, sub-

\* Ibid, p. 317.

† Ibid, p. 319.



dividing as they subdivide and ramifying with them in the different viscera. There is the coeliac plexus of the sympathetic surrounding the arterial coeliac axis, and spreading in secondary plexuses, the hepatic, splenic, and coronary, around the corresponding arteries; and these spread again in tertiary plexuses around the branches of their respective vessels, the hepatic furnishing a gastroduodenal plexus. Another division of the solar plexus, the superior mesenteric, accompanies the artery of the same name, and is distributed with it to the colon as well as to the small intestines. If we follow the splenic artery we find that it enters the spleen by six or more branches, and ramifies in its interior; "the smaller branches of the arteries terminate in the proper substance of the spleen in small tufts or pencils of capillary vessels,"\* and "the splenic plexus of the sympathetic nerve is continued on the splenic artery and its divisions into the substance of the spleen."† Here, therefore, we have the apparatus for producing and removing congestion of the spleen. Paralyse the splenic plexus of the sympathetic nerve, and the tufts of capillaries in the spleen become dilated; stimulate the nerve, and the vessels are restored to their natural calibre. We have only to suppose that the Ague poison paralyzes the splenic plexus, and that Quinine stimulates it, to understand the production of an Ague cake, and the cure of it by Quinine. That the sympathetic nerve does really influence the circulation through the spleen is proved both by anatomical investigation and by direct experiment. Kölliker remarks that the arteries of the human spleen are exceedingly muscular, which sufficiently explains, he says, the dilatation and subsequent contraction of the organ observed five or six hours after the ingestion of food noticed by many observers; and the very presence of muscular elements in a structure implies that it is subject to nervous influence; for although contraction can be excited in muscle by stimulants applied directly to it, there are reasons for believing that under all ordinary conditions the muscular function is discharged only in

\* Quain's Anatomy, vol. iii., p. 214.

† Ibid., vol. ii., p. 676.



obedience to a nerve stimulus, for where nerve energy is not required in any part, elastic tissue is found to take the place of muscular tissue for the purposes of contraction.

I am not acquainted with any experiment which shows that section of the splenic nerves produces subsequent enlargement of the spleen, and such an experiment is not easily performed; but the contrary experiment of galvanising the spleen is followed in many animals by marked contraction of that organ. In the human spleen the contraction is less evident than it is in those animals in which muscular elements exist in the coat and trabeculae of the spleen as well as in the coats of its arteries, but one case is recorded by Kölliker, in which it was observed in an executed criminal experimented upon at Wartzburg.

If these hypotheses of the action of the Ague poison and of Quinine upon the sympathetic system be accepted, there is no difficulty in accounting for all the symptoms of Ague.

The cachexia which increases with the duration of the disorder and the occasional jaundice are natural consequences of the stagnation of the blood in the viscera and of its imperfect purification. The inflammations which in protracted cases occur in the internal organs may reasonably be ascribed to the irritating effect of the depraved blood, and of the foul secretions, upon the tissues and the glands. The Ague fit also admits of a ready explanation. Internal congestion tends to produce shivering, which is brought about by reflex action. Shivering is a restorative effort, the physiological object of which must be a more equable distribution of the blood. Whether produced by the effect of cold upon the surface, causing inward propulsion of blood, or by active internal congestion, such as that produced by a loaded stomach, as is often the case in children after a full meal, or by atonic passive congestion, as in Ague, the mechanism of it must be the same. A morbid impression is conveyed by the afferent nerves to certain nerve centres, and by reflex action the muscles are thrown into spasmodic contraction. This like the more regular contraction of the muscles in bodily exercise quickens the return of the blood to the



heart. That organ is thereby excited to more energetic action, and distributes the blood with greater force throughout the body and to the periphery, producing heat of surface and subsequently perspiration. That this is a right interpretation of the purpose of an Ague fit is shown by the efficacy of certain remedial measures in warding off an expected paroxysm. For instance an accession of the rigors can sometimes be checked by the administration of an emetic just before the time of their recurrence. The effect on the system produced by the efforts of vomiting resembles that caused by shivering, the circulation being quickened by it, and the blood more equably distributed; so that the natural reaction of the system to rid itself of a source of irritation is thus anticipated and imitated by artificial means; and if the congestion is sufficiently relieved by the operation of the emetic there is no occasion for the rigors, which in that case do not occur.

The shivering fit relieves the internal congestion no doubt to a certain extent, but owing to the atonic condition of the vessels it is speedily reproduced unless the vessels can regain their tone. If the congestion has been of short duration and depends upon atony of the vessels alone, Quinine is able to work a cure of the complaint by itself; but if the congestion has led to depraved secretion and disordered action of the liver and other organs, it is necessary first to clear off the unhealthy secretions and relieve the gorged liver by the action of purgatives before the good effect of the Quinine will be manifested, but when this has been once accomplished, Quinine prevents a recurrence of congestion, by restoring tone to the vessels.

If the tendency to internal congestion remains, sooner or later another fit will come on, and the time at which it will take place will be determined by the relation between the amount of congestion which is the exciting cause of it, and the activity of the ganglia through which the reflex action is produced. The greater the irritation and the more excitable the nervous centres, the sooner they will be moved to action; and in an irritable



state of the nervous centres a smaller degree of stimulation of them from internal congestion would produce a fit than would do so if they were in a less impressible condition. Thus the time of recurrence of the paroxysms must depend, not only upon the amount of congestion of the viscera, but upon the degree of impressibility of the nervous centres at the time. This affords some explanation of the fact that the fits occur at different intervals in different persons, or even occasionally in the same person; but it does not furnish us with a reason for the very remarkable regularity observed in the return of the fits, so that after two fits have occurred it may be foretold almost with certainty at what time the next and all the subsequent fits will come on.

The periodicity of the Ague fits has been ascribed to the alternate accumulation of the influence of the Ague poison in the body, and the reaction of the vital powers against it; but no explanation has been given as to how the malarious influence reaccumulates at such a very definite rate, as to excite another effort of reaction against it after a definite period of twenty-four, forty-eight, or seventy-two hours, according to the type of the disease. Such remarkable periodicity cannot be ascribed to any development of successive crops of poison in the system, especially as there is no definite period of incubation of the poison in the first instance; and it seems most probable that the action of the poison is continuous and uniform, and that the internal congestion produced by it is continuous, except so far as it is relieved for a time by the occurrence of a paroxysm of shivering, but that the fits occur at definite intervals because the nervous centres are naturally more easily impressed at certain times, and the reflex action of shivering is then more easily produced.

It is quite in accordance with analogy to suppose that the nutrition of the nervous system proceeds in a rhythmical manner, so that the ganglia acquire alternately a greater and less amount of activity. Absolute uniformity appears to be unknown.



in nature. Every organized being has a definite period of development, and when it has arrived at maturity either proceeds to decay or is maintained, in many instances at least, by a series of organic changes periodically repeated. In one system of the human body a periodic nutrition is unmistakably evident; the monthly activity of the ovarian and uterine functions admits of no dispute; and no better explanation of it can be given than that it depends upon the law of their nutrition, just as the duration of life, or the period of utero-gestation, which is characteristic of each species, depends upon the inherent endowments of the species. And as we find a law of periodical and rhythmical nutrition prevailing generally through the organised kingdom, and markedly so in one system of the human body, it becomes probable at all events that other functions of the body are regulated by similar laws. It becomes probable that there may be a rhythmical nutrition of the nervous centres whereby their activity is periodically increased, and they are rendered more susceptible at intervals of any morbid impression. Apart from the menstrual flux, which is an inessential process superadded to the generative functions as discharged in the lower animals, we should have no more evidence of the monthly occurrence of ovarian activity in the woman than we now have of the assumed periodical activity of the nervous centres; but a rhythmical mode of nutrition being known to exist in the one case affords a strong argument from analogy for the supposition that it may exist in the other; and moreover upon this supposition we can give a better explanation of periodical symptoms occurring in certain conditions of disease, regarding them not as purely pathological symptoms, but as physiological symptoms aggravated and rendered prominent by pathological conditions.

That symptoms of periodical irritability of the nervous system do not occur more often in various conditions of disease, which must be allowed to be an argument of some weight against the theory proposed, may be accounted for by considering that many morbid processes in the body would interfere with the rhythmical



nutrition of the nervous centres, as we see that they do with the periodical nutrition of the generative system ; but the more local the disease, and the more free from constitutional symptoms, the more likely would it be to elicit evidence of, rather than to interfere with, the rhythmical nutrition which I suppose to take place in the nervous system ; and this freedom from constitutional disturbance pre-eminently characterises Ague of a mild form, and other intermitting affections ; whereas in Ague if the general cachexia becomes great, or if the system is weakened by bleeding, the periodic reaction is interfered with.

In nature nothing is strongly or definitely marked, and although general laws undoubtedly exist they are readily broken or modified, so that it is quite admissible to allow that there is evidence of such a law of rhythmical nutrition, although we may be quite unable to determine, amid the various disturbances of it, what the normal rhythm is. In the nervous system it may be of a daily type, intensified perhaps every alternate day. Cullen, speaking of the periodicity of the paroxysms of fevers, says, " But as I cannot perceive anything in the cause of fevers determining to this, I must presume it to depend upon some general law of the œconomy. Such a law appears to be that which subjects the œconomy in many respects to a diurnal revolution. . . . . The return of sleep and watching, of appetite and excretion, and the changes which regularly occur in the state of the pulse, show sufficiently that in the human body a diurnal revolution takes place." \*

To consider the manner in which Quinine acts upon the sympathetic system, that it is a stimulant to it appears evident by comparing its action with that of galvanism. Brown Séquard records that after galvanizing the cervical sympathetic the irritability of the iris and of the muscles disappears sooner than usual after death, the opposite effect being produced by dividing the nerve ; and a similar exhausting effect upon the tissues of the heart from the operation of Quinine, in excessive doses, upon its

\* Cullen's Practice of Physic, LV.



ganglia has been observed by Schlockow in his experiments upon frogs, the tissues of the heart after fatal doses losing their irritability sooner than usual after death.\* This is in accordance with the fact that slowness of the heart's action, and of the pulse, is characteristic of a state of cinchonism; and I would submit that large doses of Quinine by over-stimulating the ganglia subsequently produce exhaustion of them, and of the tissues also which they act upon, but that moderate doses promote their nutrition, in accordance with the law that nutrition is increased by functional activity, provided that the necessary waste of tissue is not too great to be counterbalanced by corresponding appropriation of new material. This agrees with the results of experience, that to obtain the good effects of Quinine it must be given in moderate doses.

With regard to Ague then I would say that the periodicity of the paroxysms is determined by the nervous centres being more impressible at certain intervals, owing to the rhythmical mode of their nutrition; that the fit is excited by internal congestion; and that the amount of this together with the degree of irritability of the nervous centres will partly determine the time of the occurrence of the paroxysms, and the type of the disease; that the internal congestion is caused mechanically by relaxation of the small vessels of the visceral organs, in consequence of their vaso-motor nerves being paralysed by the action of the Ague poison; that the cachectic symptoms which occur in Ague are produced by the impurity of the blood which results from its stagnation in the viscera; that Quinine cures Ague by curing the paralysis of the visceral sympathetic nerve; and that it effects this by stimulating its ganglia to increased action and increased nutrition.

I must now proceed to the consideration of other intermitting disorders which yield to Quinine, and endeavour to explain their pathology in conformity with the hypothesis that Quinine acts specially upon the sympathetic system.

\* N. Syd. Soc. Year Book, 1862, p. 171.



Some forms of Hyperæsthesia and of Neuralgia are brought into the same category as Ague from their occurring for the most part in paroxysms, and from their yielding readily to Quinine. It is the great characteristic of pure Neuralgia that no local lesion can be discovered at the seat of pain; there is simple pain in the part without any symptoms of inflammation; and the explanation which I would offer of it is, that the sensation of pain is caused by some slight irritation of a nerve acting upon a nervous centre which is in an hyperæmic and irritable state from loss of power in the vaso-motor nerves which should regulate the calibre of its vessels; and that the pain ceases under the influence of Quinine because improved tone is given to the vessels of the morbid ganglion by the action of that drug upon the enfeebled vaso-motor nerves. There is probably in all cases of Neuralgia some irritation of a nerve, but in many cases so slight an irritation that it would cause no sensation of uneasiness if its nervous centre was in a normal state; and the Neuralgia ceases when the irritability of the nervous centre is relieved, even though the peripheral irritation remains. Nervous Hyperæsthesia can be explained in a similar way, by supposing that there is very great irritability of certain nervous centres from a similar cause, but no constant irritation of any particular nerve connected with them; for there is absence of pain so long as no pressure is made upon the surface, although owing to the morbid condition of the centres the slightest touch produces acute pain, but the exaggerated sensibility ceases when the action of Quinine has relieved the hyperæmic condition of the nerve centres.

When the spinal cord is cut across the reflex activity of the part separated from the brain is increased; and when one lateral half of the spinal cord is divided Hyperæsthesia arises in the parts of the body behind the section on the same side of the body; and it seems probable that both the increased reflex activity and the increased sensibility are produced by injury having been inflicted at the same time upon the vaso-motor nerves, which regulate the supply of blood to the spinal ganglia, so that the latter



become hyperæmic. Brown Séquard says, "As a great many vaso-motor nerves go up to the brain and to the cerebellum along the spinal cord, the medulla oblongata, and the pons varolii, the diseases or injuries of the various parts of the cerebro-spinal axis, besides symptoms concerning sensibility and movement, present symptoms depending upon irritation and paralysis of vaso-motor nerves."\* If we suppose the spinal ganglia to be in an irritable state from paralysis of their vaso-motor nerves and consequent hyperæmia, it is easy to understand that any impression made upon them would be reflected with increased energy to the corresponding motor nerves, causing energetic reflex action; and that being transmitted with morbid activity upwards to the sensorium it would produce there a sensation of pain.

To illustrate this by a well known experiment.

If you take a frog and dip its hind feet into water it allows them to remain in it, but if you dip them into an acid solution it at once withdraws them. Make an acidulated solution so weak that a frog can just bear to have its toes dipped into it without resenting it, then divide one lateral half of its spinal cord and repeat the experiment. The leg on the side of the section will be instantly withdrawn on immersion in the acidulated fluid. The irritation which before the lesion was inflicted on the spinal cord was disregarded now suffices to produce reflex action; and similar experiments with higher animals show that Hyperæsthesia also is produced by a similar injury.†

Now the persons in whom Neuralgic and Hyperæsthetic affections most frequently occur are persons who are nervous, as it is called, from original temperament or who have become nervous from debilitating causes; and nervousness seems to consist in a great measure in a predominance of the reflex actions over the power of the will to restrain them, so that the actions of nervous persons manifest emotions out of proportion to the feelings of the mind. In a nervous condition of the body a sudden noise makes

\* Physiology of the Nervous System, p. 206.

† Bernard. Leçons sur la Physiologie du Système Nerveux. Leçon 17.



the body start to a degree quite out of proportion to the effect of the noise upon the mind, but the will is unable to restrain the involuntary action of the body, on account of the irritability of the nervous centres and the consequent energy of the reflex actions.

Both these affections, both nervousness and disorders of sensation, are in many instances curable by Quinine ; and in such cases I would attribute them to an irritable condition of the nervous ganglia from a feeble condition of the vaso-motor nerves, whereby a certain amount of hyperæmia is produced in them. The hyperæmia probably does not amount to congestion, but consists of a slight injection of the vessels, such as is often seen in the conjunctiva in states of debility, but which would leave no trace after death of its previous existence. Different statements have been made with regard to the effect of such an hyperæmia upon the nutrition of the part. Brown Séquard says that hyperæmia produced by division of the cervical sympathetic nerve leads to increased nutrition in the injected part ; Savory denies this and says, "this abnormal condition may be maintained for months and yet no visible effect upon nutrition follows."\* It is clear therefore that the effect of atonic hyperæmia upon the nutrition of the part in which it occurs cannot be very marked ; and its action upon the nervous centres can be explained in a different way. Let us suppose that the hyperæmia does not influence their nutrition at all, yet it may produce some effect upon them mechanically. The pressure of the blood, which ought to be supported by the tonicity of the small vessels, when their tone is lost must fall upon the nerve tissues. Pressure upon the nerve cells from a state of passive congestion would tend to interfere with their function, but the gentle pressure produced by slight injection of the vessels serves only to irritate them, and to make them ready to be impressed by and to respond in an exaggerated manner to the slightest stimulus, so that inordinate pain and inordinate reflex action result from comparatively feeble irritation.

\* Savory on Life and Death, p. 73.



But should the injection of the centres become excessive, paralysis may be the consequence, and the clinical cases of Paraplegia combined with Hyperæsthesia and Photophobia which get well under the use of Quinine seem capable of being explained in this way.

Upon the assumption of a rhythmical nutrition of the nervous centres it is easy to understand how a periodical Hyperæsthesia or a periodical Neuralgia may arise; for at the periods of increased irritability of the nervous centres a sensation of pain may be produced by an irritant which is too feeble to make itself felt in the intervals. The excess of pain at these periods is accounted for by supposing that there is at such times a morbid increase of irritability caused by increased blood pressure upon the nerve tissues not at all counteracted by tonicity of its vessels. Restore the vascular tonicity by the action of Quinine and the morbid symptoms cease. The supposition that in cases which yield to Quinine the irritability of the nervous centres is produced by pressure of blood upon the nerve cells derives support from the interesting case related by Dr. Watson of a gentleman with hypertrophy of the heart, who on looking upwards to the whitened ceiling of a room used to see a darkened spectrum which vanished and reappeared with great regularity synchronously as it was found with his pulse.\*

"In this case," says Dr. Watson, "it is presumable that by each contraction of the left ventricle of the heart plethora of the cerebral blood-vessels was produced, and therefore an excess of pressure upon the cerebral substance." This case surely shows how under different circumstances intermittent amaurosis may arise from pressure produced at intervals upon the cerebral substance in a different way, namely as before explained by a normal periodic plethora of the capillaries with an atonic condition of their walls; and how in such a case it would be remedied by Quinine if the hypothesis I am advocating is correct.

My remarks upon the pathology of Neuralgia and Hyperæ-

\* Watson on Principles and Practice of Physic, vol. i., p. 373.



thesia apply only to such cases as yield to Quinine,\* and of such cases those which intermit yield the most readily, because as the fact of their intermitting proves the irritating cause is not able to make an appreciable impression upon the nerve centres except at the period of their greatest irritability, and consequently the irritation must be excessively slight, and the chief fault must be in the sympathetic system. With regard to the origin of these lesions of the sympathetic and the relation of Intermittent Neuralgia and other paroxysmal affections to Ague, it is doubtful whether the former are of malarious origin. It was not supposed that they were so until it was found that they were curable by Quinine, and there is no evidence to show that they are produced more by malaria than by other debilitating causes.

It seems probable that Quinine acts as a stimulant to the vaso-motor nerve system throughout the body, but that the Ague poison acts, if not exclusively, at all events most energetically upon the abdominal portion of it; and that local lesions of the sympathetic system in other parts of the body may arise from other causes, and that they do not necessarily indicate malarious infection.

If I have succeeded in making my theory of the action of Quinine as a remedy for these nervous affections intelligible, I think it will be admitted that it affords an explanation not only of the success which attends the administration of this drug in some instances, but also of the failure of it as a remedy in other cases. If the irritability of the nervous centres arises from the circulation through them of poor and watery blood, Quinine fails to relieve the morbid state, and Iron is found to be a more efficient remedy. If the symptoms arise from plethora or from the poison of retained excreta, Quinine cannot alleviate the symptoms, and the treatment must be directed to the improvement of the unhealthy condition of the blood. If the nerve tissue itself is in a state of innutrition, Cod-Liver Oil and the Hypophosphites, as supplying ingredients of nerve structure

\* Some of the cases of Neuralgia and Hyperæsthesia which yield to faradisation are probably of a similar character.



appear to be the most efficient remedies. Quinine is of use only where the radical fault is feebleness of the sympathetic system, or so far as that system is implicated.

The good effect of Quinine upon the system generally as a tonic is also fully accounted for; because, although when the function of a vaso-motor nerve is in abeyance no visible effect upon nutrition, so far as increase or decrease of bulk is concerned, takes place, yet it must be of the utmost importance that the supply of blood to the several secreting and excreting organs should be duly regulated; and the maintenance of an equable circulation through the system at large must exercise an immeasurable influence upon the general health.

In conclusion I have only to remark that although in the affections in question, urgent symptoms, such as rigors, pain or excessive tenderness, occur only at intervals, yet that the diseased action which gives rise to these symptoms is continuous, (if at least the explanation which I have given of these disorders is the true one,) and that therefore the remedies which relieve them cannot rightly be said to possess antiperiodic properties. Drugs of the most opposite character, and possessing no single property in common, might be classed together under such a title by virtue of their modifying in very different ways different morbid conditions, which give rise to symptoms only at intervals in consequence of the nutrition of the nervous system going on in a periodic manner. But as the remedies influence only the diseased action, which is not periodic, but continuous, they cannot rightly be said to possess any antiperiodic property. For the natural periodicity of function cannot really be affected by the removal of the unhealthy condition, and we must presume that the physiological alternation of action continues, although it may be scarcely if at all perceptible when signs of it are not elicited by morbid irritation.

Briefly to recapitulate. The principal points which I have endeavoured to prove are these.

1. That as Cyanide of Potassium exerts a special paralysing

action upon the muscles, and Curara a similar action upon the motor nerves, so Quinine exerts a special stimulating action upon the sympathetic system generally, and Malaria a special paralysing action upon the visceral sympathetic.

2. That in those disorders in which Quinine acts as a specific remedy the radical fault is in the sympathetic system, which is in a more or less paralytic condition.

3. That paralytic affections of different parts of the sympathetic produce different disorders. Paralysis of the visceral portion of it giving rise from the morbid complications which follow to the symptoms which constitute Ague; whilst loss of power in any part which regulates the supply of blood to one or more of the cerebro-spinal ganglionic centres leads to disorders of motion and sensation.

4. That in all these affections the essential disorder is purely local.

5. That it gives rise to urgent symptoms only at intervals, unless the affection is very severe, because the nervous system is naturally more irritable at particular times, owing to a periodic alternation which normally occurs in its nutrition.

6. That Quinine has acquired its title of antiperiodic, by curing the morbid conditions through which the periodic alternation of action in the system is made so much more evident than it is in health, and not by exerting any control over the periodic action itself.









