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TABES AND OPTIC ATROPHY

BY

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ON looking over a series of visual fields in tabetics, one cannot help being struck by the remarkable variability that they show and the marked disproportion that exists in different cases between the loss of visual acuity and the loss of visual field. Is there anything in the underlying pathological changes which will explain this variability? To determine this, it is necessary to see what has been learned of the pathology of tabes in general and more particularly of tabetic optic atrophy. I have tried to show in the following paper in how far the process as it concerns the optic nerve, resembles or differs from the process in other parts of the central nervous system. Of necessity, as the literature on the subject is immense, I can only refer to the more outstanding papers that have come to my notice, but I think these show how varied and discordant are the views held as to the nature of tabes.

It is obvious that if tabes is a clinical entity, a homogeneous disease, and not simply a heterogeneous collocation of manifestations of later syphilis, there must be some definite relationship in the pathology of the conditions that are found in different parts of the central nervous system; and the variations that occur must be due more to variations in the nature of the tissue attacked than to variations in the virus.

The Lesion in Tabes

In tabes, we have one of the most common diseases of the central nervous system, and yet one in which the pathological process at work is the subject of the most diverse views. Much of the difficulty is due to two causes; in the first place almost invariably the investigations have been made in cases where the disease has reached a most advanced stage, and secondly, as tabes is a late manifestation of syphilis, a patient with this lesion is likely to present many other lesions resulting from syphilitic infection. In consequence of these two facts, it becomes a very difficult matter to separate out and define which of the pathological changes found are essentially parts of the clinical entity tabes, and which are to be regarded as complications due to other syphilitic conditions. And this is more especially difficult since syphilis can produce so many diverse effects on the central nervous system, *e.g.*, meningitis, myelitis, and all the variety of lesions resulting from syphilitic vascular lesions. We find accordingly that when a writer is supporting any particular hypothesis, he always adduces a co-ordinate syphilitic complication to explain away all the facts that are not in accordance with the hypothesis he favours.

A. Position of Originating Lesion

The present-day theories of tabes may be subdivided into three main groups according to the position in which the pathological changes are supposed to begin.

1. The posterior columns.
2. The posterior root ganglion.
3. The posterior roots.

The placing of the origin of tabes in the posterior columns is a perpetuation of the older hypothesis of the disease. Strümpell's⁽⁴⁷⁾ support of it is based on three points:—

- (a) Certain tracts in the posterior columns remain unaffected.
- (b) The affection always shows a certain distribution involving more intense implication of certain zones and relative freedom of other regions which are equally of post root-fibre origin.
- (c) The symmetrical nature of the distribution.

Flechsigs⁽⁸⁾ has supported the theory of the elective action of the tabetic virus on certain fibre tracts in the posterior columns on biological grounds. He considers that there is variation in the vulnerability of tracts according to the variation in the time of development of their myelin sheaths (*v.* also Kaufmann¹²).

Both these writers support the hypothesis of a systemic elective action of a tabetic toxin (meta-syphilitic) directly on nerve fibres of the posterior column, *i.e.*, a parenchymatous action of the virus.

In the second hypothesis, the posterior root ganglion is sug-

gested as the point of origin of the degeneration, and tabes is regarded as a typical neuronc degeneration commencing in the ganglion cells of the posterior root ganglion. The degeneration of the posterior roots and posterior column tracts is, on this theory, regarded as secondary to the degeneration of the ganglion cells. This hypothesis has been strongly supported by Stroebe⁽⁴⁴⁾, Marinesco⁽²⁰⁾ and Köster⁽¹⁴⁾, and again the toxin is supposed to act on parenchymatous tissue.

It is on the third hypothesis of a primary affection of posterior root fibres that most of the discussion in recent years has taken place.

According to the hypothesis of Obersteiner and Redlich⁽³⁰⁾, the posterior root fibres are primarily attacked as they pass through the pia mater to enter the posterior columns. There is at that point a diminution in the myelin sheath which renders the fibres more vulnerable. The bundles are, at this point, constricted partly by a meningitis and partly by arterio-sclerotic changes in the branch of the artery which comes into relationship with these entering bundles.

Orr and Rows⁽³³⁾ also are of opinion that the process has its starting place at the point of entry of the posterior root into the cord, but they do not agree with the Obersteiner-Redlich idea of a primary meningeal cause. They consider that it is primarily a parenchymatous degeneration, and that the reason that the toxin produces its effect at this particular place is that here the nerve fibres lose their neurilemmal sheath which blends with the pia, and at the same time the myelin sheath much diminishes in thickness, so that, generally, the nerve fibre is less protected than elsewhere. In addition, the main lymph channels enter the cord along with the posterior roots, and as they convey the virus the posterior roots are more exposed to its attack at this point. Their work on other infective conditions in the central nervous system has shown the importance of the lymph channels in the conveyance of infections, and especially the lymph channels which accompany the afferent nerves from the periphery to the cord.

According to Nageotte's⁽²⁴⁾ hypothesis, the lesion of the posterior roots is completely extra-pial, and the root is primarily attacked in the portion nearest the ganglion where the dura and arachnoid sheaths have joined up into one, but where there still exists a definite subarachnoid space, forming a pocket or recess which is carried further out along the posterior root than along the anterior root. The portion of nerve lying in this space, the "radicular nerve of Nageotte," is supposed to be the part of the nerve first affected. (v. Fig. 1.)

This theory of Nageotte has been very strongly supported by the recent work of Richter⁽³⁸⁾.

Nature of Pathological Lesion

The discovery of spirochaetes in the brain of paretics by Noguchi⁽²⁵⁾ in 1913 rendered it increasingly probable that sooner or later these would also be found in cases of pure tabes, and their localization would help to give a clue to the point of origin of the disease. The difficulty again was likely to lie in the other syphilitic complications that so frequently accompany and complicate tabes. If Richter's⁽³⁸⁾ discovery of spirochaetes in a few cases of tabes in the granulation tissue in the sub-arachnoid recess which surrounds the radicular nerve is confirmed, it will go far to solve the problem of tabes. Before dealing with Richter's views, I will briefly state some of the earlier hypotheses as to the nature of the pathological lesion.

FIG. 1.

A—B RADICULAR NERVE (Nageotte).

To illustrate Nageotte's and Richters' Hypotheses.

I. That the condition is one of primary nerve fibre degeneration, brought about by the selective action of a meta-luetic toxin on certain nerve tracts, and that the proliferation of connective tissue and glial tissue and the other signs of chronic inflammatory change are secondary to and consequent on the nerve atrophy. This hypothesis can be sub-divided into two sub-groups:—

(a) Where the primary degenerative process takes place in the posterior columns.

(b) Where the primary degenerative process takes place in the posterior roots.

I have already referred to the work of Orr and Rows⁽³³⁾ which would place tabes under this heading. On the same lines runs the work of McIntosh, Fildes⁽²¹⁾, Head and Fearnside⁽¹¹⁾. According to these writers, the essential features of syphilis are the same in

all its stages, and both interstitial and parenchymatous tissue may be affected. There may be evidence not only of perivascular proliferation and small celled infiltration, but also of intoxication of the parenchyma itself. "The difference between the interstitial tissues and the parenchyma is, that in the former the reaction is marked—proliferation and infiltration—while the degeneration is slight, and in the latter the reaction is trivial and the degeneration extensive."

This applies both to the acute and chronic stages of the disease. The parenchymatous tissue has little or no reparative power, and consequently degeneration in it means loss of function.

In the tertiary stages, the number of spirochaetes has markedly diminished, and "there is a remarkable lack of correlation between the amount of virus and the extent of the lesions. This disproportion is due to the poisoning of the tissues in the secondary stages producing a great increase in the susceptibility of the tissues to the virus (hyperallergie), so that the awakening into activity of even a small number of spirochaetes produces a very marked tissue reaction or tissue degeneration. These spirochaetes having escaped the general destruction which takes place towards the end of the secondary stages (which destruction may be caused by the development of antibodies or by drugs), may remain dormant for years until awakened into activity by some cause as yet obscure."

In dementia paralytica the pia is in a state of inflammation, showing infiltration by large numbers of lymphocytes and plasma cells and proliferation of the endothelium of the capillaries and small vessels. In addition to these changes in the mesoblastic tissues, there are changes in the ectoblastic tissues, degeneration of ganglion cells and increase of neuroglial cells. But the changes in the parenchyma are more marked than those in the interstitial tissue, *i.e.*, the disease is essentially a parenchymatous encephalitis.

In tabes, the essential lesion "also is due to an inflammatory reaction on the part of the nerve fibres and neuroglia induced by the presence of the spirochaeta pallida." "The degeneration of the nerve fibres following on this intoxication will occur in those parts only which have been deprived of the neurilemma." The writers adopt the theory of Orr and Rows as to the primary site of the lesion being where the neurilemmal sheath leaves the roots to blend with the pial sheath and the thinner nerve root passes into the cord tissues, and also with their theory that the lymph channels convey the virus to this position.

II. That there is a co-ordinate action of the virus on nerve fibres and supporting tissue, and that the changes in the two tissues are to that extent independent of one another.

Against this hypothesis, as Richter points out, there is the fact that there is never nerve degeneration without the presence of

granulation tissue, but there is frequently found well-marked development of granulation tissue preceding nerve atrophy, and it is only in the immediate neighbourhood of granulation tissue that nerve degeneration is found.

III. That the nerve degeneration is the consequence of the development of the granulation tissue, and is brought about partly by the disturbance of nutrition caused by granulation tissue developing in and blocking the normal lymph channels and finer connective tissue spaces by which the nerve fibres obtain their nourishment, and partly by the mechanical constriction of the fibres by the growth of neuroglial tissue, *i.e.*, the process is partly bio-chemical and partly mechanical.

According to Obersteiner and Redlich⁽³⁰⁾, this process of constriction and blockage takes place in the pial region, and is consequent on a primary meningitis, of which the evidence is the existence, not only of fibroblastic cells, but also of lymphocytes and plasma cells. To this exudative process is superadded a further constriction by arterio-sclerotic changes in a small branch of the posterior spinal artery.

In 1894 Nageotte⁽²⁴⁾ published his first paper, in which he described the changes as commencing round the nerve roots towards the outer portion where they come close together and lie in a common sheath. He describes the nerve roots as consisting of three parts:—

1. Inside the cord until they pierce the pia mater.
2. Lying more or less free and in several fascicles in the sub-arachnoid space. In this portion, they get a partial sheath of sub-arachnoid tissue which gradually thickens into a more definite lamella as the bundles fuse together to form the third portion.
3. Fused bundles joined up and surrounded with a sheath composed of combined dura and arachnoid which closes in on the combined anterior and posterior roots before the ganglion is reached. This last portion, which he calls *nerf radulaire*, is, as I have already said, the point of origin of the lesion. Pathologically, both Nageotte and his latest supporter, Richter, describe the changes as commencing in the sub-arachnoid tissue surrounding this portion of the nerve.

In Richter's words⁽³⁸⁾—"the recognisable nerve changes in tabes depend upon a direct lesion of the nerve root fibres in the area of Nageotte's radicular nerve caused by syphilitic granulation tissue which is produced in the lymph spaces of the connective tissue sheaths by the irritation of spirochaetes deposited there, and this spreading along the lymph channels in the nerve bundle causes local patches of disturbance."

The granulation tissue originally described by Nageotte in 1894 as an *infiltration embryonnaire*, results from the proliferation of

endothelial cells in the lymph spaces and of the fixed connective tissue cells. According to Richter, there are no cells of haematogenous origin, no lymphocytes nor plasma cells, but only pure fibroblastic cells. These first develop in the lymph spaces of the combined dural-arachnoid sheath, and from there the granulation tissue makes its way into the looser tissue of the sub-arachnoid space and invades the nerve bundles, making its way by lymph channels and spaces up the nerve towards the cord and down towards the ganglion.

The process in tabes differs from that found in general paralysis or tabo-paresis in the absence of haematogenous cells. In general paralysis and tabo-paresis, both lymphocytes and plasma cells are found invading the tissues, and in the perivascular lymph spaces.

Affections of Cranial Nerves other than the Optic Nerve

Of the cranial nerves other than the optic nerves the oculo-motor nerves are more frequently attacked in tabes than any other. The general opinion of the majority of workers has been in favour of regarding tabetic oculo-motor palsies as of nuclear origin. In the paper on "Ocular Palsies" I read in March, 1921, at the Royal Society of Medicine (*B.J.O.*, June, 1921), I stated this hypothesis somewhat baldly and dogmatically. The extent of the subject to be covered in that discussion must be my excuse. It is far from being generally accepted. If it be true, it places tabetic oculo-motor palsies in a different position from the tabetic affections of the cord. In none of the theories of tabes is the primary lesion supposed to be in the grey matter of the cord. The nearest analogous theory is that which places the primary lesion in the posterior ganglion cells. Again it is the nucleus of origin of an efferent nerve which is here supposed to be affected, and in the cord the afferent nerve is always the more affected and the anterior root shows a much greater resistance to the disease and is much later in yielding to it. On this point, the idea suggested by Sherrington⁽⁴²⁾, mainly based on the work of de Kleijn, that the fleeting diplopias of early tabes are due to disturbances in the afferent proprioceptive impulses from the oculo-motor muscles and muscles of the head and neck, should be remembered. The point is of importance as hinting that here also, as in the other tabetic lesions, the primary disturbance may be in afferent fibres. In the case of the eyes, however, the afferent impulses from the retina and from the semi-circular canals predominate to such an extent over all other afferent impulses that the diplopia produced by disturbances of the latter is speedily compensated and proves but evanescent. This disturbance of afferent impulses probably plays no part in the production of the permanent oculo-motor palsies of late tabes. The

hypothesis that this is not primarily a nuclear degeneration but an affection of the nerve stem, has the support of many writers, *e.g.*, Oppenheim⁽³²⁾, Dejerine⁽⁴⁾, Nonne⁽²⁸⁾ and Cassirer⁽²⁾, and, more recently, Stargardt⁽⁴³⁾ and Richter⁽³⁸⁾.

The hypothesis of Stargardt is that the affection of the oculo-motor nerves commences by an infiltration of the sheath and vessels of the oculo-motor nerve. In the central nervous system, the Grenz-membrane shuts these off from the fibres themselves, but in the extra-cerebral nerve roots, the ecto-dermal Grenz-membrane is represented only by the sheath of Schwann surrounding individual fibres, so that the infiltrating tissue passes in among the nerve fibres. The primary point of invasion is where the nerve passes through the dura; and the infiltrating tissue contains cells of haematogenous origin, plasma cells and lymphocytes. In Richter's hypothesis, the process commences in the perineurium of the extra-cerebral portion of the nerve, and the granulation tissue developing in this area is of exactly the same nature as that which he finds in the posterior nerve roots. He admits that cells of haematogenous origin are to be found in the pial zone, but in the tissue actually invading the nerve, he finds only fibroblasts and no lymphocytes nor plasma cells. The difference between his findings and Stargardt's he ascribes to the fact that he was only dealing with pure tabetics, while Stargardt's cases included tabo-paretics and paretics.

Optic Atrophy

Various and discordant as are the theories advanced to explain the pathology of the changes in the posterior roots and columns, we find that the theories of optic atrophy are just as diverse. The possibilities may be briefly grouped into:—

1. A primary neuronc degeneration with secondary fibrosis:—
 - (a) Commencing in the ganglion cells (Gowers⁽¹⁰⁾, Erb⁽⁷⁾, Charcot⁽³⁾, etc.).

- (b) Commencing in the nerve fibres or axones (Uhthoff⁽⁴⁵⁾, etc.).

2. A primary peripheral and interstitial neuritis with secondary degeneration of nerve fibres.

- (a) The primary changes commencing in the papilla (Elschnig⁽⁶⁾).

- (b) The primary changes commencing in the pial and subpial regions in the peripheral portion of the nerve (Léri⁽¹⁶⁾, Wilbrand and Saenger⁽⁴⁹⁾).

- (c) The primary changes both axial along the central vessels and peripheral in the subpial zone.

- (d) The primary changes commencing in the optic foramen (a periostitis and pachymeningitis resulting in strangling of the nerve (Schlagenhauer)).

(e) The primary changes commencing in the intra-cranial portion of the nerve including the chiasma and optic foramen and mainly in the pial and subpial zone (Stargardt and Richter).

3. The interstitial changes and the parenchymatous changes in the nerve are co-ordinate results of the activity of the tabetic virus and not mutually dependent on one another.

Hypotheses of Primary Neuronic Degeneration

Parsons⁽³⁴⁾ in "The Pathology of the Eye," Vol. IV, p. 1344, gives what may be taken as the commonly accepted view up to the end of the nineteenth century—"the primary seat of the disease is in the retina, commencing in the ganglion cells and nerve fibre layer. In the nerve, the atrophy is generally most marked near the globe, diminishing towards the cerebrum; changes in the chiasma and tracts are absent in the early, and are slight even in the later stages." This view of a primary neuronic degeneration commencing in the ganglion cells was held by Erb, Charcot, Gowers, Popow⁽³⁶⁾, Moxter⁽²³⁾, v. Michel, de Grosz⁽⁴⁶⁾, Klippel⁽¹³⁾, Gliksmann⁽⁹⁾, Wagenmann⁽⁴⁸⁾ and Coppez, but the arguments against it are numerous. These were summarized by Léri in 1904. Holden in 1899 argued that the changes in the ganglion cells were secondary to degeneration of nerve fibres. Léri found numerous ganglion cells intact in the retina where every fibre in the nerve had disappeared, and in all cases there was a marked disproportion between the ganglion cell and nerve fibre layer degeneration and the degeneration in the nerve itself. From the examination of the retina and nerve in eleven cases of blind tabetics, he concluded that the origin of tabetic atrophy could not be in the retina itself.

Stargardt summarises his conclusions as regards the retinal origin of the optic atrophy in tabes and general paralysis in the following eight clauses:—

1. The retina never shows, during the course of optic atrophy in tabes or general paralysis, a special pathological histology. The changes which occur in the retina are throughout analogous with those which occur in any descending atrophy, such as may result from the pressure of an arterio-sclerotic internal carotid. The pyknomorphic ganglion cells are found in both conditions indicating a definite reparative attempt. Also the slight changes in the inner nuclear layer are similar in character.

(Nissl's pyknomorphic ganglion cells are supposed to indicate a reparative effort in the nervous tissues. The nucleus, which in degeneration has become pushed to the side, gets back to the centre of the cell. Immediately round it, large Nissl granules develop, and then later similar large Nissl granules develop in the periphery. The Nissl granules are all larger and more numerous than in the ordinary ganglion cell.)

2. The retinal changes in tabes and general paralysis are in all essentials similar to those found after experimental section of the nerve. In animals, however, there are no pyknomorphic ganglion cells found, nor changes in the inner nuclear layer.

3. There are no changes found in the outer retinal layers such as are found after certain poisons, *e.g.*, quinine, aspidium, filix mas, and atoxyl.

4. There are no changes found in the retina unless there are undoubted changes in the optic nerve.

5. In the earliest stages of optic atrophy, no changes are found in the retina.

6. In partial optic atrophies, the retinal changes found are strictly confined to the portions which correspond to the part of the nerve affected.

7. In partial optic atrophy, the amount of retinal change found is relatively less than the amount of optic nerve change.

8. After complete optic atrophy, quite normal ganglion cells, though few in number, can be found in the retina.

His general conclusion from retinal examinations is that the retina cannot be the seat of the primary change in tabetic atrophy.

The hypothesis of a neuronc degeneration beginning in the nerve fibres in the nerve itself has become widely accepted amongst ophthalmologists on account of its advocacy by Uhthoff in his article in Graefe-Saemisch, and later by Wilbrand and Saenger⁽⁴⁹⁾ in "Neurologie des Auges," Vol. V, p. 585. Uhthoff describes the process as commencing in a fatty degeneration and absorption of the myelin sheaths followed by changes in the axis cylinders. These first show varicosities and subsequently also degenerate, leaving only the fine threads of collapsed nerve fibre sheaths. In the later stages, all that is left is fatty drops, myelin drops, and amyloid bodies.

The changes in the interstitial tissue follow on these parenchymatous degenerations. The finer septa and processes of supporting tissue disappear and the larger septa become more swollen. There is no evidence of any chronic inflammatory process producing these changes, neither cell infiltration nor nuclear proliferation, only that with the disappearance of the nerve fibres the larger septa become more prominent. It is only in the latest stages that glial proliferation comes into evidence. Such, briefly, is Uhthoff's description of the process which he regards as a neuronc degeneration commencing in the nerve fibres and due to a tabetic or metasyphilitic toxin. He considers that the process commences in and is most marked in the peripheral portion of the nerves and diminishes in intensity towards the intra-cranial portion and the chiasma, and is mostly absent above the chiasma. "A primary starting point of the degeneration in the chiasma or in the optic

tract, or in the primary centres of the optic nerves, seems to be excluded." He considers that the early appearance of disc changes points to the peripheral origin of the lesion.

Hypotheses of Primary Peripheral and Interstitial Neuritis

I now come to the consideration of the hypotheses which regard the primary changes as taking place in the peripheral and interstitial tissues. Of the sub-divisions of this group, three require only very brief mention.

Elschnig⁽⁶⁾, in 1899, after the examination of a case of tabes with marked atheroma, suggested the hypothesis that "the cause of the optic atrophy could be found in the overgrowth of thick glial tissue in the disc replacing the nerve fibres." ("Das dichte Gliagewebe, welches das Nervenfasergewebe in der Papille substituiert, wohl ganz in diesem Sinne als Ursache des Schwundes der Nervenfasern angesehen werden könnte.")

Elschnig, in advancing this hypothesis, seems to have been influenced greatly by Obersteiner and Redlich's hypothesis of the origin of tabetic degeneration by strangulation of the posterior root in its passage through the pia.

Schlagenhafer⁽⁴¹⁾ ascribed the optic atrophy to a strangling of the nerve in its passage through the optic foramen in consequence of a syphilitic periostitis or pachymeningitis. Probably a process somewhat similar to this is the cause of the optic atrophy in oxycephaly, but in that case, there is evidence also in some cases of a true optic neuritis. The interest of this hypothesis also lies in its analogy with that held by Obersteiner and Redlich for tabes.

There seem to be very few authorities prepared to support an axial origin of the interstitial changes. Peltesso⁽³⁵⁾ found in one patient with commencing tabes, a patch of central atrophy in the optic nerve. Clinically, the great rarity of cases of central scotoma is a strong argument against it, and a still stronger argument against it is the fact that the retinal vessels show little or no alteration in their calibre, even when the atrophy is very advanced and the sight almost gone.

The great majority of writers in favour of the interstitial theories describe the process as commencing in the periphery of the nerve. Léri⁽¹⁶⁾, in his paper published in 1904, recorded the results of his examination of the optic nerves of 84 cases. Of these, 21 were tabetics, 19 were completely blind and 2 not completely blind. Three were cases of blind general paralytics, 16 tabetics and 18 general paralytics without evidence of visual loss, were examined. The rest were mostly cases of different forms of syphilis affecting the central nervous system. He describes in detail the macroscopic and microscopic appearances seen. His conclusion is that the lesion is an interstitial neuritis, a syphilitic cirrhosis of vascular

origin and a syphilitic meningitis. The meninges (especially the sub-arachnoid and the pia), are infiltrated with lymphocytes which are specially abundant round vessels; but the vessels which penetrate the nerve are only to a slight extent surrounded by lymphocytes.

In the nerve itself, there is an intense proliferation of vascular connective tissue and of neuroglia, with a subsequent sclerosis and obliteration of the vessels, both pre-existing and new-formed. The atrophy of the nerve fibres depends on the loss of nutrition resulting from the obliteration of the vessels and not on any direct toxic effect on the nerve fibres, and it commences round the vessels, especially in the peripheral subpial zone. According to Léri, the process is primarily a periarteritis and an endarteritis, with subsequent degeneration of nerve tissue. He found the changes in the intracranial portion of the nerve and the chiasma exactly similar to those found in the orbital portion.

The conditions are exactly the same in general paralysis, in tabes, and in other cases of syphilitic atrophy.

Stargardt⁽⁴³⁾ published his first account of his researches at the Heidelberg Congress in 1911. His full account was published in 1913. He describes the earliest changes as taking place in the intracranial or foraminal portion of the nerve and in the chiasma, and it is only in the fairly late stages that the orbital portion of the nerve, the tract and the external geniculate body show any evidence of change. An exudative process, in which lymphocytes and plasma cells predominate, precedes any evidence of nerve degeneration. This exudation is found mainly in the pial sheath, and the septa spreading in from it. In the pia the plasma cells may be diffusely scattered, but as a rule, they are thickest in the neighbourhood of the vessels. In the septa the plasma cells mostly lie in the Virchow-Robin spaces, but they may permeate all the connective tissue spaces. Not only the larger vessels, but also the capillaries, show plasma cells between the elastic membrane and the thin adventitial layer, and it is along the vessels that they make their way into the nerve. The subsequent degeneration of the myelin sheath and axis cylinder process seems to progress contemporaneously. The disappearance of the degeneration products is due to phagocytic action of cells of glial origin.

His work is summarized briefly in the following paragraphs:—

1. There is no fibre degeneration unless there is an exudative process in some part of the course of the nerve. The exudative process belongs just as much to the picture of optic atrophy as to tabes and general paralysis.
2. The chief sites of the exudative process are the intracranial and foraminal segments of the nerve, and after them the chiasma.

The orbital portion, the tract and the corpus geniculatum are only rarely affected.

3. There is no regularity in the localization and spread of the exudative process.

4. In general paralysis, the exudative process generally spreads from the brain to the optic tracts, etc. In tabes it is an isolated process in the optic nerves or chiasma and may spread to the brain. "All sorts of variations are possible." The exudative process precedes the degenerative changes.

"It is only when distinct degeneration shows in the chiasma that evidences of degeneration in the optic nerve and retina become manifest. The cell degeneration is to be regarded as entirely secondary."

His conclusion is that "the simple optic atrophy in tabes and general paralysis is the result of an extraordinarily chronic inflammation which commences in the neighbourhood of the chiasma, the tract and the intracranial portion of the optic nerve, and makes its way along the lymph sheaths of the vessels into these tissues."

Richter⁽³⁸⁾ finds himself, as the result of an examination of three cases of tabes and one of tabo-paresis, in complete agreement with Stargardt. The changes in the optic nerve are the same in tabes and tabo-paresis, so that, as far as optic atrophy is concerned, the granulation tissue no longer plays the predominant rôle that he ascribes to it in other tabetic processes. It is an exudative process in which cells of haematogenous origin are predominant, and in this respect the changes are more closely allied to those found in general paralysis than to those found in other tabetic manifestations. Is this a reason for regarding cases in which optic atrophy occurs as really belonging to the category of general paralysis? Mott⁽³⁹⁾ speaks of the greater tendency of cases with early optic atrophy to pass on to general paralysis; but Richter thinks that the different reaction of the optic nerve can be explained on other grounds. The optic and olfactory nerves differ from all the other nerves of the body. They are of purely ectodermal origin, and their parenchyma is ectodermal in its constitution. Only the septa grow from the sheath into the nerve substance. The more intimate supporting structure of the optic nerve is of glial origin. In the other nerves it is of mesodermal origin. The granulation tissue—Nageotte's "*infiltration embryonnaire*"—is of mesodermal origin and can spread freely in tissues built up on a mesodermal framework, but can find no entry into ectodermal structures. In posterior root lesions the primary changes are in the tissue formed from the combined dural-arachnoid sheaths, and the pia is not represented. In the optic nerve the primary changes are in the pial zone, and the dura and arachnoid sheaths show only scanty signs of granulation tissue. The pia is essentially the

vascular member of the meninges, and when the lesion takes its origin in this the reaction shows a vascular character. In the optic nerve, the primary lesion and its cause, the spirochaetes, have their site in the pia, and in consequence of this, the reaction is of a vascular nature with cells of haematogenous origin.

Summary. Pathological Conclusion

The old hypothesis of a metaluetic toxin, the result of tissue degenerations produced by earlier syphilitic manifestations, must, in light of all the recent work, be finally abandoned. The toxin was always a purely hypothetical substance evoked to explain degenerations taking place where no active organisms could be found. In the light of the work of Noguchi, Levaditi, Mott, Head, Fearnside, McIntosh and Fildes, it must now be allowed that all the manifestations of syphilis are due to the local production of toxins in the presence of the spirochaete, but that the reaction between the spirochaetes and the tissue varies at different periods and in different tissues, either because of a diminution in the number and virulence of the spirochaetes, or because of differences in the resisting power of the tissues to the action of the toxin. Further, this tissue resistance may vary from time to time owing to variations in the strain on it (Ehrlich) or to the establishment of a condition of *allergie* (von Pirquet).

There still remains, however, the unsettled question as to whether this locally produced toxin acts directly on nerve tissue, producing a parenchymatous degeneration, or primarily on connective, vascular and lymphatic tissues, with a consequent secondary nerve degeneration; or a third possibility, that the nerve degenerations and the connective tissue degenerations are co-ordinate results due to the presence of the spirochaetes in both tissues.

I have failed to find in the course of my reading any strong advocacy of this last hypothesis. Yet I believe there is much to be said for it, and it would bring the causation of optic atrophy into line with the causation of general paralysis as described by McIntosh and Fildes, and it would also be in agreement with the hypothesis as to the origin of tabes which Schaffer⁽⁴⁰⁾ very strongly supports. As will be evident from the next part of my paper, I think the clinical evidence tends rather to support this hypothesis.

Functional Disturbances in Tabetic Optic Atrophy

The variability of the functional disturbances found in tabetic optic atrophy is a feature of the condition which has been frequently remarked on. This variability shows itself in the relationship that exists between visual acuity, visual fields and ophthalmoscopic appearances, as well as in the progress of the

disease. Recently the work of Behr⁽¹⁾ has brought into prominence another important functional disturbance, the loss of dark adaptation. This he regards as a most important early symptom of a tabetic atrophy, and he says it may precede any evidence of atrophic change in the fundus. In tabes "there appears regularly a typical and marked loss of dark adaptation, often without the smallest obvious change in the visual acuity, the visual fields or the colour sense." . . . "A tabetic optic atrophy is always associated with a disturbance of dark adaptation." Uthoff's⁽⁴⁵⁾ dictum that "every visual disturbance in tabes which precedes the ophthalmoscopic signs of optic atrophy is to be regarded as probably unconnected with the progressive optic atrophy," must then be definitely modified. Apart altogether from Behr's work, I consider that Uthoff's statement is much too sweeping.

Behr divides the clinical course of tabetic atrophy into four stages:—

1st Stage.—Isolated disturbance of adaptation with *normal* ophthalmoscopic appearances, visual acuity, visual fields and colour sense.

2nd Stage.—Disturbance of adaptation with definite signs of atrophy, but other functions normal.

3rd Stage.—Disturbance of adaptation, optic atrophy, loss of visual fields for white and colours, and diminution of visual acuity.

4th Stage.—Optic atrophy and amaurosis.

It is outside my brief to discuss the various theories of dark adaptation, but it would seem, if Behr is correct, that the centrifugal fibres are concerned in dark adaptation, and that, for some reason or another, they are specially liable to undergo early degenerative change in the course of tabes.

A rarer phenomenon, which is possibly also associated with changes in the centrifugal fibres, is the occasional development of coloured vision. It is mostly described as a blue-green or purple coloration, but Doyne has recently brought forward instances of red coloration in cases of tabes, and Uthoff⁽⁴⁵⁾ mentions a case in which there was a golden shimmer over things on waking in the morning, later turning into a silver shimmer. Eight weeks later the patient complained that in the dark he saw red, and in daylight a blinding whiteness.

Furthermore, it is probable, as a consequence of the diminution of the power of functional adaptation, that some of these patients see much better in diffuse light than in full daylight. When taking the fields of some tabetics, it is very noticeable that on testing along any radius the patient may see the test object very much further out at some times than at others. In most patients, the limits are quite defined, but every now and again

one comes across a patient who gives most variable responses and one cannot get any certain field. This, again, is probably due to disturbance of functional adaptation.

The Visual Fields

In discussing the visual fields of tabetic atrophy, Uhthoff distinguishes between two main classes of defect:—

1. The whole field seems to suffer simultaneously with an early loss of colour fields and early loss of visual acuity. There is a relative peripheral contraction of the fields for white, but a full field may still be obtained in the course of an ordinary investigation, *e.g.*, with 10 mm. white at half metre distance.

2. The area of defective visual fields is sharply delimited from unaffected areas, showing full normal vision, and central acuity may be quite good.

Stargardt gives a more elaborate classification of the visual fields:—

1. Peripheral loss of white and colours with simultaneous loss of function in other parts of the field. With advancing peripheral loss, the visual acuity falls and at the same time, the distinction between red and green, and later blue and yellow.

2. Peripheral loss for white and colours with good function in the untouched fields.

3. Peripheral loss of colours with full fields for white. Visual acuity may be normal or diminished.

4. Partial (sectorial) loss with more or less perfect functioning in the rest of the field.

5. Normal limits to the peripheral fields with diminished visual acuity and colour sensation.

6. Central scotomata.

7. Hemianopic defects.

My first two fields illustrate in the most characteristic way Uhthoff's two classes.

Case I. E.W.M. (age 45), noticed failure of his sight first in January, 1921. He consulted two oculists during 1921, who both told him that nothing could be done for him. Seen February, 1922. Ophthalmoscopically, he showed typical discs of tabetic atrophy. The fields for 10 mm. white test object at 15 inches were quite full, but his visual acuity in each eye was less than 6/60. An attempt to map out colour fields proved quite hopeless as he could see a 2 mm. red or green disc in the most patchy manner over most of the central portion of the field. He would see the colour quite clearly for a moment, and then not at all, and at no time long enough or over a big enough area to allow of my trying to indicate either the outer limits of the area in which colours were visible or the size of the areas in which they were seen.

FIG. 2.

L. V. = 6/60. Not Improved.

R. V. = 6/60. Not Improved.

CASE I.—E. W. M., Feb. 9, 1922. 10 mm. white at 15 in.

Case II. H.W. (age 46). Seen first in January, 1909. He complained that for some months past he had some difficulty in seeing things with his left eye. His right eye he considered to be quite good. His pupils were unequal—Right more than Left. Neither pupil reacted well to light, but both reacted well on accom-

FIG. 3.

L. V. = 6/9.

R. V. = 6/5.

CASE II.—H.W., 1909. 10 mm. white at 15 in.

modation-convergence. R.V.=6/5. L.V.=6/9. He gave a history of syphilis in 1887, and was under treatment for one to two years. Enquiry elicited a history of shooting pains in both legs. He showed slight ulnar anaesthesia and absence of knee jerks. His right optic disc was grey, but with a fair admixture of pink still present. The left optic disc showed a condition of advanced grey atrophy with the lamina cribrosa standing out clearly. The vessels were not altered in calibre. His fields showed definite peripheral limitation, much more marked in the left eye than in the right eye, but in both eyes with definite re-entrant angles.

In this case it was only the slight complaint about the vision of the left eye that led to an examination of the right eye and the discovery of a marked loss of field with commencing grey atrophy in that eye.

These two cases are typical examples of Uhthoff's two classes.

L.V. = Fingers,
20 mm. white at 15 in.

FIG. 4.

R.V. = 6/6.
10 mm., 3 mm., 1 mm. white at 15 in.

CASE III.—T.N., March 4, 1922.

Case III. T.N. (age 39). The next field I have to show illustrates the marked inequality which may sometimes be found between the affection of the two eyes. It is, further, of great interest because it goes against the commonly accepted belief that ophthalmoscopic changes always precede functional disturbance.

In this case, the right eye shows quite a definite limitation of the peripheral field, with good visual acuity and quite a normal-looking disc. The left eye showed a completely atrophic disc, of the usual tabetic type, and the visual field, only obtainable by using a 20 mm. test object, showed only three small islands of

vision, of which one was central, one nasal and the largest one temporal. Again, here it was only the condition of the left eye which called attention to the loss of field in the right eye.

Case IV. McM. (age 51) is one of the cases in which there is quite a good peripheral field for 10 mm. white, but a very marked variability in response to examination with 2 mm. white. A 10 mm. disc had to be used to get a colour field for red, and green could not be seen at all in any part of the field. It is of interest to note that, even allowing for the marked variability in the response for 2 mm. white, there was quite a fair correspondence between the shape of the red colour fields and the 2 mm. white fields.

FIG. 5.

CASE IV.—McM., March 25, 1922. 10 mm., 2 mm. white at 15 in.

Case V. F. (age 31). Probably a tabo-paretic, rather than a pure tabes, showed the same marked variability in response. His central vision was very poor in both eyes, and the field in his left eye had to be charted with a 40 mm. disc. In the left eye, examination with a 10 mm. disc showed an indefinite scotoma passing from the blind spot to the macula. In the right eye the field charted with a 10 mm. disc showed its greatest limitation in the upper temporal region. In the left eye the greatest loss is in the upper nasal region. Again, in the right eye examination with a 2 mm. disc shows a scotoma extending up and down from the blind spot and reaching to the fixation point. Colour fields could not be charted. I am afraid it would be stressing this case too far to take it as illustrative of a quadrantic homonymous hemianopia, but Nonne⁽²⁸⁾ describes a case of partial left-sided

FIG. 6.

L.V. = P.L. 40 mm. white at 15 in.
Paracentral scotoma dotted. 10 mm. white.

R.V. 1/60. 10 mm. white. Dotted area.
Paracentral scotoma. 2 mm. white.

CASE V.—F., March 26, 1922.

homonymous hemianopia in tabes, and Wilbrand and Saenger⁽⁴⁰⁾ illustrate a similar case of partial (mainly quadrantic) homonymous hemianopia.

Case VI. B.M. (age 43), seen in March, 1918. Complaining of loss of sight which had been going on for over a year. He was

FIG. 7.

L.V. = 6/18.

R.V. = 6/36.

CASE VI.—B.M., March, 1918. 10 mm. white at 15 in. Colours lost.

sent to me with the definite diagnosis of tabes already made. His pupils were quite inactive to light, but reacted with accommodation-convergence. His corrected vision in the right eye was 6/36, and in the left eye 6/18. He complained that he saw worse in bright light than in diffuse daylight. His discs were very atrophic, but the blood vessels were of quite good calibre. His visual fields showed such a marked bitemporal quadrantic loss that I determined to ascertain whether there might not be some pituitary disease complicating the tabes, but the radiograph showed a perfectly normal fossa. His subsequent history shows a steady but slow advance, and he is still able to manage a large farm, though his R.V.=1/60, and L.V.=5/60 only.

FIG. 8

Wilbrand and Saenger, "*Neurologie des Auges*," Vol. V, p. 553.

In connection with this case, I illustrate the fields of a case cited by Wilbrand and Saenger⁽⁴⁹⁾ (*Neur. des Auges*, Vol. V, p. 553) which shows an absolute bitemporal hemianopia in a tabetic.

Case VII. M.W. (female, age 52). I cite this case for the special reason that the marked nasal quadrantic loss and the atrophy of the disc led to her undergoing an operation for chronic glaucoma in the right eye. Apart from this, there is nothing especially noteworthy about the case.

Uhthoff⁽⁴⁵⁾, in his article in Graefe-Saemisch, Vol. XI, gives an example of a purely horizontal hemianopic loss in a case of tabes. In that case the upper part of the field in both eyes is hardly

FIG. 9.

CASE VII. M.W., March 20, 1922. 10 m.m. white at 15 in.

affected, but the lower field is completely lost. I am afraid I can cite no case of that kind, and I believe that there is a greater tendency for the upper part of the field to be more affected than the lower part. That can be seen from some of the fields already shown, and also more markedly in Case VIII.

Case VIII. M.C. (female, age 42). In this case, the right eye

FIG. 10.

Uhthoff, Graefe-Saemisch, *loc. cit.* p. 198.

LEFT.

RIGHT.

FIG. 11.

L.V.=6/12.
10 mm. and 2 mm. white at 15 in.

R.V. Amblyopic eye.
V.=6/60. 10 mm. and 2 mm. white

CASE VIII.—M.C., March 27, 1922.

had always been amblyopic, and though the disc was pale, it did not show the ordinary appearances of a tabetic atrophy. The vision was less than 6/60, and there was a general slight peripheral limitation. In the left eye, the ophthalmoscope showed a typical tabetic atrophy of the disc with bluish-white appearance and sharp-cut outline. L.V.=6/12, and the limitation of the field, both for

LEFT.

RIGHT.

FIG. 12.

Uthoff, Graefe-Saemisch, " Handbuch d. ges. Augenheilk," Vol. XI, p. 200

10 mm. and 2 mm. test objects was much more marked in the upper field than in the lower field.

I have never been lucky enough to see a case of absolute central scotoma, such as Uhthoff illustrates in his article in Graefe-Saemisch, Vol. XI, p. 200, and which I reproduce here. I thought I had found one some weeks ago in a case of very old standing tabes (with a history of 25 years), but though there was an undoubted central scotoma in both eyes, it was due to tobacco poisoning and not to tabes.

Conclusions

In reviewing these different fields, which can be regarded as fairly representative, it is possible to take up the standpoint that certain of them which agree best with the particular theory that we favour are the true tabetic fields, and that the others are due to complicating syphilitic manifestations, such as syphilitic meningitis or syphilitic myelitis. I am afraid that is too commonly the standpoint of writers on the subject. The other explanation, which seems to me the more probable one, is that the variability in the fields is a true exemplification of the variability in the pathological process; that in tabetic optic atrophy we have a process in which both parenchymatous tissue and interstitial tissue are attacked by the toxin. In some cases the parenchyma suffers more severely and at an earlier stage, and then there is presented the rapid diffuse loss of function involving the central acuity, the functional adaptation and the colour fields, but often leaving an almost full field to larger white objects. In other cases, and probably more frequently, the interstitial tissue suffers the most, and the clinical result is the circumscribed loss of field with actively functioning unattacked parenchyma away from the neighbourhood of the chronic interstitial inflammation.

We have seen that as regards tabes, there still exists a very definite dispute as to whether the syphilitic toxin acts directly on the nerve fibres or indirectly through the interstitial tissue, whether, in other words, the primary lesion is parenchymatous or interstitial.

As regards general paralysis, there seems to be more general agreement that there is both parenchymatous and interstitial action of the spirochaetes.

In optic atrophy, we again find from the pathological side the same controversy; but from the clinical side, in so far as the evidence of the visual fields can help, there certainly seem to be indications that both processes may be at work, and that the variability in the type of fields is due partly to variations in the proportions in which the parenchymatous and interstitial tissue suffer, and partly to variations in the site of the primary lesion.

Further, an unbiased examination of the fields will not support the old contention of the distal origin of the tabetic lesion, but shows that, in many cases at least, the lesion must be in the neighbourhood of the chiasma, and to that extent is in accord with Stargardt's contentions.

It will always be a matter of regret that pathological work so valuable as Stargardt's was not supported by visual fields of the cases which subsequently came under examination.

I have purposely omitted any mention of the Argyll Robertson pupil in the general discussion of tabes and general paralysis. The subject is already sufficiently complicated without entering into that very dark region.

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BUTYN: A SUBSTITUTE FOR COCAIN

BY

W. M. BEAUMONT

BATH

THE pre-eminence of cocain as a local anaesthetic is challenged by butyn. This synthetic product of coal-tar was introduced by the Abbott Laboratories of Chicago for surface anaesthesia, especially in ocular, nasal, pharyngeal and dental diseases. Its chemical formula is para-aminobenzoyl gamma di-n-butylamino-propanol sulphate.

The chemical research work was done by Profs. Roger Adams and Oliver Kamm, of the University of Illinois, and Dr. E. H. Volveiller, of the Abbott Laboratories.

Butyn has been reported on by a committee on local anaesthesia appointed by the section of Ophthalmology of the American Medical Association. The members were:—Albert E. Bulson, Jun., Fort Wayne (Chairman); Wm. Zentmayer, Philadelphia; Roger S. Thomson, New York City; H. Maxwell Langdon, Philadelphia; Harry S. Gradle, Chicago.

Their report* shows that one minute after one instillation of 2 per cent. solution surface anaesthesia is sufficient to permit the removal of foreign bodies from the cornea without discomfort. Anaesthesia lasts from 15 to 20 minutes, or it may be 30 minutes. The depth of anaesthesia is not sufficient by one instillation for operations or for removal of deeply imbedded foreign bodies in the cornea, but it is sufficient for the application of astringents and

* *Journal of the American Medical Association*, February 4, 1922, p. 343.