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A Further Contribution

To the clinic and pathology of presbyophrenic dementia — the paper in which Oskar Fischer answered his critics, counted forty ordinary brains, and found the threadlets to be protein

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Oskar Fischer

German Psychiatric University Clinic, Prague · 1912

Zeitschrift für die gesamte Neurologie und Psychiatrie, Originalien XII, 99–134, with one plate

A new English translation

Benjamin Aaron Gustafsson

AdultCognitiveDisease.com · September 2026

Two cases out of two hundred and seventy-five did not fit. Fischer kept them, and reasoned from them that a lesion must exist for a time before symptoms appear, that a certain degree of it is required, and — in a parenthesis — that the degree required probably varies between individuals. Then he went to the general hospital, took forty brains of the ordinary old, and counted.

The translation is complete and unabridged; the pagination of the original is marked throughout.

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The Translation

I. Anatomical Part.

Sphaerotrichia cerebri multiplex

Part I — The Anatomical Part (original pages 371–392)

Translator's Note

This is a complete new English translation of the opening and the whole of the anatomical part of Oskar Fischer's *Die presbyophrone Demenz, deren anatomische Grundlage und klinische Abgrenzung*, published in 1910 in the *Zeitschrift für die gesamte Neurologie und Psychiatrie* (Originalien, vol. III), pages 371–471, with 13 plates. The paper carries the line (*Eingegangen am 6. August 1910*) — received 6 August 1910.

Scope. This file covers original pages **371 to 392**: the introduction, and Part I, *Anatomischer Teil*, entire — through Fischer's five numbered conclusions, his eight-stage table, and his naming of *Sphaerotrichia cerebri multiplex*. It stops at the head of Part II, *Klinischer Teil*, which runs from page 392 to page 468 and consists chiefly of 111 case histories; that part is to be translated separately.

The translation of what it covers is complete. Nothing within pages 371–392 is abridged or summarised. Fischer's paragraphing is preserved. His emphasis — set in the original by letter-spacing — is rendered here in bold. The pagination of the original is marked in the margin as **[371]**, **[372]** and so on, at the point where the original page turns. Fischer's footnotes appear at the foot of their own page, marked as he marked them. Anything supplied by the translator appears in square brackets and is marked *Tr*.

Terminology. The policy is that of the 1912 and 1907 translations in this corpus: keep Fischer's term, do not modernise it. *Drusen* is rendered **drusen**, not "plaques"; *Keulen* and *Kolben* are **clubs** and **bulbs**; *Achsenzylinder* is **axis cylinders**, with *axons* given at first occurrence and his own word kept thereafter. Note that between 1907 and this monograph Fischer has replaced his own earlier word: the lesion he called *Plaques* in 1907 is called *Drusen* throughout here.

Fischer's term	Rendered here as	Modern equivalent
<i>Drusen</i>	drusen	senile (neuritic) plaques
<i>Sternchen, Sterndrusen</i>	little stars, star-drusen	the earliest fibrillar deposit
<i>Morgenstern(form)</i>	morning star (form)	spiked-mace form of the core
<i>Fädchen, Fäserchen</i>	threadlets, fine threads	the fibrillar material of the deposit
<i>Zipfel</i>	plaits	the radiating fibrils of the corona
<i>Hof</i>	halo	plaque corona
<i>Randring</i>	marginal ring	the dense outer rim
<i>Rädchen(bildung)</i>	little wheel (formation)	the completed cored plaque

Fischer's term	Rendered here as	Modern equivalent
<i>dickfaseriger Knäuel</i>	coarse-fibred ball	the mature dense-fibred deposit
<i>Keulen, Kolben</i>	clubs, bulbs	dystrophic neurites
<i>Achsenzylinder</i>	axis cylinders	axons
<i>grobfasrige Fibrillenwucherung</i>	coarse-fibred fibrillary proliferation	neurofibrillary tangles
<i>Infiltrate, Infiltrationsstadium</i>	infiltrates, infiltrative stage	diffuse/infiltrative deposits
<i>Pelzbesatz</i>	fur-trimming	amyloid cuffing of vessels
<i>Schollen</i>	clods	granular degenerative masses
<i>Sphaerotrichia cerebri multiplex</i>	Sphaerotrichia cerebri multiplex	the plaque process as a whole

Five passages deserve to be found rather than stumbled upon.

The first is on original page **373**, and it defines the earliest form: between fibrils that are "*sonst ganz intakten*" — otherwise entirely intact — there are strewn tiny stars of the finest threads, about 2 μ across, and "*Zugrunde gegangene Elemente oder in Destruktion befindliche Gewebsbestandteile sieht man in der nächsten Nähe der Sternchen **nie***": perished elements, or tissue components in the process of destruction, are **never** seen in the closest vicinity of the little stars. Fischer repeats the point for the next form up on the same page. His initial object is a free-lying deposit in undamaged tissue.

The second is on page **381**, and it is the sentence on which any argument about Fischer's staging turns:

*"Die kolbigen Wucherungen der Achsenzylinder kommen nur in etwa 50% der Fälle vor; dabei auch nur um die größeren Drusen; am häufigsten finden sie sich um das Stadium V, dann um Stadium IV, seltener um Stadium III, **nie in der Nähe der Stadien I und II**, ebenso auch **nie** um Stadium VIII."*

The bulbous proliferations of the axis cylinders occur in only about 50% of cases; and then only around the larger drusen; most frequently around stage V, then stage IV, more rarely stage III, **never in the vicinity of stages I and II**, and likewise **never** around stage VIII. Both negatives are Fischer's. A widely circulated machine translation of this monograph renders *in der Nähe* as "in the north" and drops the second *nie* altogether, which reverses the sense; the German is quoted above so that the point cannot turn on anyone's rendering of it.

The third is on page **383**: "*Einen engeren Zusammenhang der Neuroglia mit den Drusen konnte ich nirgendwo erblicken.*" Glia were frequently proliferated around the **large, older** drusen, especially those bearing many clubs, and glial fibres sometimes penetrate into them — "*aber um die kleinen und*

kleinsten konnte eine Gliavermehrung nicht nachgewiesen werden": but around the small and the smallest, no increase of glia could be demonstrated. The deposit precedes the glial response, on Fischer's own staining, and he says so in order to refute Redlich.

The fourth is on pages **386–387**, the colour clock: the star form, as the youngest formation, always stains only black, whereas the morning stars and the plaits very often take a brownish tint — from which Fischer infers that the threadlets stain black in the youngest stages and brown in the later ones, and then uses that to argue that the **marginal ring is the youngest part** of a mature druse. It is an internal dating instrument built out of a staining artefact, and it is the most original thing in the monograph.

The fifth is on pages **391–392**: the five numbered conclusions and the eight-stage table, with Fischer's own ordering — **stages I to V are a developmental series, I the youngest and V the oldest**; VI and VII belong with the oldest; and VIII he regards as a *younger* process again, against whose advance the tissue could muster less resistance. Stage VIII is therefore not a late fate in his scheme. It is a fast one.

The Translation

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By **Oskar Fischer**.

(From the German Psychiatric Clinic in Prague).

With 13 plates.

(Received on 6 August 1910.)

In a preliminary communication I published in the year 1907 a peculiar, enigmatic alteration of the cerebral cortex, appreciated adequately neither anatomically nor clinically, which was found in a number of brains of the senile-demented and which I at that time designated as "druse-like necrosis"; in all those cases certain traits of presbyophrenia could be demonstrated clinically, whereas in the simply senile-demented the alteration was not found. A year later I communicated further findings at the annual meeting of the German Association for Psychiatry, was able to confirm their clinical significance, and drew attention at that time also to the morphological similarity of the drusen to bacterial growths. Yet a detailed publication on this subject I have until now avoided; for I was concerned in the first place with the clinical significance of this finding, and for that a larger material had first to be collected and worked through. Since my material has now grown to such an extent that its size leads to more than approximate conclusions, I proceed only now to a more detailed publication. In the meantime, however, several authors have already occupied themselves with this subject and have judged my results of that time in a more or less dismissive manner. Against all these works I have the reproach to make that they rest on too small a material, as regards both the histological working-through and the clinical evaluation of the findings. For that reason I will first describe my findings and only then pass over to the discussion of the relevant works already published.

As is evident from what has just been said, the description of the subject has to move in two directions: first, the pathological-anatomical relations must be exactly established and an explanation of them attempted; second, it must be ascertained

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whether one can trace any clinical symptoms back to this cerebral disease.

In my first communication I did indeed describe and discuss a part of the material now collected; but the material of that time was still small, the findings still showed many a gap, and for

that reason — but especially in order not to disturb the unity of the description — I will not take the details of the earlier communications into account, but will describe matters here in summary, as if nothing had yet been reported by me.

I. Anatomical Part.

The alteration of the brain that comes into consideration is best demonstrated with the method of Bielschowsky; with most of the ordinary and hitherto customary histological staining procedures the elements in question do not stain at all, or so indistinctly that they can very easily be overlooked; therein lies also the reason why this so frequent alteration became known only so late.

On the technique of Bielschowsky's method I should like to remark here that brain sections stain best when their thickness amounts to about 20 μ ; with thinner sections the staining leaves much to be desired, whereas in 20 μ sections from the same material disproportionately more fibres stain out, which holds also for the ganglion cells and the alterations that come into consideration here. One can, however, also stain thinner sections if one slides 2–3 sections one on top of another in the ammoniacal silver bath, lays these superimposed sections on the needle just as if one had a single thicker section before one, draws them quickly through the water and transfers them into formol.

The following description of the histological findings refers throughout, where nothing else is said, to preparations prepared after Bielschowsky's method. With the large material that stands at my disposal, a more exact discussion of the individual histological findings would take up too much time and space without any essential benefit resulting from it; for that reason I will describe the alterations found summarily, so far as that goes, and will proceed in such a way that one passes from the smallest traces still just visible to the coarsest alterations of this kind.

The alteration of the smallest degree is found depicted in Fig. 1 at *a* and 37 (Plates VII and XVI). **Between the otherwise entirely intact fibrils there are strewn quite small little stars, which consist of the finest black-stained threads lying together**

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in irregular star form and recall the smallest crystal stars. These smallest little stars have mostly a diameter of about 2 μ ; they lie now singly, now in groups together, and then very frequently confluence, so that one has larger convolutes of the threadlets before one. If smaller groups confluence, one still recognises the individual stars quite well in the conglomerate (Fig. 1b, Plate VII); in the somewhat larger convolutes (Fig. 1c, Plate VII), out of which the threadlets project in longer tangled strands, this is only indicated here and there. **Perished elements, or tissue components in the process of destruction, one sees in the closest vicinity of the little stars never;** they lie mostly in the not essentially altered tangle of fibres of the cortex, whereby the axis cylinders [axons — *Tr.*] run around the larger little stars always, around the small ones very

frequently, in an arc — a behaviour which can be regarded only as **the expression of a displacement of the nervous tissue by the little stars**, which I should like here also to designate for short as drusen.

The next larger forms, which on the ground of their regular construction possess a still greater similarity to crystal druses, are represented in Figs. 2 and 3 (Plate VII). In a small niche of the tissue there lie morning-star-like formations whose size varies between 8 and 30 μ ; particularly to be emphasised is a peculiar behaviour of theirs on silver impregnation: a part of these drusen stains, namely, like the previous ones, deep black, but most of them take on a brown-violet to reddish-yellow tincture, whereby they stand out very distinctly from the entirely black-stained nervous meshwork of the cortex.[1] In these drusen the individual fine threads are strictly radially arranged, run quite straight and are also mostly of equal length, so that the druse looks as if evenly cropped; only exceptionally do individual threadlets project somewhat beyond the others. On the constitution of the centre nothing certain can be said, given the smallness of the formations and the thickness of our sections.

These morning-star-like drusen too always lie free in the tissue and displace it, as is to be seen from the bending-out of the neighbouring axis cylinders. **Never can any degenerating or otherwise perishing nervous constituents be demonstrated in the closest vicinity.** Fig. 4 (Plate VII) shows a somewhat larger druse. The fine threads are stained black, joined together into a morning-star-like formation; the tissue is retracted all around, so that a free halo arises about it, and at some places there project from the periphery of the morning star fine strands composed of tangled, interwoven

[1] On the accompanying plates this "metachromatic" staining of the drusen is, for the sake of simplicity, represented in a single shade only.

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threadlets, which recall the formations of Fig. 1c. In Fig. 5 (Plate VII) one sees a druse which possesses some similarity with the last-mentioned formation, only that the threadlets have taken on a brownish tone, the plaits are somewhat more massive and longer, as indeed the whole druse is also somewhat larger than in the previous figure. In this picture too one sees the displacement of the arcuately deviating axis cylinders. To these two last-described drusen there is similar in many respects Fig. 6 (Plate VIII), which — be it remarked in passing — is drawn at a somewhat stronger magnification. Out of the distinctly morning-star-like central core there run reddish-stained strands which unite, at the margin of the nerve tissue and distinguished from it by their colour, into a half-ring. In Fig. 7 (Plate VIII) — likewise drawn at stronger magnification — the central morning star is only indicated; the radially running plaits are much longer and spread out in places in fan form; the whole formation is bordered by a ring formed of tangled fine threads, which consists of the same fine threads, which here, however, run quite tangled and form a dense meshwork which in

places hangs together with the plaits. Fig. 8 (Plate VIII) shows a formation in which the fine threads are stained black like the fibrils of the surroundings; one sees a "central morning star" from which radial plaits go out; the neighbouring nervous tissue is retracted and is bounded by a ring formed of dense tangled fine threads, which on superficial examination looks as if the fibrils of the surroundings had condensed. On closer inspection, however, especially at stronger magnification (immersion with strong eyepieces), one recognises that this ring consists of the same fine threads of which the central morning star and the plaits are composed, only with the difference that the fine threads in the ring interweave quite tangledly and irregularly. This is moreover proved also by Figs. 6 and 7 (Plate VIII), in which the whole druse together with the peripheral wreath has taken on a different colour from the axis cylinders.

A remarkable staining shows itself in Fig. 10 (Plate VIII); here the centre of the druse and the fibre-plaits are brown, the peripheral ring by contrast stained black; the brown plaits pass over into the fibre-tangle of the black-stained marginal ring, whereby at some places one sees the intermixture of the brown, more straight-running fine threads with the finer and irregularly tangled, intertwined black fine threads. Somewhat more distinctly, because drawn at stronger magnification, this behaviour shows itself in Fig. 11 (Plate VIII). One sees here very beautifully radiating broad plaits which exhibit fan and flame form, and a ring consisting of dense black fine

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threads, in which here and there the smallest convolutes of brown-stained fine threads are strewn, which no doubt derive from the brown plaits.

Here too the alteration of the tissue documents itself in the arcuately deviating axis cylinders; in certain circumstances the tissue is somewhat more retracted than was to be seen in the drawings so far. Such a behaviour is shown by Fig. 12 (Plate IX). The druse resembles in general those described above, only that here the space arising through retraction is larger and encloses grey-stained, slightly granulated, otherwise structureless and clod-like arranged masses. Among these masses there is found (upper left) an elongated perishing cell nucleus, and through the middle there runs an axis cylinder — **both otherwise a rare occurrence.**

To the previous figure there is similar in many respects Fig. 13 (Plate IX). Here too there is a central morning star out of which more or less long tufts spring; the ring of threadlets is fairly far removed from the centre, so that a large halo arises which is traversed by the strands; between these there now lie small star-like formations consisting of the same threadlets, and between them reddish-stained, slightly granulated clods. In places individual clods are bordered by the threadlets. In Fig. 14 (Plate IX) there is likewise a distinctly morning-star-like composed central core, which has taken on a red-brown staining and out of which shorter tufts, here stained quite black, step forth. The halo lying within the fairly thick and dense marginal ring is filled with reddish-grey stained, sharply demarcated clods which show distinct granulation; at some places one gains the impression

as though the skeins of threadlets passed over into the granulated masses. At \ there lies a nucleus-like formation which no doubt corresponds to a perishing cell nucleus. A formation related in many respects to Fig. 13 is shown by Fig. 15 (Plate IX). At weak magnification the druse drawn here looks as if it consisted of crumbly masses of disintegration. With immersion one sees that the crumbs consist of nothing but the finest threadlets, which are in part arranged star-like and in places form small tangled plaits; in the upper left corner one sees an indication of halo formation around a small central tuft of fibres; the margin of the druse is formed by a ring which consists of the finest tangled, intertwined threadlets and which in places also contains a mass of the finest granules. Between the convolutes of threadlets one sees slightly granulated, grey-stained masses. To the right, at a*, outside the druse, one sees quite isolated and free in the tissue a quite small star-like constructed druse.

The similarity of Fig. 13 (Plate IX) and Fig. 15 (Plate IX) lies in this, that in both the slightly granulated clods are found,

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only that the colour is different and that in Fig. 15 the bundles of fibres situated between the clods are smaller and more numerous.

A construction deviating from the previous drusen is shown by Fig. 16 (Plate X). In the tissue pushed to the side there sits a dense convolute of thicker, brown-red stained threads which, in part closed together into broader stripes, interweave in such a way that the formation acquires the appearance of basketwork.

In contrast to the earlier formations, the nervous tissue lies quite closely against the convolute of fibres, and at some places there show themselves also interweavings of the threadlets with the nerve fibrils. **Never, however, is even a trace of a transition of the nervous tissue into the masses of threadlets to be seen.**

All the formations described so far had among other things this in common, that they had a rounded form and set themselves off quite sharply from the surrounding tissue. The same fine thready masses occur, however, in yet another formation, represented in Fig. 17 (Plate X). Here one sees at weaker magnification a peculiar patchy, black staining, as if the tissue had stained in patches more densely than elsewhere; immersion shows that this darker staining is conditioned by a dense, thready-granular meshwork which sits in the tissue without showing sharp boundaries; at these places the axis cylinders appear in the Bielschowsky preparation to be, with few exceptions, completely absent; in the surroundings of the "dark patches" they are sparser than elsewhere and are not stained so darkly as in the wider surroundings. With very strong stopping-down of the diaphragm one sees, however, that at least a part of the axis cylinders still exists, but has taken on no stain.

In places these thready-granular masses have now confluesced over larger stretches of the cerebral cortex (Fig. 18, Plate X); here, over areas which are sometimes larger than the visual field of

an immersion lens, the axis cylinders and the fibrillar network have completely disappeared, and their place is taken by the masses mentioned, which sometimes also exhibit fairly sharp boundaries. Of the nervous tissue there persist in them only the ganglion cells, which are very severely shrunk and have lost the greatest part of their processes; further there lie in them here and there darkly stained cell nuclei, which no doubt belong to the glia.

A more exact comparison of these masses of threadlets with the drusen shows that they consist morphologically of the same fine threads which form the outer ring of the larger drusen and its transition into the fibre-plaits.

On examining most of the figures brought forward so far, it is striking **that the drusen are always found in the neighbourhood of some vessel**

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or other; such a coincidence could indeed, given the rich vascular branching of the cerebral cortex, also be accidental, without an inner connection between drusen and vessels having to be assumed; yet the coincidence, and especially investigated on serial sections, is so regular that chance becomes improbable. There are, however, isolated cases in which the close relations of the drusen to the vessels come to light quite unobjectionably. Fig. 19 (Plate X) shows these relations. Here the spherical drusen always lie against some vessel or ensheath it, mostly in such a way that they are localised at some bend of the vessel or between the branches of a bifurcation; in the illustration two drusen are indeed also drawn in which appear to stand in no relation to a vessel, but serial sections show that these too lie against a vessel which, however, happens to be just below or above the plane of section.

In several cases the close attachment of the drusen to the vessels shows itself in a manner which Fig. 20 (Plate XI) demonstrates. The drusen consist here of the thicker, curved, reddish-stained fibres which resemble those depicted in Fig. 16 (Plate X); in places the staining of the fibres is indistinct and as if washed out; the drusen sit throughout against the vessels, and there where, as in the figure, a larger vessel happens to be struck lengthwise, one sees the drusen lying hemispherically against the vessel; they sit throughout **outside the adventitia** of the vessel, displace the tissue, but always send a few runners into the somewhat retracted perivascular space. **In this manner (demonstrable on serial sections) whole little vascular trees are often beset with drusen.**

A quite particularly enigmatic relation of the drusen to vessels showed itself in two other cases; the same is represented in Figs. 21–24 (Plate XI). In Fig. 21 (Plate XI) one sees a peculiarly thickened vessel; one recognises the vessel lumen with an endothelial cell; the left wall of the vessel is quite thin, has a dark-brown staining and broadens eccentrically over to the right side; it there acquires a streaky appearance and splits up towards the outer periphery into the finest threadlets

arranged in tufts. The nervous tissue, represented by the deep-black-stained fibril net, is lifted off from the vessel by a somewhat widened perivascular space; the margin of the nervous tissue is interwoven by a dense network consisting of brown fine threads, which at *b* exhibits a morning-star-like formation and at one place hangs together, by means of a plait consisting of the same fine threads, with the fringe of fibres surrounding the vessel. A more exact examination, especially at strong magnification, shows that

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all the brown fine threads are identical, only differently disposed and interwoven in appearance.

A similar behaviour is shown by Fig. 22 (Plate XI), which represents two little vessels of the same case; these little vessels have laid about them a kind of fur-trimming which consists of the same fine brown threads; their intima appears stained in the form of fine black threadlets and lamellae; here and there (but not precisely in the drawing) one still sees endothelial cells. The lumen of the little vessels is patent and contains, as proof of patency, red blood corpuscles in places. On the larger vessels this fur-trimming shows itself peculiarly modified (Fig. 23, Plate XI); one notices on the cross-section of the vessel, as innermost lining, a layer of swollen endothelial cells and a quantity of black granules, which are no doubt to be regarded as their inclusions; next there follows a light, yellowish-stained layer of unequal thickness, which possesses a somewhat wavy dark margin interrupted below. Outside that is a quite lightly stained layer consisting of the finest, only slightly brownish-stained fine threads, and this again is surrounded by an outer, more darkly stained layer contoured on the inside by a still darker stripe. This outermost layer too consists of fine threads which, although at the inner boundary they stand out little distinctly, project outwards, more darkly stained, in spine form. The fine threads are strictly radially arranged, so that on oblique or longitudinal sections of the vessel they are struck obliquely or transversely; the same is also to be seen at the upper pole of the somewhat obliquely running cross-section of our illustration. In similar manner, at individual places, almost the entire vessels of one or several vascular districts are altered. Peculiar do these vascular alterations look on staining with haematoxylin-eosin or after van Gieson. Here the vessel appears surrounded by a hyaline-looking mass; only at strong magnification does one see — with this staining too — that the hyaline mass can be resolved, as with the silver staining, into the finest fine threads, and likewise one sees, although not so distinctly, the differentiation into individual layers.

In places one finds in these brains vessels of the kind represented in Fig. 24 (Plate XI). These vessels are enclosed by brownish-stained masses which have in part a crumbly structure, but in places still end outwards in the finest jagged points and thereby also exhibit morning-star-like formations; the lumen of the vessels has in places disappeared, the intima is stained black and has fallen apart into the finest fragments and granules; in these vessels no endothelial cells are stainable, and the lumen appears also to be no longer patent.

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In what relation, then, do these druse-like formations stand to the surrounding tissue? First of all it is to be emphasised that the drusen **push the nervous tissue away**, as is to be seen in most of the illustrations described above and in Fig. 26 (Plate XII). The longer axis cylinders which run in the immediate surroundings of the drusen bend in a more or less pronounced arc around the drusen and are mostly not further altered; sometimes, however, they exhibit in the vicinity of the drusen spindle-shaped swellings, which are now barely indicated, now may also show larger dimensions. These swellings are represented in Figs. 25–32 (Plates XII to XIV); they are found **not in all, but only in a part of the cases**, and are always placed wreath-like around the druse, in such a way that the thin neck stands inwards, the bulbous end is directed outwards and oversteps the area of the druse. The bulbs are of various size, the smallest $\frac{1}{2}$ –2 μ thick and about 6 μ long; yet one finds also specimens of 4–5 μ thickness and a length of up to 20 μ . In a large number of these bulbs one can demonstrate **a direct connection of the thready, centrally directed end with the axis cylinders of the surroundings**, which can be found the more frequently the thicker the sections one investigates. On these, for self-evident reasons, the axis cylinders can also be followed over greater stretches, so that, apart from other circumstances, a confusion with other elements can be excluded. Since the thready ends of the clubs are directed towards the interior of the druse, the axis cylinders must bend into the margin of the druse as well. This behaviour is shown very distinctly by Fig. 25 (Plate XII). Fibril *c* winds, after multiple vertical bendings not representable in the drawing, and after it had at one place undergone a slight thickening, into the druse, bends off in a sharp arc in order to pass over into a large club and therewith to end. Another axis cylinder likewise runs, after multiple windings, to the margin of the druse and ends here in a cloverleaf-like tripartition with three clubs (at *b*). **Frequently it shows itself that the clubs, where one can follow them and their axis cylinders over longer stretches, do not sit as terminal clubs of an axis cylinder, but present themselves as a lateral outgrowth.** Such an axis cylinder has either only one such lateral outgrowth (Plate XIII, Fig. 30b) or several (Plates XII, XIII, Figs. 28, 29, 30c, d, g). The stalk is triangularly broadened at the point of attachment and ends either with a single club (Plates XII, XIII, Figs. 28, 30b, g), or else it divides repeatedly in order to pass over into several clubs of different size and frequently also of differently tortuous shape. Thereby mistletoe-like formations frequently come about (Plates XII, XIII, XIV, Figs. 25, 28,

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29, 30, 31b). Particularly instructive and unobjectionable is the relation of the clubs to the axis cylinder shown in Fig. 28 (Plate XII), which represents a tangential section of a druse; therein an axis cylinder which runs over the druse and comes to lie precisely in its marginal portion is struck in its whole length and shows several outgrowths. Besides the more regular club forms described so far, there also frequently occur various irregular shapes of the outgrowths; they are elongated, often band-shaped, provided at the end with a small knob, have a shorter or longer stalk, go off singly or

multiply from the axis cylinder; they run straight or in several planes, often in quite tangled windings difficult to draw; their form is often quite irregular and band-like intertwined — in short, formations of an enormous multiplicity which Figs. 30a, 31a, b, d (Plates XIII, XIV) can render only approximately. The clubs, especially the smaller ones, are in most drusen placed radially at the margin, and sometimes so densely that they form a dark wreath around the drusen which springs at once to the eye (Plates XII, XIV, Figs. 25, 27, 29, 32). The greatest part of the clubs is opaque, stained black; a smaller part, especially in the somewhat more weakly stained preparations, shows a lighter grey staining (Plates XII–XIV, Figs. 25, 29, 30, 31) and contains within a dense, inextricable net. If one examines these clubs at very strong magnifications, one sees that the stalk is filled with more parallel-running, somewhat wavy, finest fine threads, which then become tangled towards the bulbous end. In Fig. 31a (Plate XIV) a club is represented out of whose entirely black-stained stalk several fibrils spring, which end in isolation in the only grey-stained club. Fig. 31b (Plate XIV) shows clubs which contain the fibrillar net only in the marginal portions, whereas the centre is only diffusely grey-stained. Cross-sections of such clubs yield, at very strong magnification, a picture like Fig. 33a (Plate XIV): at the margin a tangled meshwork of transversely struck fine threads, whereas the middle appears grey or reddish stained. In the case of smaller clubs the margin is frequently represented only by a quite narrow fringe of fibrils and the centre remains unstained (Plate XIV, Fig. 31c). The axis cylinders running in the immediate surroundings of the drusen are, as has already been mentioned, pushed aside throughout, which is most distinctly to be seen on the radial fibres running in bundles. The irregularly and transversely running fibres of the cortex apparently terminate at the margin of the drusen, but in reality they wind back and forth repeatedly and frequently then end in a club. **The peripheral zone of the drusen accordingly frequently contains a dense net of fibrils; the centre, however, is mostly free of axis cylinders and nerve**

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fibres, only exceptionally do isolated axis cylinders still run through (Plates IX, XII, Figs. 12, 25). Further, very many axis cylinders show in the vicinity of the drusen spindle-shaped swellings. Either these are only quite slight, sometimes barely perceptible thickenings (Plate XII, Fig. 26), or they are more massive and of considerable length (Plate VIII, Figs. 6, 27 and 29), or they are of a magnitude equalling the size of the ganglion cells (Plate XII, Fig. 25). An axis cylinder has either a single or several swellings (Plate XII, Fig. 29), and sometimes clubs also sit upon such a spindle-shaped swollen axis cylinder (Plates XII, XIII, Figs. 29, 30b). As a very rare occurrence one sees a splitting of an axis cylinder, which Fig. 30d (Plate XIII) represents; yet it is after all also possible that in this case the ends of the two split threads belong to cut-off clubs.

The bulbous proliferations of the axis cylinders occur in only about 50% of the cases; and then only around the larger drusen; most frequently they are found around stage V, then around stage IV, more rarely around stage III, NEVER IN THE

VICINITY OF STAGES I AND II, and likewise NEVER around stage VIII. (See the division of the stages on page 392.)

Why in individual cases the clubs are found and in others not has not become clear; in the histological behaviour no other difference was perceptible.

A peculiar alteration of the axis cylinders shows itself further in those portions of the cortex which are altered in the form represented in Fig. 17 (Plate X). There, where the thready masses infiltrate the tissue without distinct demarcation, only the thicker of the axis cylinders passing through are stained, whereas the greatest majority of them are unstained but still distinctly visible at stronger stopping-down of the diaphragm.

The ganglion cells are altered in all cases; one finds there indeed all forms of alteration of the ganglion cells, from the lighter to the most severe. The cells show indistinct fibrils; the fibrils stick together in the processes, so that the latter are stained quite black; further, the cell acquires a granular appearance, contains only few fibrils, mostly in the vicinity of the processes; or else no distinctly stained fibril at all is any longer to be seen. In severe cell lesion the silver has been deposited in the cell in irregular, clod-like masses, the cell is irregularly shrunken, has forfeited its processes, and so on. Alongside this one also sees the most various alterations of the cell nucleus and of the nucleolus. This disease of the ganglion cells is not equally severe in all regions of the brain; very severe alterations are found in those sections of the cortex which are most densely permeated by drusen, **especially when it is a matter of the early stages of these.** Thereby

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it is to be emphasised that the uppermost cell layers are always the most severely affected, and that the alteration is not restricted to the cells lying closest to the drusen, but is more diffuse.

The very strongest alterations of the cells are to be met with in those brains whose cortex is diffusely infiltrated by the thready masses, and indeed those ganglion cells are most strongly affected which are directly surrounded by the masses; these cells make the impression of perishing structures (Plate X, Fig. 18).

A peculiar, quite unclear alteration of the cells shows itself in a small number of cases; the same has been known to me for a longer time and was recently described in detail by Perusini. The alteration occurs — which I must emphasise as against Perusini — **only in a small number of my cases**, and indeed always only in those in which elsewhere the ganglion cells generally exhibit very severe destruction and mostly complete disappearance of the fibrils. There one then finds the cells, whose body has sometimes still retained the ganglion-cell form but is frequently already very strongly deformed, filled out with peculiar thick, intensely black fibres which encircle the cell nucleus in wavy, screw-shaped, spindle-form or quite irregularly running courses, end in the cell itself, or else also step out through a cell process (Plate XV, Fig. 34). The fibrils are very thick and

lumpy; sometimes, however, one finds formations of this kind in which quite fine, parallel-running fibrils are to be found in similar arrangement to that in the first-named cells, from which one can conclude that the coarser fibrils are only conglomerates of finer fibrils (Plate XV, Fig. 34a). Some of these formations are completely nucleus-less and no longer look like cells at all, but like free proliferations of fibrils; Fig. 35 (Plate XV) represents such a proliferation of fibrils of unusual form; it is possible that this too derives from a cell of that kind, only the formation is much too large for that; one would have to assume that the fibrils had then proliferated further outside the cell. A formation of this kind has come before my eyes only once, so that eventual transitional pictures are so far lacking. Likewise quite peculiar is Fig. 36 (Plate XV), which comes from the molecular layer of the cerebellum; it shows a kind of fibrillar arrangement not otherwise seen, at whose centre a nucleus-like formation lies; this convolute of fibrils may also belong in the same category. **This "coarse-fibred fibrillary proliferation of the ganglion cells," as I will call this formation for short, I found among 58 cases only 10 times, thus in 17%.**

In all cases there was found a proliferation both of the cellular and of the fibrous neuroglia, in the manner usual in atrophic

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processes. **A closer connection of the neuroglia with the drusen I could nowhere perceive**, which I should like to emphasise as against some statements from the literature to be discussed later. It is true that **in the surroundings of the large, older drusen, especially of those which also contained many clubs, the glia was frequently proliferated**, mostly in the form of the large multipolar glial cells, and the glial fibres sometimes penetrate into the drusen as well, **but around the small and the smallest no increase of glia could be demonstrated.**

The blood vessels showed, besides the fringe of threadlets already described above, further alterations such as one otherwise knows in senile and atrophying brains. These will not be gone into further here.

The descriptions so far refer throughout to preparations which were prepared after the method of Bielschowsky, because only with that did the demonstration of the structures in question succeed most completely. Besides this, however, most of the customary staining methods were also employed.

The smallest of the drusen and the infiltrating masses of threadlets I could so far demonstrate only with the silver aldehyde method. The larger drusen, by contrast, stained with most basic dyes.

After paraffin embedding one can stain them in a more or less distinct manner with almost all basic aniline dyes, best with carbol fuchsin or methyl violet with subsequent alcohol differentiation.

This staining is best suited for the medium-sized drusen. In it the central morning-star-like core stains very distinctly; one sees the radial construction similarly as in the silver preparation; by contrast the halo and the plaits are indeed also stained and demarcable as a whole from the nerve tissue, yet the thready construction cannot be recognised distinctly enough there.

Nissl staining, especially after celloidin embedding, leaves the drusen unstained.

With haematoxylin-eosin the larger drusen can likewise be demonstrated quite distinctly. The centre then stains (Plate XVI, Fig. 38) in a bluish-dark colour, the star-like, thready construction is distinctly recognisable, the marginal portions are stained in the same tone as the nerve tissue and are distinguished only by their structure. Something similar is also seen with staining after van Gieson.

All our specific stainings yielded a negative result: thus the stains for fibrin, mucin, elastin, fat, calcium, iron, and all specific bacterial stains; with all of them the drusen, or the masses of threadlets composing them, remained quite unstained.

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With Weigert's myelin-sheath staining the drusen lying in the more myelin-rich lower portion of the cortex are very distinctly to be seen as round gaps in the tissue, around which the myelin sheaths deviate arcuately (Plate XVII, Figs. 43, 44). Some of the larger drusen take on, with this staining, a somewhat darker tone than the otherwise yellowish ground tone, and thereby stand out fairly sharply and distinctly.

For weak magnification — that is, for survey preparations — the large drusen can be demonstrated very beautifully if one counterstains Weigert preparations differentiated after Pal with methylene blue or carmalum. Then the ground tissue stains greenish or lightly yellowish-red, and the drusen stand out in a more or less dark-blue or dark-red-brown tincture.

For the demonstration of the finer structure of the drusen, however, the method is not suited, but only for the survey preparations and for the larger of the drusen.

Peculiar is it that **Cajal's method stains the drusen only very indistinctly, whereas the clubs are stained deep black exactly like the axis cylinders.** By contrast, Bielschowsky's method with pyridine, in which the neuroglia remains unstained, stains the drusen exactly as does the ordinary method. Weigert's glial staining method leaves the drusen completely unstained. The clubs too remain quite unstained, even when one otherwise achieved a faultless staining-out of the glial fibres. As regards the clubs, I will mention further that they can very frequently also be demonstrated with the nuclear staining methods.

In the affected brains the drusen are present in the cerebral cortex in varying density and distribution. There are brains in which the drusen are so sparsely represented that

one must often scan many visual fields before one discovers a druse; from this so rare occurrence of the affection there are all gradations up to so dense a distribution of the drusen that there are up to 25 drusen per mm² (Plate XVII, Fig. 41); it is clear that the last case signifies a quite high-grade damaging of the brain. Thereby, however, the drusen are not always equally strongly represented in the individual regions of the brain.

Among the 58 brains so far investigated in which the drusen were present, the drusen were found equally strongly distributed in all cortical portions in only 15 cases, thus in 33%; in the majority of the cases, however, there are differences. In 29 cases, thus 50%, the frontal region is always much more strongly affected than the posterior portions; indeed in 5 cases the alteration is present only in the frontal lobe, whereas it is otherwise absent in the brain. In 10 cases (17%) the drusen are in the frontal portion

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less abundantly represented, and of these, in 2 cases the drusen are completely absent in the frontal region, whereas they are present in the posterior brain portions. Thereby the distribution is mostly such that the same parts of the two hemispheres show the same alterations; but here too there are exceptions. The distribution of the drusen is sometimes also very irregular, in that in quite closely neighbouring portions the severity of the alteration fluctuates to a high degree; I have observed one case, for example, in which in the upper half of the central convolution very abundant drusen were found, whereas the lower part of the convolutions was completely free of drusen.

The drusen are found regularly in the grey cerebral cortex, and are there most abundant in the upper layers and decrease continually towards below. In the white matter the drusen do not occur at all.

Much more rarely than in the cerebrum do they occur in the other grey masses of the brain, thus in the thalamus opticus, nucleus caudatus and lentiformis, in the cortex of the cerebellum; by contrast **I never found them in the medulla oblongata and in the spinal cord.**

The basal ganglia and cerebellum I investigated in 10 cases whose cerebral cortex was richly permeated by drusen. Of these, 2 cases had drusen in the cerebellum and one case drusen in the basal ganglia. In the cerebellum the drusen were always only very sparsely represented, sat only in the middle of the molecular layer, showed mostly stage III (vide later) and **contained never any clubs.**

With so novel, unusual a pathological alteration, not properly registrable under the processes hitherto known, one must in the first place exclude the possibility of artefacts. Apart from other circumstances still to be mentioned in the clinical part, against artefacts there speak the uniformity of the findings and the agreement with different stainings, and finally the circumstance that one can

see at least the large drusen also in the unfixed and unstained fresh frozen section. Precisely this last point excludes any discussion whatever about artefacts.

For the same reasons one also cannot regard the bulbous proliferations of the axis cylinders as artefacts. I will emphasise further that most of the brains were fixed and processed very soon after death; for in the greatest part of the cases formol was injected into the dural sac by means of a lumbar-puncture cannula immediately after death, and in this way the spinal cord and brain were fixed *in situ*.

Before we pass over to the pathological-anatomical assessment of the findings, we must first investigate whether all the formations described here

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belong together — whether they really represent only different "stages" of one and the same process.

We are accustomed, with good ground, to regard most pathological processes, when they occur in different sizes, as of different age. From this point of view the description above also began with the smallest and ended with the largest drusen. If one now considers these pictures, ranged according to size into a definite system, one cannot avoid recognising in the individual pictures also different stages of one process.

In Fig. 1 (Plate VII) the smallest of the observed forms is drawn, in which the threadlets present themselves as irregular stars. **This stage I would designate as the little-star form.** On the same figure at *b* one sees how several such little stars compose themselves and form dense groups; at the centre of this group a tangled skein forms, and at the periphery the threadlets shape themselves into strands, in which, however, one frequently (also in the figure) sees their genesis out of the little stars. The larger drusen have morning-star forms of various size (Plate VII, Figs. 2, 3); they distinguish themselves from the little-star form in that they are throughout larger and the threadlets regularly radially placed; also they do not always stain black, but sometimes brown or red. Fig. 4 (Plate VII) shows attached to this morning-star form several irregular strands or plait-like formations, which consist of the same fine threads and which are to be identified with the strands depicted in Fig. 1c.

A very frequent formation is shown by Fig. 5 (Plate VII); one sees here the strands growing out radially and fairly massively from the morning star — if I may so put it; in this stage the tissue retracts and a halo arises, which appears also in Fig. 4 (Plate VII); in the further stages there forms, as a demarcation from the nerve tissue, a dense ring-shaped zone which consists of the same fine threads and which for the greatest part stands in connection with the central morning star by means of the radially placed strands, so that **a kind of little wheel** (Plate VIII, Fig. 7) arises.

All these formations are something completely foreign to the tissue of the cerebral cortex; their mere morphology already places them quite apart from the elements of the central nervous system. The same is proved also by their behaviour on staining: the method of Cajal stains the threadlets almost not at all, even when all the axis cylinders appear stained; with Weigert's neuroglia staining they likewise cannot be demonstrated; with the method of Bielschowsky they do indeed frequently stain as black as the fibrils and axis

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cylinders, but frequently also in quite different shades differing from the staining of the nervous elements. Thereby the colours show all gradations from red, yellow to black. Were this tinctorial behaviour not to make a differentiation possible, then many a picture might perhaps be falsely interpreted. Thus with Fig. 8 (Plate VIII) one can easily gain the impression that the ring bounding the nerve tissue were represented merely by a condensation of the nerve fibrils. Against this many considerations speak. First, the different staining of the whole drusen, as in Fig. 7 (Plate VIII), where central core, strands and marginal ring present themselves in the same tincture and as built up out of the same elements; further it is to be remarked that also in the drusen in which the marginal ring is black and the strands brownish stained (Plate VIII, Figs. 10, 11), the fine threads of the latter pass over into the former or at the least interweave with them; finally, all these threadlets are far finer than the nerve fibrils and their course far more tangled and angular than one is otherwise accustomed to see in fibrils.

All the formations discussed so far must therefore be regarded as different developmental grades of one process, which begins with the little-star form, passes over into the morning-star formation and then shows the strand and spoke formations; finally the little-wheel formation arises; the marginal ring would be the youngest formation. The latter assumption gains a support in the tinctorial behaviour. We see, namely, that the star form, as the youngest formation, always appears stained only black, whereas the morning stars and the strands very frequently take on a brownish staining; we could thus also conclude from this that the threadlets stain black in the youngest stages and brown in the later ones. The same behaviour one now notices also in the stage of little-wheel formation: the central portions are there mostly brownish or reddish tinted, whereas the marginal ring always appears black (only exceptionally brown, as in Fig. 7); from which it follows that on the ground of tinctorial behaviour too the marginal ring appears as the youngest formation of the drusen.

The drusen in the stage of little-wheel formation too occur in various sizes; the smaller of them are always cell-free; in the larger ones one finds now and then nuclei or nuclear detritus, whose provenance is not clear; certain pictures to be interpreted as transitional forms speak for their being remnants of cells which were enclosed by the druse during its growth and thereby brought to destruction. Yet such occurrences are at any rate a rarity.

The nucleus-less clod-like masses occurring in some of the larger drusen (Plate IX, Fig. 14) also make the impression of remnants of perishing cells.

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With treatment after Marchi the granules enclosed in these clods become brownish to black. Peculiar and hard to explain, however, is the relation of the clods to the mass of threadlets in Figs. 13 and 15 (Plate IX). Without one's being able to demonstrate nuclear or cell remnants, one sees in Fig. 13 (Plate IX) the clods partly surrounded by the threadlets — or rather, it looks as though the masses of threadlets passed over into the clods; and in Fig. 15 (Plate IX) the grey masses are diffusely scattered as small fragments between the little stars and the plaits. Further it is striking that the clods are to be seen in the drusen disproportionately more frequently than cells and cell remnants; if now the former were to arise out of the latter, one would have to see far more transitions than is in reality the case.

The study of a larger number of such formations makes the assumption appear to me the most probable, **that at least a part of the clods is formed by products of disintegration of the masses of threadlets.** According to this explanation Fig. 15 (Plate IX) would represent an earlier stage, in which the masses of threadlets are closely mixed with the clods and the latter predominate in size; in Fig. 13 (Plate IX) the disintegration would then have progressed further, so that only sparse remnants of the threadlets become visible at the margin of the clods.

Drusen of which Fig. 16 (Plate X) brings an illustration impress one morphologically already as the oldest formations. They too consist of fine threads, which are, however, much thicker and join themselves in more or less parallel-running, somewhat wavily arranged strands into a delicate basketwork. Apart from other grounds to be mentioned later, **I regard this formation of "the coarse-fibred ball" as the oldest stage of the process,** already for the reason that it exhibits the largest dimensions among all the drusen.

To these drusen, growing from the smallest beginning in a quite definite manner, there stands in striking contrast the infiltrative accumulation of the masses of threadlets, in that on the one side we see a fairly sharp demarcation against the nervous tissue, whereas on the other the threadlets diffusely permeate the tissue and lead directly to its destruction. Despite this difference, the belonging-together of the infiltrating threadlets with the drusen can be proved by the fact that the infiltrating masses of threadlets do not differ morphologically at all from the threadlets which form the marginal ring of the drusen. Further one can demonstrate a whole series of transitions between these two kinds. Not at all rarely does one see formations as in Fig. 40 (Plate XVI); here the marginal ring has attained a particular massiveness and no longer demarcates itself sharply against the tissue, but radiates out infiltratively. If such a formation is not struck by the section precisely at its midpoint,

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one then gains the impression that one has a diffusely infiltrating disc before one. In Figs. 17, 46, 47, 48 (Plates X, XVIII) one sees how disseminated individual conglomerates of the masses of threadlets compose themselves into larger areas, whereby in places the construction out of the smallest little stars is still evident (Fig. 48, Plate XVIII). The circumstance now that these infiltrating masses of threadlets stain only black, similarly to the marginal ring and the star-drusen, **could also speak (I emphasise here the "could") for our having to do here with formations of younger date** — that is, with formations which have formed a shorter time before death than the other parts of the drusen.

After what has been described there is subject to no doubt that **in these drusen we have before us something morphologically and chemically wholly foreign to the nervous system**, and that so far neither biology nor pathology knows anything comparable to these formations. The circumstance that the drusen are found throughout in senile and atrophic brains could lead to the view that the drusen represent only a kind of breakdown product, as has indeed already been conceived several times. Against this conception something may be objected. Were the drusen, namely, merely simple masses of destruction of the nervous tissue, then they would have to be found in direct connection with tissue elements in the process of destruction. **This does not hold, at least for the smallest drusen, which are in this respect the most important; they lie abruptly in the otherwise not further destroyed nervous tissue.** In the larger drusen there are indeed found here and there cellular elements in the process of destruction, which can, however, only be regarded as cells enclosed by the growth.

Thus as masses of destruction, arising at the site of tissue disintegration, the drusen cannot be explained; by contrast they could perhaps be such breakdown products as are precipitated from an originally dissolved form far from the site of their origin, and form themselves crystal-like into drusen. Certain morphological similarities are indeed present here, but the different form, tincture and arrangement in the drusen of different size does not speak for it. If it would further at any rate have to be regarded as remarkable that unorganised precipitates should, without forming compact masses, nevertheless displace the tissue, then the behaviour of these "breakdown products" towards the vessels in the manner represented by Figs. 19 and 20 (Plates X, XI) would be still more remarkable. Further it should be remarked that it does indeed belong to the rule that breakdown products take the path of the perivascular lymph spaces, but then the masses also fill out the lumen of the cleft spaces; the drusen, however, sit, despite their perivascular arrangement, in the tissue itself.

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Still greater difficulties arise, however, if one wishes to explain the perivascular formations of Figs. 21–24 and 50 (Plates XI, XIX). A breakdown product which so beautifully and regularly

ensheathes the vessels and thereby destroys the wall of the vessel so delicately and regularly would represent something quite singular. Further there comes into consideration the circumstance that **the drusen stop strictly at the margin of the nervous tissue**, that even those cortical vessels which are enclosed by the drusen over long stretches lose this cladding at the moment they enter the meninges or the white substance.

The attempt to explain the drusen as breakdown products thus meets with great difficulties, so that one would have to accord them, as breakdown products too, a quite particularly exceptional position.

I should like to draw attention further to the fact that the drusen have in almost all their stages a great morphological similarity with filamentous fungi, and one must concede that many morphological properties might perhaps be more easily explained if it were a question here of a fungus-like organised matter: the construction out of threadlets, the different position, staining and thickness at different ages, the apparently active growth with the consequent displacement of the nervous tissue, the infiltrative overgrowth as the expression of a very rapid proliferation, in which the nervous tissue had no time left for retraction, and finally the close attachment to the vessels and the growth through the vessel wall — all these properties could in my view be ascribed somewhat more easily to a living organised matter than to a dead breakdown product.

But! — where then does the inflammatory reaction remain? In our case there is no inflammation around the drusen; the only reaction which the nervous tissue shows is the bulbous proliferations of the axis cylinders, which must at any rate be regarded as the expression of a damaging of the tissue by the foreign inclusions. But fungal growths which set up no inflammatory reaction are so far unknown. If it were now actually a question of fungi, one would have to expect that they could also be demonstrated elsewhere in the body, at least by way of indication. I have for that reason, in several cases, searched through histologically most of the organs of the body as well, but found nothing that would have recalled the drusen. Yet I must emphasise in addition that this negative result need prove nothing at all. For since we have really no specific staining of the threadlets as such, and recognise them in the brain only on the ground of their peculiar grouping — that is, only as drusen — we cannot demonstrate these threadlets at all if they do not occur as drusen

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in the other organs. Culture experiments could give more information in this direction; these were attempted in the most manifold variation, but remained quite without result. Complement-fixation experiments too were carried out with the brains containing the drusen, but likewise with negative success.

It is for the time being, in my view, a matter of indifference as what we wish to regard the drusen; always we must acknowledge that we know as yet no pathological process with which we could identify them; every attempt to attach this formation to phenomena already known still meets with a whole series of fundamental difficulties which we can bridge only with hypothetical assumptions. I will emphasise here once more that I have no absolutely conclusive explanation for the drusen, but that many morphological peculiarities would be most easily explained on the assumption of an organised, fungus-like substance. Of the clinical consequences I will not yet speak here.

We could meet yet one possible objection: one could hold against us that all these described and discussed formations need not belong to one and the same process. This can easily be refuted with two kinds of argument. First, the purely morphological connection could be demonstrated and — so far as such proofs can be conclusive at all — established; further, one can also see several of these different stages side by side in one and the same brain. I have indeed not yet seen a brain in which all stages of the drusen occurred side by side, but on the other hand **one also never finds a single stage alone, but always several represented.** Mostly one finds the youngest stages side by side, or the middle ones, or the oldest, or else also the youngest drusen with the middle ones, the middle ones with the oldest. This now occurs either in such a way that in all regions the different age-grades of the drusen are mixed, or else that different regions of the brain harbour different age-grades, which could speak for the drusen having either found a differently good soil for development, or else not having developed simultaneously in the different regions.

If I am then to summarise our morphological findings, I come to the following conclusion:

We have before us in the drusen formations:

- 1. which represent a completely novel process for pathology and biology,**
- 2. which are formed by conglomerates of the finest threadlets, which appear in the nervous system as a foreign,**

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growing mass that displaces the tissue,

- 3. which do indeed damage the tissue, but only exceptionally destroy it more severely, namely when they infiltrate it diffusely or enclose it,**
- 4. which otherwise only (in a small percentage of cases and at a definite age of the process) lead to proliferations of the axis cylinders and fibrils, and**
- 5. call forth no reactive inflammation whatever.**

The process occurs in the following stages:

	Stage	Figures
I.	Stage of little-star formation	Figs. 1, 37 (Plates VII, XVI)
II.	Stage of morning-star formation	Figs. 2, 3, 4 (Plate VII)
III.	Stage of spoke formation	Figs. 5, 6, 9, 38 (Plates VII, VIII, XVI)
IV.	Stage of little-wheel formation	Figs. 7, 8, 10, 11, 39 (Plates VIII, XVI)
V.	Stage of the coarse-fibred ball	Figs. 16, 41, 42 (Plates X, XVII)
VI.	Fur-like destruction of the vessel wall	Figs. 21, 22, 23, 24, 50 (Plates XI, XIX)
VII.	Stages of destruction of the drusen	Figs. 12, 13, 14, 15, 51 (Plates IX, XIX)
VIII.	Diffuse infiltration of the nervous tissue by the thready masses	Figs. 17, 18, 45, 46, 47, 48 (Plates X, XVIII)

Stages I–V are to be understood in such a way that I represents the youngest, V the oldest. The three last-named stages let themselves be estimated with more difficulty, yet stages VI and VII seem to me to belong to the oldest drusen; **stage VIII I should like to regard again as a younger process**, against whose advance the tissue was able to muster less resistance, so that a diffuse infiltration came about.

For all these formations, which we must regard as phases of a single pathological process, we would need a uniform designation, already for the purpose of a shorter understanding, so that we can operate in the next section with a short and distinct term. For this purpose I would propose the name:

Sphaerotrichia cerebri multiplex

an expression which is to indicate nothing other than that it is a matter of a formation of threadlets occurring in mostly spherical form.

[Here the anatomical part ends. Part II, Klinischer Teil, begins on the same page and runs to page 468; it is translated separately. — Tr.]