It will thus be seen that symptomatology is like chemistry, where the combination of elements results in the production of a great number of compounds bewildering in their variety. Nevertheless, as in chemistry, when they are subjected to strict analysis they can be resolved into their component elements. When the analysis of symptoms is studied as fully as the analysis of chemical compounds have been studied, then it will be possible to group the disturbed reflexes in an orderly manner. The next step then will be to find out the agents capable of provoking the different reflexes, so that we get nearer to the immediate cause of disease.

The employment of this method of investigation is but a return to those methods of clinical research which were so fruitful in their results in the past, especially during the early half of the nineteenth century. To realize how great the progress was during that period we have to consider the discoveries associated with the names of Addison, Bright, Graves, Adams, Stokes, Cheyne, Paget, Hodgkin, and Jenner. These observers employed the most useful of all weapons in research—the trained senses. What we aim at is to recognize the methods which these great observers employed, and by improving and refining their methods restore clinical medicine to the van of research.

Structural and Functional Symptoms.

A certain number of symptoms are due to structural changes and functional derangements. These are generally shown by physical signs, and are due to departures from the normal in various ways, as in alteration in the size and shape and consistence of organs, changes in the colour, as pallor, modification of the sounds of the heart and lungs. These are not dealt with here, but will have to be reconsidered in view of this theory of disturbed reflexes, because many apparently structural and functional signs are really disturbed reflexes, or are produced by disturbed reflexes.

A Preliminary Note

ON

THE HISTO-PATHOLOGY OF EPIDEMIC (LETHARGIC) ENCEPHALITIS.*

(With Special Plate.)

BY

C. DA FANO, M.D.,

LECTURER IN HISTOLOGY.

(From the Physiological Laboratory of King's College,
University of London.)

INTRODUCTORY.

IN a previous communication on the same subject published in collaboration with Miss Helen Ingleby, M.B., mention was made of a granular, pigment-like material occurring in the nerve cells of regions of the central nervous system where brown or black pigment is not usually found. It was also pointed out that in certain nerve cells small round or oval bodies had been detected, in the middle of which a granule could be seen. The optical impression of such an appearance, when present in Bielschowsky or Nissl preparations, was that of a sort of whitish halo surrounding each granule.

When that note was written no more detailed description of these pictures was given, both because it was meant to be only a short comment on a demonstration of preparations and because I was still uncertain as to the significance of such appearances. It was only later on that a careful examination of a great number of specimens convinced me that I had under observation something not, as far as I knew, hitherto described either in epidemic encephalitis or in other diseases of the central nervous system. As, however, the doubt of an optical illusion could not be entirely dispelled, no further communication was made on the subject, and I waited for an opportunity of somehow strengthening my conviction. This presented itself under the form of a few preparations I was able to obtain recently in Paris through the kindness of Dr. H. Durand, Chef de laboratoire of Professor Netter of the Hôpital Trousseau, and of Dr. Trétiakoff, Chef de laboratoire of Professor P. Marie at La Salpêtrière.

Though many of my doubts are still present, the new

facts observed are, in my opinion, such as to require control from those interested in the pathology of epidemic encephalitis. I propose, therefore, to give now a brief description of the already mentioned appearances and of the more recently observed facts, reserving any further discussion about the occurrence of the granular, pigment-like material for another paper.

FIRST HISTO-PATHOLOGICAL FINDINGS.

A fairly good idea of the appearances to be described is given by Fig. 1 (special plate), which is a photographic reproduction of a coloured drawing† made from a toluidine blue preparation of material fixed in alcohol and embedded in celloidin.

This large nerve cell was seen in the lower part of the medulla oblongata, near the middle line, a little ventrally to the nucleus of the hypoglossus, of the first case of epidemic encephalitis published in collaboration with H. Ingleby. As clearly shown in the figure, the Nissl substance has undergone an almost complete process of chromatolysis, all that remains of it being still visible at the edges of the cytoplasm and near the nucleus, which, though retaining its form, has become shifted to the periphery of the cell body. The whole of the cell body is beset with a great number of granules easily distinguished in the preparation because of their blue stain contrasting with the purple of the fundamental cytoplasmic framework. The granules are found in the deep as well as in the superficial parts of the cytoplasm, and nearly all of them are surrounded by a minute light area which under moderate magnification looks like a halo, but under very high power and proper illumination appears as a very delicate, though sufficiently well defined, body, whitish or slightly bluish in colour, and irregularly round or oval in form. As a rule there is one granule in each body, though in some of them two granules, arranged like diplococci, can be observed. Most of the bodies are discrete, and only a few appear united in dumbbell-shaped forms. The granules measure about $0.4\ \mu$, their surrounding light areas from 1.4 to $1.8\ \mu$ in diameter.

These are the appearances which repeatedly attracted my attention. For the sake of brevity they will henceforth be spoken of as "minute bodies," comprising in this term also the granules which appear to occupy their centre. It must be pointed out here that specimens as plain as that shown in Fig. 1 are very rare. In most instances the "bodies" are seen in altered nerve cells, together with a variable quantity of granular material which becomes stained by toluidine and polychrome-methylene blue in various shades of green. This is mentioned both because it may help other investigators in their search for the "bodies," and because it shows that their recognition is not hampered by the presence, within the nerve cells, of a granular material with which they seem, however, to have some relation.

A good instance of this is given in Figs. 2 and 3, which are likewise photographic reproductions of coloured drawings, the former being made from a toluidine blue, the latter from a polychrome-methylene blue preparation. The large nerve cell shown in Fig. 2 was found in the reticular formation of another section of the same medulla oblongata from which Fig. 1 was drawn. The diseased condition of the cell is clearly proved by the advanced chromatolysis, deformation, and peripheral shifting of the rather opaque and dark nucleus. The middle parts of the cytoplasm are occupied by a number of granules which in the preparation were stained a yellowish-green. Some of them appear here and there surrounded by a very small light area which, up to a point, imparts to them an aspect similar to that of the "minute bodies" which are particularly noticeable in the peripheral portions of the cytoplasm. These do not differ as regards form, staining properties, and situation, from those shown in Fig. 1. Outside the nerve cell two other "bodies," identical with those situated within it, can be recognized on the top of small fragments of protoplasmic material the exact nature of which could not be ascertained. In the same Fig. 2 another nerve cell has been drawn, showing for the purpose of comparison a common process of vacuolization.

The two nerve cells shown in Fig. 3 were drawn from the layer of small pyramids of a section of the first frontal

* Towards the expenses of this research a grant was made by the British Medical Association.

† All figures illustrating this paper were drawn by Mr. W. Pilgrim with the help of the Abbe-Zeiss camera lucida, comp. oc. 8 K, obj. 2 mm. Z., drawing sheet at the level of the microscopic table.

convolution from the alcohol material of the second case of encephalitis published in collaboration with H. Ingleby. Both of them have undergone a more or less advanced process of vacuolization, the vacuoles having been probably occupied by some fatty-like material dissolved by the alcohol fixation and successive treatment for embedding in celloidin. In the smaller cell a few typical "minute bodies" can be seen; in the larger one it is easy to recognize, beside the "bodies," small clumps of a granular material, stained a dark green in the preparation, and also surrounded by a light area similar to that which characterizes the typical "bodies."

FRESH EVIDENCE.

Investigations had reached this stage, but no further progress had been possible, particularly because all attempts to obtain a differential or at least more defined stain of the "bodies" had failed to give satisfactory results. The same can be said of the method commonly used for staining bacteria, their spores and capsules. The question was therefore left in abeyance until the opportunity arose of meeting Netter in Paris. During the conversation we had on the subject the following points were particularly emphasized by him: (1) The similarity existing in certain respects between epidemic encephalitis and certain forms of sleeping sickness on the one hand and rabies on the other. (2) The involvement in almost all cases of epidemic encephalitis of the salivary glands, a fact which he and Dr. Durand could support both from clinical and histo-pathological points of view. (3) His conviction that the direct etiological factor of the disease ought to be looked for in some agent similar if not akin to the Negri bodies.*

Of the preparations shown to me by Durand some were of nervous tissue, and on looking at them I had the rather vague impression of seeing within the nerve cells bodies which reminded me of those seen in my own preparations. Other specimens were from a salivary gland of an acute case of the disease, and these clearly showed in the interstitial tissue zones of small-celled infiltration very similar to that one meets with in the nervous tissue from cases of epidemic encephalitis.

As I was much interested in such an observation Durand presented me with two slides, on each of which were stuck three unstained paraffin sections of this salivary gland. When back in my laboratory the slides were cut in such a way as to obtain six separate preparations, which I stained with toluidine blue, polychrome-methylene blue, Weigert's iron haematoxylin, haematoxylin and eosin. In the areas of small-celled infiltration of three of them "minute bodies" were found similar to those detected by me in the central nervous system. The granules were stained either blue or blue-black according to the method used; their surrounding areas had again the same whitish or slightly bluish appearance as above.

As seen in Figs. 4 and 5 the dimensions only of some of the central granules are somewhat larger than those of the granules noticeable in most of the "bodies" seen both in these specimens and in the nervous tissue. This difference has been a little emphasized in the photographic reproductions illustrating this paper by the fact that Figs. 1 and 2 have had to be reduced by two-tenths, while all others are of the same size as the original drawings. It is interesting to note that some "bodies" are situated within the cytoplasm of the infiltration cells while others lie free in the tissue, or, as in the case of the two extracellular forms shown in Figs. 2 and 5, they appear situated on the top of or attached to some protoplasmic material of not quite definite nature.

The purpose of my visit to La Salpêtrière was to see the preparations of epidemic encephalitis of Marie and Trétiakoff, but particularly "les volumineuses granulations entourées chacune d'un halo clair" described by them in the nerve cells of the substantia nigra, as well as the "inclusions homogènes dans le protoplasme de volumineuses cellules nerveuses du Noyau Rouge," also observed by them in their case No. 3. It is outside the province of this paper to enter into a discussion of the significance of these inclusions, particularly of the "volumineuses granulations," considered by the authors as a phenomenon "analogue à celui décrit par Alzheimer sous le nom de dégénérescence graisseuse à gros grains."

* Professor Netter and Dr. Durand have kindly consented to the publication of the above statement.

but it should be noted that the fact corresponds to the description given by the authors, though the explanation might perhaps be different.

At La Salpêtrière both Trétiakoff and I looked for the "bodies" in the preparations kindly shown to me by him; but as nothing clear could then be found he gave me the following polychrome-methylene blue specimens for further investigation: (1) A normal preparation of the mid-brain of an individual of about 40 years of age; (2) two sections—one of the optic thalamus and one of the mid-brain—of a case (Shibler) who had died in consequence of a relapse of the malady; (3) one section of the optic thalamus of an acute case (Baudeloque).

In the normal preparation, just as in my own control specimens, I failed to find anything resembling the "bodies." The section of the optic thalamus of the case Shibler was spoiled on the journey, and no use could be made of it; but in the grey matter surrounding the Sylvian aqueduct of the mid-brain section of the same case a few nerve cells were found the protoplasm of which was beset with small clumps of granular, pigment-like material. These had stained a yellowish-green and could be distinguished with sufficient ease from a few "minute bodies" identical with those seen in my own specimens. The preparation of optic thalamus of the acute case (Baudeloque) was also damaged during the journey, but it could be dismounted and restained with toluidine blue. In this specimen, in which the small-celled infiltration was of extreme intensity, neither pigment-like material nor blue granules could be found within the nerve cells, but "bodies" similar to those observed in the salivary gland were seen scattered in the nervous tissue, particularly near areas of perivascular infiltration (Fig. 7). In a few places forms occurred of which the central particle appeared to consist of two granules arranged in pairs as described above, but in this case one only of them was stained blue, while the other had taken a metachromatically red tinge. In regard to the peculiar tetragonal form shown in the same figure and consisting of two relatively larger purple-red and two relatively smaller blue granules, I think it advisable for the time being to reserve any judgement.

GENERAL CONSIDERATIONS.

It is evident that the possible value of my observations is, in great part, connected with the fact that they were made on varied material from different cases. Indeed, it is only the knowledge of the presence of the "minute bodies" within the nerve cells that has made it possible to recognize them outside the nerve cells in the nervous tissue, as well as within and without the cells forming the small-celled infiltration of the salivary gland specimens. On the other hand, this last observation, which by itself would be worthless, has given to my old finding a fresh significance. Of course, the possibility remains that the "bodies" seen in my specimens and in those for which I am indebted to Dr. Durand and Dr. Trétiakoff might be different, in spite of the similarity in aspect and staining properties. But if so, two different suggestions ought to be put forward to explain the presence of peculiar "bodies" in tissues more or less affected by the same disease. And this seems to me the chief point to be borne in mind: the pathological process underlying these observations being the same, so ought their explanation to be.

With this object in view the following three suggestions seem to me worth briefly considering: (1) That the bodies are the result of an optical illusion; (2) that the granules alone are either bacteria or products of a cell degeneration, their bluish or whitish haloes being again an illusion produced either by light or by vacuolization; (3) that the "bodies" are appearances directly due to the presence in the tissues of an agent, cause of the disease.

As to the first supposition, it has already been said how and why it has been the cause of considerably delaying the publication of this paper. However, I wish to point out here and now that such a suggestion could explain perhaps some of my recent observations and the bluish areas surrounding each granule in evidently diseased nerve cells. But this, in any case, only up to a point, as neither pigmented nor vacuolized nerve cells in normal or pathological conditions ever give such a complete illusion, even if highly magnified and looked at by very powerful artificial light. Moreover, some other suggestion ought to be put forward to explain the occurrence within nerve cells of granules which, according to their staining properties,

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FIG. 1.—Large nerve cell beset with the "minute bodies" described in the text.

FIG. 2.—Nerve cell with "minute bodies" and granular material. In the other nerve cell a common process of vacuolization is shown.

FIG. 3.—Two nerve cells from the cerebral cortex, the smaller one with "minute bodies" only; in the other both "bodies" and small clumps of granular material are shown.

FIG. 4.—"Minute bodies" among and within the infiltration cells of a salivary gland from an acute case of epidemic encephalitis.

FIG. 5.—Somewhat larger "bodies" seen in another place of the same specimen as Fig. 4.

FIG. 6.—Large nerve cell with granular pigment-like material and a few "minute bodies." From the grey matter surrounding the Sylvian aqueduct of a mid-brain preparation of C. Trétiakoff.

FIG. 7.—"Minute bodies" and a larger tetragonal form seen in the optic thalamus of an acute case of the disease.

are to be considered as formed either by chromatin or by a similar material.

This takes us to the second supposition, about which, besides some of the reasons just mentioned, I think it useful to remark that bacteriological investigations have been attended, for the present, by negative results, and that, as far as I know, no nerve-cell degeneration has been described resembling the appearances shown in my Figs. 1, 2, 3, and 6.

As to the third hypothesis, I wish to point out that it would link up one with the other the various findings as well as these with histo-pathological changes, which most authors consider extremely like those seen in cases of trypanosomiasis. Those who recollect the aspect of some of the small (internal) forms out of which the Negri bodies appear to result will recognize that between these and the "minute bodies" described in this paper there is a morphological and structural similarity which is at least striking. I quite realize that such a suggestion will acquire value only if other investigators are able to confirm my observations, and particularly if the apparent "bodies" can be found in the nervous or other tissues of animals to which the disease has been successfully transmitted.

SUMMARY.

In the nervous tissue from cases of epidemic (lethargic) encephalitis within and without the nerve cells minute forms have been observed, to all appearance consisting of a central generally basophil particle and of a delicate little stainable body, irregularly round or oval in shape. For these forms the term "minute bodies" is *pro tempore* proposed.

The bodies are generally discrete, and provided with one granule, but dumbbell shaped forms occur as well as others with two central particles arranged in pairs. An as yet not quite definable relation seems to exist between these forms and a granular, pigment-like material occurring within the nerve cells in places where brown or black pigment is not generally found.

Minute forms, similar in shape, structure, and staining properties to those observed in the nervous tissue, have been traced within and without the cells infiltrating a salivary gland from an acute case of the disease.

After discussing the supposition that such findings might be the product of an optical illusion, associated perhaps with degenerative changes caused by the malady, the suggestion is tentatively put forward that they may be due to the presence in the tissues of a living agent, cause of the disease.

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"HARLEQUIN FOETUS" (HYPERKERATOSIS CONGENITALIS).

BY

JAMES T. McAUSLIN, F.R.C.S.,

SENIOR RESIDENT SURGEON, ROYAL MATERNITY HOSPITAL, EDINBURGH.

(With Special Plate.)

THE comparative rarity of this condition appears to warrant the following case being reported; only one case has been recorded here in fifty years.

The mother of the foetus was a girl of 16 years, admitted in labour. On vaginal examination, a breech presentation could be made out, but it was obvious one was dealing with an unusual case. The os was well dilated and the skin of the foetal buttocks had the feel of "crocodile skin." One could not employ a more apt term to describe this, as the hard thickened skin was broken up into numerous irregular patches similar to that of crocodile hide.

The full-time foetus was born dead and weighed 7 lb. It presented a repulsive appearance, as the photographs show. The skin was dead white in colour, cornified and cracked in all directions, making the foetus appear as if clad in a horny armour. The distribution of these changes was universal. When a portion of the hardened skin was removed a red raw-looking area was exposed underneath.

The appearance of the eyes was interesting: no differentiation into the various parts, iris, pupil, etc., could be made out, the eyes appearing as two sacs filled with blood.

An examination was made by Dr. F. J. Browne (Assistant Physician, Ante-natal Department), who was unable to make out any definite morbid changes in the internal organs, except in the thymus, which, although of normal size, contained numerous small scattered abscesses throughout its substance. No spirochaetes could be demonstrated, but the appearance of the thymus was suggestive of syphilis. The microscopic sections were, I regret, not a success, owing to *post-mortem* changes. A Wassermann test in the mother, who made an uneventful recovery, yielded a negative result.

This condition has been confused with congenital ichthyosis, but "it is distinguished from it by the fact that it is present at birth, whereas ichthyosis appears towards the end of the first year of life; and by its distribution, which is universal, whereas ichthyosis is rarely very widespread at first, and hardly ever affects the palms and soles, which this disease always does" (Norman Walker).

I am indebted to Dr. Haig Ferguson for permission to publish this case.

ROTATION-DISLOCATION OF THE ASTRAGALUS.

BY

ROBERT OLLERENSHAW, M.D., F.R.C.S.ENG.,

HONORARY SURGEON IN CHARGE OF ORTHOPAEDIC DEPARTMENT, SALFORD ROYAL HOSPITAL.

(With Special Plate.)

DISLOCATION of the astragalus alone is not a very common accident. The usual displacement is of the astragalus forwards—a condition which often results in a compound dislocation.

A more uncommon displacement is of the astragalus backwards, in which event it is to be felt lying between the tendo Achillis and the malleoli. Dislocation of the bone by rotation in its bed is rare, and when it does occur it is not possible to effect a reduction by manipulative measures. In this form of dislocation the astragalus is frequently detached from all its ligaments. Open operation is necessary, and removal of the astragalus has been the general procedure in the recorded cases. Stimson,¹ in his well-known book, describes dislocation by rotation of the astragalus and refers to seven cases. He insists that the description should only include those cases in which the astragalus has undergone rotation round a vertical or an antero-posterior axis, but still remains mainly within the tibio-fibular mortise. Barwell² reports a case in which he removed the astragalus and where good function was obtained. He recommends primary removal of the astragalus in all cases of rotation-dislocation in which "certain and sufficient, but not too persevering, attempts at reduction" have failed.

For this reason the present case, in which a rotation-dislocation with complete tearing of all ligaments was operated upon and completely reduced with an ultimate restoration of full function, appears to be a circumstance which it is essential to record in some detail.

W. W., male, aged 42 years, was working at the Manchester Ship Canal Docks on May 20th, 1920, and whilst walking with the right foot well advanced a heavy piece of timber fell from a height and struck the back of his left heel. He was admitted to the Orthopaedic Department of Salford Royal Hospital on the same day.

On examination there was an obvious dislocation of the astragalus, the upper articular surface being palpable below the skin on the outer aspect of the dorsum of the foot. There was also a fracture of the fibula two inches above the tip of the malleolus. X-ray examination showed the nature of the dislocation to be a rotation of 90 degrees round the vertical axis (Figs. 1 and 2).

Manipulation was entirely unsuccessful, and operation was decided upon with the idea that astragalectomy would probably be required.

Operation.

A curved incision was made from a point one and a half inches above and behind the outer malleolus curving across the prominence of the astragalus to the mid-line of the foot. The upper and outer surfaces of the astragalus were exposed lying immediately under the skin, and the tendon