pulmonary œdema. It sometimes assumes a course similar to that of Landry's paralysis. The condition is always serious when the patient's general health is poor in consequence of a recent infectious disease, or in severe types of chronic alcoholism, etc. When the vagus or phrenic nerves become involved, the life of the patient may be in constant danger, although recovery has occurred even under such circumstances. When the paralysis is confined to the distal portions of the extremities, the prognosis is more favorable. In exceptional instances the course may become chronic and progressive. In the majority of cases, however, in the absence of complications the disease terminates in complete recovery. Even in favorable cases the affection may last from several months to two years or more, depending upon the underlying cause, the extent and intensity of the nerve degeneration, and the recuperative powers of the patient. The prognosis is always materially influenced by the course and virulence of the toxæmia. When the sphincter of the bladder is involved, it is usually indicative of extension of the inflammatory process to the spinal cord, thus rendering the prognosis as to recovery more doubtful.

Treatment.—The treatment of polyneuritis is essentially symptomatic. Aside from the cause of the toxæmia the various forms receive practically the same treatment. It is essential to discover, if possible, the cause of the neuritis, and to remove it or discontinue its further action. This should be the first consideration, particularly in cases due to alcohol. The sudden withdrawal of the customary stimulant is not always advisable, particularly when cardiac weakness is present. This can usually be successfully accomplished, however, by the administration of suitable heart tonics. Rest in bed, with general supporting treatment, is desirable or absolutely necessary in the majority of cases. A local or general warm wet pack for the purpose of producing diaphoresis, if the patient's strength admits, is often followed by excellent results in the early stage, or, if the patient is strong enough to bear the necessary procedures, a warm bath for fifteen or twenty minutes daily often proves beneficial. General constitutional treatment applicable to the special condition constituting the toxæmic process should never be forgotten. In order to prevent deformities, faulty positions of the extremities should be corrected by giving the necessary support to paralyzed muscles. Thus when there is "foot-drop" the feet should be kept at right angles with the leg by means of sand-bags, pillows, etc. For the purpose of relieving the pain anodynes should be administered when necessary in the same manner as mentioned in the description of the treatment of mononeuritis. When the diaphragm becomes paretic or paralyzed, artificial respiration and the hypodermatic injection of strychnine must be resorted to. Indications of heart failure are to be met by absolute rest and the administration of cardiac stimulants. When deglutition is interfered with, the patient should be fed through the œsophageal tube in order to prevent the entrance of food into the larynx or bronchi.

Fortunately such emergencies arise only in exceptionally severe cases. After all of the acute symptoms have subsided, massage and electricity will prove useful.

William M. Leszynsky.

NEURODIN, acetyl-p-oxy-phenyl-urethane, $C_2H_4.OCOCH_3.NH.COOC_2H_5$, is prepared by acetylation of the compound formed by the interaction of chlorocarbonic ether and amidophenol. It is a colorless, odorless, crystalline substance, soluble in 1,400 parts of cold water and readily in boiling water. It is antipyretic and antineuralgic in dose of 0.5–1.5 gm. (gr. viij.–xxiv.).

W. A. Bastedo.

NEUROEPITHELIOMA.—The name of neuroepithelioma was first given by Simon Flexner in 1891 to a peculiar tumor of the retina in which were found collections of cells resembling the rods and cones of the external nuclear layer. Flexner believes this tumor to have had its origin not in the supporting cells, but in the neuroepithelial cells of the external nuclear layer, and to be therefore not a glioma but a neuroepithelioma. In this tissue he found the tubular or alveolar arrangement of the cells, so common in glioma of the retina; and among the cells of the tubules he found tiny rosettes composed of long cylindrical cells, the pointed extremities of which were turned toward the lumen of the rosette and formed there a membranous ring. These cells he considered rudimentary rods and cones. He answers the objection of Iwanoff to the formation of tumors from any cells except supporting cells by quoting Klebs' opinion that all the elements of the nervous system are capable of proliferation.

Three years later, Wintersteiner reported a case of so-called neuroepithelioma of the retina in which rosettes similar to those described by Flexner were found. Wintersteiner mentions Flexner's work, but claims to have made his discovery quite independently of the latter, and does not give him credit for the name "neuroepithelioma." He found transitions between the rods and cones and the tumor cells, and considers the membrane formed by the processes of the cells to be analogous to the membrana limitans externa. In a later monograph Wintersteiner discusses eleven tumors with epithelial rosettes which he found among thirty-two gliomata, and in two cases of microphthalmos. He regards these tumors as originating in misplaced cells of the rod-and-cone layer. Several other authors have reported similar tumors, but without giving them the same interpretation. Thus Becker describes rosettes of cylindrical cells in a tumor with a marked alveolar structure which he called "tubular angiosarcoma." Bochert, Eisenlohr, Jung, Thieme, and Van Duyse probably were also dealing with the same kind of tumor under the name of glioma or gliosarcoma, or angiosarcoma. Two observers, Greef and Hertel, working with the Golgi method, were able to demonstrate the presence of true ganglion cells among the ordinary spider cells which formed the mass of the tumor in both cases. They did not, however, apply the term neuroepithelioma to these tumors, but preferred to use the name neuroglioma ganglionare, after similar tumors in the central nervous system.

The best criticism of the views of Flexner and Wintersteiner is given by Ginsberg, who examined two tumors from a case of microphthalmos, and found in them the same rosettes of epithelial cells described by the two former. Ginsberg, however, regards these as cylindrical cells from the pars ciliaris retinæ, not rods and cones. These cylindrical cells are undifferentiated cells of the original Anlage of the retina, formed before the neuroblasts and spongioblasts. As these primitive cells are of epithelial origin he suggests the name "carcinoma retinæ," instead of neuroepithelioma. He bases his theory not only on the appearance of the cells composing the rosettes, but also on the fact that these primitive, undifferentiated cells are capable of proliferation, while in the case of highly specialized cells, such as the rods and cones, there is great doubt as to the possibility of their proliferation. The tumors which Wintersteiner has called neuroepithelioma Ginsberg regards as probably formed from primitive epithelial elements, and not from the highly specialized neural epithelium.

Alice Hamilton.

NEUROFIBROMA. See *Fibroma.*

NEUROMA. See *Fibroma.*

NEUROMA OF THE SKIN, PAINFUL.—This is an exceedingly rare affection, but two cases in which the skin was primarily affected being on record. Duhring's "Case of Painful Neuroma of the Skin," *American Journal of the Medical Sciences*, October, 1873, was the first noted and was followed by Kosinski's case in the *Centralblatt für Chirurgie*, No. 16, 1874. Both cases occurred in men, aged seventy and thirty years respectively. In Duhring's case the tumors had been developing for ten years and in Kosinski's for fourteen. The tumors, varying in size from a pinhead to a filbert, confluent and disseminated, were thickly studded over the areas affected. In the first case they extended from the left scapula over the shoulder down the arm to the elbow, occupying principally the area of distribution of the circumflex nerve, and in the second case over the buttocks and upper part of the thigh, corresponding to the area supplied by the small sciatic and external cutaneous nerves. The lesions were arranged irregularly, not corresponding exactly to the course of the nerves mentioned, and formed firm, flat, or oval, elastic nodules, fixed in and extending below the skin, and movable only with it. The integument between the nodules was normal, they being purplish or pink in color. In Duhring's case the skin over the nodule was slightly scaly. At the outset pain was variable, but later it became excruciating and occurred in violent paroxysms, lasting an hour or more.

Since they are never malignant these neuromata are best not interfered with unless great distress is caused by the pain. In both the above cases resort was had to a removal of portions of the nerve supply with resulting quick relief from pain and gradual and almost complete subsidence of the nodules.

The new growth is composed of firm connective tissue and non-medullated nerve fibres.

Charles Townshend Dade.

NEUROMIMESIS. See *Joints, Chronic Diseases of.*

NEURONE, GENERAL PATHOLOGY OF THE.—Introduction.—Notwithstanding the liberal number of papers which have been published in recent years upon the pathology of nerve cells, we have still, in an essay to construct a general pathology of the neurone, only fragmentary data at our disposal. The neuropathologist, like all other special pathologists, meets with insuperable difficulties, due to the fact that a well-developed pathology of the cell in general is still lacking. Investigators are coming more and more to the opinion that in order to build up a satisfactory pathology of the cell, research ought not to be limited to the cells met with in the special tissues of highly differentiated animals, but should be extended to unicellular forms, in which the conditions of life are simpler and with which the possibilities of experiment are more manifold, and the experiments themselves are more easily subject to control. Indeed, at the present time, part of the pathology of each of the special types of cells of the vertebrate animal is based directly upon inferences drawn from work done upon one-celled species. Thanks to the very extraordinary distribution of the protoplasm of the nerve cell in space, however, it has been possible, in nerve cells or neurones, better than in any other specialized type, to study the results of injury to a part of the cell; indeed, this kind of injury can perhaps be better studied in them than in any of the simplest organisms. It is owing to this circumstance, doubtless, that such a goodly portion of that pathology of the neurone which has thus far been evolved has to deal with degenerative and regenerative processes following upon damage to some one of its parts, particularly its axone.

In view of the variety of hypotheses still advanced concerning the ultimate structure of the protoplasm of the normal nerve cell (see this Handbook, Vol. II., article, *Brain, Histology of*), it is by no means surprising that there is lack of unanimity of opinion regarding the fundamental nature of the changes which are met with in the neurone when it is diseased.

The studies of the botanist Fischer, of Leipsic, have shaken microscopical histology at its foundations. Now that we know the varying results which can be obtained, not only by the use of fixing reagents of different chemical constitution, but by the employment of the same reagent in different degrees of concentration, we must needs be chary of the conclusions we arrive at from the examination of fixation pictures in nerve cells, not only in health, but also and perhaps more particularly in disease.

The scepticism excited by these recent observations has, in some quarters, probably become excessive. Realizing that the stainable substance of Nissl can be precipitated in granules of different size by alcoholic solutions of varying strengths, that by treating nerve cells by one series of vigorous reagents, the so-called neurofibrils of Apáthy or of Bethe may be demonstrated, while by treating the same nerve cells by a different series of powerfully modifying solutions the honeycomb structure of Bütschli or the neurosome rows of Held may be put in evidence; and bearing in mind, further, that microscopic appearances similar to karyokinetic figures, centrosomes, and cytoplasmic radiations may be produced by the action of fixing reagents upon albuminous solutions injected into the empty cellular spaces of cork, there are those who would go so far as to say that the microscope and microscopical histological methods have been and can be of very little help to us in unravelling the structure and deciding upon the functions of cells. Such pessimists, however, forget the wonderful advances in neurological knowledge, anatomical and pathological, which are directly attributable to the use of the microscope. It would be as illogical for the student of the nervous system to give up the study of fixation pictures as it would be for the chemist to abandon the method of precipitation as a means of acquiring knowledge concerning the composition of solutions. It may be that the protoplasm of the nerve cell, as well as protoplasm in general, consists chiefly of colloidal particles held in suspension by virtue of the electric charges which they possess; if so, we may expect that some day new and desirable information will be derived from a study of artificially prepared colloidal solutions. Such a line of investigation, attractive and promising as it is, will unquestionably be that along which many can profitably work; but it is to be hoped that there will be others who will continue and extend those studies by histological methods which have done so much for us in the past, and which, many of us are convinced, are capable of supplying us with still more valuable information in the future.

In the brief sketch of the general pathological morphology of the nerve cell to be made here, the changes due to functional activity will first be referred to; next a description of the processes of necrosis and necrobiosis as they affect the neurone will be given, followed by a brief discussion, (1) of the various degenerations which involve the whole neurone or parts of it; (2) of regenerative phenomena; and (3) of the changes consequent upon various forms of intoxication.

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Changes due to Functional Activity in the Neurone.

In this connection the studies of Hodge upon the histology of fatigue are by far the most important hitherto undertaken. His researches were made upon the nerve cells of various animals, including sparrows, swallows, pigeons, and honeybees. A comparison of the cells of such animals captured in the morning with cells of animals of the same species killed after a long day's exercise

showed alterations both in the protoplasm and in the nuclei of the fatigued cells. The nuclei were smaller than normal in the tired cells, had irregular margins, and stained with unusual intensity. An examination of the protoplasm revealed a shrunken appearance, and it stained more feebly than normal. The changes in the cells of the occipital cortex in the pigeon, as depicted by Hodge, are very convincing. Hodge's earlier reports did not contain satisfactory data with regard to the behavior of the stainable substance of Nissl, as he used osmic acid fixation for some of the cells and sublimate fixation with Gaule's stains for others.

Later on Mann, working with other methods, compared the pyramidal cells of the cerebral cortex and the motor cells of the ventral horn of the spinal cord of a dog at rest with those of another dog after a long period of muscular activity. In a further series of experiments he bandaged one eye of dogs leaving the other exposed, killed the animals after twelve hours, and compared the retinal neurones, those of the corpora quadrigemina, of the lateral geniculate body, and of the occipital cortex of the one side with those of the other. He concludes that the stainable substance of Nissl increases in amount in nerve cells which are resting; it diminishes during functional activity, owing to direct utilization by the cell protoplasm. In addition, Mann describes an increase in the size of the cell bodies and of the nucleus and of the nucleolus in the early stages of functional activity; if the activities be prolonged to fatigue, there are shrinking of the protoplasm and contraction of the nucleus, the borders of the latter becoming irregular. Similar investigations have been made by De Moor and Pergens.

The studies just described refer to the changes which occur in nerve cells as the result of that normal excitation of cells which accompanies muscular activity or normal retinal illumination. Opportunities for studying other forms of normal functional activity might well be taken advantage of. It is desirable, too, that methods should be devised for testing the effect of alterations of temperature, light, moisture, and non-poisonous chemical stimuli upon different groups of neurones.

The effects of electrical stimulation have been investigated to a certain extent. For example, Hodge stimulated the peripheral sensory nerves of cats and afterward made sections of the spinal ganglia. In the ganglion cells on the side of excitation he found a decrease in the size of the nucleus and a change in its shape. The cell body, also, gradually diminished in size. Vas, on the other hand, stimulating the sympathetic for fifteen minutes, found a distinct increase in the size of the cell body, and a disappearance of the stainable substance of Nissl in the region of the perikaryon immediately adjacent to the nucleus. The nucleus itself, Vas states, becomes swollen and tends to be displaced toward the periphery, sometimes even causing a bulging at the periphery of the cell. The somewhat conflicting statements of Hodge and Vas have been reconciled by the experiments of Lugaro, who demonstrated during the early period of excitation a state of turgescence in the protoplasm of the cell body, while later on, when the stimulation had been continued long enough to cause fatigue in the cell, progressive diminution in the size of the cell body was met with. According to Lugaro the tigroid substance slowly increases in amount during the earlier period of stimulation; after the cell has become fatigued, it is decreased in amount and tends to be more diffusely distributed throughout the cell body.

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Necrosis and Necrobiosis of the Neurone.

By the term necrosis of the neurone is meant that condition or set of conditions in which the cell is relatively suddenly killed; by necrobiosis of the neurone is indicated the process which leads, through a series of pathological changes, gradually to the death of the cell.

Necrosis of nerve cells is met with in trauma, in infectious processes directly involving the nerve tissues, in sudden cutting off of the oxygen supply (*anæmic necrosis*) and possibly under other conditions.

The classification of direct necrosis introduced by Klebs is perhaps the most satisfactory one we possess. If the noxious agent which kills the cell affects it equally in all its parts, one gets a microscopic picture not unlike that met with in the artificial killing brought about when we fix the nerve tissues in the fixing reagents of the laboratory; the structure of the protoplasm and nucleus is relatively well preserved. The nucleus is, however, in some cases, first attacked by the noxa, in which event it may either be dissolved (*karyolysis*) or become fragmented (*karyorrhexis*); in such instances the alterations in the cell body may at first be slight, consisting perhaps merely of cloudy swelling. In forms of cell death, on the other hand, in which the protoplasm appears to be first attacked, a primary vacuolar degeneration of the cell body (*plasmarrhexis*) may be encountered.

A cell is doomed to death if its nucleus be destroyed or injured beyond a certain degree. The studies of Condorelli upon the effect of mechanical injury to cells have shown us that rupture of the nucleus not infrequently occurs as a result of trauma. Schmaus has suggested that we may here have an explanation of the direct necroses of ganglion cells which may be assumed to take place in commotio cerebralis and commotio spinalis. Tissues under these conditions should be studied in the early stages and with the aid of modern methods. A beginning has been made in this direction (*cf.* Barbacci, *loc. cit.*, p. 819).

We know but little of the effect of powerful electric currents acting directly upon the neurones. A few cases of electrocution have been examined post mortem without, it must be confessed, adding much to our knowledge. There is here room for fruitful experimentation in the light of the results which were obtained by Eschle upon artificial necrosis due to electrical influences (see also work of Corrado, cited by Barbacci).

In diseases associated with peripheral neuritis (diphtheria, lead poisoning, etc.) we have exquisite examples of partial nerve-cell necroses, the poison killing the axones of the neurones through a distance of from a fraction of 1 mm. to several millimetres. The effect on the whole neurone is the same as that which follows upon artificial section of the axone (*vide infra*).

Careful studies of karyolysis and karyorrhexis in nerve cells have still to be made. There are only fragmentary remarks upon the subject in the bibliography. The difficulty of the study is aggravated by the unusual distribution of the chromatin in the normal nuclei of nerve cells.

The so-called condition of pyknosis in which there is a condensation of the nucleus and cell body is worthy of mention. Schmaus assumes that the so-called "sclerosis" described by Friedmann in acute myelitis is closely allied with pyknosis. This author found in cells otherwise nearly intact glistening masses which stained intensely with nuclear dyes; such masses appeared at first in the periphery or in the interior of the cells, as though they had resulted from fusion of the spindles and granules of

the stainable substance of Nissl. Later, the cells diminished in size, though the glistening staining increased. The nucleus was often well preserved for a long time. It may be that some of the "chromophile" cells of Nissl belong in this category, though in most instances it would seem that they are to be regarded as artefacts due to the fixing reagent.

A series of necrobiotic changes have been described by Pándi in nicotine, bromide, and cocaine poisoning. In chronic poisoning with nicotine, the nucleus of the cell becomes shrunken, the cell body is diminished in size, and the paraplasm and the nucleus stain of a dark color. In cocaine and bromide poisoning the nuclei show enlarged nucleoli; the chromatic threads in the protoplasm lie closely pressed together, sometimes becoming merged with the deeply stained ground substance of the nerve-cell body.

The experimental work of Klemm upon plant cells has shown the way for a series of experiments upon nerve cells, which, it is hoped, some one in the near future may be induced to undertake. According to Klemm, when a cell is suddenly killed there is never any contraction of it, nor any considerable alteration in configuration. These are the signs of a much slower dying process. The visible alterations in the protoplasm of plant cells on sudden killing are, according to Klemm, of three kinds: (1) Precipitates: usually granular structures giving an increased granular appearance to the cell. Such granules may be united in the form of chains, networks, and dendritic structures. Instead of granular precipitates a fibrillary appearance may be produced. (2) Phenomena of solution: vacuole formation, foam formation, and the like. (3) A mixture of granulation (coagulation) in the plasma with formations of fewer and smaller vacuoles.

Where death is not so sudden and yet very intense effects are suddenly produced, the most marked alterations in configuration are met with. In the still slower "physiological" death the terminal phenomenon is usually coagulation of the protoplasm, and there is a tendency to various forms of degeneration—granular degeneration, vacuolar degeneration, etc. Dying protoplasm has the tendency to break up into small clump-like masses which assume a more or less spherical shape.

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Atrophy of Neurones.

Hodge, of Clark University, has made us familiar with some of the changes which take place in neurones in senile atrophy. In a man ninety-two years old, dead of marasmus, the ganglion cells as a rule looked fairly normal, though he describes a diminution in the number of the Purkinje cells in the cerebellum and slight shrinking of those which were present. His study of the spinal ganglion cells demonstrated that the nucleus nearly always had an irregular contour, was more or less shrunken, and often devoid of nucleolus. The cell protoplasm was rich in fat and pigment, which were absent in the fœtus. Hodge's description of fat and pigment in a forty-seven-year-old man is accompanied by the suggestion that the man suffered from premature senescence due to alcoholism. I am of the opinion that the pigment which he describes is visible in the nerve cells of nearly all human beings and probably at all ages, except in the fœtus and in early childhood. I have been struck with the comparatively large number of times the so-called lipochrome of normal nerve cells has been described as a pathological product. Some of those who have studied the Gasserian ganglion in *tic douloureux* have fallen into this error.

Hodge studied the changes due to age in bees, as well as in human beings, and described shrinking of the nuclei, vacuole formation in the protoplasm, as well as diminution of the total number of cells.

Studies of a similar nature have been undertaken by Vas. This investigator made use of the method of Nissl in examining the nerve cells of old people. He describes various alterations in the stainable substance of Nissl, and states that in the last stage the cell body is transformed into a strongly staining, formless mass, which may be broken up into clumps. It does not seem impossible that Vas may have had to deal with artefacts, perhaps the "chromophile" cells of Nissl. They can be obtained occasionally in nerve tissues from individuals of any age. I have pictured one in a former publication (see Fig. 73, "The Nervous System," p. 124).

According to Babes, the processes in the anterior horn cells of the spinal cord are reduced in number in old age. In a group of intact nerve cells one sometimes finds in old people shrunken, colloid, or very pale elements without nucleus or nucleolus, or with a strikingly pale nucleus. The tigroid masses are pale and few in number, or they may be entirely absent in the periphery of some of the cells. In other old people the nerve cells appear to be nearly normal, which proves, Babes thinks, that the capacity for resistance varies greatly in different individuals.

The pigment (lipochrome) is certainly more abundant in older people, a fact repeatedly confirmed by Marinesco, Rosin, myself, and others.

The more one studies the descriptions of atrophy of the nerve cells in old age, the less he feels satisfied with the studies which have thus far been made. The subject should be taken up again now that we have better methods and are more familiar than formerly with changes in the neurones due to causes other than senility.

One of the later studies is that of Marinesco, according to whom the senescence of the nerve cells is due to a defect of metabolism. The anatomical changes include a decrease in the size and number of the tigroid masses; sometimes the Nissl bodies are transformed into granules of variable size (senile chromatolysis), especially around the nucleus, but often throughout the whole cell. Marinesco believes that the "pigment" really represents a product of the involution of the cell, and that when it is increased in amount it reduces the nutritive and respiratory capacity of the cell. The number of dendrites diminishes and their branches disappear. Finally the volume of the perikaryon itself decreases. He denies neuronophagocytosis due to senility. Instead of an increase in the glia cells, these cells disappear *pari passu* with the vanishing of the nerve cells.

Of the atrophy which may take place in a neurone when its axone is injured, or when impulses which normally come to it are cut off, mention will be made in connection with secondary and tertiary degenerations of the neurone.

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Degenerations of the Neurone.

Under this heading will be considered (*a*) Primary Degenerations of the Neurone, including (1) cloudy swelling, (2) fatty degeneration, (3) vacuolar degeneration, (4) pigmentary degeneration, (5) albuminous degeneration; and (*b*) Secondary Degenerations of the Neurone.

(*a*) Primary Degenerations of the Neurone.—(1) *Cloudy Swelling.*—In view of the fact that parenchymatous degeneration or cloudy swelling has been described in connection with the acute infections and intoxications in most of the organs of the body, it is rather surprising that we find so few references in the bibliography to this form of degeneration in the nerve cells. The changes which accompany infection and intoxication are so characteristic and constant in the various secreting cells that it seems probable that a similar degeneration has been frequently met with in the nervous system, but has been described under a different name. Doubtless the presence of the peculiar tigroid masses in the protoplasm of nerve cells has been responsible for the difficulty in studying this change. If one reads Benario's careful review of the whole subject of cloudy swelling and then examines the articles by Ewing, Marinesco, and others on the pathological changes in the nerve cells in acute infections, he cannot but feel that the preliminary swelling of the nucleus and protoplasm and swelling of the tigroid masses followed by their breaking up into fine granules, described by these writers, correspond more or less closely to the cloudy swelling which affects gland cells. The alterations described by Franca in the nerve cells in plague, and by Camia in the nerve cells in influenza, are very suggestive in this connection.

References Bearing on Cloudy Swelling.

Benario: Die Lehre von der trüben Schwellung in ihrer Entwickelung und Bedeutung, Würzburg, 1891.
Ewing, J.: Studies on Ganglion Cells. Arch. Neurol. and Psychopathol., New York, vol. i., pp. 263–440.
Marinesco, G.: Recherches sur quelques lésions peu connues des cellules nerveuses corticales. Roumanie med., Bucarest, vol. vii., 1899, p. 913.
Franca: Contribution à l'étude des altérations des centres nerveux dans la peste bubonique humaine. Le Névraxe, Louvain, 1900.
Camia, M.: Due casi di psicosi consecutiva ad influenza, con autopsia. Riv. d. patol. nerv. e ment., Firenze, vol. v., 1900, p. 100.

(2) *Fatty Degeneration.*—Fat droplets of smaller or larger size are frequently met with in nerve cells in the most different pathological processes, but especially in infections and intoxications. These are usually met with in the protoplasm of the perikaryon and are visible as yellow, glistening droplets in frozen sections, or as black spherules in Marchi preparations. I have often seen black droplets in the nuclei of nerve cells in Marchi specimens; in some instances they appear to be coincident with the nucleolus.

(3) *Vacuolar Degeneration.*—The study of vacuolar degeneration of the nerve cell has had an interesting history. In the older publications, where the studies were nearly all made upon Müller's fluid preparations, nothing was more common than to read of extensive vacuolar degenerations in the cells of the brain and spinal cord. We know now that the majority at least of these were nothing more nor less than artefacts due to the action of the hardening reagent (work of Kreyssig and of Trezebinski). In some of the more recent studies, however, true vacuolization of both protoplasm and nucleus of the nerve cells has been described. Nerlich has investigated the origin of vacuoles in a case of cerebral tetanus in which the nucleus nervi hypoglossi, the nucleus nervi facialis, and the nucleus motorius nervi trigemini contained vacuolated ganglion cells. He found occasionally as many as twenty vacuoles in a single cell. The cell body was swollen, though often surrounded by a large pericellular space. The nuclei were not altered, though they were sometimes displaced from the normal position by the vacuoles.

Besides in tetanus, vacuolization of the nerve cells has been described in various infectious diseases, in acute poisoning with mineral acids (ganglion cells of the heart), and in fasting. Sometimes the nucleus, as well as the cell protoplasm, is vacuolar (Kazowsky).

The study of vacuole formation in cells generally has been approached recently from the experimental side. Two kinds of vacuoles may be distinguished according to their origin: (1) solution vacuoles, which increase in size with the diffusion and endosmosis of the agent producing them; (2) expulsion vacuoles which are formed suddenly as a result of coagulation and do not usually increase in size.

References Bearing upon Vacuolar Degeneration of the Nerve Cell.

Schmaus, H., u. E. Albrecht: Vakuoläre-fettige Degenerationen. Ergebn. d. allg. path. Morphol. u. Physiol., Wiesb., 1895, SS. 151–161.
Nerlich: Ein Beitrag zur Lehre vom Kopftetanus. Arch. f. Psychiat., etc., Berl., Bd. xxiii. (1892), S. 672.
Popoff, N. M.: Pathologisch-anatomische Veränderungen des Centralnervensystems bei der asiatischen Cholera. Arch. f. path. Anat. [etc.], Berl., Bd. cxxxvi. (1894), S. 42.
Kazowsky, A. D.: Ueber die Veränderung in den Herzganglien bei akuten Mineralsäurevergiftungen. Centralbl. f. allg. Path. u. path. Anat., Jena, Bd. v. (1894), S. 1020.
Statkewitsch: Ueber Veränderungen des Muskel- und Drüsengewebes, sowie der Herzganglien beim Hungern. Arch. f. exper. Path. u. Pharmakol., Leipz., Bd. xxxiii. (1894), SS. 415.
Ströbe, H.: Experimentelle Untersuchungen über die degenerativen und reparationischen Vorgänge bei der Heilung von Verletzungen des Rückenmarks, etc. Beitr. z. path. Anat. u. Physiol., Jena, Bd. xv. (1894), S. 383.
For a list of diseases in which vacuolar degeneration has been described, see Barbacci: *loc. cit.*, p. 805.

(4) *Pigmentary Degeneration.*—In frozen sections and in Nissl preparations of adult nerve cells in various parts, a yellowish pigment can be made out. This is said to be entirely absent in the newly born. According to Pilcz, Obersteiner, and others it appears at different periods of life in different nerve cells, at the sixth year in the spinal ganglia; at the eighth year in the anterior horn cells. The amount of pigment increases as age advances (*vide supra*, Atrophy).

This pigment is not identical with that of the locus cœruleus, substantia nigra, or substantia ferruginea. It may be improper to speak of it as pigment at all. It stains black with osmic acid, and thus is easily visible in Marchi preparations. It seems to be related to the fats (Rosin). Ramón y Cajal regards it as a metabolic product of the cell, which the latter cannot rid itself of. Whether it arises from the stainable or from the unstainable substance of Nissl is not known. Obreja and Tatuses believe that this pigment is of a fatty or myelinic nature, probably related to lecithin. They therefore look upon it as a store of nutrient substance in the cell; according to their findings it is diminished in amount in the anterior horn cells in strychnine poisoning and in tetanus, while after prolonged rest it is increased. Against this view van Gehuchten urges that the substance is absent from the nerve cells in early life, and further that in a case of tetanus which he examined there was no diminution in the amount of pigment. The whole matter requires further investigation.

References Bearing upon So-Called Pigmentary Degeneration.

Rosin, H.: Ein Beitrag zur Lehre vom Bau der Ganglienzellen. Deutsche med. Wchnschr., Leipz. u. Berl., Bd. xxii., 1896, SS. 395–397.
Ramón y Cajal, S.: Textura del sistema nervioso del hombre y de los vertebrados, Madrid, 1899, t. i., pp. 129–130.
Obreja et Tatuses: Le pigment des cellules nerveuses. Compt. rend. Soc. Sc. Méd., Bucarest, November, 1898 (*cf.* Rev. Neurol., Par., 1899, p. 326).
Barker, L. F.: The Nervous System and Its Constituent Neurones, New York, 1899, pp. 107–108.

(5) *Albuminous Degenerations.*—Accepting the definition of Klebs, by albuminous degenerations are to be understood those disturbances of nutrition in which insoluble albuminous bodies are deposited in the tissues. In the nervous system we have to deal with two such albuminous deposits: (*a*) the so-called Russell's fuchsin bodies, and (*b*) the corpora amylacea.

Ad (*a*). Russell's fuchsin bodies described in cancer, in 1890, have since been proven non-specific as far as these tumors are concerned. They occur under normal conditions in various tissues of the body, including the nervous system, but are greatly increased in numbers under pathological conditions. They are usually extracellular in situation but may occur also inside of cells. As a rule, several of them exist together. They are small, round, homogeneous bodies, varying from 0.5 to 20 μ in diameter. Under the microscope they appear as glistening masses looking not unlike fat droplets, when examined in water. They stain intensely by Gram's method and in acid fuchsin. In Ehrlich's triacid stain they are tinged sometimes with the acid fuchsin, sometimes with the orange. In Heidenhain's iron hæmatoxylin they stain black. Lubarsch found them in large numbers in atrophic conditions of the brain. The probability is that they are products of the cell protoplasm, rather than of the nucleus. Some of them may be swollen and altered cell granules. It is not impossible that fine granules in the cell protoplasm undergo chemical change and fuse to form the fuchsin bodies. Again it has been suggested that they may have their origin from lecithin. Lubarsch found that pure lecithin yields the same staining reactions as do the fuchsin bodies; on the other hand, pure lecithin is easily soluble in alcohol, while the fuchsin bodies are not.

Ad (*b*). Corpora amylacea have long been known in the central nervous system. Their origin and significance have been much disputed, but there can be no doubt that they are very numerous in atrophic and degenerated portions of the brain and spinal cord. Under normal conditions they appear in the third decade of life and are never absent in people over forty. In the cerebrum they are found in the lining of the ventricles and in the tractus olfactorius; they are less frequently found in the cerebellum. Redlich supposed that they had their origin in the nuclei of neuroglia cells. According to a widespread opinion they arise from the coagulation of myelin. It is not unlikely that some of them at least have their origin through the union with normal tissue juices of altered cell protoplasm exuded from the cell. Spiller believes that at least a portion of the corpora amylacea have been derived from altered blood-vessels. The colloid bodies described by Bevan Lewis and also by Spiller would seem to be closely related either to Russell's fuchsin bodies or to the corpora amylacea.

Recent studies make it seem certain that greater differentiation among these structures than that ordinarily made is necessary. Thus Siegert has divided them into corpora versicolorata (including the "corpora amylacea" of th central nervous system) and corpora flava (including the "corpora arenacea" of the central nervous system). The corpora versicolorata, so-called because they take a variegated tint in iodine or bromine, yield the "amyloid reaction" with aniline dyes, and are further characterized by their brittleness and their morphology. They may be, (*a*) spherical, ovate, or polygonal with rounded angles; (*b*) concentrically lamellated, and (*c*) sometimes radially striated. They never arise through direct transformation of cells, nor do they become calcified. The corpora flava, on the other hand, behave differently in solutions of the halogens (chlorine, bromine, iodine), staining of a yellow color only in Lugol's solution; they do not yield the amyloid reaction with the aniline dyes. They are waxy rather than brittle; they vary greatly in their morphology, being sometimes smoothly spherical, sometimes very irregularly shaped. Concentric lamellation may not be visible in them and they are never radially striated. Unlike the corpora versicolorata the corpora flava are said to arise directly from the transformation of cells and to show a decided tendency to become calcified.

References Bearing upon Albuminous Degenerations.

Klebs, E.: Handbuch der allgemeinen Pathologie, Bd. ii., S. 100.
Redlich, E.: Die Amyloidkörperchen des Nervensystem. Jahrb. f. Psychiat., Bd. x. (1892), 1–68.
Siegert: Untersuchungen über die Corpora amylacea sive amyloidea. Arch. f. path. Anat., etc., Berl., Bd. cxxix., S. 513.
Lubarsch, O.: Die albuminösen Degenerationen. Ergebn. d. allg. path. Morphol. u. Physiol., Wiesb., 1895, SS. 180–200.
Spiller, W. G.: On Amyloid, Colloid, Hyaloid, and Granular Bodies in the Central Nervous System. N. York M. J., 1898, August 13th.

(*b*) Secondary Degeneration, and Modifications in the Neurone following upon Injury to the Axone.—The nutritive centre of a neurone is in the perikaryon. The trophic influence emanates from the nucleus. If any part of a neurone be severed from its connections with the nucleus, the separated part dies. In case it is a medullated axone, which suffers solution of continuity, not only does the whole axone, distal from the lesion, undergo disintegration, but the myelin sheath degenerates in the same area and the nucleated sheath of Schwann or neurilemma undergoes important modifications. These phenomena taken in their totality are usually designated as secondary or Wallerian degeneration.

In the early part of the last century it was known that interruptions of the connection of peripheral nerves with the central system could lead to their degeneration (Nasse, Valantin, Stannius). The first careful study of the subject, with establishment of a law, was that undertaken by Waller, and from him the process has derived its name. He described it in detail—the coagulative breaking up of the myelin sheath and the dissolution of the axis cylinder. If a motor nerve is cut, all the fibres in the peripheral end degenerate completely as far as the muscles which they supply, the central end either remaining entirely intact or perhaps, as a result of the trauma, degenerating as far as the first node of Ranvier. If a sensory nerve be cut distalward from the spinal ganglion, all the sensory fibres of that nerve degenerate to the very periphery, though the portion of the nerve still in connection with the ganglion, as well as the central intramedullary continuation of the nerve, remain undegenerated. On the other hand, if a dorsal root of a spinal nerve is severed between the ganglion and the spinal cord, the portion of the nerve attached to the ganglion does not undergo degeneration, but that connected with the cord degenerates typically, not only in the portion outside the cord, but also throughout its whole intramedullary extent. This is the proof which has been brought for the view that the cell bodies in the spinal ganglia are the trophic centres for the peripheral sensory neurones. Following upon Waller's investigations came the observations of Türck, which demonstrated that the same law holds within the confines of the central nervous system—for example, for the pyramidal tract. Since Türck's studies a host of observations have established the general validity of the law for all groups of neurones. When an axone degenerates, the retrogressive process involves not only the main axone but also its terminals, together with the collaterals belonging to it with their terminals.

The study of secondary degenerations has been much facilitated by the introduction of Weigert's myelin sheath stain and the osmic-bichromate method of Marchi and Alghieri.

The finer histology of secondary degeneration has been studied by Homén, Howell and Huber, Tooth, von Notthaft, Ceni, and others. Von Notthaft subdivides the changes which occur in the nerve after section into two stages, the first including the alterations which take place during the first three days (fragmentation of myelin and of axone for a distance of one or two internodes on each side of lesion), probably due to trauma. The second stage, beginning on the second or third day and confining itself to that part of the fibre cellulifugal from the lesion, represents the true Wallerian secondary degeneration; it is not the direct result of the trauma, but is due to the severance of that part of the neurone from the trophic influence of the nucleus. In this second stage the axone swells up and undergoes fragmentation, and