NEUROPATHOLOGY.

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THIS review is based on neuropathological contributions which have either a direct or indirect relation to mental disease or are of major general interest. Notwithstanding these restrictions the field which had to be covered remains vast, and no claim can be made that the survey of the literature is complete, although it is hoped that it is, to some extent, representative. In order to counteract this defect, recent reviews or comprehensive papers on special problems have been recommended, whenever they were available. They will enable the reader to trace references which for lack of space had to be suppressed. For the same reason of economy, a number of quotations have been made from reviews. This does not mean that the original papers have not been consulted.

GENERAL PROBLEMS AND TRENDS OF NEUROPATHOLOGY.

The apparent failure of neuropathology to supply pathological information in a large group of psychoses has emphasized the need for new avenues of approach, and in particular, for the improvement of existing methods and the introduction of new ones. During the period under review, attempts in various directions have been made, of which the following may serve as examples:

Examination in polarized light, already established as a method for some time past, has been employed by Weaver (1941) in studies of nerve fibres after artificially produced hyperpyrexia. The author regards this as the most sensitive and accurate technique available for studying early (reversible and irreversible) degeneration of myelinated nerve fibres.

There has been a marked revival of interest in terminals, which represent the anatomical substrate of synapses. Extensive anatomical work in this field had been done by Cajal, Bielschowsky and others, for the most part with a view to establishing or refuting the neurone theory. Recent work which has been reviewed by Bodian (1942) is more directed to pathological problems. Experimental changes occurring in end bulbs after axon sectioning, carried out in sympathetic ganglia and anterior horn cells of the spinal cord, have conclusively demonstrated the reality of synaptic knobs. Recently Glees and Le Gros Clark (quoted from Bodian, 1942) have clearly shown degeneration of end bulbs in the lateral geniculate body after lesions of the retinal endings of the optic nerve. Minkler (1942) has made studies in a variety of inflammatory

https://doi.org/10.1192/bjp.90.378.152 Published online by Cambridge University Press

and degenerative pathological conditions of the spinal cord. The technique has been considerably simplified by Bodian, Glees and Le Gros Clark and others, and Minkler even claimed successful results on material that had been in formalin for a long time. The difficulties of adequate assessment remain however, considerable, owing to the vagaries of fixation, silver staining and, particularly, the great number of boutons (which run easily into a thousand around a single anterior horn cell). Moreover, despite the quality of earlier work, little is known concerning the different forms of terminals, and, in particular, their variation in different parts of the brain. According to Glees (1942) there is a certain amount of evidence that it may be a general phenomenon of the central nervous system that terminals do not end freely, but have a definite end apparatus. Further work along these lines may well contribute new information in various directions.

Histochemical methods have been employed for the demonstration of various structures and substances. Staining of the erythrocytes by benzidine has become increasingly popular for the investigation of normal and abnormal vascularity, and disturbance of the blood circulation (*cf.* section on vascular disease). Pickworth, who first advocated the application of this method to the central nervous system, published in 1941 a modification, allowing a differential staining of red and white blood corpuscles.

To the demonstration of vitamin C in the nervous system by means of the silver nitrate method reference will be made later in this review. The distribution of alkaline phosphatase in the brain was studied by Landow, Kabat and Newman (1942), using Robison's histochemical test. They found greatest activity in the endothelial cells, in the brain stem of the chick, in various tumours, and also in plaques of disseminated sclerosis. Intravital staining has been particularly used for the elucidation of problems concerning the blood brain barrier. Friedemann, in a recent review (1942), has emphasized the importance of newly gained information about the electrical charge governing permeability to problems such as incubation period, neurotropy of micro-organisms, etc. Intravital staining has been advocated as an aid to neuro-surgery by Sorsby, Dickson-Wright and Elkeles (1943), who demonstrated that Kiton fast green, a basic dye with acid properties, stains connective tissue in mesodermal tumours, degenerating gliomas and cortical scars in epilepsy. This new approach may lead to further interesting developments.

Micro-incineration has been in use since Policard first devised a suitable technique in 1923. While its results, so far, have been limited in scope, systematic investigations, chiefly by Alexander (1938) and Alexander and Myerson (1938), have yielded undoubtedly valuable information about the neurone in normal and pathological conditions, and it is chiefly due to their labours that micro-incineration is becoming progressively more useful as a supplementary method in many neuropathological conditions. Heat-resistant ash is more marked in the cerebellum and allocortex than in the isocortex and basal ganglia, and there are significant differences in relation to architectonic boundaries. Immature nerve cells contain more ash than mature ones. The heaviest deposits have been found in the nucleolus and the Nissl substance of cytoplasm and dendrites, while the rest of the nucleus, neurofibrils, hillock, axis cylinder and myelin

sheaths contain no ash or only a small amount. Many interesting observations have been made in a variety of pathological conditions. Hypermineralization has been found in haemorrhages, inflammation, tumour, tuberosclerosis, and in the neurofibrils of Alzheimer's disease; on the other hand, necrosis, softening, plaques of disseminated sclerosis, and the cell disease of amaurotic idiocy are characterized by loss of minerals. Alexander and Myerson (1938) also made an attempt at supplementing these results by spectroscopy, which with experience and careful manipulation yields reproducible results, although these are not always in accordance with those obtained from micro-incineration. Normal cerebral grey matter of the adult brain is richer than white matter in iron, calcium, magnesium and sodium, while white matter is richer in phosphorus. In the newborn most elements except iron are increased. In oedema there is an increase of sodium and calcium particularly within the white matter. No absolute increase of iron was found in dementia paralytica, despite heavy perivascular and intraglial deposits of this metal. This is explained by the concomitant decrease of the vascular bed in this condition. Lead, in lead encephalopathy, is mainly deposited in the grey matter. Meningiomas contain ten times as much calcium as normal grey matter, while spongioblastomas contain more potassium. Mention will be made of other results in later sections of this review.

Greenfield (1938), reviewing histochemical and cell physiological work on the neurone, came to the conclusion that so far little has been done to alter the conceptions formulated by Cajal and Nissl. Examination of the living and unfixed nerve cells had even established the real existence of cell constituents such as tigroid bodies and neurofibrils. In the meantime, however, there have been interesting general developments in the cytological field, as is shown in reviews by Gersh (1941), and particularly in the excellent book edited by Bourne (1942). New techniques of fixation have been developed, such as the Altman-Gersh method of freezing-drying which (since the application of liquid air stops all metabolic processes at once) has proved of immeasurable value for cytological studies. At the present time, however, its application to nervous tissue appears to be difficult.

The advent of fluorescence and electron microscopy is naturally of great interest. Fluorescence microscopy (Ellinger, 1940) has proved successful in investigations of certain pigments, vitamins and viruses. So far, little has been achieved in the nervous system, but it must be admitted that no appreciable systematic work has yet been done with fluorescent dyes in this field.

There are great and almost insuperable difficulties in regard to a direct application of electron microscopy to cytological studies, and especially to studies of nervous tissues. Its success, however, in virus diseases (Stanley and Anderson, 1941), other micro-organisms including the syphilitic spirochaetes (Mudd, Polevitzky and Anderson, 1942), and the reaction of micro-organisms to antibodies (Anderson and Stanley, 1941) is of indirect value to neuropathology, and, e.g., constitutes a challenge to workers in the field of neurosyphilis. Recently electron microscopy has been developed in combination with micro-incineration after fixation by the Altman-Gersh method (Scott and Packer, quoted from Bourne, 1942). This appears to open

an almost unlimited field for studies of minerals in tissues, with a much greater accuracy of localization than was obtainable in ordinary histospectrographic analysis.

Bensley and Hoerr (quoted from Bourne, 1942) have devised a bold technique of dissecting out of liver cells, organelles, such as mitochondria, which have been subsequently submitted to various chemical investigations. New information is thus being collected about the composition and the normal and abnormal function of this and other cell constituents. In investigations of this kind much help will be derived from ultramicrochemical methods introduced by Linderström-Lang-Holter (quoted from Bourne, 1942), which are applicable to minute pieces of tissue and to microtome sections alternately used for chemical and histological examination. One of these methods, the Cartesian diver technique, enabled, for example, Boell and Nachmansohn (1940) and Nachmansohn and Steinbach (1942*a* and *b*) to estimate the content of cholinesterase, diphosphothiamine and succinic dehydrogenases separately in myelin sheaths and axoplasm in the giant fibre of the squid.

It has been said that the biochemist wants his material in test-tubes, whereas the histologist is merely interested in structure. However, the histologist's preoccupation with structure is a fairly recent development, and there are now unmistakable signs of a *rapprochement* between the two branches of science. This process is already extending to neuropathology, and will extend further in a measure, as new methods become applicable to the central nervous system. It will be closely watched by all workers in the psychiatric field.

Special Neuropathology: Inflammatory Diseases.

The problems concerning *syphilis* have been comprehensively reviewed by Reynolds, Mohr and Moore (1942). They mention two apparently spirochaetal conditions resembling syphilis which might be interesting subjects for comparative research: *Maladia del Pinta*, which may affect the central nervous system, and *Bejel*, occuring in the Euphrates Valley and producing predominantly bone lesions. With the help of the electron microscope, investigations have yielded some interesting new information about the structure of spirochaetes. Granular inclusions, lateral buds, and constrictions were clearly seen, and the organism was shown to be surrounded by a sheath which forms thin projecting tendrils. Further results, particularly in connection with the action of antibodies, may be confidently expected in the near future. Among other contributions to the spirochaetal problem may be mentioned that by Steiner (1940). Miliary necrosis in dementia paralytica and other syphilitic conditions is, according to him, due to spirochaetal conglomerations, forming reproduction centres in the living tissues of the host, and not the result of a vascular factor assumed to be operative by previous workers. The so-called silver cells described by the same author have been investigated by Blackman and Putnam (1938) and Hassin and Diamond (1939). The existence of granules was confirmed, but their spirochaetal origin denied. The last-mentioned authors doubted the cellular nature of the structures.

Several cases of stationary general paralysis have been investigated histo-

logically (Galbraith, 1940; Urechia and Mueller, 1940; Pinto, 1941). The condition in Galbraith's case lasted 31 years. The pathogenesis of the Lissauer type of general paralysis has been under renewed discussion for some years, and the various views put forward have been reviewed in the light of a particularly early case by Galbraith and Meyer (1942), who found that the focal symptoms were produced by a local intensification of the inflammatory process rather than by an independent vascular factor or syncretic process. Morel and Duman (1941) made an attempt at assessing the relation between varieties of psychotic manifestations in general paralysis and changes in macroglia, microglia and oligodendroglia.

Studies have been made in Torula meningitis (de Busschaer, Scherer and Thomas, 1938), Rocky Mountain spotted fever (Hassin, 1940), pink disease (erythroedema polyneuritis) (Ratcliffe, 1941), and toxoplasmic encephalomyelitis (Cowen, Wolfe and Paige, 1942). This latter condition is of some interest, as its onset is congenital or soon after birth, and may result in various neurological and mental defects. Pathologically it is characterized by multiple foci of intracerebral calcification due to the tendency of the granulomas set up by the organism to calcify.

Boeck's disease (sarcoid), regarded by some as an unusual type of tuberculosis, was the subject of a study by Erickson, Odom and Stern (1942). The central nervous system was involved. The absence of necrosis in the granulomas produced would argue against tuberculosis and syphilis.

While fundamental discoveries about *neurotropic virus diseases* have been made in a period prior to that covered by this review, there have been none the less some noteworthy recent developments. A general review which includes also other neurological and psychological conditions in man and animals has been made by Findlay and Innes (1940), and the most recent developments have been discussed by Brain, Greenfield and Russell (1943). The new types of encephalomyelitis due to virus infection include Japanese B, St. Louis, Western and Eastern forms of equine encephalitis and Russian encephalitis. Equine encephalitis, which occurs also in man, has received the greatest attention (Adler, 1941; Baker and Noran, 1942; Weil and Breslich, 1942). According to the last-named authors all the various infections enumerated above have in common intense monocytic inflammation, with formation of dense foci of gliosis and diffuse astrocytosis. The inflammatory reaction is most marked in the grey masses of the mid-brain. The description given by the other authors differs, however, in some points from that given by Weil and Breslich.

While none of these virus infections has been observed in this country, Henson and Russell (1942), Russell (1943) and Greenfield (1943) reported cases of the type of encephalitis described by Hurst (1941) as "haemorrhagic leucoencephalitis." As the name suggests, it is characterized by polymorphonuclear exudate, perivascular necrosis, focal demyelination and microglial reaction confined almost exclusively to the white matter. The occurrence of polymorphonuclear leucocytes distinguishes this condition from post-vaccinial, post-influenzal, Baker's haemorrhagic encephalitis and purpura. According to Hurst, it forms a link between these last-mentioned inflammations and the demyelinizing diseases. It must also be distinguished from the encephalopathy

occasionally following treatment by sulphanilamides (Fisher and Gilmour, 1939; Rosemann and Aring, 1941), which is interesting in view of the wide use of these drugs.

A rare type of encephalitis associated with the name of Dawson has been studied recently by various workers (Smith, Lennette and Reames, 1941; Akelaitis and Zeldis, 1942; Brain, Greenfield and Russell, 1943). It seems to occur predominantly in children; its course is subacute; involuntary movements are characteristic. The cerebro-spinal fluid is normal or contains only a few lymphocytes. In one case a virus identical with herpes simplex was isolated from the brain. The characteristic histological sign is the occurrence of eosinophil intranuclear inclusion bodies in the cortical neurones associated with perivascular exudation of lymphocytes and plasma cells, microglial reaction and astrocytosis. Inclusion bodies were also found in oligodendrogliocytes, but no demyelination ensued.

Bodian and Howe (1940) made a comprehensive experimental investigation on poliomyelitis. They concluded that nerve-cell pericarya are more important for the spread of the infection than fibre connections. The invasion was checked if the nerve cells were degenerated, e.g. in the thalamus. Kempf *et al.* (1941) were unable to infect rabbits by intracranial injections of poliomyelitis virus when the animals were kept in a condition of hypoglycaemia. The lowered susceptibility is possibly due to the decrease of cellular oxidation.

The significance of primary thrombosis in the pathogenesis of disseminated encephalomyelitis has been again stressed by Putnam and Alexander (1939). Apart from local infection as a pathogenic factor they consider the role of allergy, as had been done also by Finley (1938). The problem of anaphylaxis as cause for lesions in the brain has been the object of several experimental studies. Ferraro and Jervis (1940) and Jervis, Ferraro, Kopeloff and Kopeloff (1941) sensitized monkeys by sterile extract of rabbit brain and egg white respectively. The results were in accordance with previous experiences by other workers: scattered foci of demyelination and accumulation of fat-containing scavenger cells. There was also a local ("Arthus") phenomenon at the site of the intracerebral injections (necrosis, oedema, leucocytic infiltration). Kolb and Bolton (1940) were unable to produce demyelination in rats by injections of rabbit serum containing brain antibodies.

Intoxication.

Studies on intoxication, particularly if conducted on a comprehensive experimental and comparative scale, have obtained considerable importance as a means of investigating the reactions of the central nervous system to known agents. This is stressed by Ferraro, Jervis and English (1938), who, summarizing earlier work, point out the differential attack of various substances. Metallic salts, inorganic acids, histamine, etc., produce changes of nerve cells, cyanides affect the myelin, arsenic has a specific action on blood vessels, and guanidine appears to act upon the macroglia. In the same paper they report experimental results with phosphorus, which seems to act on nerve cells (vacuolation), on the blood vessels (focal cortical necrosis, haemorrhages and

endothelial proliferation), and on the glia. In particular, a swelling of the microglia is described which is considered to be a counterpart to that of the oligodendroglia. Fatty degeneration, often regarded as specific of phosphorus poisoning, was absent in their animal material, as it was in the eight human cases investigated by Takeyo-Sikō (1939).

Encephalopathy produced by arsenicals, and especially arsphenamine, was the subject of several studies (Roseman and Aring, 1941; Ecker and Kernohan, 1941). Alterations in the nerve cells, perivascular necrosis due to endothelial damage of the small vessels and inflammatory reaction were the main features, while petechial haemorrhages were less important.

A study of deposits of gold in the central nervous system in animals after injection of gold salts (Roberts, 1939) is of some interest in view of its therapeutic use. The metal was found in nerve and glial cells in the nuclei of the intracranial nerves, supraoptic and infundibular nuclei, Purkinjë cells and anterior horn cells.

Scholz and Hsü (1938), following up earlier experimental work, investigated late damage from X-ray radiation of the human brain. Extensive foci of necrosis were found, due to severe degeneration of the blood vessels, the walls of which contained homogeneous hyalin-like deposits.

Of greater interest to the psychiatrist are experiments carried out by Schube and Raskin (1940) with benzedrine. It appears that after large doses congestion and stasis of meningeal and intracerebral vessels, including those of the choroid plexus, occur, leading to haemorrhages in the cerebellum and other parts of the brain. Only guinea-pigs and rats were used and no illustrations are given.

A number of contributions has been made in relation to so-called anoxic poisons, including carbon monoxide, cyanide, and carbon bisulphide, anaesthetics, and barbiturates. Their study is not only interesting because of the mental changes that often ensue, but also in view of their close liaison with problems of a general nature, such as selective regional vulnerability, demyelination, etc.

Carbon monoxide poisoning is the oldest and best known member of this group. Raskin and Mullaney (1940) have recently given a comprehensive review of its nervous, mental and histological sequelae, to which they added a new and thoroughly examined case which had survived the acute poisoning for 15 years. Hsü and Ch'Eng (1938) studied the "myelinopathy" in carbon monoxide poisoning, an already well-known lesion which they consider to be the direct effect of anoxaemia. An investigation into the pathogenesis of demyelination was also the aim of histological and biochemical experimental studies in cyanide poisoning by Hurst (1940, 1941) and Windham (1941). Their results indicated that anoxaemia is more important than the inhibition of cellular enzymes (succinic dehydrogenases, cytochrome oxidase and catalase). Sodium azide, though in its biochemical action resembling cyanide, has no histological effect. The histological lesions vary according to the degree of poisoning: in severe poisoning the cerebral and cerebellar cortex suffer most; in less severe intoxication lesions of the basal ganglia (putamen and globus pallidus) are predominant; in repeated slight poisoning there is, apart from the

necrosis of the basal ganglia, demyelination of the white matter. While, in the opinion of the present writer, it is of great interest that demyelination of the white matter can be produced by carbon monoxide, cyanide and other poisons, there is no record of any case of true demyelinizing disease with selective lesions of the globus pallidus such as occur characteristically after poisoning. It may be added in this connection that according to Verhaert (1941) demyelinization may be produced in lead poisoning, while Jervis and Kindwall (1942) describe a case resembling Schilder's disease clinically and pathologically following ergotamine poisoning.

The clinical and pathological sequelae of anaesthesia have been the subject of a number of papers during the period under review. Steegman (1939) described the pathological lesions in four fatalities. Abbot and Courville (1938), Batten and Courville (1940) and Winblad (1940) dealt with the ill effects of nitrous oxide poisoning, while Courville (1941) paid attention to ether anaesthesia. Again, lesions localized in the cerebral and cerebellar cortex, globus pallidus, Sommer sector, etc., figure foremost in nitrous oxide poisoning and they have been also previously described, after respiratory failure caused by prolonged ether anaesthesia (Meyer and Blume, 1934). Although lack of oxygen is recognized as the primary cause of the lesions in all these intoxications, there are differences in the pathogenesis, which in the opinion of Courville (1941) warrant the introduction of the concept of a "selective anoxia." Batten and Courville (1940) were particularly interested in the mental changes following nitrous oxide anaesthesia which they studied in 10 personal cases, reviewing also 11 cases described by earlier workers. Confusion, stupor, coma, and progressive dementia were the chief psychotic symptoms, while choreathetosis and rigidity indicated involvement of the basal ganglia. Ether tremor and ether convulsions, which have attracted considerable attention in recent years, are according to Courville (1941), of anoxic origin, and not due to hyperpyrexia, acidosis, etc.

It is interesting that selective necrosis of the globus pallidus may occur after barbiturate poisoning (de Groat, 1940; Alexander, 1942*b*). In the case of Alexander, softening of the cerebellar cortex and widespread thrombosis of veins in the cerebral white matter were additional features. Lesions of the lenticular nucleus and, in particular, of the globus pallidus have been described in carbon bisulphide poisoning by Alpers and Lewy (1940), Ferraro, Jervis and Flicker (1941). In addition, there are diffuse and circumscribed changes in other parts of the brain which are not yet fully understood. Carbon bisulphide poisoning deserves attention because of its industrial importance and the frequency of mental changes.

The vulnerability of the globus pallidus and other centres in this group of anoxic conditions (which incidentally comprise, in addition to the above-mentioned poisons, morphine, dinitrobenzol, ether, manganese and severe anaemia) has, in the past, aroused the interest of many workers, including the present writer. The latest attempt to solve the problem has been made by Alexander (1942*a* and *b*). On the strength of pathological investigations and painstaking re-examination of the blood supply to the basal ganglia, this author concludes that the softening of the globus pallidus is due to thrombosis of the

anterior choroid artery, which he suggests renaming the pallido-hippocampo-capsular artery, in accordance with the main regions supplied. This artery is prone to undergo thrombosis during circulatory disturbances because it has the longest subarachnoid course and the greatest "undivided length" of any cerebral vessel of similar calibre. Detail must be consulted in the original papers. The author, summarizing, states that "the two most vulnerable structures of the human brain, the globus pallidus and the cornu ammonis, are both supplied by the anterior choroid artery." Next to this artery, the long thin venules in the cerebral white matter are most susceptible to thrombosis.

It remains to be seen how generally Alexander's interesting claim will be accepted. Most previous workers who have agreed that peculiarities in the blood supply and oxygenation determine the susceptibility of the centres concerned have vigorously denied thrombosis as a primary cause. Moreover, while lesions in the globus pallidus and cornu ammonis occur frequently together in anoxic conditions, the absence of globus pallidus lesions in epilepsy would require an additional explanation. As at an earlier stage of the discussion, comparative experimental studies will prove useful for the solution of the problem. In this regard, an interesting contribution has been made by Scharrer (1940). He found that in the opossum the cornu ammonis is the chief site of lesions in carbon monoxide poisoning. The vessels in this region are arranged in a rake-like pattern which, according to the author, explains why the blood pressure can drop locally below a critical level before this condition occurs in the rest of the brain.

Vascular Disease and Disturbances of Circulation.

A useful general survey of recent work on gross vascular disease has been presented by Scupham, de Takats, van Dellen and Marcus (1942). It includes pathogenic, symptomatological, pathological and therapeutic aspects of arteriosclerosis, hyperpiesis, thromboangiitis obliterans, etc. Original contributions deal with periarteritis nodosa, which affects the brain in about 20 per cent. of cases (Malamud and Foster, 1942), lesions in the central nervous system associated with subacute bacterial, chronic verrucose and other types of endocarditis (Bruetsch, 1938, 1939; Kernohan, Woltman and Barnes, 1939), cerebral arteriosclerosis (Winkelman, 1939), malignant hypertension (Rosenberg, 1940), granular or verrucose atrophy in hyperpiesis and progressive vascular disease of the cerebral cortex on an arteriosclerotic basis (Greenfield, 1938).

Of special psychiatric interest is the increasing frequency with which the vascular changes characteristic of thrombo-angiitis obliterans are found in the brain, leading to various types of organic mental disorder (Meves [clinical report on four cases], 1938); Nils Antoni, 1941). Krücke (1940) described the formation of true bone during the organization of the thrombus in this disease.

Scholz and Nieto (1938) and Scholz (1938) made an anatomical and histochemical analysis of certain vascular affections which are often confused with arteriosclerosis. One of them ("*drusige*" degeneration) is related to the perivascular type of senile plaques and is only found in the highest age-group.

An attempt at correlation between mental symptoms in cerebral arterio-

sclerosis and neuropathological changes was made by Rothschild (1942) on the strength of 28 cases. There were marked discrepancies between the degree of anatomical change and psychosis. In some cases no anatomical substrate was found at all. This discrepancy is explained by the differing capacity of the individual to compensate for brain damage. The same explanation had been given by this author in an earlier paper (1937) for the lack of correlation between senile anatomical changes and intellectual impairment.

The discussion on the pathology of apoplexy, which was very lively at an earlier period, has quietened down. K. Stern (1938), while accepting the importance of vasomotor factors, points out that no single theory is as yet wholly satisfactory. The preference for haemorrhages to occur in the area of the basilar artery (as found in hyperpiesia) may be due to oedema, or the rapid increase of intracranial pressure. This author advocates more work on the venous side of the circulation in order to understand the phenomena of the apoplectic insult. In parenthesis, Schlesinger (1939, 1940) has, in the course of his experimental work, investigated anatomical and pathological problems related to venous circulation in the brain, particularly the galenic system.

Interest in cerebral fat embolism has been considerable, partly in association with war and air raid injuries, partly in relation to occasional complications of convulsive treatment of psychoses (Nightingale and Meyer, 1940; Silverstein and Konzelman, 1940; Robb-Smith, Russell, Greenfield, 1941; Winkelman, 1942). No new points of major importance have been introduced. In this connection neuropathological investigations in sickle cell anaemia are of interest. Gross neurological symptoms are occasionally seen in this condition (Skoog, 1940). Wertham, Mitchell and Angrist (1942) found, in addition to small areas of softening and haemorrhages, intravascular lipoids which, however, did not give the reactions of neutral fat. They make the interesting suggestion that the lipoid material is derived from the disintegrating lipoid cell membrane of the red blood corpuscles, which for this reason assume the sickle form.

It is impossible to give even a superficial account of the results of studies made in relation to disturbance of the cerebral circulation. Many of the problems are of a physiological nature and will be dealt with elsewhere in this volume. It is now generally accepted that there are myelinated and unmyelinated fibres on cerebral vessels, and that their function is the maintenance of the intracranial blood-flow (Forbes and Cobb, 1938; Forbes, 1940). The benzidine stain has been increasingly employed to demonstrate normal and abnormal circulation (Putnam and Alexander, 1938; Alexander and Putnam, 1938; Campbell, Alexander and Putnam, 1938; Fazio, 1938; Sahs and Alexander, 1939; Hardman, 1940). It has been found useful in the diagnosis of stasis, thrombosis and embolism. Perivascular haemorrhages are shown to be netlike in the grey, and nodular in the white matter. Certain characteristics of the vascular arrangement in recent and old softenings, scars, Wernicke's disease, various tumours, etc., come out well. Size, density and regularity of the sinusoids have a definite relation to the differentiation of the tumours, which have in common inadequacy and awkwardness of the blood supply. In dementia paralytica and other organic psychoses a considerable

loss of the vascular bed of the cerebral cortex is demonstrable, and this is borne out by investigations of the cerebral blood-flow, which in severe cases is reduced by about a third (Rosenbaum, Roseman, Aring, Ferris, 1942). An interesting study of the correlation between vascularity (as demonstrated by benzidine stain) and the oxidase reaction has been carried out in the cat brain by Campbell (1939). There exists a parallelism between the amount of the enzyme and vascularity. Both are low in the archicortex, while within the isocortex the highest values are found in laminae 3 and 4. Of the centres of the basal ganglia, the globus pallidus is lowest and the lateral geniculate body highest in the scale; the values in the cerebellum approach those found in the isocortex.

Many other investigations into the normal vascular bed of various centres of the brain cannot be discussed here.

Dreszer and Scholz (1939) made an interesting use of benzidine stains for investigations into the pathogenesis of cardiazol convulsions. They claimed that anaemia of the brain could be demonstrated preceding the onset of the convulsion. Whitehead *et al.* (1940) made a similar observation in one animal, but A. Meyer (1939), working with Watterson and M. Meyer, failed to confirm this result in a series of controlled experiments. Severe irregularities of the blood circulation were, however, seen in later stages of the convulsions, and also after injection of vasodilator drugs. This would be in accord with the clinical and physiological experiences of Penfield and other workers, for the detail of which the exhaustive monograph on epilepsy and cerebral localization by Penfield and Erickson (1941) should be consulted.

In sudden arrest of the circulation of the brain, Weinberger, Gibbon and Gibbon (1940) found permanent damage after interruption of 3′ 10″ (three minutes, ten seconds), necrosis and softening after 3′ 25″, and complete destruction and liquefaction after 7′ 30″. In order of susceptibility, visual and motor cortex rank first, while orbital, olfactory and temporal cortex are least vulnerable. Laminae 3 and 4 are most affected. Among other structures the order is: Purkinjë cells, lateral geniculate body, hypothalamic nuclei, thalamus, globus pallidus, caudate nucleus. The brain stem and spinal cord are usually uninjured. It is interesting to note that there is much agreement with Campbell's results above, and also, that the individual susceptibility after arrest of circulation does not correspond to that in anoxia, which seems to be quite a different mechanism. The presence of much inflammatory change is also an interesting phenomenon. Kabat and Schadewald (1941) found the susceptibility to arrest of circulation of synaptic terminals much lower than that of the nerve cells on which they end. They regard this as strong evidence against structural continuity.

In the period under review work has been done with regard to the chemical and histological clarification of cerebral oedema and brain swelling. Most of it has been reviewed by Greenfield (1942). According to him there are physical, chemical and histological criteria of oedema. He does not recognize an essential difference between oedema and swelling, which differ only by degree. As physical criterion he accepts the statement by Alexander and Looney (1938), who define oedema as an increase of brain size beyond 96 per cent. of skull capacity. Chemical criteria have been summarized by Stewart-

Wallace (1939), who found increase of fluid and of Na and Cl ions in the white matter with the exception of the big commissural and associational fibre tracts. Cortex and basal ganglia do not participate. The excess fluid is probably derived from the blood. The histological criteria are best studied in oedema associated with malignant tumours (Greenfield, 1939). In myelin-stained slides the centrum ovale is pale, but the large commissural tracts are not affected. The reduced stainability is due to separation of the fibres, but after some time true degeneration ensues in severer cases. The axis cylinders are less affected, although there is frequently some swelling and beading. Clasmatodendrosis is one of the most constant signs, and not a chance finding as it was believed to be by earlier workers. In cases of longer standing this may pass over into a proliferative type of astrocyte. The oligodendroglia shows little change, and abnormalities of the microglia depend on the stage of myelin degeneration. The changes in the white matter are ill defined, gradually merging with the normal tissue. There is much confusion about the naked-eye identification of oedema. Neither wetness of the surface nor congestion are characteristic. The only certain criterion in the fresh brain is diffuse yellowish discoloration of the white matter. The commonest cause of oedema is thrombosis of the cerebral vessels; next come cerebral tumours, granulomas and abscesses. In the experience of Greenfield trauma leads only rarely to generalized oedema, which is usually limited to the neighbourhood of the bruised area.

Senile and Presenile Conditions.

The problem of presenile dementias has been dealt with in a discussion at the Royal Society of Medicine in which Mayer-Gross, Critchley, Greenfield and A. Meyer took part (1938). More recently it has been the subject of a comprehensive review by McMenemy (1941). The tendency was to widen the conception of presenile dementia beyond what McMenemy calls the essential group, i.e. Alzheimer's disease and Pick's disease, which form only a small part of organic conditions presenting themselves at this age-period. This broader conception should be welcomed, as there are undoubtedly other presenile conditions which have not yet been fully explored. One of them, the Jakob-Creutzfeld syndrome, has aroused increasing interest, contributions having been made by A. Meyer (1938), Stadler (1939), Jansen and Monrad-Krohn (1939), Davison and Rabiner (1940), Jervis, Hurdum and O'Neill (1942). Worster-Drought, Greenfield and McMenemy (1940) and McMenemy and Pollack (1941) published further important cases of presenile psychosis, so far unclassifiable. K. Stern's (1939) case of thalamic degeneration associated with dementia (discussed later) belongs also to this group, as does the acute catatoniform psychosis described under the heading of Kraepelin's disease by Best (1941). In this process of exploring the presenile dementias on a wider scale, it would be a mistake, however, to include conditions such as the epilepsies, demyelinizing diseases and others whose incidence at this age-period is more or less fortuitous. It should also not be forgotten that the "essential dementias"—although only a small group—have a particularly close relation to the process of ageing, and they are, thus, the natural object of fundamental

pathological studies in this field. They will be, therefore, the principal subject of this review.

In the period under review there have been published numerous new cases of Alzheimer's disease (Liebers, 1939; McMenemy, Worster-Drought, Flind and Williams, 1939; van Bogaert, Maere and Schmedt, 1940; McMenemy, 1940; Grünthal and Wenger, 1940; Ferraro and Jervis, 1941; Hemphill and Stengel, 1941; English, 1942), and of Pick's disease (Davison, 1938; Nichols and Weigner, 1938; Löwenberg, Boyd and Salon, 1939; Bouton, 1940; Bosch and Orlando, 1940; Malamud and Boyd, 1940; Hassin and Levitin, 1941). In the contributions on Alzheimer's disease particular attention has been paid to familial or hereditary aspects and to onset before the presenium (Grünthal and Wenger, van Bogaert, Maere and Schmedt, Ferraro and Jervis). Van Bogaert *et al.* divide cases into early, middle-aged and presenile, occurring either sporadically or in families. In the brain of one of the two familial cases investigated by Grünthal and Wenger neither plaques nor neurofibrillar changes were found; instead there was a circumscribed atrophy of the frontal lobes. The authors argue that plaques, etc., may not be an essential feature of Alzheimer's disease, but may possibly be due to a superimposed factor of hypovitaminosis. There is, however, at least the possibility that the authors had been dealing with the equally interesting familial concurrence of Alzheimer's and Pick's disease.

In the case of Hemphill and Stengel the interesting observation of hemiatrophy with crossed cerebellar degeneration was made.

There have not been any major advances in the pathology of Pick's disease, which Nichols and Weigner suggest renaming idiopathic circumscribed presenile cerebral atrophy. Attention has been focused on the interpretation of the clinical symptomatology in the light of the localization of the lesion. The frequent presence of a hereditary factor and of early manifestation of the disease has been stressed by Löwenberg, Boyd and Salon. These authors and also Malamud and Boyd confirm the earlier view that the condition is a system disease affecting—though not exclusively—the highest centres within the frontal, temporal and parietal lobes. Hassin and Levitin emphasize the discrepancy between mild parenchymatous and severe neuroglial proliferation. They favour a toxic etiology in view of the similarity to changes produced by metrazol. It is interesting that the gliosis of the white matter may be so intense as to cause hypermineralization (Alexander and Looney, 1938*b*).

The occurrence of argentophilic structures in these conditions has stimulated much further research into their pathogenesis and relation to the problem of ageing. A good historical survey has been given by McMenemy (1940). From this it appears that the theory associated with the names of Ruzicka, Grünthal and von Braunmühl has been, in principle at least, accepted by most workers. Accordingly ageing is essentially a change of the brain colloids from a highly dispersed to a less dispersed state, resulting in condensation and coagulation (hysteresis). This process is alleged to take place in the so-called ground substance. Plaques and the thickening of the neurofibrils are secondary phenomena. It is possible that dehydration is a related factor. Its importance in regard to the pathology of senility has been stressed by Alexander and Looney

(1938*a*), who found the post-mortem water-binding capacity decreased in senile brains.

With regard to detail there have been, however, many divergencies of opinion. It has been said that von Braunmühl's colloidal experiments do not account for all forms of senile plaques (Müller, 1939; Jakob, 1939). The mechanism of the perivascular plaque, for example, is regarded as different, and explained by vessel wall changes described by Scholz as "*drusige Entartung*" (to which reference has been made in the paragraph on vascular diseases). King (1942), using impregnation with ammoniacal silver without further chemical treatment, also accepts the vascular change described by Scholz as responsible for perivascular plaques, and, in addition, found that in the Ammon's horn plaques may develop from degenerating neurofibrils. While he reserves this mechanism for one type of plaque only, Soniat (1941) regards it as operative in the great majority of plaques. Alexander and Looney (1938*b*), using micro-incineration, found hypermineralization at the site of argentophilic neurofibrils and other intracellular argentophil inclusions in senile dementia, Alzheimer's disease, Pick's disease, pellagral ganglion change and the change experimentally produced by soaking. They failed, however, to demonstrate either increase or decrease of ash at the site of plaques, which they regard as metaplasias of the glial reticulum, and not as a reticulum containing an excess of inorganic substances. This is, according to the authors, at variance with von Braunmühl's theory.

Müller (1939) found that the silver impregnability of plaques is reduced if unstained sections have been previously treated with acetone or xylol. He also failed to demonstrate argentophil structures in the brains of old animals. It is difficult to accept his explanation that this might be due to the shorter life period of animals as compared with that of man.

There remain, thus, many obscurities in the pathogenesis of plaques and related phenomena. As Soniat (1941) points out, our chemical methods are not yet adequate enough to elucidate the complex biochemical processes involved in the formation of plaques. One point, however, seems to emerge clearly, that is, that glial cells are not primarily concerned with plaque formation (McMenemy, 1940; Soniat, 1941; King, 1942). The proliferation of microglia and astrocytes is a reaction to the formation of the plaque, and the oligodendroglia is apparently involved for spatial reasons only. The reaction of the various glial cells, however, seems to account for certain morphological variations in the final appearance of the plaque (McMenemy, 1940).

According to Korenchevsky (1942), ageing is associated with hypoplasia of all organs which commences soon after birth. The prime of life is, thus, in early infancy. In addition there is a fall in the nucleocytoplasmic ratio parallel with increasing age. There are also reports of a progressive reduction of anterior horn cells and spinal roots (Gardner, 1940), of olfactory nerves (Smith, 1942), of *boutons terminaux* in the spinal cord (Minckler, 1942), of increase of lipoids in afferent neurones (Truex and Zwemer, 1942), and increased neuronophagia (Andrew, 1939, 1940). It is obvious that these localized findings are only of limited value. They must be considered in relation to other anatomico-pathologic, biochemical and endocrinological aspects.

Head Injuries.

The war has, naturally, stimulated much work on injuries of the central nervous system. From the pathological point of view the problem of concussion and the pathogenesis of blast injuries have received particular attention, and it is proposed to confine this review to the developments made in these conditions.

As regards concussion, Greenfield (1938) has given a survey of different pathogenic theories, both historical and current. According to him these theories may be divided into vascular, humoral and mechanical. The vascular theory most popular in this country is Trotter's modification of Kocher's theory, which attributes loss of consciousness to sudden anaemia. The classical example of humoral theories is that of Duret, supported by Berner, which presupposes a wave of cerebrospinal fluid being driven from the lateral ventricles towards the foramen magnum, distending on its way the third and fourth ventricles and Sylvian aqueduct. The theories of a direct mechanical effect on the nervous tissue may be conveniently subdivided into three: compression, vibration, and deformation and stretching.

The investigations made within the period covered by this review differ in their support to the main theories just outlined. Among those who favour a vascular pathogenesis are Schaller, Tamaki and Newman (1941). These authors submitted rats to a propulsion impact to the head by dropping them from variable heights. Diapedetic petechiae, thrombosis and hyalin change of the blood vessels were produced, which they regard as identical with those observed in human brains after concussion, and which they strictly separate from the changes seen in contusion, laceration and tearing. They are, according to the authors, the result of vascular dilatation, stasis and anoxaemia. Some of the changes, through resorption of petechiae, are reversible, and there is also a tendency to reparation by final obliteration of the damaged vessels with ensuing replacement gliosis. No large haemorrhages nor softenings were seen, nor was there a tendency to progression.

Vasomotor changes operating as outlined by Ricker are held by Helfand (1939) to be responsible for most of the changes seen in the brains of 22 cases of head injuries. Mechanical factors, e.g., resulting in displacement of Purkinjë cells, play only a minor part. In a later paper Helfand (1941), using the Pickworth method, demonstrates local disturbances in the vascular pattern.

Dixon (1940) suggests an explanation somewhat along the lines of Trotter's, with the difference that it is not the blood driven out of the brain vessels, but the cerebrospinal fluid drawn out of perivascular and perineuronal spaces, thus depriving the neurones suddenly of their nutrition, and in particular of the sugar which is essential for their normal action.

There is no doubt that the great majority of contributors to the problem of concussion adhere to a mechanical pathogenesis in one or other manner. Greenfield (1938) thinks that the theory of deformation and stretching, already accepted for spinal concussion, fits also best with the known facts of cerebral concussion. The alterations in the shape of the brain which result from a blow on the head produce sudden stretching of nerve fibres and other tissues, especially blood vessels, at various places in the brain, especially where the impact is

resisted by dural septa or bony ridges. The tearing of the vessels need not result in rupture, but may well damage the endothelial lining and the local contractile mechanism by which the arterioles react to changes in internal pressure. This seems to the author a more satisfactory way of accounting for dilatation of vessels than Ricker's theory of traumatic paralysis of vasomotor nerves. A local dilatation of small vessels may also account for oedema, but Greenfield (1938, 1942) makes the important point that general oedema is rare in head injuries. It may occur locally beneath an area of bruising, and is then often followed by severe local demyelination and gliosis. The area around the anterior horns of the lateral ventricle is a favourite site for this lesion, in which the humoral mechanism as outlined by Duret and Berner may have at least a partial significance. The sudden loss of consciousness in concussion may possibly result from tearing of fibres in thalamic and hypothalamic centres. It cannot be explained by the small haemorrhages frequently found in the grey matter around the Sylvian aqueduct, and more deeply in the tegmentum. These are seen, in connection with other haemorrhages, in severe cases of head injury and are not pathognomonic of concussion.

The important experimental investigations by Denny-Brown and Ritchie Russell (1941) also support a mechanical explanation of concussion. The only limitation of the value of their work, as stated by the authors themselves, lies in the fact that states of unconsciousness cannot easily be studied in animals (cats, dogs, and monkeys were used), particularly in animals under anaesthetic. The main points arrived at are, that concussion of short duration can occur without histological changes in the brain. There was no evidence of vascular spasm or stasis in the brain. If, in severer types of head injury, haemorrhages (petechial, or large ones) are produced, they are due to distortion and tearing of blood vessels, and not to a paralysis of vasomotor nerves as suggested by Ricker. The phenomena of concussion are produced by a general physical injury of great complexity to the neurones, which causes reflex paralysis of respiratory and vasomotor mechanism *via* centres in the medulla and pons. This effect is produced when the forebrain is absent (after decerebration), and when vestibular influences are excluded (after cutting the eighth nerve). It is necessary to distinguish between "acceleration concussion," which occurs when the skull is subjected to a sudden change of velocity, and which is associated with only a negligible rise of intracranial pressure, and "compression concussion," produced by a blow on the head supported on a hard surface. In this latter type the rise of pressure is considerable, but must be about ten times the normal in order to be effective in the animals used.

Scott (1940) observed in dogs whose heads were held in a specially designed apparatus while a mechanical force was applied, increase of intracranial pressure. He was obviously dealing with "compression concussion." No histological changes were demonstrable.

Williams and Denny-Brown (1941) found in experimental concussion always instantaneous generalized reduction of cerebral electrical activity, which they interpret as a direct result of mechanical violence to cerebral cells, and not of secondary changes such as oedema, anoxia or hypoglycaemia.

Views expressed by Dawson (1939), Hassin (1940), and de Gutierrez-Mahoney

(1941), are, as a whole, in keeping with a theory of direct action on the neurones in concussion. Hassin bases his opinion on his observation of tearing of large vessels in electrocution. Hassin, as well as Scheinker (1940) and Courville (1942), however, differ from the views of Greenfield on traumatic oedema, to which they attribute much importance. Gutierrez-Mahoney also stressed the occurrence of fat embolism in brain vessels, which he regards as being derived from shattered myelin. The shortness of time in his human cases required to break down the myelin lipoids to neutral fat is, however, surprising.

The important problem of *blast injuries* has been the subject of several discussions and papers (Zuckerman, 1941; Stewart, Russell and Cone, 1941; Krohn, Whitteridge and Zuckerman, 1942). The conclusions are based predominantly on experimental investigations in animals of various species (mice, rats, guinea-pigs, rabbits, cats, monkeys, and pigeons). Stewart and his associates were able to study the effects of blast in a pheasant injured during an air raid. The most important effect of the blast waves is directed against the body wall, resulting in haemorrhage of internal organs, foremost in the lungs. If the trunk is protected no changes in the internal organs are found, indicating that there is no pressure or suction through nose or mouth. In the nervous system haemorrhages around thoracic spinal roots are constant, but meningeal, ventricular and intracerebral haemorrhages are rare, and occur only on exposure to highest pressures. Zuckerman (1941) reports that detailed investigation of the brains of his experimental animals by Greenfield and Le Gros Clark failed to demonstrate significant changes; these results were confirmed by Hadfield, speaking in the discussion. Changes in the brain if they occur are not regarded as due to a direct concussion-like effect, but are probably secondary to fall of blood pressure following changes in pulmonary blood-flow (Krohn, Whitteridge and Zuckerman, 1942), or violent venous back-pressure resulting from the sudden compression of the thoracic cage (Stewart and associates, 1941). It is worth mentioning that the electro-encephalogram demonstrates either no changes, or those characteristic of secondary anoxemia. Fat embolism is not an integral factor in the pathogenesis of blast injuries (as was contended), but, if found, it is a complication, as are also occasionally the sequelae of asphyxia, carbon-monoxide poisoning, burns, and drowning.

Deficiency Diseases.

Valuable reviews are available on the whole problem of nutritional deficiency (Butt, Leary and Wilder, 1942), vitamin B deficiency and nervous diseases (Aring and Spies, 1939), tissue changes in vitamin deficiency (Wolbach and Bessey, 1942), pathologic anatomy in avitaminosis (Hsü, 1942), pathologic effects produced by deficiency of single metallic and non-metallic elements (Follis, 1942). They should be consulted by all who want complete information about the numerous data concerning the pathology of nutrition. In this review it is not possible to give more than a rough outline of the principal and most striking advances.

It has now been established that nervous lesions produced by ***vitamin A*** deficiency are wholly of mechanical origin through disproportionate growth

of the central nervous system in relation to surrounding bone (Wolbach and Bessey, 1941). This appears to solve previous controversies regarding experimental production of nervous lesions in A-avitaminosis. There is indeed very little of the vitamin in the normal central nervous system, as has been recently shown by Popper (1941) and Ragins and Popper (1942), who made a comparative study by means of fluorescence microscopy. Likewise deficiency of *vitamin D* is of very little importance to the central nervous system. Damage had been reported after repeated administration of massive doses, but Vollmer (1941) was unable to confirm this.

Vitamin C has been the subject of histochemical investigations by Wolf-Heidegger (1942), who used Giroud-Leblond's silver nitrate injection method. In normal animals silver deposits are found in the cytoplasm of nerve cells, microgliocytes, oligodendrocytes, and the epithelial cells of the choroid plexus, while none were seen in the ependymal cells. No reduction of the silver salt took place in the brains of vitamin C deficient animals. The apparent spatial relationship of the silver granules to the Golgi apparatus and the mitochondria is of great histochemical interest (Wolf-Heidegger, 1942 ; Bourne, 1942).

The chief neuropathological advance has been made in the field of *vitamin B deficiencies*, and among these the most striking is that which led to the clarification of the Wernicke syndrome. Although in Wernicke's first case the lesion followed pyloric stenosis from sulphuric acid poisoning, subsequent opinion was that it was more or less specific of chronic alcoholism. It is Neubuerger's (1937) merit to have first drawn attention to its wider occurrence. Campbell and Biggart (1939) stressed the nutritional aspect as a common link, and even suggested vitamin B_1. The aetiology was finally clinched by the experimental work of Alexander (1939, 1940), who was able to produce lesions comparable to the Wernicke syndrome in pigeons fed on thiamine-free diet rich in other food-stuffs and containing A, the remaining Bs, C and D in excess. Alexander's results were in accordance with earlier work of Prickett (1934) and Zimmerman (1939–40, 1940), who both confirmed retrospectively his findings.

Apart from these main steps in the elucidation of its pathogenesis, there has been a vast literature on various pathological aspects of the Wernicke syndrome. It is now recognized that it may occur in the course of chronic gastric conditions, cholecystectomy with persistent vomiting, hyperemesis gravidarum (Sheehan and Sinclair, 1939), chronic febrile disease (Chang, Suh and Ling, 1941), depression associated with anorexia, pernicious anaemia, etc. Vonderahe (1939), describing haemorrhages around the third and fourth ventricle in 14 cases of peptic ulcer, may have been dealing, at least in some instances, with the Wernicke syndrome. He points out that certain signs of visceral and emotional irritability commonly associated with peptic ulcer may be of central origin. Moodiness, emotional lability, etc., have been clinically recognized as symptoms of slight thiamine deficiency. Chastek paralysis in foxes fed with a fish diet is an interesting counterpart of Wernicke's syndrome and likewise due to a deficiency in thiamine (Alexander, Green, Evans and Wolf, 1941 ; Evans, Carlson and Green, 1942). Ferraro and Roizin (1941) described similar changes in cats which had been starved.

Alexander (1940) is of the opinion that thiamine has an anti-angiodegenera-

tive action, but he failed to explain why the lack of this factor should produce angiodegeneration in selected areas of the brain only. More recently Swank and Prados (1942) and Prados and Swank (1942) regarded the vascular changes in the Wernicke syndrome as secondary to an affection of the neurones. Faulty metabolites in the neurones due to the deficiency of thiamine produce vasodilation, haemorrhage, interstitial proliferation and sclerosis.

The neurohistology of pellagra, which is mainly, but not entirely identical with nicotinic acid deficiency (as, in a similar way, beri-beri is not wholly identical with thiamine deficiency [Leblond and Chaulin-Servinière, 1942]) has been competently reviewed by Hsü (1942). Of the triad, hyaline change of capillaries, diffuse fatty changes and primary irritation of large nerve cells, the latter seems to be the most constant histological symptom. Sclerosis of the posterior and lateral tracts is frequent. It is, however, more in the nature of a Wallerian degeneration than of the patchy honeycombed appearance in subacute combined degeneration. Aring, Bean, Roseman, Rosenbaum and Spies (1941), counting the fibres in peripheral nerves in pellagrins, found a reduction in 8 out of 10 cases.

Aring, Ryder, Roseman, Rosenbaum and Ferris (1941), and Loman, Rinkel and Myerson (1941), demonstrated after intravenous injection of nicotinic acid increase of blood-flow which seems to be more marked in the periphery than inside the cranium. This vasodilator effect is not shown by nicotinamide, which has the same therapeutic usefulness.

Although the biochemical aspects of Wernicke disease and pellagra are outside the scope of this review, they may be of great importance for the understanding of the pathogenesis of the structural changes. Since thiamine is necessary for complete combustion of carbohydrates, Wortis, Bueding, Stein and Jolliffe (1942) and Wortis, Bueding and Jolliffe (1942) studied pyruvic acid in Wernicke disease and peripheral neuropathy respectively. They found hyperpyruvaemia in patients suffering from Wernicke disease and acute peripheral neuropathy. Himwich, Spies, Fazekas and Nesin (1940), by studying the difference in arterial and venous circulation, found a decrease in metabolism of the brain in pellagrins and more marked still in beri-beri.

A few remarks are necessary about the remaining components of the B group and other vitamins which appear to be of little importance to human neuropathology. There is much controversy about the involvement of the central nervous system in riboflavin deficiency. Phillips and Engel (1938) described myelin degeneration, fragmentation of axis cylinders, degeneration of neuromuscular endplates and proliferation of Schwann cells in peripheral nerves, and gliosis and chromatolysis in the spinal cord of chicks fed on a diet low in riboflavin. They concluded that riboflavin is necessary for the growing chick, and might be specifically associated with myelin metabolism. Zimmerman (1939–40) considers the spinal cord lesions in pellagra to be due to riboflavin deficiency, quoting work by Sebrell and Onstott, and also unpublished work by Street, Cowgill and Zimmerman as proof. Sinclair (1943) refers to peripheral neuropathies observed during the siege of Madrid, and in particular to retrobulbar neuritis, in which deficiency of riboflavin appears to be the most likely cause. On the other hand, Lightner and Forbus (1940) were not able

to produce any change in the central and peripheral nervous system, and Wolbach and Bessey (1942), although their work was not specifically concerned with the central nervous system, did not find any changes which could be regarded as other than the effect of starvation. They confirm, however, the important observation that riboflavin deficiency in various species of animals and possibly in man may lead to sudden collapse, associated with ataxia, inability to stand, loss of deep reflexes, coma, failing respiration and death. In the absence of any morphological pathology they postulate a chemical disturbance resulting in cellular asphyxia.

There is also some controversy with regard to the neuropathology of vitamin B_6 complex (pyridoxine) deficiency. Street, Cowgill and Zimmerman (1941) reported some degenerative changes in myelin sheaths of peripheral nerves and spinal cords of dogs, but at least the peripheral changes were to some extent found also in control animals. Antopol and Unna (1942) observed in rats the typical hyperkeratosis and acanthosis of ears, paws, and snouts, and a failure of spermatogenesis, without mentioning the nervous system, whilst Lightner and Forbus (1940) failed to discover any changes in the peripheral and central nervous system.

Vitamin E (*α-tocopherol*) deficiency produces in young chicks an apparently ischaemic neuromalacia of the cerebellum and occasionally the cerebrum (Adamstone, 1941). Monnier (1941) reported in adult rats after prolonged deficiency degeneration of the dorsal tracts of the spinal cord, sclerosis of anterior horn cells and vegetative lateral horn cells. There was also slight demyelination of spinal roots and nerves, including their end apparatus in the muscles. The muscle itself was degenerated. The author believes that the clinical amyotrophy is essentially myogenic, but may include a neurogenic component. The most recent experimental investigations by Pappenheimer (1942) and Wolf and Pappenheimer (1942) demonstrate that the central nervous system is unaffected and that the "amyotrophy" is not a progressive condition, but is due to a muscular degeneration of the Zenker type. That this is probably not far from the truth is borne out by the failure to influence amyotrophic disease in man by α-tocopherol therapy.

There have been no reports on pathological changes in the nervous system in deficiency of vitamin K and pantothenic acid. As regards biotin (vitamin H), Shaw and Phillips (1942) failed to produce in rats changes of the nervous system despite the fact that the animals died in a condition of extreme spasticity. This is in contrast to earlier findings (Findlay and Stern, quoted by the authors) of diffuse infiltration with small round cells and definite myelin changes in peripheral nerves. Biotin deficiency leads to involution of thymus and atrophy of testicles, and may have, thus, some relation to the process of ageing.

Although the neuropathology of *chronic alcoholism* has been to a very large extent merged with that of thiamine and nicotinic acid deficiency, many of the workers have stressed the great complexity of the pathogenesis of the nervous lesions. Jolliffe and Wortis (1941), Jolliffe, Wortis and Fein (1941) deal with various clinicopathological aspects of the Wernicke syndrome. Their main point among many others, which cannot be discussed in detail, is that the

clinical symptomatology is due to multiple deficiencies, and not only to that of thiamine. Alexander (1941) has made an attempt at correlating the various neuropathological lesions with the pathogenic factors operative in chronic alcoholism. According to him the shrinkage of the brain may be due to atrophy or dehydration. Subdural haemorrhage may be caused by deficiency of vitamin C, the blood level of which has been found lowered. As regards the microscopic findings, he attributes the vascular Wernicke lesion to deficiency of thiamine, while the affection of the neurones (neuronitis) may be due to a deficiency of thiamine (as in peripheral nerves), or nicotinic acid (as in central nerve cells), or of the anti-anaemic factor (as in the long tracts). The same author (1942) found associated with the alcoholic cirrhosis of the liver changes in the putamen which he claims to be similar to those seen in hepato-lenticular degeneration. This combination suggests to him a possible avitaminotic basis of the latter condition.

Jamaica ginger (triorthocresyl phosphate), which may occasionally give rise to neuritis and spinal cord symptoms, produces different histological lesions, consisting chiefly of hyperplastic fibrosis of arterioles and capillaries (Aring, 1942).

In view of the emphasis laid on the Wernicke syndrome as the basis for the clinical symptomatology, it is also worth mentioning that Morel (1939) described in four cases of chronic alcoholism a laminar astrocytosis in the third layer of the cerebral cortex, using a silver impregnation method. None of these cases had a Wernicke lesion, but this was present in a case which was the subject of a later communication (Morel and Duman, 1940), and in which there was found, in addition, a diffuse granular degeneration of nerve cells of the pre-frontal and frontal areas.

The complex problem of *demyelinizing disease* has been approached from various angles, and some of them (such as the inflammatory, allergic, toxic and vascular approach) have been mentioned in other sections of this review. Naturally, the possibility of a nutritional deficiency has been frequently discussed, although none of the known vitamins have so far been found deficient. There are, however, a few notable exceptions. One that has been known for a long time is subacute combined degeneration in pernicious anaemia, due to the absence of the anti-anaemic principle. It is not yet settled whether a similar condition in captive monkeys has the same aetiology (Hamerton, 1942). Swayback, a congenital disease of lambs with certain affinities to Schilder's disease, has been found to be due to lack of copper in the feed of the mother animal. It can be prevented in the offspring by giving copper to the pregnant animal (Innes, 1939). While it is not permissible to identify swayback with the demyelinating diseases of man, it is interesting to note that recently Winkelman and Moore (1942) have described a human equivalent to swayback. Mitchell (1941), who experimented with pigs under various avitaminotic conditions, found in both the avitaminotic and control animals a demyelination of the posterior tracts which appeared to be the result of the lack of an essential inorganic micro-constituent of the diet, probably copper.

A nutritional deficiency has been recently suggested for Marchiafava's disease which is characterized by demyelination of the corpus callosum and

occasionally of some other large fibre tracts. Both Lolli (1941) and Bohrod (1942) regard thiamine deficiency as cause of the condition, which is, thus, a counterpart of the Wernicke syndrome. This suggestion is based on the fact that it occurs almost exclusively in alcoholics belonging to the poorer classes of the population. All the 50 cases so far reported were of Italian extraction. However, Bohrod (1942) quotes an earlier paper of Jervis, who produced a lesion of the corpus callosum by poisoning cats with cyanide of potassium (*cf.* also the investigations by Hurst and associates, discussed in the section on intoxication).

It would be beyond the scope of this survey to include many other papers dealing with various aspects of demyelinizing disease ; the whole problem has been comprehensively reviewed by Einarson and Neel (1938).

Lesions of the Hypothalamus and Thalamus in Relation to Mental Disease. Neuropathology of So-called Functional Psychoses.

There has been a wealth of evidence, and much of it convincing, that the hypothalamus controls vital bodily functions, such as cardiovascular regulation, body temperature, sleep, gastro-intestinal function, metabolism of water, carbohydrates and fat, pituitary function, etc. Those interested in these aspects will find all the necessary information in two excellent books on the hypothalamus (1938 and 1940), and in shorter reviews (Ingram, 1939 ; Kuntz, 1942).

These great advances have, naturally, aroused hopes that something might be gained from investigations in this part of the brain towards the solution of normal and disturbed psychological function, and, in particular, of those psychoses whose pathology is not yet known. While there is little doubt about a connection of the hypothalamus with vital psychological processes and the make-up of personality, the earlier and too sanguine expectations have not been fulfilled, and a distinct note of caution in regard to the speculative character of many current concepts has been sounded in recent papers reviewing the situation (Grinker, 1939 ; Alpers, 1940 ; Masserman, 1942). Indeed, as far as the anatomical aspect is concerned, only a few clear-cut facts have emerged so far.

One of the best known is the very constant association, in the Wernicke syndrome, of confusional states and the Korsakoff syndrome with an affection of the mamillary bodies and of the neighbouring grey matter around the third ventricle. Much thought has been given to explaining the anatomical and psychological mechanisms. Grünthal (1939) has drawn attention to the connection of the mamillary body with the dorsal agranular frontal cortex, *via* the anterior nucleus of the thalamus, and in accord with earlier theories of his own and of others, is inclined to regard the Korsakoff syndrome as the result of a general reduction of activity and tension.

A number of cases have been reported in which tumours or other lesions of the hypothalamus have given rise to hallucinatory disturbances, mostly of a visual type, memory defects, personality disorder, and particularly, manic excitement. Grinker (1939) and Alpers (1940), in their reviews, stress the

frequency of manic syndromes. Stern and Dancey (1942) add their observation of mania associated with a glioma of the diencephalon. Like previous workers they were not able to give a more precise localization within the hypothalamus. Change of personality and sudden episodes of temper, and violence in the later stages of the illness, were described by Collins (1942), in a case in which the hypothalamus was also found destroyed by a tumour. The relationship of these reported psychological abnormalities to those encountered in patients with the Wernicke syndrome requires further elucidation.

Investigations of the hypothalamus have been also made in uncomplicated cases of so-called functional psychoses and in mental defectives. Larson (1939) found in all of his 14 cases of manic-depressive psychosis petechial haemorrhages in the midbrain and hypothalamus. It is hardly conceivable that these recent haemorrhages, which might occur as an agonal phenomenon, could have been primarily associated with the psychosis. Morgan (1939, 1940) found a notable reduction of the number of cells in various nuclei of the hypothalamus in the major psychoses, epilepsy and mental deficiency. Chromatolysis in the remaining cells indicates a chronic process, chromatolysis without cell loss signifies an early process, while absence of the cell change with marked reduction in number is typical of an end stage. The part most consistently involved is the substantia grisea and nucleus tuberis lateralis. Masserman (1942) rejects these results on "various technical and observational grounds," and it is indeed difficult to understand why conditions of such widely differing symptomatology should have almost the same anatomical substrate.

It may be mentioned that no variations in the secretory phenomena of hypothalamic cells have been observed in relation to any type of mental disorder (Scharrer and Scharrer, 1940).

The thalamus has figured in investigations designed to demonstrate secondary degeneration of those of its nuclei which receive fibres from diseased cortical areas. The purpose of these important studies is primarily anatomical to gain information in the human brain about the cortico-thalamic connections, which so far have been mainly established by experimental work. Le Gros Clark and Russell (1940) were able to demonstrate in a case of total cortical atrophy that all thalamic nuclei had degenerated with the exception of the centre median nucleus, whose function remains, thus, obscure. Stern (1941–42) examined the thalamus in a case of frontal lesion. He found that the medial part of the ventrolateral nucleus was degenerated, although the cortical area 4 was intact. Cases dying some time after leucotomy from intercurrent disease will be valuable for studies of this kind, but so far no such investigations have been published.

The important observation has been recently made by Alexander (1942), viz., that the myelo-architectural pattern of the normal thalamus shows a surprising number of individual differences. According to him, "one is led to the conclusion that human thalami are almost as different in appearance as human faces." So far he has not been able to correlate this variability with any peculiarity of behaviour, such as motor and emotional patterns, awkwardness and other normal variations.

A Korsakoff syndrome, rapidly developing into dementia, has been attributed

by Stern (1939) to a presenile bilateral degeneration of the thalamus. The ventral, arcuate, midline nuclei and also both the lateral and medial geniculate bodies were preserved. The intellectual degeneration is explained by the repercussion of the thalamic degeneration upon the function of the cerebral cortex with which the thalamus is intimately connected. The cerebral cortex as well as the white matter were, however, not free from changes such as fatty degeneration of nerve cells and astrocytic gliosis, but they were not regarded as sufficient to explain the severe mental symptoms. The author refers to his and Smith's earlier experiences with thalamic tumours, which were often found to be associated with dementia. The case is so far unique in the literature; in cases of thalamic hypertrophy published by Nevin (1938) there were widespread additional blastomatous changes in other parts of the brain which could account for the mental symptoms.

In conclusion, a few remarks are necessary about the slender structural changes which have been often described in the brains of schizophrenics and other functional psychoses. They are now almost universally disregarded as a substrate of the psychosis (Peters, 1938*a* and *b*; Scheidegger, 1942). The occasional extensive vascular lesions found in the brains of patients dying suddenly are not directly associated with schizophrenia, but are the result of a vasomotor lability (Malamud and Boyd, 1939). In this connection, whether the pathological structure of cutaneous capillaries described by Olkon (1939) has any significance remains to be seen.

A very original and in its results startling approach to the anatomical problem of schizophrenia, manic-depressive psychosis and other mental disorder has been made by Elvidge and Reed (1938). They found swelling of the oligodendroglia in biopsy material taken from the brains of mental patients. It was found in the white matter. No such change was seen in biopsies of cases without mental change, as was also confirmed in the discussion by Penfield, who drew attention to the fact that the oligodendrogliocytes are the most frequent cells in the brain, and that they contain gliosomes which may indicate secretional properties. So far, apparently, no re-examination has been made. Campoma's (1939) paper on the same subject was not available for this review. It is difficult to understand that a somewhat labile phenomenon such as swelling of the oligodendroglia should be a permanent symptom in chronic psychoses without ever giving rise to more severe pathological changes. It is interesting that the authors were able to confirm their findings in the same patient at different intervals.

It is beyond the scope of this review to discuss the endocrinological, physiological and biochemical aspects of this group of psychoses.

The Neuropathology of Shock Treatment.

The flood of publications, both experimental and pathological, which started soon after the introduction of shock treatment has not yet abated during the period under review, although there has been a notable shift of interest towards the effects of convulsive therapy, particularly electrically induced convulsions, whereas hypoglycaemia had its peak period earlier.

The most recent review on the neuropathology of *hypoglycaemia* has been given by Lawrence, Meyer and Nevin (1942), who after giving a historical survey on previous work, describe the pathology in six personal cases. Their review shows that gross vascular lesions (haemorrhages and softenings) are relatively rare. The main type of lesion is a widespread, often continuous necrosis, the nerve cells showing ischaemic or more often homogenizing or severe cell change. The cerebral cortex and the striatum (caudate nucleus and putamen) are most frequently affected, the cerebellum less so, whilst lesions in the remaining centres are usually slight. The cortical necrosis is often of the pseudo-laminar type, affecting especially the upper layers. In a small number of cases a gliosis of the cerebral and cerebellar white matter is the main lesion. It is impossible to give here a full account of the various pathogenic theories which have been put forward in the course of time; the review shows that the majority of workers adopting Ricker's and Spielmeyer's suggestions have considered vasomotor disturbances as the cause of the lesions. In addition, the importance of a chemical factor is increasingly realized. Lack of the substrate glucose results in non-utilization of oxygen. Although the effect on the nervous parenchyma is more or less identical with that of anoxia, it is hardly correct to describe the hypoglycaemic mechanism by this term, since the oxygen concentration of the arterial blood is not decreased. The term oxyachrestia (cf. achrestic anaemia, from χρῆσις = use) is therefore suggested as useful and accurate.

The lesions described above are seen in fatal cases in which the coma has become irreversible. There has been much interest in the factors, both clinical and histological, which determine the irreversibility of the coma. Nerve-cell changes, most of them of a reversible nature, and some neuroglial and microglial proliferation, have been seen after therapeutic doses (Schmid, 1936), while Neumann, Cohn and Katzenelbogen (1942), under similar conditions, did not see any changes which could not be found in control animals. Winkelman and Moore (1940), who found severe cell damage, expressly stated that their cats died in secondary coma. According to Tyler and Ziskind (1940), the degree of brain damage is parallel to the dose of insulin. Cats must be kept for at least 100 minutes in a "medullary stage" of decerebration for irreparable damage to be produced. Finley and Brenner (1941) found in animals that single insulin comas of up to four hours' duration leave only reversible changes, while after a coma lasting about nine hours, severe cell change of an irreversible nature and acute reaction of the glia were observed. Repeated prolonged shocks led to extensive damage to the nerve cells of the cerebral cortex and basal ganglia, and to gliosis in these regions and generally within the white matter. It is difficult, however, to state from clinical experience the length of time required to produce irreversible changes, as the brain cells of different individuals probably vary in their ability to recover from an attack (Lawrence, Meyer and Nevin, 1942). Experience suggests to these authors that coma of one to three hours is usually associated with complete recovery, while longer periods are dangerous.

A number of fatalities occurring after therapeutic application of *metrazol* and related drugs have been investigated pathologically. Death was attributed

to organic disease of the heart and blood vessels (endocarditis, Buerger's disease) by Hayman and Brody (1939), and Michael and Wittenbrook (1940). The first-mentioned authors also refer to earlier, similar observations of death caused by aortic disease, pelvic thrombo-phlebitis, bilateral hypernephroma, etc. In the case described by Pessin and Reese (1939) acute cardiac dilatation may have been a contributory cause of death. A rare fatal complication appears to be fat embolism from a fracture produced during the convulsions (Nightingale and Meyer, 1940).

Various cerebral lesions have been described in fatal cases: Focal changes in the cortex and basal ganglia (Fellows and König, 1939); petechiae, oedema and acute swelling of nerve cells in striate body, thalamus and cerebellum (Pessin and Reese, 1939); generalized ischaemic disease of nerve cells and gliosis (Petersen, 1939); bilateral softening of the frontal lobe (Jansen and Waaler, 1940); oedema and softening of the cerebellum following injection of triazol (Wyllie, 1940). Marked diffuse hypertrophy and hyperplasia of astrocytes and, to a lesser degree, of the microglia was the outstanding feature in six cases investigated by Weil and Liebert (1940), and a similar glial proliferation was briefly described by Meyer (1939) in two cases complicated by myocardial degeneration and pellagrous change following ulcerative enteritis respectively.

There has been much controversy about the severity of the lesions after convulsions, produced by metrazol, in experimental animals. Reitman (1938), and Cleckley, Bowles and Mettler (1940) found serious lesions, especially gross haemorrhages and necrosis, but they obviously did not use "therapeutic" doses. Arieti (1941) observed only mild or even no changes, although he continued the injections until four of the five monkeys died spontaneously in protracted convulsions. The severity of the lesions was not proportional to the dosage or the number and duration of the fits. All the animals had an interstitial or parenchymatous nephritis, possibly of tuberculous origin.

The following groups of workers arranged their experiments in order to imitate strictly the therapeutic situation. Liebert and Weil (1939), using rabbits, found hyperplasia and hypertrophy of all types of glial cells more pronounced in the striate body and hippocampus than in the cerebral cortex. The nerve cells showed some shrinkage of cytoplasm and nuclei. Strecker, Alpers, Flaherty and Hughes (1939) described vacuolization of nerve cells and subarachnoid haemorrhage in four out of seven monkeys. Winkelman and Moore (1940) found no degenerative changes of nerve cells apart from occasional nuclear pyknosis. Whitehead, Neubuerger, Rutledge and Silcott (1940) found in three dogs and four rabbits small local areas of cortical necrosis with slight glial reaction, in addition to diffuse degenerative changes in nerve cells. Similar slight changes were seen by Finley and Brenner (1941) in monkeys. Neumann, Cohn and Katzenelbogen (1942) described in cats petechial haemorrhages and scattered cytolytic changes in nerve cells, which they also saw, however, in normal controls.

An original approach to the problem of the immediate and reversible changes produced by convulsions has been made by Heilbrun and Liebert

(1941). Using biopsy material they studied nerve-cell changes after administration of metrazol, monobromidated camphor, thujone, insulin, nitrogen, air embolism and electricity. Pieces of the brain were taken out 2, 5, 10, 20, 30, 45 and 60 minutes after administration of the convulsive agent. Swelling, tigrolysis, eccentricity of the nucleus in nerve cells and swelling of the astrocytes and oligodendrogliocytes were observed, commencing five minutes after administration, and gradually disappearing after 30 minutes unless a new convulsion occurred. The changes were—surprisingly—most marked in electrically produced convulsions, and occurred even after subconvulsive doses, eliciting only myoclonic twitchings. The same authors (Liebert and Heilbrun, 1940) studied cell changes by means of microincineration. Dust formation, hypomineralization and even complete demineralization, particularly marked in Ammon's horn, were seen to follow immediately after the seizure, and they were to some extent reversible. Nissl stain need not reveal any changes when hypomineralization was readily demonstrable.

Apparently no human brains after electro-convulsive treatment have been investigated, but a few experimental investigations have been carried out. Heilbrun and Weil (1942) found in most of their experimental animals haemorrhages in meninges, brain stem, spinal cord, and also in lungs and kidneys. They considered a combination of pathogenic factors such as sudden rise of arterial pressure, vasospasm and venous stasis. Neither generalized nerve-cell changes nor glial reaction were seen. Although the authors considered the shock given to their animals to be similar to that given in psychoses, it is noteworthy that 16 of their 28 rabbits were paralysed afterwards, 7 even after the first shock. In the discussion Hassin stressed the discrepancy between these results and negative findings in human brains after electrocution. Alpers and Hughes (1942) used threshold currents in 30 cats. Subarachnoid haemorrhage of mild degree was found in 14 animals; intracerebral haemorrhages, usually of the punctate type, were produced in the cerebral cortex, white matter, cerebellum and the grey matter around the third ventricle of nine animals. No relationship existed between the severity of the lesion and the number of shocks and the interval at which they were given. Dogs were used in so-called "therapeutic" experiments by Neubuerger, Whitehead, Rutledge and Ebaugh (1942). The animals were rather unruly during the period of the "treatment." Histological examination revealed petechiae, widespread changes of the cortical nerve cells (tigrolysis, swelling, vacuolation and—focally—ischaemic and severe degeneration) and a slight proliferation of the neuroglia and microglia. All the changes were especially marked in the pathway of the electric current. Both a direct effect upon the nervous parenchyma and a general contraction of intracranial arteries are considered as factors operative in the causation of the lesions, which, although definitely pathological, are regarded as light, and as undoubtedly less severe than after metrazol convulsions.

In conclusion, the present situation may be summarized as follows: The nature and extent of the lesions produced in irreversible hypoglycaemic coma are now comparatively well known, but there remains some uncertainty as to what happens after uncomplicated insulin treatment. No systematic investigations in treated cases dying from intercurrent diseases have been so far made,

and the experimental approach to the problem, although supplying valuable information, has not yet been wholly satisfactory.

It seems to be established that the lesions in cases dying from convulsive treatment are, on the whole, less severe than those seen after fatal hypoglycaemia. With regard to the sequelae of uncomplicated convulsive treatment we again depend almost entirely on experimental work, and although recently workers have tried to imitate the therapeutic procedure, the experimental conditions are not wholly comparable to those in man. Generally speaking, the reported changes in the brain did not appear to be serious—after electroconvulsive treatment even less so than after metrazol convulsions. Many of the acute changes, including small haemorrhages, may be reversible, and others such as a mild proliferation of the glia need not be of great importance. It is too early, however, to pass a final judgment upon this point.

Some of the changes seen after artificially produced convulsions are, in quality at least, similar to those seen in idiopathic epilepsy, although the characteristic necrosis of the Sommer sector in the Ammon's horn and of the Purkinjë cells in the cerebellum do not appear with the same frequency. It remains to be seen whether this difference is due to the relative smallness of our present experience, or possibly to more fundamental causes.

It is beyond the scope of this review to deal with the purely metabolic aspects and theories of shock treatment, but it may perhaps be useful to mention a few recent biochemical investigations on the effect of insulin and convulsive treatment. Loman (1941), examining sugar and oxygen metabolism during and after hypoglycaemia, failed to detect any sign of metabolic stimulation. There was no appreciable difference in the gaseous constituents of the blood before and after insulin and metrazol treatment (Harwitt, Liebert and Wiltrakis, 1940) nor any effect on blood pyruvates, lactates and glucose (Elliott, Rivers, Elliot and Platt, 1941). An alteration of the albumen : globulin ratio in the cerebrospinal fluid has been reported after insulin and metrazol shocks by Kingsley and Freed (1941). For earlier references the reviews by Lawrence, Meyer and Nevin (1942) on hypoglycaemia and by Kennedy (1940) on convulsive treatment should be consulted.

Oligophrenia.

Various aspects of the group of diseases known as *lipoidosis* have recently been investigated. New cases with unusual features were described and attempts made at clarifying the relationship between the individual members of the group, particularly from the chemical point of view.

Hallervorden (1938*a*) investigated a late case of amaurotic idiocy, with onset at the age of 33, progressing slowly for about 20 years. The clinical symptoms pointed to a predominant affection of extrapyramidal centres. Histologically the most intensive lipoid deposits were found in the cells of the striate body, hypothalamus and the cornu ammonis.

Norman and Wood (1941) described a congenital form of amaurotic idiocy with onset in foetal life. An unusual feature was heavy extracellular lipoidal deposits in the white matter, which have some resemblance to those seen in

https://doi.org/10.1192/bjp.90.378.152 Published online by Cambridge University Press

the Schüller-Christian type. This latter condition has been the subject of a study by Hallervorden (1938*b*). He separates two groups: the Schüller-Christian syndrome, in which cholesterolesters are deposited in the brain, the lesions being patchy, and cholesterinosis characterized by cholesterol deposits and diffuse lesions. Cholesterol is hydrophobic and remains in the tissues after secretion from the blood, while the esters are more easily taken up by cellular elements. The brain stem and cerebellum are predominantly affected; only in one case previously described by Davison had the cerebral hemispheres been found involved.

There have been no noteworthy developments regarding the pathology of gargoylism (chondro-osteo-dystrophy of the Hurler type) since Ashby, Stewart and Watkin (1937) established the similarity of the nerve cell changes with those found in the juvenile form of amaurotic idiocy. The six cases occurring in one family, described by Jervis and Thiells (1942) showed some unusual features, especially later onset, absence of the grotesque facial appearance, and no enlargement of liver and spleen, which in the opinion of the authors separate them from the closely allied Hurler condition.

The relationship between Niemann-Pick disease and amaurotic idiocy has been much investigated. Scheidegger (1941) believes that both conditions are identical, and Hagedorn (1940) said the same with regard to the retinal changes. Rothstein and Welt (1941), however, while acknowledging an interesting interrelationship, advocate that the term amaurotic idiocy be reserved for cases with involvement of the central nervous system only. They give a comprehensive review of all types of lipoidosis, with the main differentiating pathological findings in tabular form. The difference between the two conditions has been also pointed out by Jervis (1940). In amaurotic idiocy some lipoids of the "protagon" type are increased and not sphingomyelin. The chemical investigations by Klenk (1939, 1940), which were not available for detailed study, apparently support this separation, which had previously been suggested by Epstein. In an interesting experimental approach Ferraro and Jervis (1940), using rabbits and monkeys, found after intravenous injections of sphingomyelin changes strikingly similar to Nieman-Pick disease. They failed, however, to produce a storage of sphingomyelin in the brain, which, in their opinion, indicates a difference between this condition and amaurotic idiocy.

Sjövals' theory that the lipoid storage in nerve cells in amaurotic idiocy is the expression of a rapid and premature senescence has been repudiated by Dide and van Bogaert (1938) and Jervis (1941), the latter pointing out that in contrast to senile changes there is no cell atrophy in amaurotic idiocy.

Norman and Wood (1941) have criticized the term lipoidosis as being too vague, since in most cases the lipoid deposits are confined to certain organs and are not generalized. This objection may have been met, to some extent, however, by Jervis and Thiells (1942), who advocate the concept of "localized lipoidosis."

Alexander and Myerson (1939) studied the brain in amaurotic idiocy and other conditions by means of micro-incineration. The nerve cells in amaurotic idiocy are demineralized, while the glia contains an excess of heat-resistant ash. Hypermineralization is, as in all blastomatous cells, the characteristic sign of

tuberosclerosis. The periventricular spongioblastoma often associated with this condition may even show gross hypermineralization. The nerve cells in mongolian idiocy appear normal.

The problem of *mongolism* has been studied from many aspects within the period under review. Benda (1939*a* and *b*) studied the thyroid and pituitary glands cytologically. In the former involutional changes were very constant, indicating preceding hyper- or dysfunction. The changes resembled those seen after administration of thyrotropic hormone. In the pituitary the frequency of relative eosinophilia may be caused by pituitary deficiency of the mother during pregnancy. Several papers by the same author (1939*c* and *d*, 1940) deal with problems of growth and physical development in mongolism, 120 cases serving as basis of the investigation. Mongolism must be due to prenatal factors, since it is already present at birth. Rate of growth is low during the first nine years, and usually stops after the fifteenth year. Dystrophia adiposogenitalis is frequent after puberty. The peculiar shape of the skull is due to arrest of development of the base. An irregularity of ossification can be demonstrated by X-rays and by histological examination.

All the changes suggest to this author a congenital absence or deficiency of hypophysial or extrahypophysial hormones stimulating differentiation and growth. There is, however, no evidence that the " growth " hormone of the anterior pituitary is responsible.

Bixby (1939, 1940, 1941) has contributed several biochemical investigations into mongolism ; his main points are that the blood groups are those of the average American population, thus excluding any relation to the Mongolian race. The basal metabolic rate, serum cholesterol, blood sugar, glucose tolerance, although singly within normal range, may collectively indicate hypofunction of the anterior pituitary. This is also suggested by a delayed glycaemic response after insulin. The initial lesion may have been caused by temporarily or permanently high levels of cholesterol in the maternal blood. The author himself admits, as does Schachter (1941), the difficulties of interpretation of the biochemical findings. Himwich and Fazekas (1940), examining samples of arterial and venous blood, concluded that less sugar and oxygen are utilized by the brain in mongolism, as well as in phenylpyruvic oligophrenia.

A neurohistological study of mongolism has been made by Meyer and Jones (1939) ; they found histological changes, often of marked degree, in a large percentage of mongols, but do not consider that they represent the pathological substrate underlying mongolism. They may be caused, however, by concomitant factors in mongolism, such as frequency of birth injury, congenital heart disease, susceptibility to infection, etc.

Norman (1938*b*) made a *cytoarchitectonic* study of the supragranular cortex in 30 normals and 30 mental defectives (cases with gross pathological lesions being excluded). He used frozen sections in order to avoid shrinkage and he chose three areas for comparison (OA, FE, PF). He found no significant differences between the two groups in regard to average depth of the cortex and the number of cells, but he occasionally found an excess of neurones in the visuopsychic area of oligophrenics. The arrangement of the neurones in the middle portion of the supragranular cortex was less uniform and regular than in

the normal brain. Diminution of normal spacing between poorly developed nerve cells is highly characteristic of the oligophrenic. There were no significant differences between mongols and other varieties of mental deficiency.

A number of authors have studied various types of *malformation* of the brain. Jakob (1938) tried to group the different types from a genetic point of view, based on the earlier theories of Bielschowsky. Benda (1941) made a histological analysis of a microcephalic case showing both macrogyria and microgyria interna. In another microcephalic, cystic degeneration, probably due to birth injury, was found. Walker (1942) described the changes in a case of lissencephaly (agyria). Only five similar cases were found in the literature. The cerebral cortex was arrested at the stage of development normally occurring in the third month. Except for the "*Randschleier*" no cortical lamination was seen. The white matter was narrow and heterotopias frequent. The basal ganglia and brain stem were well developed, but the cerebellum and olives were hypoplastic. Arhinencephaly was the subject of a paper by Stewart (1939*a*). Despite complete absence of olfactory bulbs and tracts, there was no abnormality in the hippocampal convolutions. Only the fascia dentata was reduced in size. There is no obligatory parallelism in the development of the frontal lobe and hippocampus, although maldevelopment of both may occasionally occur together. An important study into the problem of porencephaly has been made by Yakovlev and Wadsworth (1941). They discriminate between schizencephalies (developmental abnormalities) and encephaloclastic porencephalies. In the former variety there is a continuity of the walls of the cavity with the ependyma of the underlying ventricle through a pia-ependymal seam. The clefts follow the gyral pattern.

A comprehensive review on *cerebral diplegia* based on the histological examination of 50 cases has been given by Stewart (1942). He arrives at the conclusion that no single cause common to all cases can be assumed in view of the diversity of the lesions. The frequency of micrencephaly and of normal birth suggests that birth injury as a causal factor has been overrated. Many of the lesions can be explained by Collier's conception of primary degeneration. In others, anoxaemia and nutritional deficiency may be important factors. With regard to anoxaemia, the frequency of cerebellar changes, especially the loss of Purkinjë cells, which are known to be particularly susceptible to oxygen want, is of interest. Nutritional deficiency is suggested by the prevalence of demyelination, and by certain other characteristics. For more detailed information the original paper should be consulted.

It is impossible to give a complete survey of the numerous papers dealing with rare conditions and even rarer combinations which may occur in defectives. Only a few examples can be incorporated into this review.

Peters (1939) introduces a new theory to explain the hemiatrophy in Sturge-Weber disease. According to him, the multiple angiomatosis is congenital. The cortical atrophy, however, is probably produced by chronic disturbance of the circulation due to the diseased meningeal blood vessels and also to the vasomotor disturbances accompanying the epileptic convulsions. The calcification in the cortex originates to a large extent from the blood vessels.

The condition known as status marmoratus has been the subject of several important contributions. Scholz, Wake and Peters (1938), after giving a comprehensive review of the literature, reported the results of histological investigation of eight new cases. They confirm the view first introduced by Scholz, and subsequently held by other workers, including the present writer, that the marbling occurs within glial scars. There is evidence, illustrated by ischaemic changes, in an early case of their material, that the original lesion giving rise to hypermyelinized scars is caused by oxygen want. Norman (1938*a*) found also extensive glial scarring in his case, but he was not convinced that this is directly connected with the production of status marmoratus, which may be due to malformation, as it had been originally assumed to be by C. and O. Vogt. An interpretation also based on the theory of malformation, but in many regards quite novel and almost sensational, has been offered by Alexander (1942). Studying four cases of this condition by a careful histological technique, including examination in polarized light, microincineration, and benzidine stains, this author arrived at the conclusion that the assumption of a hypermyelinized glial scar is incorrect. The corpus striatum in all its histological components is normal. The marbling fibres constitute an accessory tract (fasciculi marmorantes) and are branches of the tractus marmorans, which probably is part of the fronto-pontine fibres in the internal capsule. In cases of striatal status marmoratus the caudal portion of the fronto-pontine tract in the midbrain and pons is absent or reduced in size, corresponding in degree to the number of marbling fibres in the striate body. The occurrence of marbling within the thalamus is explained similarly; it is followed by diminution in size or paucity of fibres in the reticular substance of the medulla. The occurrence in the normal striate body of the shrew of a fibre tract to some extent resembling marbling is taken as evidence in favour of malformation.

It would be premature and also beyond the scope of this review to comment upon Alexander's important investigation, which is likely to arouse a lively discussion and stimulate new work.

A comprehensive review has been written by Fitzgerald, Greenfield and Kounine (1939) on the sequelae of "*Kernicterus*." They were able to add two personal cases with pathological investigation. In both cases the globus pallidus, nucleus subthalamicus, Ammon's horn and fascia dentata were affected. The condition is interesting because of its relation to similarly localized lesions encountered in defectives; for example, it may throw light on the pathogenesis and certain histological features of status dysmyelinisatus. Icterus in the adult does not usually stain the brain, but nerve cells and scavenger cells in areas of degeneration have an increased affinity to the pigment, as has been recently shown by Rutledge and Neubuerger (1942).

A lesion in some of the hypothalamic nuclei has been found by Stewart (1938) in a case showing the symptoms of pseudo-aphroditism, adiposity, polyuria and hypoglycaemia. The same author (1939*b*) investigated the brain and organs of a case of the syndrome of Rud (combination of congenital ichthyosis with infantilism, idiocy and epilepsy).

BIBLIOGRAPHY.

General Neuropathology.

ALEXANDER, L., and MYERSON, A. (1938), *Arch. Neurol. Psychiat.*, **39**, 131.
ALEXANDER, L. (1938), *Brain*, **61**, 52.
ANDERSON, T. F., and STANLEY, W. M. (1941), *J. Biol. Chem.*, **139**, 339.
BODIAN, D. (1942), *Physiol. Rev.*, **22**, 146.
BOELL, E. J., and NACHMANSOHN, D. (1940), *Science*, **92**, 513.
BOURNE, G. (1942), *Cytology and Cell Physiology*. Oxford University Press.
ELLINGER, P. (1940), *Biol. Rev.*, **15**, 323.
FRIEDEMAN, U. (1942), *Physiol. Rev.*, **22**, 125.
GERSH, I. (1941), *ibid.*, **21**, 242.
GLEES, P. (1942), *J. Anat., Lond.*, **76**, 313.
GREENFIELD, J. G. (1938), *J. Neurol. Psychiat.*, **1**, 306.
LANDOW, H., KABAT, E. A., and NEWMAN, W. (1942), *Arch. Neurol. Psychiat.*, **48**, 518.
MINCKLER, J. (1942), *Amer. J. Path.*, **18**, 1061.
MUDD, S., POLEVITZKY, K., and ANDERSON, T. F. (1942), *Arch. Path.*, **34**, 199.
NACHMANSOHN, D., and STEINBACH, H. B. (1942*a*), *J. Neurophysiol.*, **5**, 109.
Idem (1942*b*), *Science*, **95**, 76.
PICKWORTH, F. A. (1941), *J. Ment. Sci.*, **87**, 50.
SORSBY, A., DICKSON WRIGHT, A., and ELKELES, A. (1943), *Proc. R. Soc. Med.*, **36**, 137.
STANLEY, W. M., and ANDERSON, T. F. (1941), *J. Biol. Chem.*, **139**, 325.
WEAVER, H. M. (1941), *J. Lab. Clin. Med.*, **26**, 1295.

Inflammatory Diseases.

ADLER, A. (1941), *Amer. J. Path.*, **17**, 407.
AKELAITIS, A. J., and ZELDIS, L. J. (1942), *Arch. Neurol. Psychiat.*, **47**, 353.
BAKER, A. B., and NORAN, H. H. (1942), *ibid.*, **47**, 565.
BLACKMAN, N., and PUTNAM, T. J. (1938), *ibid.*, **39**, 54.
BODIAN, D., and HOWE, A. (1940), *Brain*, **63**, 135.
BRAIN, R., GREENFIELD, T. G., and RUSSELL, D. S. (1943), *Proc. Roy. Soc. Med.*, **36**, 319.
DE BUSSCHAER, J., SCHERER, H. J., and THOMAS, F. (1938), *Rev. Neurol.*, **70**, 149.
COWEN, D., WOLF, A., and PAIGE, B. H. (1942), *Arch. Neurol. Psychiat.*, **48**, 689.
ERICKSON, T. C., ODOM, G., and STERN, K. (1942), *ibid.*, **48**, 613.
FERRARO, A., and JERVIS, G. A. (1940), *ibid.*, **43**, 195.
FINDLAY, G. M., and INNES, J. R. M. (1940), *Proc. Roy. Soc. Med.*, **33**, 161.
FINLEY, K. H. (1938), *Arch. Neurol. Psychiat.*, **39**, 1047.
FISHER, J. H., and GILMOUR, J. R. (1939), *Lancet*, ii, 301.
GALBRAITH, A. J. (1940), *J. Ment. Sci.*, **86**, 112.
Idem and MEYER, A. (1942), *J. Neurol. Psychiat.*, **5**, 22.
HASSIN, G. B. (1940), *Arch. Neurol. Psychiat.*, **44**, 1290.
Idem and DIAMOND, I. B. (1939), *ibid.*, **41**, 471.
HENSON, R. A., and RUSSELL, D. S. (1942), *J. Path. Bact.*, **54**, 227.
HURST, E. W. (1941), *Med. J. Aust.*, **2**, 1.
JERVIS, G. A., FERRARO, A., KOPELOFF, L. M., and KOPELOFF, N. (1941), *Arch. Neurol. Psychiat.*, **45**, 733.
KEMPF, J. E., PIERCE, M. E., and SOULE, M. H. (1941), *Proc. Soc. Exp. Biol., N.Y.*, **48**, 187.
KOLB, L. C., and BOLTON, B. (1940), *J. Neurol. Psychiat.*, **3**, 111.
MOREL, F., and DUMAN, R. (1941), *Schweiz. Arch. Neurol. Psychiat.*, **46**, 276.
PINTO, R. G. (1941), *Rev. Clín. Españ.*, **3**, 234.
PUTNAM, T. J., and ALEXANDER, L. (1939), *Arch. Neurol. Psychiat.*, **41**, 1087.
RATCLIFFE, T. A. (1941), *J. Ment. Sci.*, **89**, 545.
REYNOLDS, F. W., MOHR, C. F., and MOORE, J. E. (1942), *Arch. Intern. Med.*, **70**, 836.
ROSEMANN, E., and ARING, C. D. (1941), *New Engl. J. Med.*, **224**, 416.
SMITH, M. G., LENNETTE, E. H., and REAMES, H. R. (1941), *Amer. J. Path.*, **17**, 55.
STEINER, G. (1940), *Arch. Path.*, **29**, 189.
URECHIA, C. I., and MUELLER, M. (1940), *Confinia Neurol.*, **3**, 157.
WEIL, A., and BRESLICH, P. J. (1942), *Arch. Neurol. Psychiat.*, **48**, 349.

Intoxications.

ABBOTT, C. N., and COURVILLE, C. B. (1938), *Bull. Los Angeles Neurol. Soc.*, **3**, 46.
ALEXANDER, L. (1942*a*), *Proc. A. Research Nerv. and Ment. Dis.*, **21**, 77.
Idem (1942*b*), *ibid.*, **21**, 334.
ALPERS, B. J., and LEWY, F. H. (1940), *Arch. Neurol. Psychiat.*, **44**, 725.
BATTEN, C. T., and COURVILLE, C. B. (1940), *Anesthesiology*, **1**, 261.
COURVILLE, C. B. (1941), *ibid.*, **2**, 44.
DE GROAT, A. (1940), *Arch. Path.*, **29**, 271.
ECKER, A. D., and KERNOHAN, J. W. (1941), *Arch. Neurol. Psychiat.*, **45**, 24.

FERRARO, A., JERVIS, G. A., and ENGLISH, W. H. (1938), *Psychiat. Quart.*, **12**, 294.
FERRARO, N., JERVIS, G. A., and FLICKER, D. J. (1941), *Arch. Path.*, **32**, 723.
HSÜ, Y. K., and CH'ENG, Y. L. (1938), *Brain*, **61**, 384.
HURST, E. W. (1940), *Australian J. Exp. Biol. Med. Sci.*, **18**, 201.
Idem (1941), *Med. J. Aust.*, **2**, 661.
JERVIS, G. A., and KINDWALL, J. A. (1942), *Amer. J. Psychiat.*, **98**, 650.
MEYER, A., and BLUME, W. (1934), *Z. ges. Neurol. Psychiat.*, **149**, 678.
RASKIN, N., and MULLANEY, O. C. (1940), *J. Nerv. Ment. Dis.*, **92**, 640.
ROBERTS, W. J. (1939), *Arch. Psychiat. Nervenkr.*, **109**, 744.
ROSEMAN, E., and ARING, C. D. (1941), *New Engl. J. Med.*, **224**, 550.
SCHARRER, E. (1940), *Arch. Neurol. Psychiat.*, **44**, 483.
SCHOLZ, W., and HSÜ, Y. K. (1938), *ibid.*, **40**, 928.
SCHUBE, P. G., and RASKIN, N. (1940), *Psychiat. Quart.*, **14**, 264.
STEEGMAN, A. T. (1939), *Arch. Neurol. Psychiat.*, **41**, 955.
TAKEYO, S. (1939), *Arch. Psychiat. Nervenkr.*, **109**, 113.
VERHAART, W. J. C. (1941), *Amer. J. Dis. Child.*, **61**, 1246.
WINBLAD, S. (1940), *Dtsch. Z. ges. Gerichtl. Med.*, **33**, 73.
WINDHAM, R. A. (1941), *Australian J. Exp. Biol. Med. Sci.*, **19**, 243.

Vascular Disease and Disturbance of Circulation.

ALEXANDER, L., and LOONEY, J. M. (1938), *Arch. Neurol. Psychiat.*, **40**, 877.
ALEXANDER, L., and PUTNAM, T. J. (1938), *Proc. A. Research Nerv. and Ment. Dis.*, **18**, 471.
ANTONI, N. (1941), *Acta Med. Scand.*, **108**, 502.
BRUETSCH, W. L. (1938), *Amer. J. Psychiat.*, **95**, 335.
Idem (1939), *Z. ges. Neurol. Psychiat.*, **166**, 4.
CAMPBELL, A. C. P. (1939), *Arch. Neurol. Psychiat.*, **41**, 223.
Idem, ALEXANDER, L., and PUTNAM, T. J. (1938), *ibid.*, **39**, 1150.
DRESZER, R., and SCHOLZ, W. (1939), *Z. ges. Neurol. Psychiat.*, **164**, 140.
FAZIO, C. (1938), *Riv. Pat. Nerv. Ment.*, **51**, 125.
FORBES, H. S. (1940), *Arch. Neurol. Psychiat.*, **43**, 804.
Idem and COBB, S. S. (1938), *Brain*, **61**, 221.
GREENFIELD, J. G. (1938), *Proc. Roy. Soc. Med.*, **31**, 1443.
Idem (1939), *Brain*, **62**, 129.
Idem (1942), *Proc. Roy. Soc. Med.*, **35**, 525.
HARDMAN, J. (1940), *Brain*, **63**, 91.
KABAT, H., and SCHADEWALD, M. (1941), *Amer. J. Path.*, **17**, 833.
KERNOHAN, J. W., WOLTMAN, H. W., and BARNES, A. R. (1939), *Arch. Neurol. Psychiat.*, **42**, 789.
KRÜCKE, C. (1940), *Arch. Psychiat. Nervenkr.*, **111**, 233.
MALAMUD, N., and FOSTER, D. B. (1942), *Arch. Neurol. Psychiat.*, **47**, 828.
MEVES, H. (1938), *Nervenarzt*, **11**, 127.
MEYER, A. (1939), *J. Ment. Sci.*, **85**, 927.
NIGHTINGALE, G. S., and MEYER, A. (1940), *ibid.*, **86**, 819.
PENFIELD, W., and ERICKSON, T. C. (1941), *Epilepsy and Cerebral Localization*. Springfield, Illinois: C. C. Thomas.
PUTNAM, T. J., and ALEXANDER, L. (1938), *Proc. A. Research Nerv. and Ment. Dis.*, **18**, 544.
ROBB-SMITH, A. H. T., RUSSELL, D. S., and GREENFIELD, J. G. (1941), *Proc. Roy. Soc. Med.*, **34**, 639.
ROSENBAUM, M., ROSEMAN, E., ARING, C. D., and FERRIS, E. B. (1942), *Arch. Neurol. Psychiat.*, **47**, 793.
ROSENBERG, E. F. (1940), *Arch. Intern. Med.*, **65**, 545.
ROTHSCHILD, D. (1937), *Amer. J. Psychiat.*, **93**, 757.
Idem (1942), *Arch. Neurol. Psychiat.*, **48**, 417.
SAHS, A. L., and ALEXANDER, L. (1939), *ibid.*, **42**, 44.
SCHLESINGER, B. (1939), *Brain*, **62**, 274.
Idem (1940), *ibid.*, **63**, 178.
SCHOLZ, W. (1938), *Z. ges. Neurol. Psychiat.*, **162**, 694.
Idem and NIETO, D. (1938), *ibid.*, **162**, 675.
SCUPHAM, G. W., DE TAKATS, G., VAN DELLEN, T. R., and MARCUS, P. L. (1942), *Arch. Intern. Med.*, **70**, 444.
SILVERSTEIN, A., and KONZELMAN, F. (1940), *Confinia Neurol.*, **3**, 129.
SKOOG, A. L. (1940), *South. Med. J.*, **33**, 714.
STERN, K. (1938), *J. Neurol. Psychiat.*, **1**, 26.
STEWART-WALLACE, A. M. (1939), *Brain*, **62**, 426.
WEINBERGER, L. M., GIBBON, M. H., and GIBBON, J. H. (1940), *Arch. Neurol. Psychiat.*, **43**, 961.
WERTHAM, F., MITCHELL, N., and ANGRIST, A. (1942), *ibid.*, **47**, 752.
WHITEHEAD, R. W., NEUBUERGER, K. T., RUTLEDGE, E. K., and SILCOTT, W. L. (1940), *Amer. J. Med. Sci.*, **199**, 352.
WINKELMAN, N. W. (1939), *Arch. Neurol. Psychiat.*, **41**, 98.
Idem (1942), *ibid.*, **47**, 57.

Senile and Presenile Conditions.

ALEXANDER, L., and LOONEY, J. M. (1938*a*), *Arch. Neurol. Psychiat.*, **40**, 877.
Idem (1938*b*), *ibid.*, **40**, 1075.
ANDREW, N. V., and ANDREW, W. (1940), *J. Comp. Neurol.*, **72**, 525.
ANDREW, W. (1939), *ibid.*, **70**, 413.
BEST, C. R. (1941), *Mschr. Psychiat. Neurol.*, **103**, 308.
BOSCH, G., and ORLANDO, R. (1940), *Bol. Acad. Nac. de Med. de Buenos Aires*, p. 537.
BOUTON, S. M. (1940), *J. Nerv. Ment. Dis.*, **91**, 9.
DAVISON, C. (1938), *Amer. J. Psychiat.*, **94**, 801.
Idem and RABINER, A. M. (1940), *Arch. Neurol. Psychiat.*, **44**, 578.
ENGLISH, W. H. (1942), *Psychiat. Quart.*, **16**, 91.
FERRARO, A., and JERVIS, G. A. (1941), *ibid.*, **15**, 3.
GARDNER, E. (1940), *Anat. Rec.*, **77**, 529.
GRÜNTHAL, E., and WENGER, O. (1940), *Mschr. Psychiat. Neurol.*, **102**, 302.
HASSIN, G. B., and LEVITIN, D. (1941), *Arch. Neurol. Psychiat.*, **45**, 814.
HEMPHILL, R. E., and STENGEL, E. (1941), *J. Neurol. Psychiat.*, **4**, 97.
JAKOB, H. (1939), *Z. ges. Neurol. Psychiat.*, **166**, 313.
JANSEN, J., and MONRAD-KROHN, G. H. (1939), *Acta Psychiat., Kbh.*, **14**. 179.
JERVIS, G. A., HURDUM, H. M., and O'NEILL, F. J. (1942), *Amer. J. Psychiat.*, **99**, 101.
KING, L. S. (1942), *Arch. Neurol. Psychiat.*, **48**, 241.
KORENCHEVSKY, V. (1942), *J. Path. Bact.*, **54**, 13.
LIEBERS, M. (1939), *Arch. Psychiat. Nervenkr.*, **109**, 363.
LÖWENBERG, K., BOYD, D. A., and SALON, D. D. (1939), *Arch. Neurol. Psychiat.*, **41**, 1004.
MCMENEMY, W. H. (1940), *J. Neurol. Psychiat.*, **3**, 211.
Idem (1941), *ibid.*, **4**, 48.
Idem and POLLAK, E. (1941), *Arch. Neurol. Psychiat.*, **45**, 683.
Idem, WORSTER-DROUGHT, C., FLIND, J., and WILLIAMS, H. G. (1939), *J. Neurol. Psychiat.*, **2**, 293.
MALAMUD, N., and BOYD, D. A. (1940), *Arch. Neurol. Psychiat.*, **43**, 210.
MAYER-GROSS, W., CRITCHLEY, M., GREENFIELD, J. G., and MEYER, A. (1938), *Proc. Roy. Soc. Med.*, **31**, 1443.
MINCKLER, J. (1942), *Amer. J. Path.*, **18**, 1061.
MÜLLER, W. (1939), *Arch. Psychiat. Nervenkr.*, **109**, 147.
NICHOLS, I. C., and WEIGNER, W. C. (1938), *Brain*, **61**, 237.
SMITH, G. (1942), *J. Comp. Neurol.*, **77**, 589.
SONIAT, T. L. (1941), *Arch. Neurol. Psychiat.*, **46**, 101.
STADLER, H. (1939), *Z. ges. Neurol. Psychiat.*, **165**, 326.
STERN, K. (1939), *Brain*, **62**, 157.
TRUEX, R. C., and ZWEMER, R. L. (1942), *Arch. Neurol. Psychiat.*, **48**, 988.
VAN BOGAERT, L., MAERE, M., and DE SCHMEDT, F. (1940), *Mschr. Psychiat. Neurol.*, **102**, 249.
WORSTER-DROUGHT, C., GREENFIELD, J. G., and MCMENEMY, W. H. (1940), *Brain*, **63**, 237.

Head Injuries.

COURVILLE, C. B. (1942), *Bull. Los Angeles Neurol. Soc.*, **7**, 55.
DAWSON, J. G. (1939), *Proc. Roy. Soc. Med.*, **33**, 51.
DENNY-BROWN, D., and RUSSELL, W. R. (1941), *Brain*, **64**, 93.
DIXON, K. C. (1940), *Lancet*, ii, 360.
GREENFIELD, J. G. (1938), *Proc. Roy. Soc. Med.*, **32**, 43.
Idem (1942), *ibid.*, **35**, 525.
DE GUTIERREZ-MAHONEY, W. (1941), *War Medicine*, **1**, 816.
HASSIN, G. B. (1940), in *Injuries of Skull, Brain and Spinal Cord* (S. Brock). London: Baillière, Tindall & Cox.
HELFAND, M. (1939), *J. Nerv. Ment. Dis.*, **90**, 157.
Idem (1941), *Psychiat. Quart.*, **15**, 33.
KROHN, P. L., WHITTERIDGE, D., and ZUCKERMAN, S. (1942), *Lancet*, **1**, 252.
SCHALLER, W. F., TAMAKI, K., and NEWMAN, H. W. (1941), *Arch. Neurol. Psychiat.*, **45**, 1.
SCHEINKER, J. (1940), *Mschr. Psychiat. Neurol.*, **102**, 39.
SCOTT, W. W. (1940), *Arch. Neurol. Psychiat.*, **43**, 270.
STEWART, O. W., RUSSELL, C. K., and CONE, X. V. (1941), *Lancet*, i, 172.
WILLIAMS, D., and DENNY-BROWN, D. (1941), *Brain*, **64**, 223.
ZUCKERMAN, S. (1941), *Proc. Roy. Soc. Med.*, **34**, 171.

Deficiency Diseases.

ADAMSTONE, F. B. (1941), *Arch. Path.*, **31**, 603.
ALEXANDER, L. (1939), *Arch. Neurol. Psychiat.*, **42**, 1172.
Idem (1940), *Amer. J. Path.*, **16**, 61.
Idem (1941), *Quart. J. Stud. Alcohol*, **2**, 260.
Idem (1942), *Proc. A. Research Nerv. and Ment. Dis.*, **21**, 334.

Idem, GREEN, K. G., EVANS, C. A., and WOLF, L. E. (1941), *Trans. Amer. Neurol. A.*, **67**, 119.
ARING, C. D. (1942), *Brain*, **65**, 34.
Idem, BEAN, W. B., ROSEMAN, E. V., ROSENBAUM, M., and SPIES, T. D. (1941), *Arch. Neurol. Psychiat.*, **45**, 772.
Idem, RYDER, H. W., ROSEMAN, E., ROSENBAUM, M., and FERRIS, E. B. (1941), *ibid.*, **46**, 649.
Idem and SPIES, T. D. (1939), *J. Neurol. Psychiat.*, **2**, 335.
ANTOPOL, W., and UNNA, K. (1942), *Arch. Path.*, **33**, 241.
BOHROD, M. G. (1942), *Arch. Neurol. Psychiat.*, **47**, 465.
BOURNE, G. (1942), *Cytology and Cell Physiology*. London: Oxford University Press.
BUTT, H. R., LEARY, W. V., and WILDER, R. M. (1942), *Arch. Intern. Med.*, **69**, 277.
CAMPBELL, A. C. P., and BIGGART, J. H. (1939), *J. Path. Bact.*, **48**, 245.
CHANG, Y. C., SUH, T. H., and LING, C. C. (1941), *Arch. Neurol. Psychiat.*, **45**, 658.
EINARSON, L., and NEEL, A. V. (1938), *Acta Jutlandica Aarsskrift for Aarhus Universitet*. Copenhagen.
EVANS, C. A., CARLSON, W. E., and GREEN, R. G. (1942), *Amer. J. Path.*, **18**, 79.
FERRARO, A., and ROIZIN, L. (1941), *Trans. Amer. Neurol. A.*, **67**, 477.
FOLLIS, R. H. (1942), *Arch. Path.*, **34**, 451.
HAMERTON, A. E. (1942), *Brain*, **65**, 193.
HIMWICH, H. E., SPIES, T. D., FAZEKAS, J. F., and NESIN, S. (1940), *Amer. J. Med. Sci.*, **199**, 849.
HSÜ, Y. K. (1942), *Arch. Neurol. Psychiat.*, **48**, 271.
INNES, J. R. M. (1939), *J. Neurol. Psychiat.*, **2**, 323.
JOLLIFFE, N., and WORTIS, H. (1941), *Amer. J. Psychiat.*, **98**, 340.
Idem and FEIN, H. D. (1941), *Arch. Neurol. Psychiat.*, **46**, 569.
LEBLOND, C. P., and CHAULIN-SERVINIÈRE, J. (1942), *Amer. J. Med. Sci.*, **203**, 100.
LIGHTNER, C. M., and FORBUS, W. D. (1940), *Amer. J. Path.*, **16**, 670.
LOLLI, G. (1941), *Quart. J. Stud. Alcohol*, **2**, 486.
LOMAN, J., RINKEL, M., and MYERSON, A. (1941), *Amer. J. Med. Sci.*, **202**, 211.
MITCHELL, D. (1941), *Brain*, **64**, 165.
MONNIER, M. (1941), *Z. Vitaminforsch.*, **11**, 235.
MOREL, F. (1939), *Rev. Neurol.*, **71**, 280.
Idem and DUMAN, R. (1940), *Mschr. Psychiat. Neurol.*, **103**, 1.
NEUBUERGER, K. (1937), *Z. ges. Neurol. Psychiat.*, **160**, 208.
PAPPENHEIMER, A. M. (1942), *Amer. J. Path.*, **18**, 169.
PHILLIPS, P. H., and ENGEL, R. W. (1938), *J. Nutrit.*, **16**, 451.
POPPER, H. (1941), *Arch. Path.*, **31**, 766.
PRADOS, M., and SWANK, R. L. (1942), *Arch. Neurol. Psychiat.*, **47**, 626.
PRICKETT, C. O. (1934), *Amer. J. Physiol.*, **107**, 459.
RAGINS, A. B., and POPPER, H. (1942), *Arch. Path.*, **34**, 647.
SHAW, J. H., and PHILLIPS, P. H. (1942), *Proc. Soc. Exp. Biol., N.Y.*, **51**, 406.
SHEEHAN, H. L., and SINCLAIR, H. M. (1939), *Proc. Roy. Soc. Med.*, **32**, 581.
SINCLAIR, H. M. (1943), *ibid.*, **36**, 169.
STREET, H. R., COWGILL, G. R., and ZIMMERMAN, H. M. (1941), *J. Nutrit.*, **21**, 275.
SWANK, R. L., and PRADOS, M. (1942), *Arch. Neurol. Psychiat.*, **47**, 97.
VOLLMER, H. (1941), *Arch. Pediat.*, **58**, 9.
VONDERAHE, A. R. (1939), *Arch. Neurol. Psychiat.*, **41**, 871.
WINKELMAN, N. W., and MOORE, M. T. (1942), *ibid.*, **48**, 54.
WOLBACH, S. B., and BESSEY, O. A. (1941), *Arch. Path.*, **32**, 689.
Idem (1942), *Physiol. Rev.*, **22**, 233.
WOLF, A., and PAPPENHEIMER, A. (1942), *Arch. Neurol. Psychiat.*, **48**, 538.
WOLF-HEIDEGGER, G. (1942), *Confinia Neurol.*, **4**, 121.
WORTIS, H., BUEDING, E., and JOLLIFFE, N. (1942), *New Engl. J. Med.*, **226**, 376.
WORTIS, H., BUEDING, E., STEIN, H. M., and JOLLIFFE, N. (1942), *Arch. Neurol. Psychiat.*, **47**, 215.
ZIMMERMAN, H. M. (1939–40), *Yale J. Biol. Med.*, **12**, 23.
Idem (1940), *Amer. J. Path.*, **16**, 668.

Lesions of Hypothalamus and Thalamus in Relation to Mental Disease.

ALEXANDER, L. (1942), *Proc. A. Research Nerv. and Ment. Dis.*, **21**, 334.
ALPERS, B. J. (1940), *ibid.*, **20**, 725.
CAMPOMA, A. (1939), *Riv. Pat. Nerv. Ment.*, **54**, 461.
CLARK, W. E. L., and RUSSELL, D. S. (1940), *J. Neurol. Psychiat.*, **3**, 123.
COLLINS, V. P. (1942), *Arch. Neurol. Psychiat.*, **48**, 774.
ELVIDGE, A. R., and REED, G. E. (1938), *ibid.*, **40**, 227.
GRINKER, R. R. (1939), *Psychosom. Med.*, **1**, 19.
GRÜNTHAL, E. (1939), *Confinia Neurol.*, **2**, 64.
INGRAM, W. R. (1939), *Psychosom. Med.*, **1**, 48.
KUNTZ, A. (1942), *Confinia Neurol.*, **5**, 78.
LARSON, C. P. (1939), *Amer. J. Psychiat.*, **95**, 971.
MALAMUD, N., and BOYD, D. A. (1939), *Arch. Neurol. Psychiat.*, **41**, 352.

MASSERMAN, J. H. (1942), *Amer. J. Psychiat.*, **98**, 633.
MORGAN, L. O. (1939), *Psychosom. Med.*, **1**, 496.
Idem (1940), *Proc. A. Research Nerv. and Ment. Dis.*, **20**, 753.
NEVIN, S. (1938), *J. Neurol. Psychiat.*, **1**, 342.
OLKON, D. M. (1939), *Arch. Neurol. Psychiat.*, **42**, 652.
PETERS, G. (1938*a*), *Allg. Z. Psychiat.*, **108**, 274.
Idem (1938*b*), *Nervenarzt*, **11**, 521.
SCHARRER, E., and SCHARRER, B. (1940), *Proc. A. Research Nerv. and Ment. Dis.*, **20**, 170.
SCHEIDEGGER, S. (1942), *Confinia Neurol.*, **5**, 65.
STERN, K. (1939), *Brain*, **62**, 157.
Idem (1941–42), *J. Anat., Lond.*, **76**, 302.
Idem and DANCEY, T. E. (1942), *Amer. J. Psychiat.*, **98**, 716.
The Hypothalamus (1938). Edinburgh: Oliver & Boyd.
Ibid (1940), *Proc. A. Research Nerv. and Ment. Dis.*, **20**.

Neuropathology of Shock Treatment.

ALPERS, B. J., and HUGHES, J. (1942), *Arch. Neurol. Psychiat.*, **47**, 385.
ARIETI, S. (1941), *Amer. J. Psychiat.*, **98**, 70.
CLECKLEY, H., BOWLES, L., and METTLER, F. A. (1940), *Arch. Neurol. Psychiat.*, **43**, 948.
ELLIOT, K. A. C., RIVERS, T. D., ELLIOT, F. H., and PLATT, B. (1941), *J. Lab. Clin. Med.*, **26**, 1928.
FELLOWS, R. W., and KÖNIG, F. (1939), *J. Nerv. Ment. Dis.*, **90**, 358.
FINLEY, K. H., and BRENNER, C. (1941), *Arch. Neurol. Psychiat.*, **45**, 403.
HARWITT, M. K., LIEBERT, E., and WILTRAKIS, G. A. (1940), *ibid.*, **43**, 1248.
HAYMAN, M., and BRODY, M. W. (1939), *J. Amer. Med. Assoc.*, **112**, 310.
HEILBRUN, G., and LIEBERT, E. (1941), *Arch. Neurol. Psychiat.*, **46**, 548.
HEILBRUN, G., and WEIL, A. (1942), *ibid.*, **47**, 918.
JANSEN, J., and WAALER, E. (1940), *Arch. Psychiat. Nervenkr.*, **111**, 62.
KENNEDY, A. (1940), *J. Neurol. Psychiat.*, **3**, 49.
KINGSLEY, G. R., and FREED, H. (1941), *Arch. Neurol. Psychiat.*, **45**, 289.
LAWRENCE, R. D., MEYER, A., and NEVIN, S. (1942), *Quart. J. Med.*, **35**, 181.
LIEBERT, E., and HEILBRUN, G. (1940), *Arch. Neurol. Psychiat.*, **43**, 463.
LIEBERT, E., and WEIL, A. (1939), *ibid.*, **42**, 690.
LOMAN, J. (1941), *ibid.*, **45**, 282.
MEYER, A. (1939), *J. Ment. Sci.*, **85**, 927.
MICHAEL, N., and WITTENBROOK, J. (1940), *Arch. Neurol. Psychiat.*, **43**, 560.
NEUBUERGER, K. T., WHITEHEAD, R. W., RUTLEDGE, E. K., and EBAUGH, F. G. (1942), *Amer. J. Med. Sci.*, **204**, 381.
NEUMANN, M. A., COHN, R., and KATZENELBOGEN, S. (1942), *Amer. J. Psychiat.*, **98**, 668.
NIGHTINGALE, G. S., and MEYER, A. (1940), *J. Ment. Sci.*, **86**, 819.
PESSIN, J., and REESE, H. H. (1939), *Amer. J. Psychiat.*, **96**, 393.
PETERSEN, F. (1939), *Allg. Z. Psychiat.*, **111**, 366.
REITMANN, F. (1938), *Psychiat. Neurol. Wschr.*, **40**, 391.
SCHMID, M. H. (1936), *Ann. Med. Psychol.*, **94**, 658.
STRECKER, E. A., ALPERS, B. J., FLAHERTY, J. H., and HUGHES, J. (1939), *Arch. Neurol. Psychiat.*, **41**, 996.
TYLER, D. B., and ZISKIND, E. (1940), *Proc. Soc. Exp. Biol., N.Y.*, **44**, 622.
WEIL, A., and LIEBERT, E. (1940), *Arch. Neurol. Psychiat.*, **44**, 1031.
WHITEHEAD, R. W., NEUBUERGER, K. T., RUTLEDGE, E. K., and SILCOTT, W. L. (1940), *Amer. J. Med. Sci.*, **199**, 352.
WINKELMAN, N. W., and MOORE, M. T. (1940), *Arch. Neurol. Psychiat.*, **43**, 1108.
WYLLIE, A. M. (1940), *J. Ment. Sci.*, **86**, 248.

Oligophrenia.

ALEXANDER, L. (1942), *Proc. A. Research Nerv. and Ment. Dis.*, **21**, 334.
Idem and MYERSON, A. (1939), *Amer. J. Psychiat.*, **96**, 77.
ASHBY, W. R., STEWART, R. M. and WATKIN, J. H. (1937), *Brain*, **60**, 149.
BENDA, C. E. (1939*a*), *Proc. Amer. Ass. Stud. Ment. Def.*, **44**, 47.
Idem (1939*b*), *Arch. Neurol. Psychiat.*, **41**, 83.
Idem (1939*c*), *ibid.*, **41**, 243.
Idem (1939*d*), *ibid.*, **42**, 1.
Idem (1940), *Amer. J. Path.*, **16**, 71.
Idem (1941), *Amer. J. Psychiat.*, **97**, 1135.
DIXBY, E. M. (1939), *Proc. Amer. Ass. Stud. Ment. Def.*, **44**, 59.
Idem (1940), *Amer. J. Ment. Def.*, **45**, 201.
Idem (1941), *ibid.*, **46**, 183.
DIDE, M., and VAN BOGAERT, L. (1938), *Rev. Neurol.*, **69**, 1.
FERRARO, R., and JERVIS, G. A. (1940), *Arch. Path.*, **30**, 731.

FITZGERALD, G. M., GREENFIELD, J. G., and KOUNINE, B. (1939), *Brain*, **62**, 292.
HAGEDOORN, A. (1940), *Amer. J. Ophthal.*, **23**, 735.
HALLERVORDEN, J. (1938*a*), *Mschr. Psychiat. Neurol.*, **99**, 74.
Idem (1938*b*), *Z. ges. Neurol. Psychiat.*, **161**, 384.
HIMWICH, H. E., and FAZEKAS, J. F. (1940), *Arch. Neurol. Psychiat.*, **44**, 1213.
JAKOB, H. (1938), *Z. ges. Neurol. Psychiat.*, **160**, 615.
JERVIS, G. A. (1940), *Amer. J. Dis. Child.*, **60**, 88.
Idem (1941), *ibid.* **61**, 327.
Idem and THIELLS, N. Y. (1942), *Arch. Neurol. Psychiat.*, **47**, 943.
KLENK, E. (1939), *Z. Physiol. Chem.*, **262**, 128.
Idem (1940), *ibid.*, **267**, 128.
MEYER, A., and JONES, T. B. (1939), *J. Ment. Sci.*, **85**, 206.
NORMAN, R. M. (1938*a*), *J. Neurol. Psychiat.*, **1**, 7.
Idem (1938*b*), *ibid.*, **1**, 198.
Idem and WOOD, N. (1941), *ibid.*, **4**, 175.
PETERS, G. (1939), *Z. ges. Neurol. Psychiat.*, **164**, 365.
ROTHSTEIN, J. L., and WELT, S. (1941), *Amer. J. Dis. Child.*, **62**, 801.
RUTLEDGE, E. K., and NEUBUERGER, K. T. (1942), *Amer. J. Path.*, **18**, 153.
SCHACHTER, M. (1941), *Z. Kinderpsychiat.*, **8**, 47.
SCHEIDEGGER, S. (1941), *Schweiz. Z. Path. Bact.*, **4**, 27.
SCHOLZ, W., WAKE, J., and PETERS, G. (1938), *Z. ges. Neurol. Psychiat.*, **163**, 193.
STEWART, R. M. (1938), *J. Neurol. Psychiat.*, **1**, 68.
Idem (1939*a*), *ibid.*, **2**, 303.
Idem (1939*b*), *J. Ment. Sci.*, **85**, 256.
Idem (1942), *Proc. Roy. Soc. Med.*, **36**, 25.
WALKER, A. E. (1942), *Arch. Neurol. Psychiat.*, **48**, 13.
YAKOVLEV, P. I., and WADSWORTH, R. C. (1941), *Trans. Amer. Neurol. A.*, **67**, 24.