between the time of injury and death. It is hoped that such a curve will serve as a basis for any future computation of mortality statistics. By studying the curves in the various type of automobile injuries, it is observed that they are inclined to follow the same general pattern (fig. 2). A curve of the mortality rate of all cases and from all causes is shown in figure 3. It can be divided into three parts. Beginning with a large number of individuals who are killed outright, the first part of the curve shows an abrupt descent. The group of individuals who are killed outright or die within a short time interval do not always reach a hospital and therefore are not included in hospital mortality statistics. In Los Angeles, for example, most injured individuals are taken to a receiving hospital where they may be kept for a number of hours before transfer to a hospital for permanent care.

TABLE II

Causes of Fatal Craniocerebral Injury

	CASES
Pedestrian struck by automobile	266
Collision between automobiles	237
Falls (accidental 152, suicidal 9)	161
Automobile striking stationary object	107
Automobile and train collision	43
Assault	35
Struck by falling objects*	15
Pedestrian struck by train	14
Fights	9
Explosion	6
Miscellaneous	5
Type of injury not known	21

This fact would explain the lower death rate in Los Angeles institutions below that of hospitals of other cities which receive patients directly from the scene of the accident.

The second portion of the curve covers the period between two and eight hours. The great majority of this group of cases are destined to die regardless of the form of treatment administered. The third part of the curve is the flattened portion which continues with but minor fluctuations for the remainder of the twenty-four hour period. It is this group that may possibly be influenced by proper therapy. As is frequently the case, these rules are not absolute but the exceptions cannot be considered in this connection.

If the mortality rate is plotted on the basis of the survival period in days rather than in hours, a similar type of curve is produced (fig. 4). The first portion of the curve drops steeply to the end of the

*Including six deaths resulting from falling masonry in the earthquake at Long Beach, March 10, 1933.

three day period. The second part drops more gradually in the first eight days. The final portion gradually flattens out to coincide ultimately with the ordinate.

DISCUSSION

From a study of the records of a large number of fatal cases of injury, it seems obvious that they should be divided into two groups, (1) those with other serious injuries, contributing to if not actually causing the individual's death and (2) those in which the craniocerebral injury is the only serious lesion. In the former group, wide variations exist in the influence of the cerebral lesion in causing

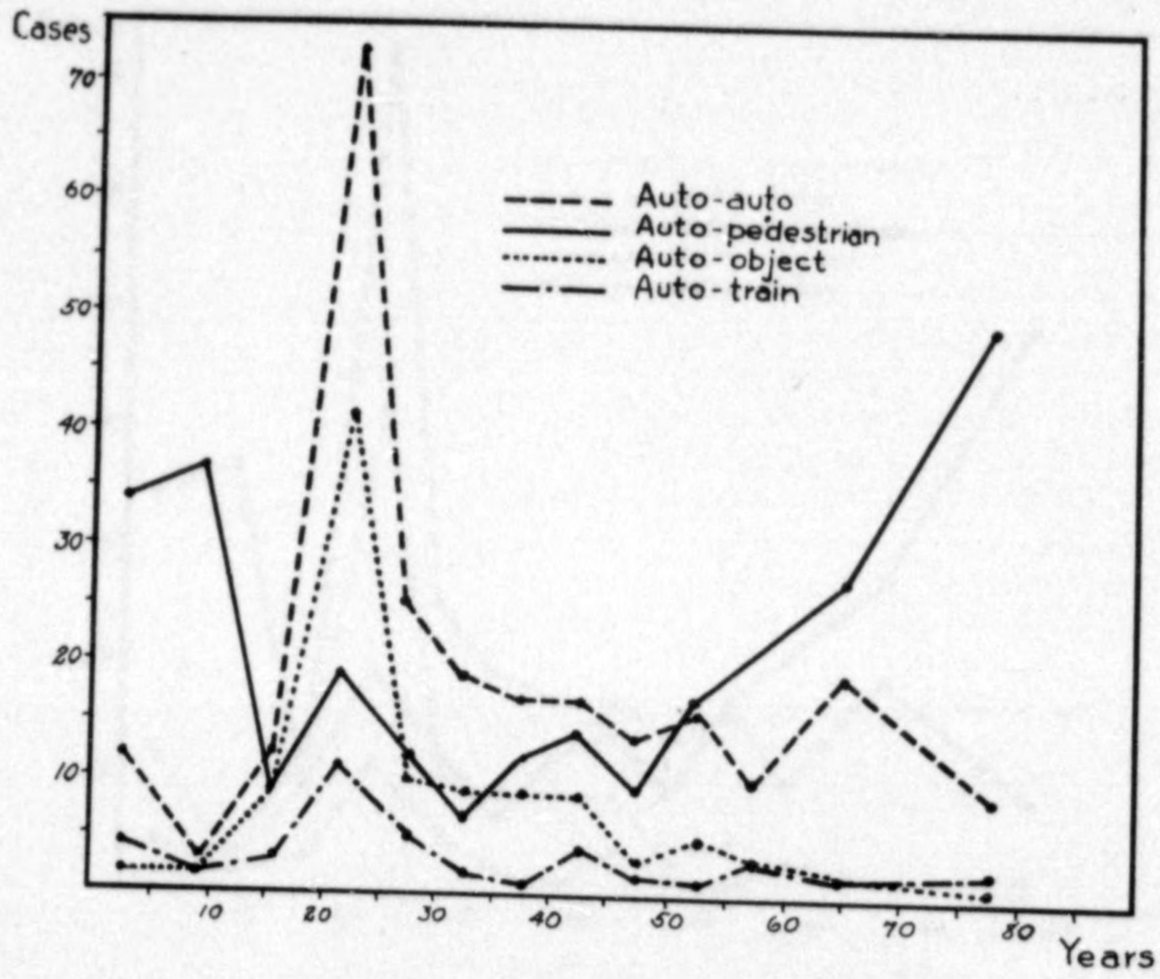

FIG. 1. Graph showing incidence of fatal cases of craniocerebral injury from auto accidents at various age periods.

death and, in many instances, honest difference of opinion would exist as to which was the major lethal factor. In attempting to establish a "normal" curve, it has seemed best to exclude this group entirely. When the remaining second group is studied on the basis of length of their survival period, it is found that a fairly characteristic curve is produced. In its first portion at least, it is likely that this curve approaches an irreducible minimum, a mortality which present day therapy is not likely soon to lower.

From a study of a relatively large series of fatal cases, it seems evident that the mortality curve alone cannot be taken as a criterion

of effectiveness of treatment. The time interval between injury and hospitalization, the complicating factors, such as injury to other parts and the varying bases for inclusion of cases (the matter of hospitalization, the matter of coma, radiographic evidence of fracture, etc.), all contribute to make the problem so complex as to be of little use in evaluating the effectiveness of a given form of treatment.

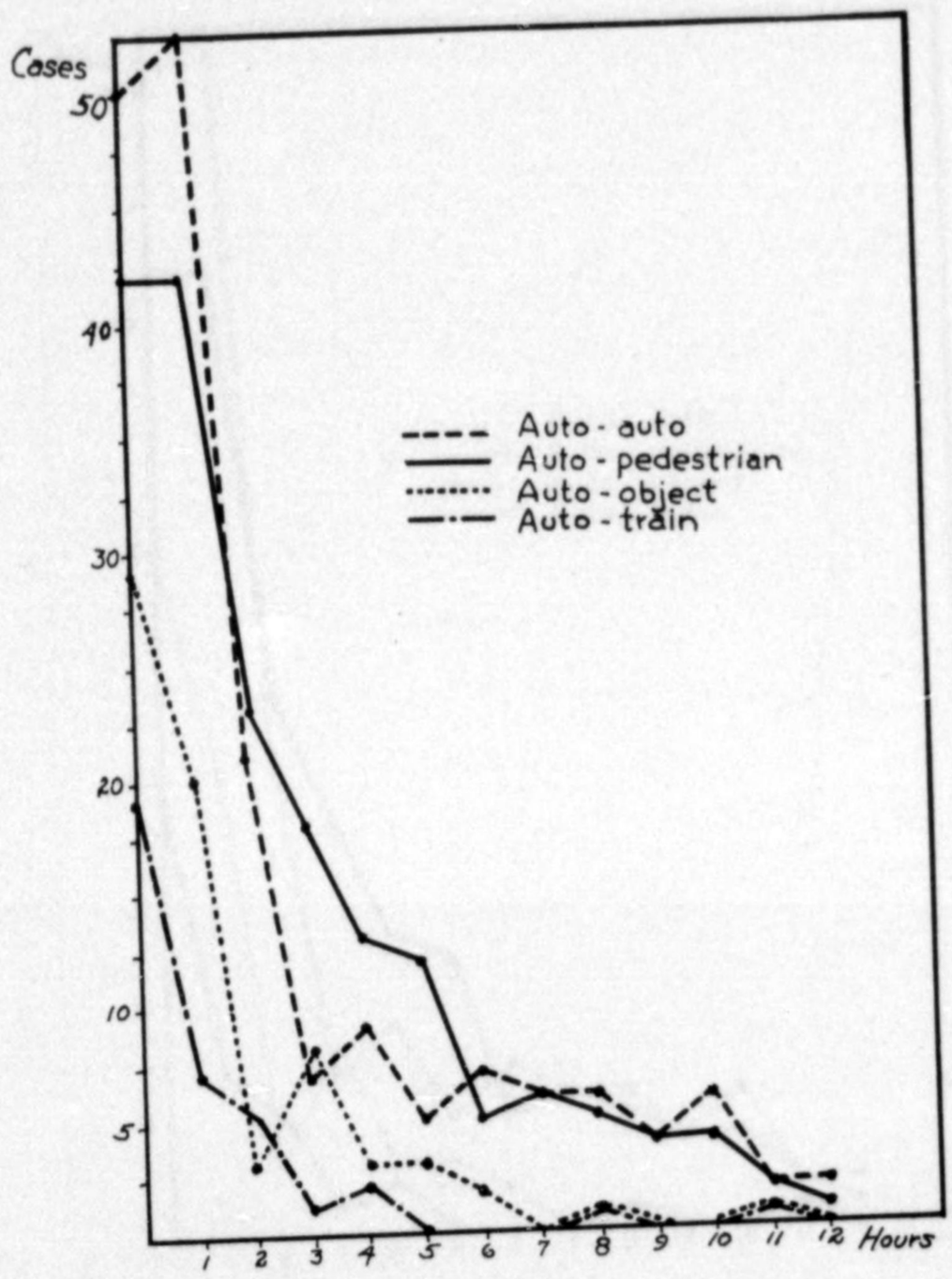

FIG. 2. Graph showing survival period in first twelve hours of fatal cases of craniocerebral injury due to auto accidents.

Perhaps a more useful criterion would be the promptness and completeness of recovery after administration of treatment if suitable clinical standards could only be established. The prominence of symptoms entirely subjective in character which constitute the postconcussion syndrome would add to the difficulty in utilizing such a basis for effectiveness of therapy.

One very practical criterion as to the effectiveness of diagnosis and treatment is to be had in a study of lesions found at autopsy. If death has occurred from a preventable or curable cause, the case should be charged up as a diagnostic or therapeutic failure. If fatal cases could be scrutinized from this viewpoint by an impartial judge, some valuable lessons would be learned.

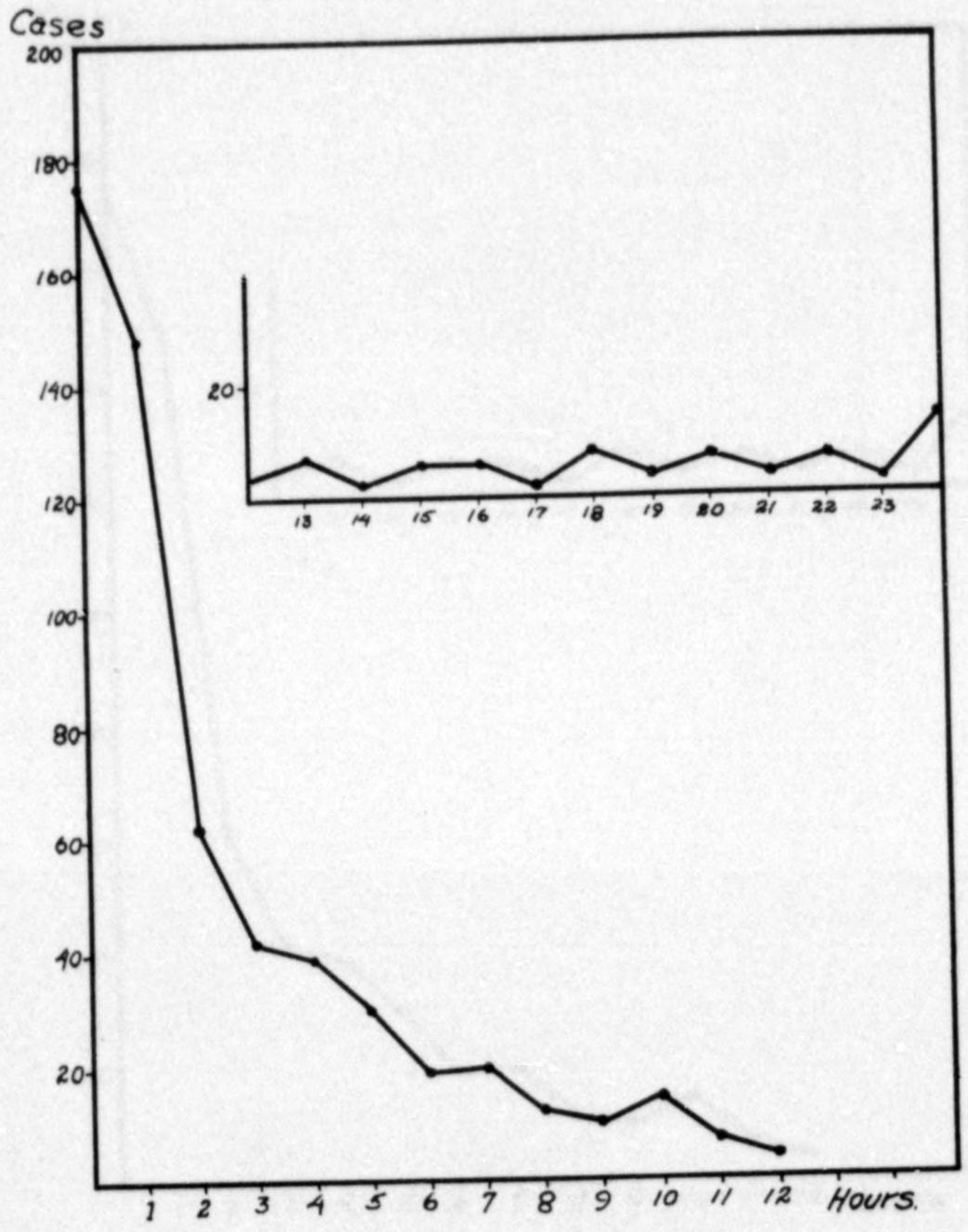

FIG. 3. Graph showing average survival period in the first twelve hours of fatal cases of craniocerebral injury. Death from all causes.

SUMMARY

1. More than one-half of all individuals dying as the result of trauma reveal at autopsy some evidence of injury to the brain or its envelopes. About half of those dying after an injury to the brain, die as a direct result of this injury alone.

2. About seventy-five per cent of the fatal cases of craniocerebral injury occur in males.

3. The automobile is responsible for more than two-thirds of the deaths resulting from injury to the head.

4. The greatest number of deaths in any age period occur in early adult life. The automobile assumes here an even greater role as a death producing agent.

5. Based on the survival period, the fatal cases describe a characteristic curve. In order to evaluate properly those mortality statistics,

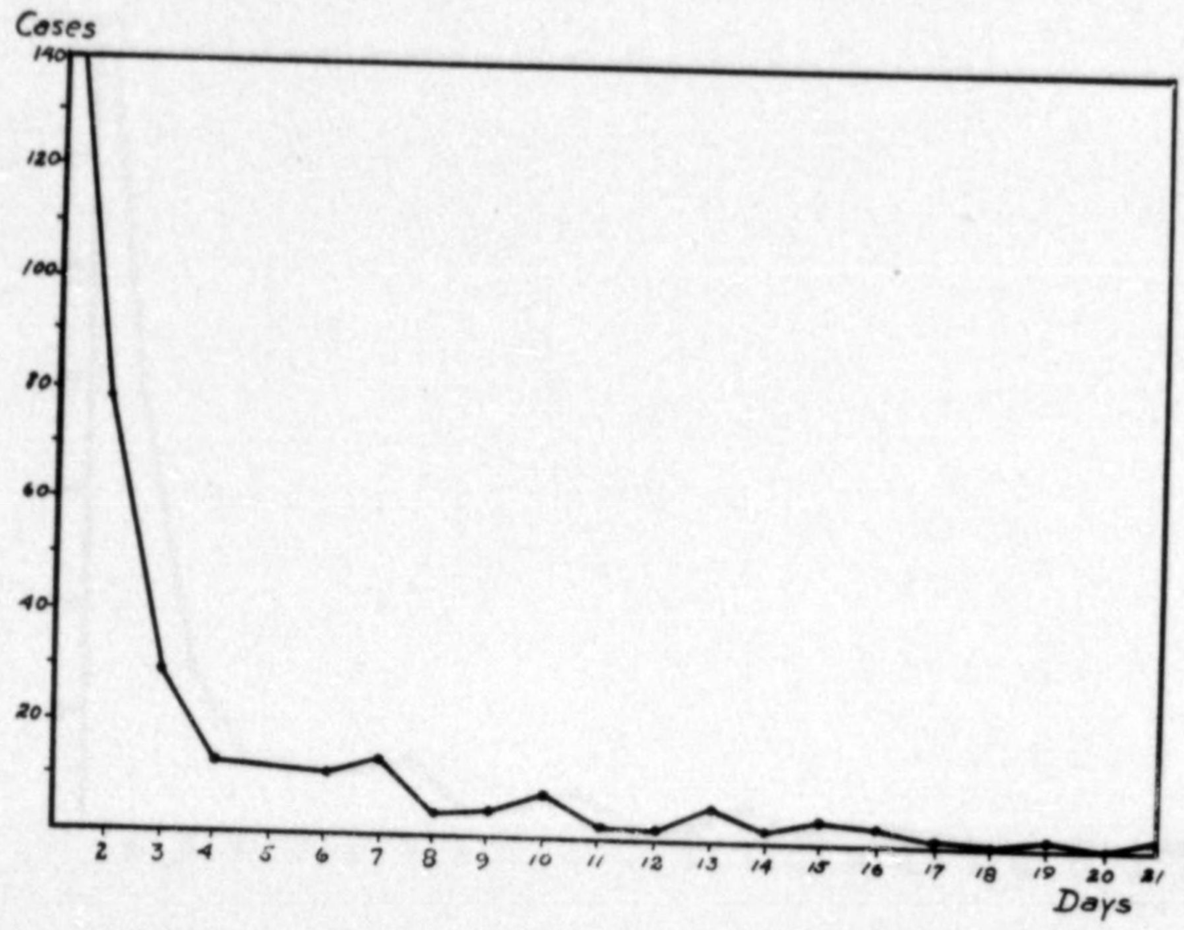

FIG. 4. Graph showing survival period for twenty-one days. Death from all causes.

it is necessary to consider the survival period of the patients who ultimately die. Most of those who die within the first eight hours and many of those who die thereafter cannot be saved by any form of treatment. Effective treatment may tend to lower the curve in its remaining portion.

6. Because of the complexity of the statistical problem, it seems unlikely that the study of mortality will be of any great use in the determination of effectiveness of treatment.

7. One practical approach to the problem is a study of the post-mortem lesions. When a preventable or curable lesion is found at autopsy, the case must be considered a diagnostic or therapeutic failure.

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THE PRESENT STATUS OF EXPERIMENTAL NEUROEMBRYOLOGY*

A RE-EVALUATION OF THE FUNDAMENTAL PRINCIPLES OF DEVELOPMENT OF THE NERVOUS SYSTEM

CYRIL B. COURVILLE, M.D.

There was a time not so long ago when it was possible for an individual interested in Science to maintain a fairly comprehensive view of its entire realm and to be especially conversant with the particular subscience in which he chose to interest himself. The accelerated tendency in recent years to more detailed specialization, the process of "knowing more and more about less and less," has made it increasingly difficult for any one individual to maintain his contacts with other fields of investigation. Between two interests, the straddle becomes increasingly wide and, sooner or later, he must jump to one side or the other. To those with clinical responsibiilities, the gap between bedside medicine and the basic sciences ultimately becomes a wide one, and a once capable and enthusiastic laboratory investigator is apt to find himself a stranger in the Elysian Fields where he formerly felt quite at home. It is therefore profitable for the clinician from time to time to resurvey the advances which have been made in the basic sciences upon which his speciality is founded to see how his concepts need be revamped to suit the facts.

To bring these generalizations to a focus, it is the object of this short review to call attention to some pertinent discoveries in the relatively new science of Experimental Embryology, which discoveries are likely to shed some light on the problems of Neuropathology and Clinical Neurology. Evidently without general recognition amongst us, certain important observations as to the mechanism and potencies of development of the nervous system have been recorded in recent years. The possible significance of conclusions based on these observations demands a reconsideration of the theories of development proposed in the latter half of the nineteenth century, which theories, although now recognized to be falsely founded, still too largely dominate scientific neurologic thought in the twentieth. This is especially true in some circles where a strong tendency exists to account for the etiology and pathogenesis of certain diseases in deviations from the normal development of the nervous system. In this short recapitulation of experimental neuroembryology, an effort will be made to point out some of the pertinent newer developments in this field and to show how such facts demand a new philosophy as to their causal implications.

In this review, a survey of certain experimental observations on the development of the central nervous system will be made, viz., the causal significance of egg-maps, egg-types and "determination", the action of the organizer in the development of the central nervous system, the influence of the axial and field

* From the Cajal Laboratory of Neuropathology, Los Angeles County Hospital, and the Department of Neurology and Psychiatry, College of Medical Evangelists, Los Angeles California.

gradients, early or visible differentiation versus late or functional differentiation, and the characteristics of nerve growth *in vivo* and *in vitro*. In the light of these observations, some important biologic generalizations will be discussed. A more critical analysis of these discoveries as they pertain to malformations and tumors of the nervous system must await another occasion.

EGG-MAPS AND THEIR SIGNIFICANCE

One of the most interesting and fundamental facts which has been brought to light by experimental embryology is one which shows that the potential pattern of future development is already sketched out in the fertilized egg or ovum.

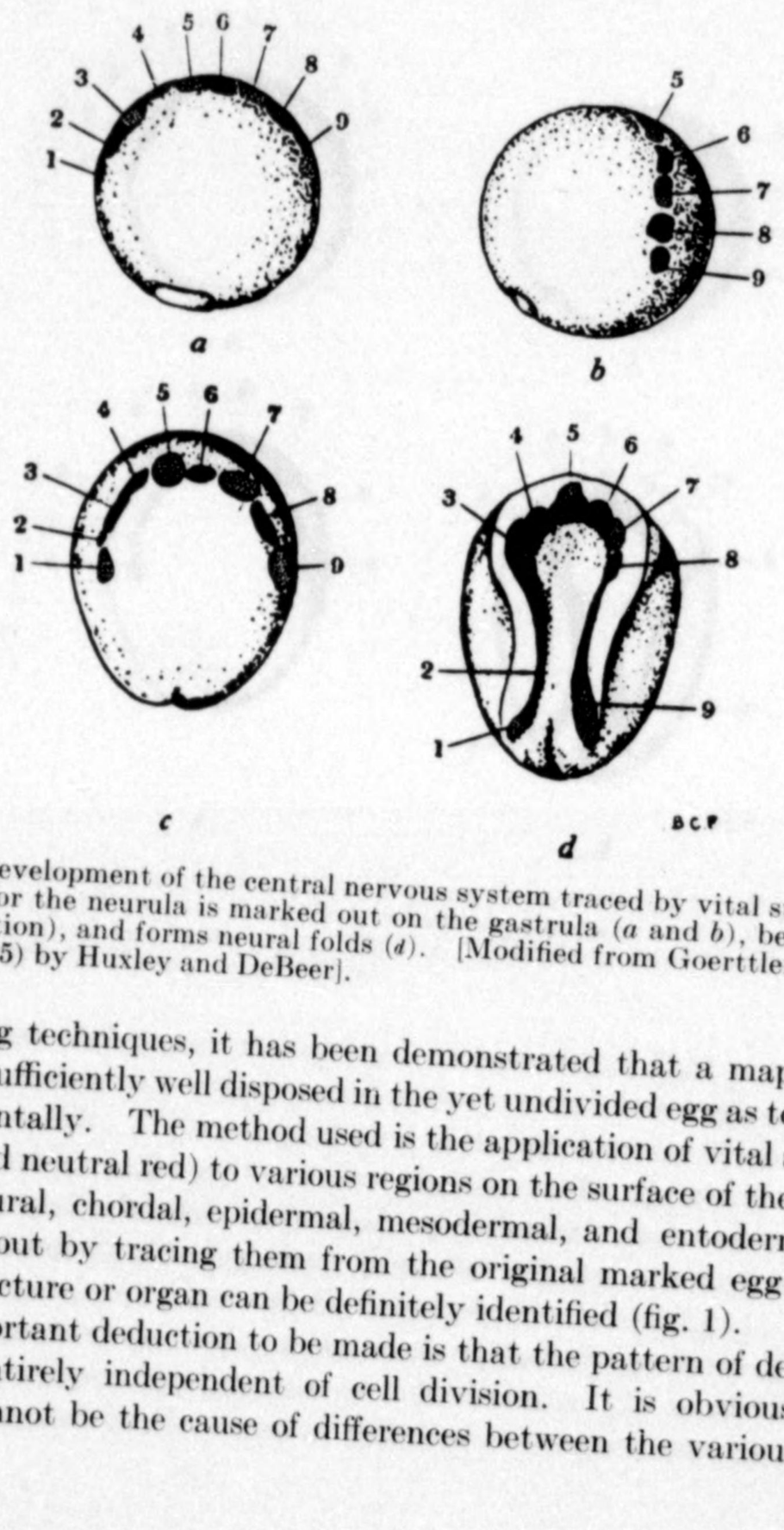

FIG. 1. Early development of the central nervous system traced by vital staining. Presumptive region for the neurula is marked out on the gastrula (*a* and *b*), becomes curved (*c* end of gastrulation), and forms neural folds (*d*). [Modified from Goerttler (*Arch Entwmech.* Vol. 106, 1925) by Huxley and DeBeer].

By vital staining techniques, it has been demonstrated that a map or plan of development is sufficiently well disposed in the yet undivided egg as to be demonstrable experimentally. The method used is the application of vital stains (nile-blue sulphate and neutral red) to various regions on the surface of the egg. The presumptive neural, chordal, epidermal, mesodermal, and entodermal regions can be mapped out by tracing them from the original marked egg to a stage in which the structure or organ can be definitely identified (fig. 1).

The most important deduction to be made is that the pattern of development is maintained entirely independent of cell division. It is obvious that cell division itself cannot be the cause of differences between the various germinal

regions, for the pattern of cleavage and subsequent cellular proliferation, may follow an entirely different and independent scheme. The actual process of development must therefore antedate the formation of the two blastomeres. Cell division is but the mechanism by which development is carried out, and is itself subject to some controlling influence in the egg.

It is also evident from a study of the germ patterns of eggs of different animals that the presumptive areas of the various structures and organs do not form the same pattern (fig. 2), nor does the involved protoplasm follow the same course of migration to its ultimate position. This migration may come

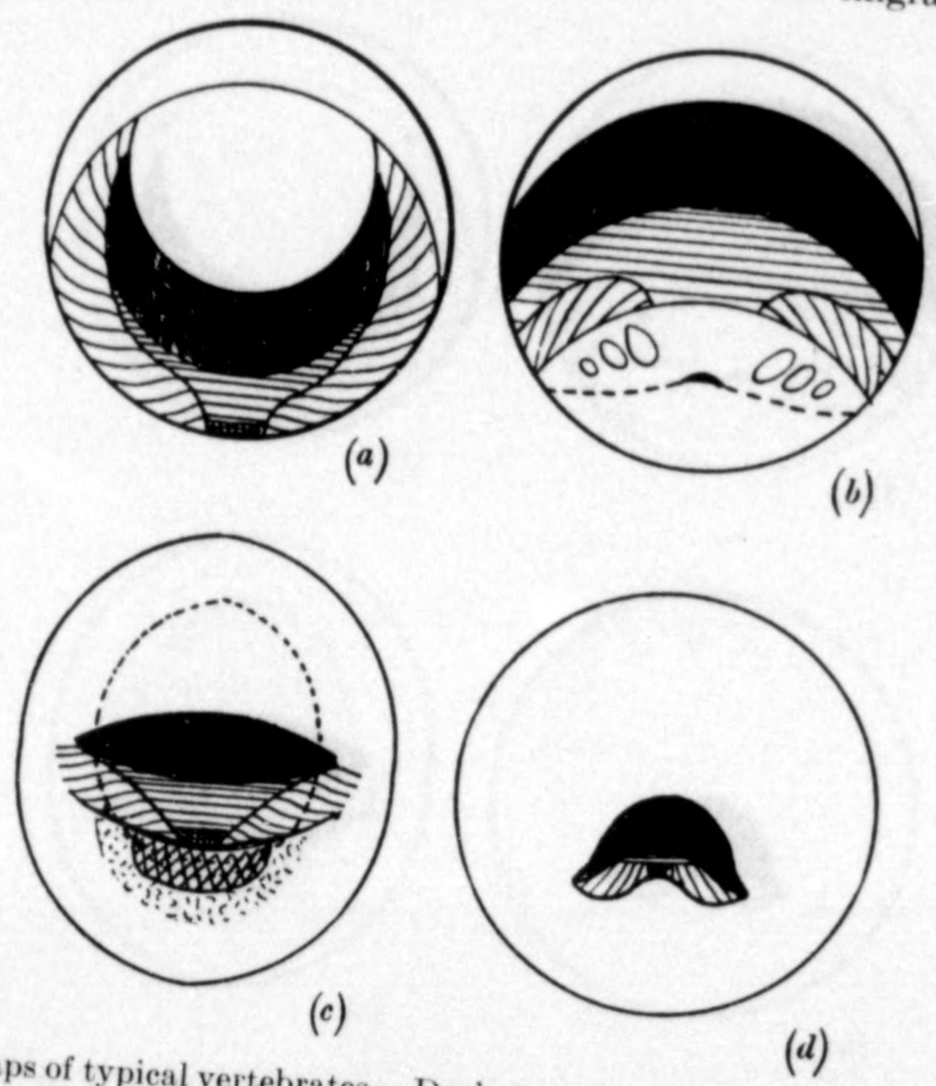

FIG. 2. Egg maps of typical vertebrates. Dark area indicates presumptive region for the central nervous system. (a) Teleosts (trout), (b) Amphibians (toad), (c) Reptiles (tortoise), and (d) Birds (chick). (Modified from Dalcq, *Form and Causality in Early Development*, Cambridge University Press, 1938).

about by mass movement or by movement of individual cells (Dürken, 1932). It is best described as an 'amoeboid movement' of the substance of the entire germ plasm. In spite of its division into many cells the formative plasm moves as an integrated mass, the process taking place coincident with, and undoubtedly controlling, the process of cell division.

One important point needs to be established in anticipation of other phenomena of development. Almost paradoxical and not easy of comprehension is the conclusion that while the various presumptive organ-regions can be mapped out in the fertilized egg, it cannot be said that each organ is specifically preformed in a particular region of the egg. This is clearly proven by the fact that upon

separation of the two blastomeres of the fertilized egg (as of the newt *Triton* for example), each will develop into a complete animal. It is therefore evident that the original pattern of the central nervous system, for example, is promptly readjusted in each half of the egg to form a perfect whole. Obviously this process is one beyond simple analysis or measurement by known biologic standards.

Several important deductions are to be made on the basis of these observations. In the first place, it is evident that the wide variability in egg-maps should destroy any notions of a purely historic interpretation of the egg. In his 'law of biogenesis' Haeckel suggested that the egg was to be compared with a presumed one-celled progenitor of all animal life. Even ignoring the wide variation in size and structure of the various types of eggs, it now becomes evident that the variation of potency-distribution shows relatively as wide differences in the egg as in the adult. The only causal implication that one can draw from a comparative study of eggs is that before there was an egg there was a predestined plan for its development, a conclusion which fails to find any place in phylogenetic interpretation.*

Another important deduction to be made from a study of egg-maps is that, from an embryologic standpoint, the principle of homology has no causal significance. DeBeer has so well pointed out this situation in the following words:

> "It might seem, then, that in considering the homology of any given structure it is necessary to consider not only the tissues from which they arise but the organizers which have induced their formation. . . . But the important point to notice is that the *structures can owe their origin to different organizers without forfeiting their homology*. . . . The fact is that correspondence between homologous structures can not be pressed back to similarity of position of cells in the embryo or of the parts of the egg out of which the structures are ultimately composed."

This important truism, for which there is ample support in experimental embryology, makes it idle to attempt to compare homologous parts of structures of the nervous system in an effort to establish phylogenetic relationships. One can make causal conclusions only when it can be proven, as DeBeer has stated, that the tissues in both cases come from identical regions and were constructed under the influences of the similar organizers.

EGG-TYPES AND DETERMINATION

As a result of experimental studies, it has become evident that there are two general groups of eggs dependent on the relative ability of the two blastomeres

* It was this failure to take into account the unseen potencies in embryologic development which was the greatest defect in the 'biogenetic law' of Haeckel. The purely deductive theory of recapitulation was elaborated solely on the basis of structural comparisons between embryos, and while at the hands of critical students the theory failed to measure up to expectations even before the experimental method was introduced, it now becomes evident that an understanding of the unseen factors at work completely destroys any remaining usefulness of the historic method (Courville, 1941). This tends to bear out in embryology the generalization of the ancient theologist-philosopher, St. Paul, who said that the things which are seen are transitory, while the things which are unseen are perpetual (II Cor. 4:18).

to form separate embryos. It has been found that in some cases (i.e., sea urchin) a separation of the two blastomeres formed by division of the fertilized egg resulted in the formation of two normal larvae. These are called *regulation-eggs*. This term indicates that organ-forming substances are developed slowly and that equal amounts of potentially equivalent cytoplasm are distributed to the two divisions of the egg which can be regulated to form a larva from each blastomere. Even in regulation-eggs this power of regulation is not long maintained and, in the case of the sea urchin, is not continued beyond the 4-cell stage. In a second group of eggs (i.e., ascidians) separation of the two blastomeres results in two more or less imperfect larvae. In these *mosaic-eggs*, the elaboration

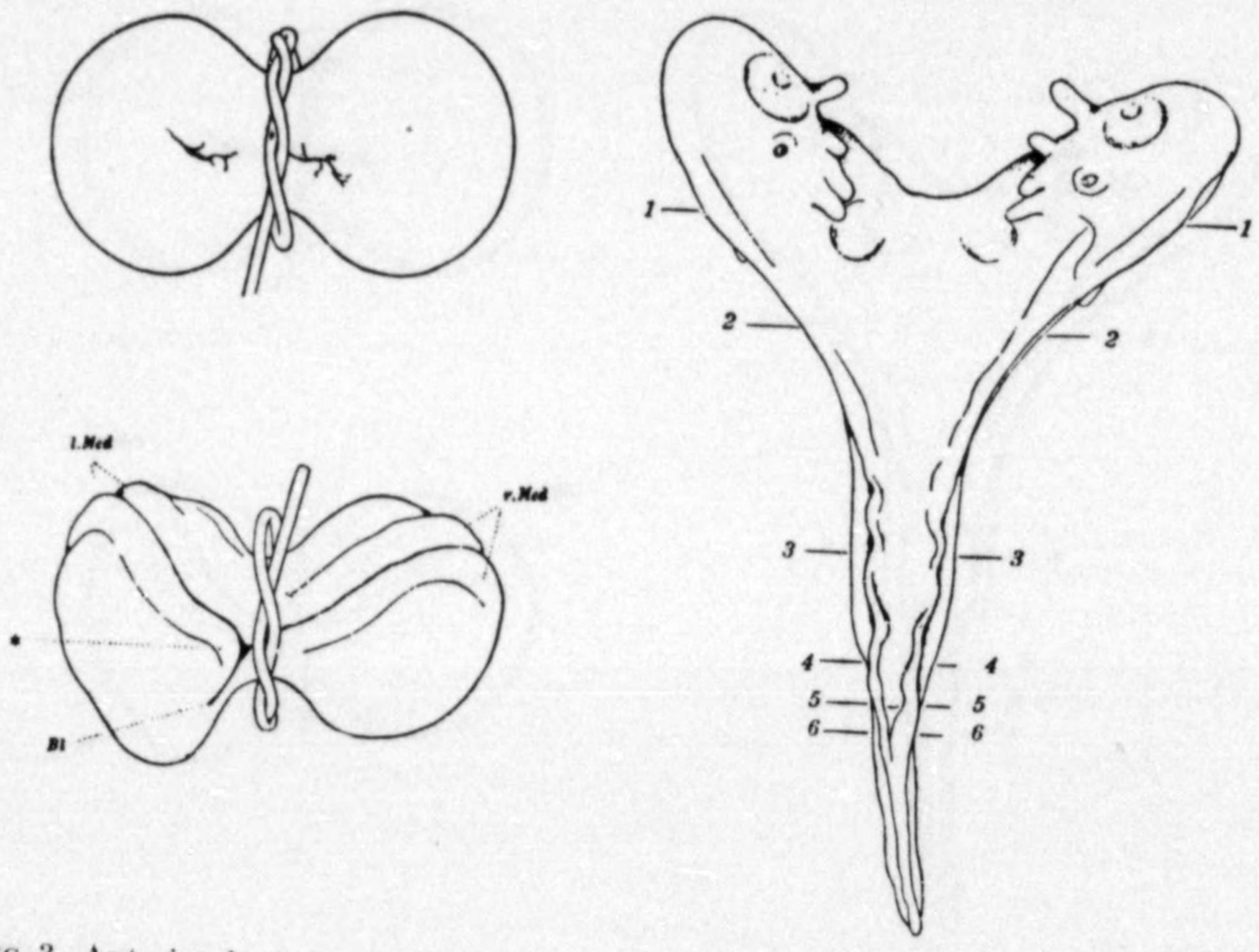

FIG. 3. Anterior doubling (*Triton*) due to partial constriction of early gastrula in plane of symmetry (Spemann, *Arch. Entwmech.*, Vol. 16, 1903).

of organ-forming substances is more rapid and takes place before cleavage. At the time of cleavage, there is an unequal distribution of qualitatively different cytoplasmic material between the two blastomeres. The term 'mosaic-egg' signifies that in the single-cell stage of development its structure is already a mosaic, the different regions being capable of developing independently of one another. The loss of a small segment is sufficient to disturb the mosaic, and an imperfect embryo results (DeBeer). As is to be expected, the line of separation between these two types of eggs is not a sharp one, and transitional types do occur.

This discussion of 'regulation' would not be complete without brief mention

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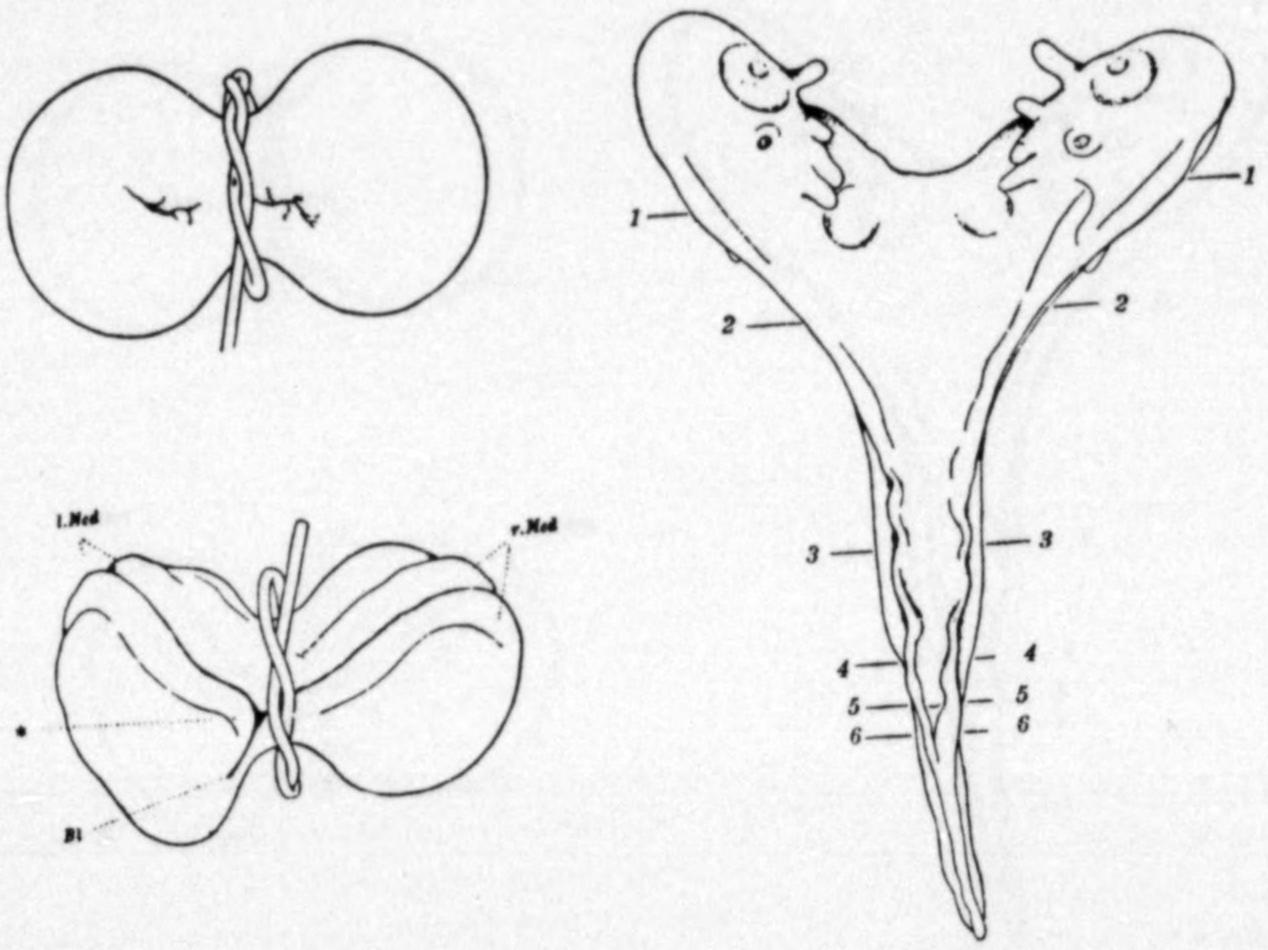

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of the two classic experiments that emphasize the principle. Among the earliest of experiments in this field were those performed by Driesch who demonstrated that in some germs separation of the two blastomeres resulted in the formation of two embryos, and conversely that two cells could be fused to form a single embryo. Partial division of a germ by a constricting hair resulted in partial doubling (fig. 3), a gross malformation sometimes seen in vertebrate embryos as a 'natural' phenomenon, or one which may be produced experimentally by lessening the oxygen supply or disturbing the chemical equilibrium of the solution in which fish eggs were being hatched (Stockard).

While this matter of regulation-eggs and mosaic-eggs is obviously only remotely concerned with development of the central nervous system, a closely related principle does have such a relationship, i.e., that of *determination*. This principle is illustrated in the following experiment: If a piece of presumptive neural tube removed from one newt embryo in the stage of early gastrulation is transplanted into the gill region of a second, this transplanted tissue will develop into an external gill. Or, if a bit of presumptive epidermis is grafted into the neural region of a second embryo, it will develop into part of the brain and the eye. It is demonstrated by these experiments that up to this stage the various tissues are plastic, developing in harmony with their surroundings and regardless of their actual origin. Not only individual regions but also the germ layers are plastic in this sense. After this stage, however, the fate of these regions is irrevocably 'determined'. Some invisible process, evidently chemical in nature (*chemo-differentiation*), has occurred to determine the fate of the various presumptive areas, and the embryo has become a mosaic of separately determined regions. As might be expected from the early development of the neural tube, at least in the newt, this structure becomes determined before the other tissues. This is but a subsequent step following determination of the dorsal lip of the blastopore, which from a very early stage has had the irrevocable function of organizer to initiate the development of the entire axial complex. This will be described more fully in the subsequent section.

The important 'law' which is to be deducted from these experiments is that *early in its development the brain is irrevocably determined, therefore takes the lead of the surrounding structures toward which it very likely acts as a secondary organizer.* In this respect, its determination is preceded only by that of the organizer itself.

ORGANIZER ACTION IN THE DEVELOPMENT OF THE CENTRAL NERVOUS SYSTEM

Perhaps the greatest single contribution of experimental embryology to the study of development is the organizer concept. By this concept is meant the control of embryonic development by certain potencies, apparently chemical, which direct the organization, first of all of the axial structures, then by action of secondary organizers of adjacent organs and structures, and so on until the formation of all the more detailed features of the embryo have been induced. In that portion of the wall of the blastula which forms the dorsal lip of the

blastopore, the chorda-mesoderm material (the presumptive notochord* and surrounding mesoderm) exerts a profound influence on the material supradjacent to it, 'inducing' it to form the neural plate, mesodermal somites, and other structures in the long axis of the embryo. Because of its ability to organize the processes of development in the surrounding tissues, this region is called the *organizer* or *organization center*. This power is not inherent alone in these regional tissues. Tissue from other parts of the embryo can be grafted into this region, which grafted tissue will then become the organizer. The potent element in the organization center seems to be of a chemical nature, something resembling a sterol. This substance apparently diffuses through the tissues of the organizer until it reaches the epidermis. It therefore exerts its effect by direct contact.

The potency of this organizer is clearly shown in what has become a classic experiment. If the dorsal lip of the blastopore is grafted into the lateral aspect of the same or another embryo, a second complex of axial organs, including the medullary rudiment, somites, auditory pits, pronephric ducts and a tail, will be induced to develop; a parasite embryo thus forms from the tissues of the host. To show its relative non-specificity, the organizer of a different species, genus or even order, may be capable of inducing the secondary axial complex in a given embryo. For example, the organizer from the toad *Bombinator* is capable of inducing the axial complex in the germ of the newt *Triton*. The action of the organizer is not the same even in closely-allied species. For instance, if the notochord of *Triton alpestris* is grafted into the *Triton taeniatus*, a new medullary plate will develop, but without any associated mesoderm. The organizer retains its potency often for a considerable time, probably variable in duration from one species to another.

Another experiment, also performed on amphibia, contributes further to our knowledge of these potencies which control the development of the central nervous system. If the organizer is removed from the young germ, development of the brain with its constituent tissues and cell complexes will still proceed to its adult state. It is evident that in these animals at least secondary concomitant factors exist which aid the chief one in inducing the axial complex. On this point Dürken writes:

> "In the determination of the actual organs we see, then, a phenomenon which may be called *double assurance* ('making doubly sure'), or to use a more general term, *multiple assurance*. Such multiple assurance of causation of a developmental process rests upon the fact that all the cells of the germ have the same specific reaction basis and upon the other fact that the germ is not a mosaic of heterogenous parts, but a unit and a whole . . . . Development is thus ultimately an integral process."

We see in this law of 'double assurance' an example of a more general anatomico-physiologic law which functions in the central nervous system, parti-

* The historic method of accounting for developmental phenomena made much of certain similarities or 'parallelisms' of embryos which were said to be at least 'reminiscent' of their phylogenetic history. Among these structures the significance of the notochord has been especially emphasized. The highly important embryonic function of this structure as a center or 'organizer' of development of the axial complex demands a different explanation of its presence other than as a vestigial structure.

cularly evident in the occurrence of double pathways (i.e., those of tactile and auditory sensation and the spinocerebellar tracts) which doubly assure the transmission of impulses from the periphery to the central organ.

It becomes obvious, therefore, that the development of the central nervous system, as of other parts of the body, is dependent upon unseen, rather simple chemical substances which control the process. Beginning at first as a single organization center in the dorsal lip of the blastopore, this influence spreads to all parts of the embryo, setting up an entire series of centers of influence until an entire 'hierarchy' of organizers is set up, 'wheels within wheels,' constructing the new individual. Applying the process specifically to the central nervous system, the original medullary plate which is induced by the primary organizer goes on to develop the neural tube. In the elaboration of the more complex structure of the brain, secondary, tertiary, or even more refined centers of influence lead out in the formation of the ganglionic masses and nuclear cell groups.

Therefore, in any consideration of development of the nervous system, we have to deal, not only with the constantly elaborating and shifting masses of cells, but also with an intricate system of chemical potencies which stimulate and direct these processes. It is no longer sufficient to speak only of the evident abnormal, excessive, or incomplete movement of cell groups as the cause of malformations. The fault presumably lies with some disturbance of, or interference with, the unseen chemical potencies which control the destinies of these cell groups.

INFLUENCE OF THE AXIAL- AND FIELD-GRADIENTS

One of the earliest developmental processes to take place in the germ is the establishment of the central axis, which in general determines the antero-posterior alignment of the individual and in particular marks the line of development of the central nervous system. In contrast to the nature of the organizers, the establishment of the axis is not dependent upon chemical activity, but rather on an orientation of the various regions in respect to the whole. In this regard, the formation of the axis seems to be closely allied with the arrangement of the egg-map already described.

Along the line of this axis there is a graded distribution of developmental potencies. This *axial gradient* is explained on the basis of 'some physical or quantitative regional differences' in protoplasmic activity (DeBeer). This difference in rate of metabolic activity ultimately results in qualitative differences in structure. While proof of this conclusion does not concern us in this connection, the relatively rapid development of the brain as compared to the spinal cord indicates the existence of the gradient, with declining potency from the cephalic to the caudal end of the embryo.

Once the axial gradient is established, the embryo becomes divided up into a number of separate and distinct *fields*, each one of which gives rise to some particular organ. The development of each of these fields is likewise under the control of a *field gradient*. In the amphibians there are fields for the development of the neural tube, the eye, the lens, and the hypophysis, as well as for the development of external structures. Once these fields have become estab-

lished by 'chemo-differentiation', development of the individual structures continues with the aid of secondary organizers. It seems to be the function of the gradient to control the development of each part so that it is properly oriented with respect to the whole.

The practical application of the principle of the gradient is that it explains the order of development of various organs. The secondary or field gradients have the function of maintaining the correct orientation of development in that field to the development of the embryo as a whole.

VISIBLE VERSUS FUNCTIONAL DIFFERENTIATION

When the axial structures have been laid down, the various regions, structures and organs begin to take form. This process of formation of a given member or organ from the protoplasmic ground substance of the embryo is called *differentiation*, and is divided into two stages, *early* or *visible differentiation* and *late* or *functional differentiation*.

Early or visible differentiation of a given part may be said to begin once the region has become 'determined'. From this moment, the ground substance of the region will go on to form the predestined organ independent of its surroundings. The ultimate potentialities of development therefore come to be resident in the tissues in question. This process of visible differentiation of the parts of the central nervous system is shown by an interesting experiment. If a dorsal segment of the newt embryo is resected and replaced after rotating it 180°, it will continue to differentiate in the reversed position. Instead of being in front, the eye cups will develop posteriorly. The underlying visceral organs —the heart, stomach and liver—however, become reversed because their differentiation is *dependent* upon (rather than *independent* of) the position of the axial structures which have thus become an organizer of second degree.

The eye cup likewise is self-differentiating at least in amphibia. When transplanted to other parts of the body, it will continue to form a typical optic cup. The differentiation of the lens, however, may be dependent or independent. In some frogs (*Rana fusca, temporaria, palustris*) its development is dependent upon the proximity of the eye cup, while in another frog (*Rana esculenta*) it is self-differentiating, or independent, and will develop whether the eye cup is present or not.

The labyrinth is likewise self-differentiating. If the presumptive optic vesicle is resected and replaced upside down, the labyrinth will differentiate in this abnormal position.

It is also of interest to note that the complete development of the pars nervosa and pars intermedia of the hypophysis is dependent upon the presence of the pars anterior. If the pars anterior is removed, the pars nervosa attains only half its normal size.

It may be said by way of summary that, *once chemo-differentiation has determined or fixed the destiny of a given region, visible differentiation begins the process of forming an organ.* This process may be concerned with the formation of the organ as a whole or only with certain histologic portions of it.

There comes a time in the formation of an organ when further differentiation becomes dependent upon function. This stage has been designated as that of *late* or *functional differentiation*. The significance of this factor is shown by the experimental removal of the hind-leg buds of the frog, in which case the hind brain fails to develop (fig. 4, a). If the embryonic eye is removed, the optic lobes likewise fail to develop (fig. 4, b).

This principle of functional differentiation is illustrated in a special way in the development of the human brain. Functional differentiation continues both histologically and physiologically months after a child is born. It is well known that myelination of the nerve fibers subservient to the association areas of the brain is not completed until some months after birth. In the light of experimental neuroembryology, this is very likely dependent upon the function of the associated cortical areas to complete the process. Physiologically, development

FIG. 4. Evidence of functional differentiations. *a*, Inhibition of growth of midbrain (right half) following removal of limb rudiment in the frog (*Rana fusca*) (Dürken, *Biol. Gen.*, Vol. 6, 1930). *b*, Inhibition of growth of midbrain after removal of eye at an early stage in the frog (*Rana fusca*) (reproduced from *Experimental Analysis of Development* by Bernhard Dürken, published by George Allen & Unwin, London).

of the speech centers is not completed until actually assisted by function. This probably explains why totally deaf children may also remain mute. Without the aid of hearing, the motor speech centers, perhaps structurally intact, cannot complete their late development.*

The following remarks of DeBeer will serve as a pertinent conclusion to this problem of differentiation.

"It is seen, therefore, that following on the period of early differentiation, when self-differentiation of parts is the rule, and there is no necessity for function, there is a period

* There is a great deal of evidence accumulated on the basis of experimental embryology which controverts the whole mechanistic concept of living matter. To this conclusion, in the stage of late or functional development we have the paradox of a machine constructing itself while operating and requiring meanwhile its operation in order to be perfected. The basis of Driesch's concepts of "vitalism" (elaborated as a result of his experiences in experimental embryology) may be easily appreciated even though in their application by this author they seem fuller of rhetoric than of logic. At any rate, no comprehensive view of the phenomena of development is possible on a purely mechanistic basis.

of functional differentiation. During the first period differentiation determines the function that any particular tissue will perform; in the second, function reacts on the tissue and perfects it.

"The finer adjustments of structures in an animal are thus not simply 'inherited': they are created afresh in every generation by functional differentiation."

HISTOLOGIC DIFFERENTIATION

Because most of the observations in experimental neuroembryology are necessarily made on very young embryos, morphologic changes tend to overshadow the more detailed ones. Nevertheless, there are some pertinent histologic facts to be deducted from experiments on developing nervous systems of simple animals. The process of differentiation of tissues has been designated as *histologic differentiation* or simply *histo-differentiation*. It is worth while repeating to say that, during the period of early or visible differentiation, also called the *prefunctional period*, both morphologic and histologic differentiation is directed to the end of making an organ ready to enter upon its functions. On the other hand, during the period of late or *functional differentiation*, the process of final perfection of detailed structure is aided by the actual function of the organ in question. It will be useful to note certain general features of histologic differentiation which may subsequently serve as points of departure for some anatomic and pathologic deductions.

As just stated, morphologic and histologic differentiation takes place at the same time. It is important to recognize, however, that histologic differentiation is not necessarily dependent upon morphogenesis. This is shown in the cultivation of the eye-rudiment of the chick *in vitro*. When the eye cup and lens are removed from the chick embryo and incubated and then cultured in extract-enriched plasma, these structures will remain relatively small in size. On the other hand, differentiation of the retinal cells is found to have proceeded at almost a normal rate. One might safely conclude that, unless there is some serious mechanical interference such as displacement, cellular development may follow its own course. The converse of this law is also true, at least in some animals. For example, if a portion of the presumptive brain region is resected and reversed in position the anterior incision being made through the presumptive eye region, it will be found that four optic vesicles will be formed, two large anterior ones and two small posterior ones. The smaller pair of vesicles will differentiate into fairly well-formed cups even though their histologic differentiation may be imperfect or abnormal. This is in accord with the observation that certain histologic malformations occur with grossly normal morphologic structures.

It would seem that purely morphologic differentiation is influenced by certain physical and mechanical factors such as the amount of material available, the space it has in which to work, and the pressure effects of adjacent developments. As shown above, at least in later stages, histologic differentiation is largely independent of these factors. This is further shown by still another experiment. By grafting a bit of presumptive neural fold material into another embryo in a position perpendicular to the direction in which it would normally develop, it is found that the tissue will differentiate morphologically into neural folds regardless of its orientation.

Further evidence of this independence of morphologic and histologic differentiation is produced by grafting pieces of presumptive neural fold or presumptive epidermis from the late gastrula or neurula stage into foreign situations. Those sections will follow, by self-differentiation, their destined histologic course. Their usual morphologic differentiation, however, is not always achieved. Conversely, if similar pieces are transplanted from an earlier stage (early gastrula) they will undergo normal morphologic but only imperfect histologic differentiation.

While morphologic differentiation is independent of histologic development, it *is* dependent upon its relationships with surrounding structures. For example, it is shown that the presence of the notochord is responsible for the formation of the ventral sulcus of the central canal. At the same time the presence of the lateral myotomes is responsible for the formation of the thick

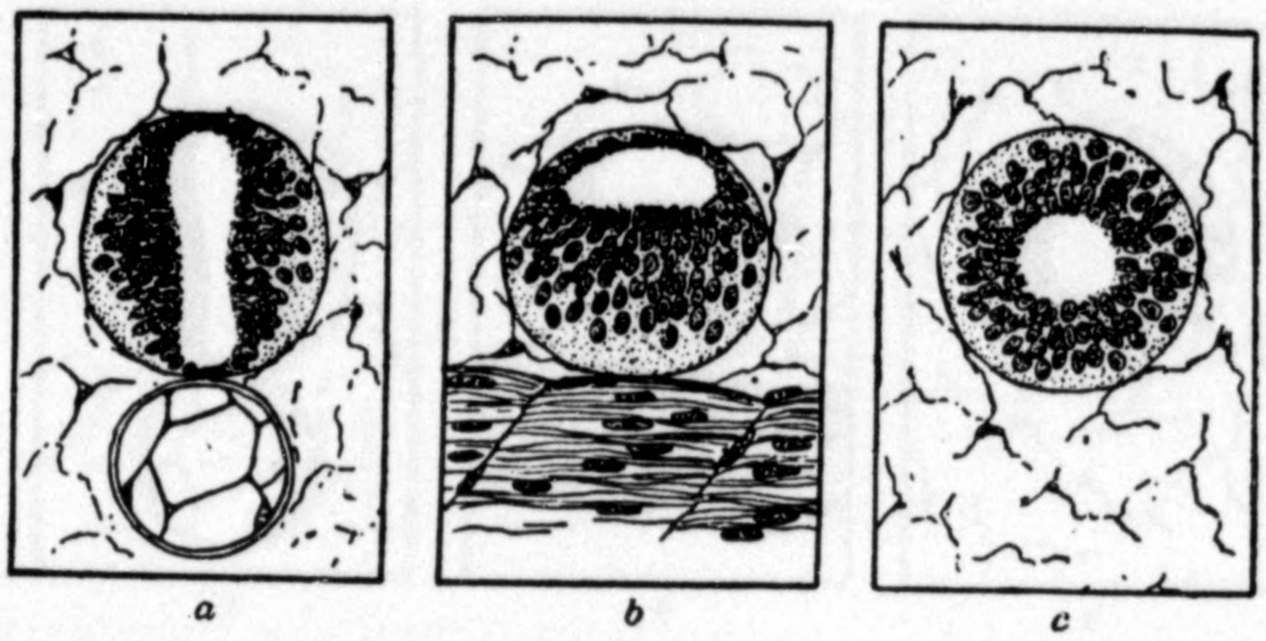

FIG. 5. Influences affecting morphogenesis of the neural tube. *a*, proximity of notochord without myotomes. *b*, proximity of myotomes without notochord. *c*, absence of both notochord and myotomes. (Holtfreter, *Arch. Entwmech.*, Vol. 127, 1933).

lateral walls of the neural tube. If a segment of neural tube is embedded in mesenchyme, therefore being free from the influence of either, it forms a radially symmetric tube (fig. 5). It is an interesting corollary that the complex differentiation of the brain occurs in a region free from the influence of the myotomes.

The degree of potency of histologic differentiation seems to be dependent upon the age of the tissue at the time of its isolation. For example, fragments of unincubated blastoderms of the chick grafted into the chorio-allantoic membrane of other embryos will differentiate only into epidermis and gut. After incubation for two hours, the fragment will also differentiate into nervous tissue. After four hours' incubation, such an implant will form brain, eye, cartilage and muscle. Similar evidence if obtained from transplanting pieces of the eye. It may thus be concluded that *the older the piece, the more completely it will differentiate.*

Histologic differentiation is not only influenced by the age of the tissues under consideration but also by a number of other factors. This is very clearly evident by transplantation experiments in which certain regions of the cord are inter-

changed. As a result of a variety of experiments, it has been concluded (Detwiler) that:

1. There are different rates of cellular proliferation in given regions and at different stages of development of the neural tube. These regions are evidence of a relatively high potential for cellular multiplication which is inherent in the region, and are not dependent on the influence of entering nerve roots. Differentiation of the cells is most active when proliferation is relatively quiescent and *vice versa*. These alternating waves of proliferation and differentiation pass along the neuraxis in a cephalocaudal direction and are apparently dependent upon the influence of the axial gradient.

2. The cellular hyperplasia observed in the brachial region of the spinal cord is due to some factor within the central nervous system and not upon the presence of the fore-limb. The fact that any segment of the cord transplanted to this region will demonstrate this hyperplasia indicates that this process is not inherently and irrevocably fixed in any given segment.

3. The medulla seems to exert a dominant influence over the spinal segments below it, provoking an increased cellular activity possibly through an increase in number of caudally-directed projection fibers.

4. The proliferative activity of certain regions of the neuraxis is evidently dependent upon hereditary factors, an activity which is closely related to developing early behavior patterns.

5. In some regions, the inherent capacity for cellular proliferation is quite fixed, while in other regions this is more labile.

6. To a considerable degree, the so-called inherent rates of proliferation can be increased by changes in environment. This indicates that the prospective potency of a part is greater than its prospective significance (Detwiler).

7. Acceleration of proliferation within a given segment seems to influence the ingrowth of regional nerve roots, while actual entrance of the nerve into the wall of the neural tube further stimulates the regional neuroblasts to increased activity.

Neurobiotaxis and Histologic Differentiation. Much has been made of the principle of neurobiotaxis in the development of the detailed structures of the nervous system. It is therefore pertinent to inquire how differences of potential enter into the general scheme of histologic differentiation. As has already been shown, the earlier potencies which lead out in development are definitely chemical in nature, usually associated with increases in metabolic rate. Any influence of an electric nature must enter into the process at a later time.

An experimental study which seems to shed some light on the problem of neurobiotaxis is that concerned with the gradients in the *Amblystoma* embryo. It has been shown that two axial gradients are present in this embryo. The dorsal *ectodermal gradient* has its high potential at the head end, while the ventral *mesodermal gradient* has its high potential at the tail end, of the embryo. To this same point is the evidence that an electric current can induce a similar axis of polarity and a gradient when tissue is exposed to such a current. It is assumed that the growth of neurons up and down the spinal cord is dependent upon these two gradients. This is suggested by the extension of the axons of the nerve cells anteroposteriorly along the long axis of the neural tube (fig. 6). In the dorsal part of the tube, the axons spread cephalically toward the point of high potential as established by the ectodermal gradient. This phenomena would

explain the cephalic course of the sensory tracts of the spinal cord. On the other hand, as Huxley and DeBeer suggest, the axons of the ventral neurons extend caudally in the direction of the high potential of the mesodermal gradient to form part of the efferent or motor system.*

This philosophy is also applied (Huxley and DeBeer) to the segmental arrangement of the paired spinal nerves. It is believed that the sensory axons are attracted to develop in the direction of the current (in the neuraxis) and extend to the adjacent portion of the spinal cord. This principle would obviously not account for the migration of the cells of the neural crest which form the sensory

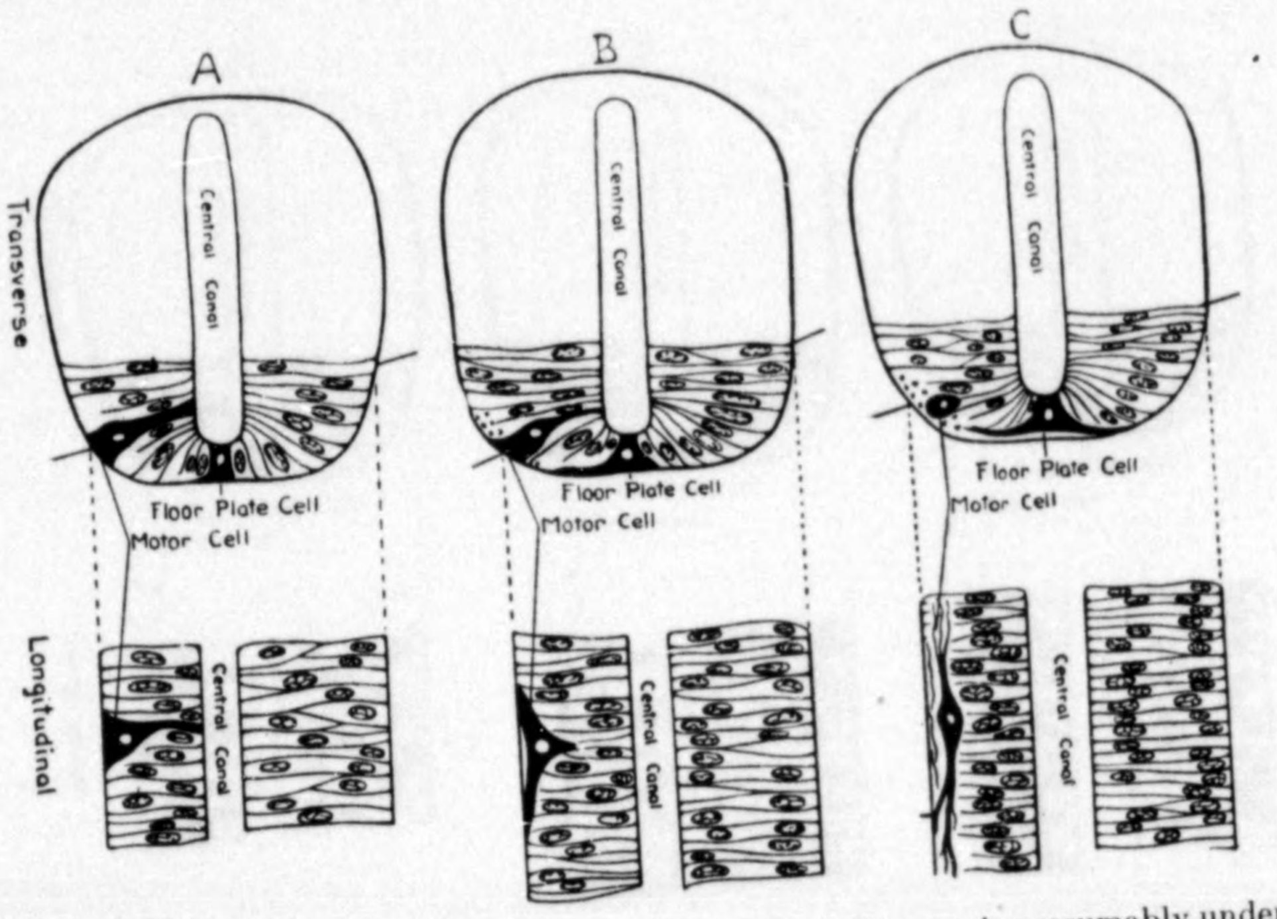

FIG. 6. Orientation of nerve cells in neural tube along its long axis presumably under the influence of the axial gradient. (Coghill, *Anatomy and the Problem of Behavior*, Cambridge University Press, 1929.)

ganglia, nor would it account for the peripheral extension of the distal axon which evidently must be under the influence of a greater potential in the corresponding field in which it develops. In case of the limbs, nerve growth would be parallel to the line of the field gradient. The direction taken by the motor axon is accounted for by the establishment of regions of secondary gradients in the center of the myotomes. These centers of high potential are presumed to attract the

* The difficulty with this presumption is that the axons which form the pyramidal and extrapyramidal systems come from the prosencephalon where the influence of the high end of the *mesodermal* gradient must be feeble indeed. However, there is no clear evidence that axons of such intercalated motor neurons as may be found in the spinal cord have a predominant caudad direction.

motor neurons and thus insure the nerve supply of the muscles. As a result of experimental studies on the question, Detwiler concludes that:

> "The atypical arrangement of the spinal nerves in animals lacking somites experimentally removed, the failure of complete and orderly segmentation of the ganglia, and the occasional complete loss of a spinal nerve, all support the view that typical segmentation of the peripheral nerves is dependent upon a normal mesodermal metamerism."

Thus it is seen that, while both the neural tube and somites are induced by the organizer, they react together to form the segmental arrangement of the nervous system.

To trace experimentally this principle of neurobiotaxis in the ultimate detailed development of the brain is obviously impossible. The fact remains that the growth of axons, at least in the neuraxis, is evidently influenced by the passage of electric current, even though these currents be ever so feeble (2 billionths of an ampere in some of the embryos studied). At some time in the early life of the germ the chemical factor which constitutes the organizer and its subsequent centers of potency is aided by the appearance of an electric factor which acts along the embryonic axial gradient to further the process of neural development. The transformation bespeaks an influence beyond the limits of a purely mechanistic concept.

OBSERVATIONS OF THE DEVELOPMENT OF PERIPHERAL NERVES

The development of the peripheral nerves offers further opportunity for the study of influences which control nerve growth which is not possible to obtain from the axonal structures within the central nervous system. It will therefore be germane to our thesis to give some attention to certain experimental observations. These observations are largely based on the development of nerves in transplant grafts of limb rudiments in an abnormal position (fig. 7). It is learned that the transplanted limb will acquire a nerve supply from the region which it occupies. On the basis of these studies, the following conclusions may be drawn:

1. Regardless of the segmental sources of the peripheral nerves, the intrinsic distribution of nerve fibers is exactly that of a normal limb. Therefore, the pattern of nerve distribution seems to be dependent upon the differentiation and growth of the muscles in accord with Nussbaum's law (the course of a nerve is an index of the direction in which the muscle has grown).
2. There is no specificity of a given motor neuron for any particular nerve fiber. Ultimate distribution of the nerve is therefore not an intrinsic factor.
3. The limb rudiment exerts an influence on the growing nerve and determines the path taken by them in effecting innervation. This is probably the result of a relatively high degree of metabolic activity within this rudiment. It may be concluded that "the nerves are guided by some force toward the developing limb rudiment" (Detwiler).
4. Whatever be the character of this force in the grafted limb, it has no influence on normal nerves once they have completed their growth.
5. In the general growth of nerves, the forces seem to be non-specific, while those which lead to the actual connection of the nerves with their end-organs are quite specific.

The growth of nerves *in vitro* has also contributed somewhat to our knowledge of the development of these elements. Small bits of neural tube from early embryos are planted in clotted frog's lymph. After incubation for varying periods, observations as to the rate of growth and of influences which may affect such growth may be made. It is found that growth of nerve fibers under such circumstances may be oriented by mechanical influences (Weiss) and, to some extent, by non-specific chemical factors (Detwiler). In accord with the principle of neurobiotaxis, nerve fibers are found to grow in a vertical direction toward the conductor of current (Ingvar). This last conclusion has been disputed by Weiss but has been accepted by others (Kappers).

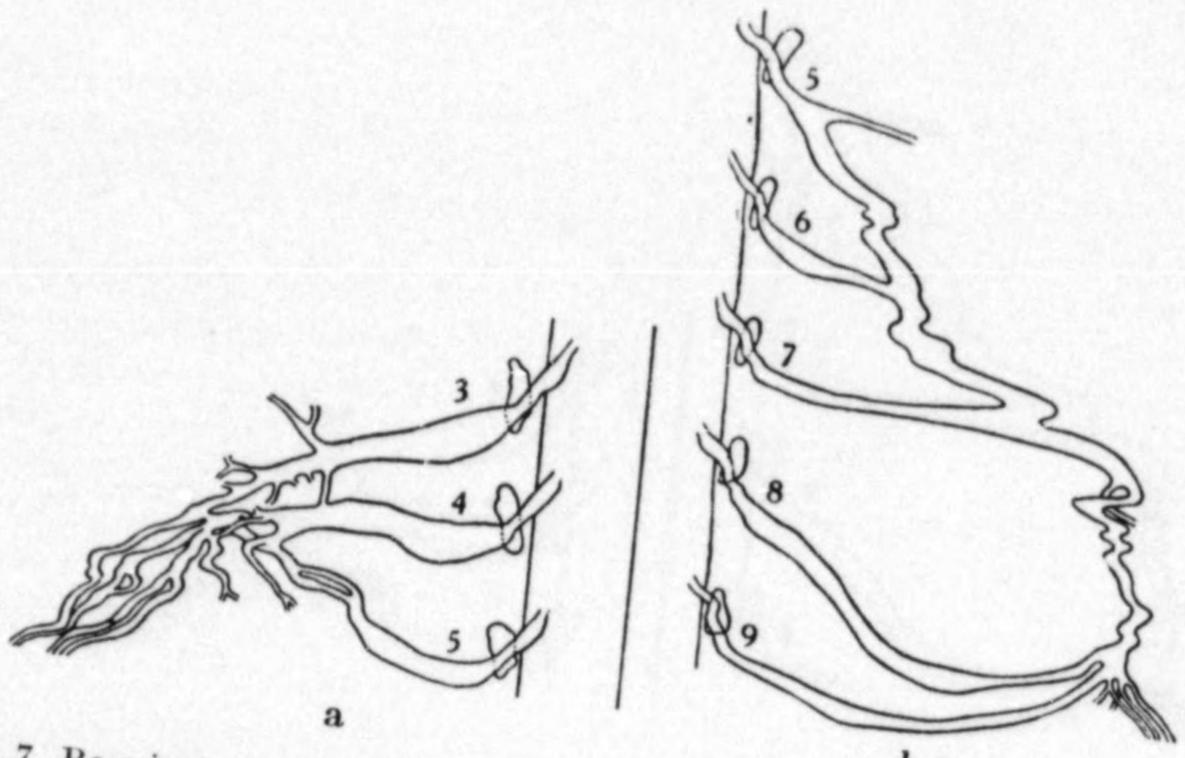

FIG. 7. Re-orientation of peripheral nerves to supply abnormally situated limb of axolotl. *a*. Normal brachial plexus. *b*. Modified plexus after transplantation of limb bud 5 segments back. (Modified from Detwiler, *Neuroembryology*, The Macmillan Company, 1936.)

GENERAL CONSIDERATIONS

The various and important contributions of experimental embryology in general, and of experimental neuroembryology in particular, are recognized by critical students to lead to conclusions of rather far-reaching importance in the field of Biology, conclusions which are bound to have their repercussions in Neurology. Perhaps the most important deduction of all is that developmental phenomena can no longer be interpreted on a purely historic basis. The presence of remarkable and complex potencies in the fertilized egg, sufficient not only to govern the course of development but also to maintain the vital functions throughout the life of the individual, makes futile any effort to compare it to a presumed one-celled ancestor. This is all the more true when the significance of a wide variation in egg-maps, even in the relatively simple animals, is fully appreciated. As DeBeer has so clearly pointed out, this also means that homology, which is so commonly used to establish phylogenetic relationships, has

actually no value in this respect unless one can prove that two compared structures came from similar regions in the germ and were developed under the influence of similar potencies.

From the viewpoint of embryology, DeBeer has recently restudied the whole problem of recapitulation and, rejecting the basis upon which Haeckel reconstructed his scheme of ancestral relationships, attempted to revise the system. His conclusion had best be put in his own words.

> "Clearly, phylogeny does not explain ontogeny at all. Even if we had a *complete* phylogenetic series of adults ancestral to any given descendant, it would not help us to understand the processes of fertilization, cleavage, differentiation, organogeny, etc., which takes place in the ontogeny of that descendant. The historically descriptive study of evolution has no bearing on the causal analytic study of embryology. . . ."

These observations should make it evident that any pathologic or clinical deductions made on the basis of alleged phylogenetic relationships must be largely guesswork and are very likely to lead its proponents into blind alleys, if not into gross error.

These newer developments in embryology have likewise settled once and for all the age-old controversy between preformation and epigenesis. The preformation theory (also called the 'old theory of evolution') was essentially mechanistic in its implications and held that the egg is a miniature and preformed adult, embryonic development simply being an unfolding or enlargement of this small form. On the other hand, epigenesis implied a more vitalistic view that ontogenetic development involved a coming into existence of new complexity of form and function, a 'fresh creation of diversity.' As DeBeer so pertinently states:

> "The inevitable conclusion is that development involves a true increase of diversity, a creation of differentiation where previously none existed, and that the interpretation of embryonic development must be sought along the lines of some epigenetic theory."

The purely mechanistic concept of embryonic development therefore cannot be maintained in the light of experimental embryology. The awakening of developmental powers in the fertilized ovum, the establishment of a plan or map of development within it, one which can be completely and immediately readjusted into two such maps if the two blastomeres are separated, the establishment of an entire system of organizers or potencies of a chemical nature, the subsequent establishment of both axial and field gradients with variations in electrical potential, and the final perfection of the organism by the harmonious interaction between structure and function, speaks clearly for 'a creation of differentiation where previously none existed,' rather than for a 'brick by brick' mechanistic construction of a new individual.

While there are those who question what may be included in the term 'mechanistic' (Huxley and DeBeer), unless one wishes to confuse the whole question by multiplication of words as some have done, the general issue seems to be clear. Dürken's remarks to this end are pertinent:

"The way is cleared [by experimental embryology] for an evaluation of the organism other than a purely mechanistic one. For the latter arises from the untenable analytical-summative conception of the reaction-basis, and must conflict with the results of analytical embryology when questions of potency and regulation arise. Thus, however paradoxical it may sound, the study of 'the mechanics of development' (*Entwicklungsmechanik*) leads away from the mechanistic conception to a really organismic conception of the organism and therefore of life itself."

While there are relatively few supporters today who hold for the vitalistic view as originally proposed by Driesch, which theory unfortunately obscures by philosophic effusion the truth upon which it is based, the fact remains, as Needham rightfully avers, that the epigenetic view of development as now understood is essentially a vitalistic one.

The practical application of these contributions of experimental neuroembryology can only be hinted at in this short survey. It becomes evident, even to the superficial investigator, that many of the mechanisms of grosser malformations of the central nervous system and clues to the occurrence of minor ones are thus made clear. The way is also open for a re-evaluation of the concept of the origin of intracranial tumors on the basis of cellular misplants during embryonic development. Nothing that experimentation has as yet brought to light can account for the occurrence of multiple tumors affecting any given tissue system or the abiotrophic 'system' diseases, although some deductions may be made in this direction. We are as yet quite remotely removed from a satisfactory solution of the exact etiology of some of the familial or hereditary diseases with defects in multiple systems. A critical discussion of these problems must await another occasion.

SUMMARY

The light shed on the problems of development of the nervous system by experimentation on early embryos demands a re-evaluation of our concepts of development and of the conclusions drawn therefrom. It is learned that a very well-defined pattern of the central nervous system is laid down in the egg soon after fertilization, a plot which differs considerably in the various animal forms studied. This 'brain-plan' can be completely readjusted to be duplicated in each of separated blastomeres arising from regulation-eggs. However, early in development the various regions become 'determined' by chemo-differentiation and, regardless of their relationships, proceed to the development of the predestined organ.

This entire process is initiated by the 'organizer', a chemical substance (of the nature of a sterol) located in the dorsal lip of the blastopore, which induces the formation of the axial structures including the neural plate. The center of influence seems to reside in the notochord. The axial gradient with its high potential in the head of the embryo is thus established. With the 'determination' of the various organ regions, secondary or field gradients are established which keep the developing structures oriented in relationship to the whole.

The early period of development has for its objective the elaboration of organs and structures capable of functioning. This period is called the stage of early

or 'visible differentiation'. It is succeeded by the late stage of 'functional differentiation' in which the structure of organs is actually perfected by function. This is well demonstrated by the process of myelination of the central nervous system, a process which continues for some months after birth. This fact suggests that function is anticipated by structure and not the reverse as some have maintained in their philosophy of origins. This function perfects structure is in perfect accord with the laws of post-embryonic as well as embryonic life.

Histologic differentiation and morphologic differentiation may be, and probably are, quite independent of each other. This fact suggests that the external form of an organ is adapted to its environment while its detailed structure is adapted to ultimate function. As far as the nervous system is concerned, the original chemical (or metabolic) initiation and promotion of cellular development is further aided by a superimposed electrical influence (neurobiotaxis) whose chief function is the development of pathways and their connections. While this concept is not so clearly applicable to the peripheral nervous system in its ultimate distribution (where the course of the nerves and their ultimate connections are rather influenced by the organs which they serve), the segmental distribution of the nerve roots are possibly to be accounted for on a similar basis.

There are two general conclusions to be drawn from a study of experimental neuroembryology. It is no longer in accord with the progress of science to explain developmental phenomena on the untenable concept that 'ontogeny is a recapitulation of phylogeny.' Those who persist in the practice can expect only to be led into blind alleys, if not gross errors, in their reasoning. The other deduction is that developmental phenomena cannot be accounted for on a purely mechanistic basis. It has become necessary to accept the vitalistic theorem of 'a fresh creation of divergence' to account for the constant addition of powers or potencies which did not exist in the unfertilized egg.

REFERENCES

(NOTE: In this brief survey it would be unwarranted to append a complete list of references to individual experimental studies which deal with development of the nervous system. Aside from a few references specifically cited or of special import, this list contains only references to certain outstanding monographs which are available in any scientific library. In which these monographs more or less extensive biobliographies are to be found.)

Brachet, A.: The Localization of Developmental Factors, Quart. Rev. Biol. 2:204 (June) 1927.

Courville, C. B.: The Recapitulation Theory. Some Notes on Its History and Present Status, Bull. Deluge Geol. 1:21 (Aug.) 1941.

Dalcq, A. M.: Form and Causality in Early Development, Cambridge University Press. 1938.

DeBeer, G. R.: An Introduction to Experimental Embryology, 2nd ed., Oxford University Press, London. 1934.

DeBeer, G. R.: Embryos and Ancestors, Oxford University Press, London. 1940.

Detwiler, S. R.: Neuroembryology. An Experimental Study, New York, Macmillan. 1936.

Dürken, B.: Experimental Analysis of Development, Trans. by H. G. and A. M. Newth. New York, W. W. Norton & Co. 1932.

Huxley, J. S., and DeBeer, G. R.: The Elements of Experimental Embryology, Cambridge University Press. 1934.

Morgan, T. H.: Experimental Embryology, New York, Columbia University Press. 1927.

Needham, J.: History of Embryology, Cambridge University Press. 1934.

Needham, J.: Biochemistry of Morphogenetic Hormones or Organisers, Chem. Weekblad., Vol. 35, No. 16. 1938.

Needham, J.: Developmental Physiology, Ann. Rev. Physiol. 1:63, 1939.

Spemann, H.: Embryonic Development and Induction, New Haven. Yale University Press. 1938.

Stockard, C. R.: Developmental Rate and Structural Expression. An Experimental Study of Twins, Double Monsters and Single Deformities, etc., Am. J. Anat. 28:115, 1921.

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CEREBRAL LESIONS FOLLOWING ADMINISTRATION OF NEOARSPHENAMINE

MULTIPLE SYMMETRIC FOCI OF HEMORRHAGIC NECROSIS OF THE BRAIN

CYRIL B. COURVILLE, M.D.
AND
CLEMSON MARSH, M.D.
LOS ANGELES

Much has been written on the effects on the body in general and on the brain in particular of the arsphenamine group of drugs. The pathologic picture of what has been called postarsphenamine hemorrhagic encephalitis or, more recently, pericapillary encephalorrhagia [1] is well known to pathologists. Multiple petechial hemorrhages scattered throughout the white matter of the brain of a patient in whom symptoms of encephalitis have developed after repeated injections of some form of arsphenamine are not likely to be mistaken for any other lesions. Somehow the occurrence of associated symmetric foci of hemorrhagic necrosis as a specific entity and their possible significance apparently have been overlooked even by clinicians and pathologists who have given attention to the general problem. It is the purpose of this study to describe this unusual and interesting lesion and to consider its evident relation to hemorrhagic encephalitis, with which it is frequently associated. In an approach to this question, we shall briefly review the etiologic concepts of perivascular hemorrhage following administration of arsphenamine, make a survey of the literature on the question and finally attempt to analyze the observations made by us and discuss their probable significance.

SIGNIFICANCE OF POSTARSPHENAMINE CEREBRAL VASCULAR CHANGES

The cause of the peculiar production of petechial hemorrhages in the brain has been the subject of much discussion since the time of Ehrlich, who first postulated the possible mechanism of its production.

From the Cajal Laboratory of Neuropathology, Los Angeles County Hospital, and the Department of Neurology and Psychiatry, College of Medical Evangelists, Loma Linda, Calif.

1. Globus, J. H., and Ginsburg, S. W.: Pericapillary Encephalorrhagia Due to Arsphenamine, So-Called Arsphenamine Encephalitis, Arch. Neurol. & Psychiat. **30**:1226-1247 (Dec.) 1933.

Ehrlich [2] concluded that the essential cause of this condition was a dilatation of the small blood vessels of the brain, a process which is followed by edema and perivascular bleeding. He stated the belief that this vascular change was produced by some derivative of arsphenamine which had to be formed within the body, as suggested by the delay of several days after the injection of the drug. It was thought that this derivative was an oxidation product, paraaminophenylarsenoxide. It was also stated by Ehrlich that this excessive dilatation of the small blood vessels was due to an insufficient amount of epinephrine in the circulating blood. This conclusion was based on the observation that several patients who had been treated with the drug and who were becoming stuporous promptly recovered when vigorously treated with epinephrine. The possibility of a too rapid destruction of spirochetes was also entertained as playing a part in the process.

As time went on, other theories were proposed to account for this condition, among which were renal disease with faulty elimination, Herxheimer's reaction due to sudden release of large amounts of endotoxin and the precipitation of blood proteins with the production of multiple small emboli, all of which possible factors have been discussed by Scott and Moore.[3] In a more detailed consideration of the likely causes of the small perivascular hemorrhages following arsphenamine therapy, Globus and Ginsburg [1] indicated what seems to be the truth of the situation when they stated that the essential factor was an injury to the blood vessel wall, although they were not just sure what the cause of that injury might be. It was their belief that the hemorrhages were the direct and selective effect of arsphenamine on the vascular endothelium. They also emphasized an evident fact when they stated that the Herxheimer reaction had no possible influence, since the same sort of lesion followed the use of arsphenamine in nonsyphilitic conditions. Landsteiner and Jacobs,[4] on the basis of their experience with guinea pigs, showed that preliminary sensitization very likely was responsible in no small degree for the ultimate lesion. In describing the histologic changes of the lesion, Russell [5] suggested that the small hemorrhages in the brain were due to increased permeability of and perhaps actual damage to the vessel wall. It was thought that peri-

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2. Ehrlich, P.: Deaths After Salvarsan, Brit. M. J. **1**:1044-1045 (May 9) 1914.

3. Scott, E., and Moore, R. A.: Fatalities Following the Use of Arsphenamine, Am. J. Syph. **12**:252-262 (April) 1928.

4. Landsteiner, K., and Jacobs, J.: Studies on Sensitization of Animals with Simple Chemical Compounds: Anaphylaxis Induced by Arsphenamine, J. Exper. Med. **64**:717-721 (Nov.) 1936.

5. Russell, D. S.: Changes in Central Nervous System Following Arsphenamine Medication, J. Path. & Bact. **45**:357-366 (Sept.) 1937.

vascular necrosis and demyelination were due to the escape of toxic material into the surrounding nerve tissues. The additional possibility of stasis was suggested by Smith and Newhill,[6] who observed that hemorrhages were most apt to occur where the blood vessels branched. With many others, they also concluded that personal idiosyncrasy played an important role in any case.

In this report we plan to show that, in addition to the focal vascular lesion, which permits escape of blood into the perivascular tissues and produces in some instances a perivascular necrosis or demyelination, some larger vascular influence is at work which in some cases favors the occurrence of groups of these individual lesions in symmetric situations in the nuclear masses as well as in the white matter of the brain.

COLLECTED EXAMPLES OF SYMMETRIC FOCI OF NECROSIS

As stated previously, the lesion which forms the subject of this study has not been specifically described by any known previous writer on the subject, although in the descriptions of the brain in cases of hemorrhagic encephalitis such foci of hemorrhagic necrosis have been mentioned, and in a few cases an illustration of the lesion has been furnished. Scott and Moore,[3] for example, described small dark necrotic areas in the roof of both lateral ventricles with similar areas in the posterior thalami, the crura cerebri and the pons. Globus and Ginsburg[1] described in their first case diffusions of extravasated blood in both thalami, with similar areas in the hippocampus, the tegmentum of the midbrain and the pons and cerebellar cortex. In their second case the lesions were small and generally distributed in the white matter of the cerebral hemispheres. These lesions proved to be confluent petechial hemorrhages. A symmetrically disposed lesion was also found in the brain stem. Black[7] found lesions in both caudate nuclei, in the right corona radiata and at the bases of both temporal lobes, which may well have been confluent petechial hemorrhages. In the case reported by Smith and Newhill[6] a good photograph of such a lesion was reproduced, bilateral lesions being found in the claustrum and internal capsule. In the case of Kuehn, Keating and von Haam[8] areas of softening were found in both thalami of a pregnant woman, aged 24, who died after the third injection of neoarsphenamine. Undoubtedly, many other cases have been observed throughout the years since neoarsphenamine was introduced for the treatment of syphilis, but a survey of available literature failed to bring to light any additional instances.

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6. Smith, D. C., and Newhill, H. P.: Arsenical Encephalitis, South. M. J. **32**:381-387 (April) 1937.

7. Black, W. C.: Death from Hemorrhagic Encephalitis Following Treatment with Sulpharsphenamine, Am. J. Dis. Child. **51**:609-613 (March) 1936.

8. Kuehn, C.; Keating, R. A., and von Haam, E.: Arsenical Encephalitis During Pregnancy [case 2], Am. J. Obst. & Gynec. **36**:122-126 (July) 1938.

REPORT OF CASES

CASE 1.—*Extreme nervousness, involuntary urination and aphasia in a young Mexican woman following an unknown number of injections of arsphenamine. Development of mild meningeal signs and status epilepticus. Death. Focal hemorrhagic necrosis in the basal ganglia of both cerebral hemispheres.*

J. M., a young Mexican woman (whose exact age could not be determined) was admitted to the Los Feliz Hospital on June 15, 1922, with the complaint of extreme nervousness. It was learned that the patient had been treated with an unknown number of injections of what was called "salvarsan" (possibly neoarsphenamine). Soon after the patient was admitted involuntary urination developed. On June 17 it was noticed that the patient did not speak (probably aphasia) and signs of mild meningeal irritation were discovered. It was also observed that she was somewhat cyanotic.

Because the patient's condition was evidently getting worse, she was referred on June 17 to the Los Angeles County Hospital. While she was still in the examining room, a generalized convulsion developed, and she was comatose by the time she reached the ward in the neurologic service. During the next few hours she had one convulsion after another, in spite of efforts to control them.

On examination, the patient was found to have contracted, fixed pupils. She had repeated episodes of extensor rigidity, followed by residual spasticity in the arms. Both Brudzinski and Kernig signs were elicited. The knee jerks were bilaterally sluggish, and an equivocal Babinski sign was present on the right.

A lumbar puncture disclosed increased pressure of the cerebrospinal fluid. The fluid itself was clear and colorless and contained 12 lymphocytes per cubic millimeter. The Wassermann reaction of the spinal fluid was strongly positive, and the colloidal gold curve was 1233320000.

Death occurred on June 18, about three days after the onset of symptoms and the day following the patient's admission to the hospital.

At autopsy, performed by Dr. George D. Maner, a study of the viscera failed to disclose any gross lesions of any sort, the only abnormalities being found in the brain. The superficial leptomeningeal vessels were considerably congested. The convolutions of the brain were generally flattened, suggesting an edema of the brain. The brain tissue was softer than usual. Coronal sections of the brain disclosed numerous petechial hemorrhages which had a definite tendency to be grouped together, giving the affected areas a stippled appearance. These areas were located in the optic thalami and the posterior portions (tail) of the caudate nuclei in approximately symmetric positions. The average size of these fairly circumscribed areas was 0.8 cm. Three separate and distinct foci were discovered in each hemisphere. These lesions were stated by the pathologist to be the result of administration of arsphenamine.

This was the first of a series of verified cases of symmetric foci of hemorrhagic necrosis which have been disclosed at autopsy at the Los Angeles County Hospital. It is unfortunate that the exact character of the drug administered, its dosage and the number of injections administered could not be ascertained. Emergency admission to the hospital in an aphasic condition, persistent coma between convulsions and episodes of decerebrate rigidity and the absence of information as to when or where she had received the treatment made the clinical history

incomplete. It seems clear, however, that the patient had had some arsenical in the treatment for syphilis and from this treatment fatal cerebral lesions developed in the form of multiple symmetric foci of hemorrhagic necrosis.

CASE 2.[9]—*Three injections of neoarsphenamine for Vincent's angina. Coma two days after last injection. Partial recovery. Lethargic state for three months. Progressive failure to death three and a half months after onset. Old necrotic areas in the basal ganglions of both cerebral hemispheres.*

A 32 year old Caucasian woman was admitted to the hospital on Nov. 6, 1936, service of Dr. Samuel D. Ingham. It was learned that she had been given three injections of neoarsphenamine for a peridental infection diagnosed as Vincent's stomatitis. The exact amount of the drug administered at each injection could not be determined. The last injection was given on July 23, 1936. Two days later the patient became irrational and a few hours later lapsed into coma. After a few days in this state, the patient recovered to the point where she could be fed. However, she did not improve beyond this point and remained in a lethargic condition until October 31, when she began to fail. She was no longer able to eat and had to be fed by tube. The temperature was irregular. The patient became restless and then lapsed into coma. It was in this condition that she was admitted to the Los Angeles County Hospital on November 6.

On examination the patient was found to be deeply stuporous. The general examination showed no essential abnormalities. On neurologic examination, the upper extremities were found to be flaccid and the lower ones spastic. Irregular clonic contractions were occasionally observed. The neck was slightly rigid. The deep reflexes were present, active and bilaterally equal.

The Wassermann reactions of the blood and spinal fluid were negative. The spinal fluid pressure on November 9 was found to be only 40 mm; 4 lymphocytes per cubic millimeter and a total protein content of 0.071 Gm. were found to be present. The colloidal benzoin curve was 00000331000000.

On November 9 the patient was reported as crying and moaning constantly, being unable to eat. On November 12 the temperature rose to 105 F. and pulmonary edema developed, resulting in death the following day.

At autopsy, performed by Dr. P. C. Humphreys, a resident pathologist, a terminal bronchopneumonia, evidently the immediate cause of death, was found, but there were no visceral lesions. The essential lesions were found in the brain. A generalized thickening of the leptomeninges was found, together with a moderate degree of cortical atrophy in both frontal regions. Coronal sections of the brain disclosed small symmetric areas of yellowish discoloration and softening in the external capsule beginning at the point opposite the head of the caudate nuclei and extending backward to the anterior limits of the thalami. Similar areas of softening were found in the optic thalami (fig. 1). These different lesions varied between 0.5 and 1.3 cm. in diameter. The section through the posterior parietal region showed a gross yellowish discoloration of the cortex in this region.

A detailed microscopic study showed a thickening of the meninges by fibrous proliferation. The cortex showed some increase in the glial elements. A section

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9. This case has been reported under another title by Dr. Elinor Ives, then resident in the neurologic service (Disseminated Areas of Necrosis in the Brain Following Intravenous Injection of Neoarsphenamine, Bull. Los Angeles Neurol. Soc. **2**:140-143 [Sept.] 1937).

through the area of gross discoloration in the calcarine area showed some focal necrosis of the superficial layers with edema of the gray matter. In the preserved areas there was an increase in number of the oligodendroglia, particularly those about the nerve cells (perisatellitosis). The walls of the blood vessels appeared thickened.

Sections through the margins of the gross necrotic lesion in the external capsule showed a central defect surrounded by a loose glial scar composed of hyalinized astrocytes, infiltrated with round cells, a few fibroblasts and phagocytic cells. The regional blood vessels were surrounded by a thick cuff of lymphocytes.

Sections through similar areas in the optic thalami showed a similar reaction, suggestive of those following foci of softening due to vascular occlusion. Some pigment was deposited in this area, suggesting the presence of previous hemorrhage.

In this unusual case, the patient evidently had an encephalitis following the three injections of neoarsphenamine for Vincent's stomatitis, and in the process a group of focal necrotic lesions of the brain had

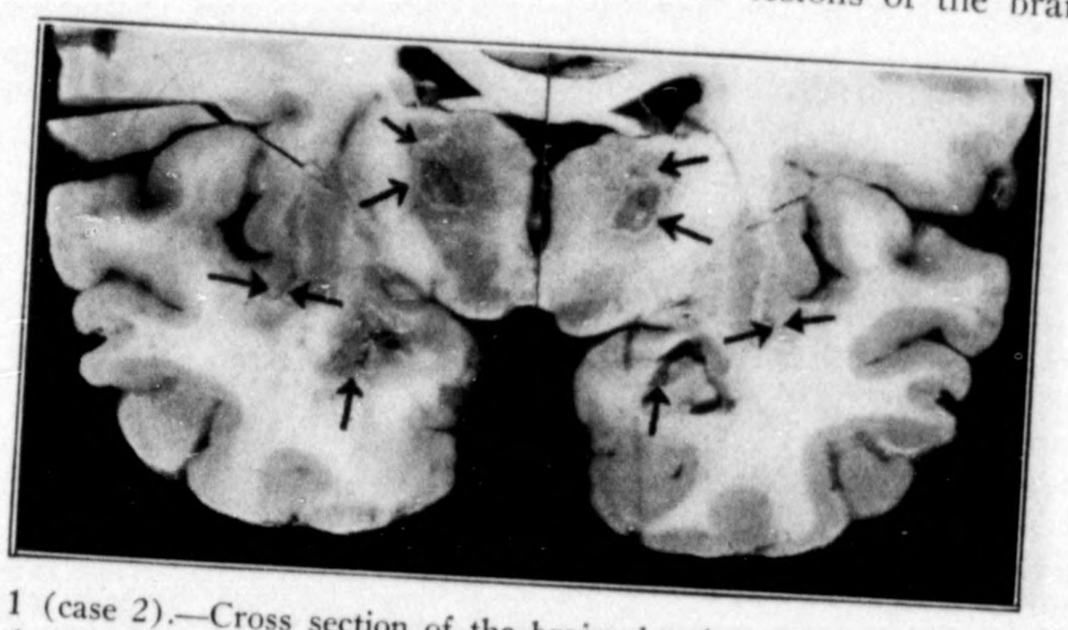

Fig. 1 (case 2).—Cross section of the brain showing old areas of hemorrhagic necrosis in the right and left lateral thalamic nuclei, external capsules and terminal portion of right and left hippocampus.

developed. The patient made a partial recovery but ultimately succumbed to a terminal bronchopneumonia. This case seems to indicate that such focal lesions, as well as the more generalized involvement of the brain with petechial hemorrhages, are not necessarily fatal if they are not too large and too numerous. After three months we were privileged to see the residuals of the lesion described in its acute stage in the 6 other cases. The peculiar localization in the thalami seems, for some reason or other, to be fairly typical of the condition.

CASE 3.—*Headache, anorexia, collapse and convulsions in a young woman three days after a second injection of neoarsphenamine for syphilis. Death seven days after the injection. Multiple symmetric foci of hemorrhagic necrosis in the centrums of the cerebral hemispheres.*

A Mexican woman aged 24, admitted to the hospital in the service of Dr. Harold P. Hamilton, was in good health until a pregnancy in 1937, during which

vomiting was persistent. About a week prior to the delivery of a normal child, on April 7, 1937, a mild toxemia of pregnancy developed. About a year later, on April 20, 1938, she was admitted to a local health center for routine antisyphilitic treatment because she was found to have syphilis. She was seven months pregnant at the time. She was given 0.3 Gm. of neoarsphenamine intravenously on this occasion. One week later she was given a second injection of 0.45 Gm. of neoarsphenamine. A few hours after this injection the patient complained of pain at the site of injection. Two days after the injection she complained of headache,

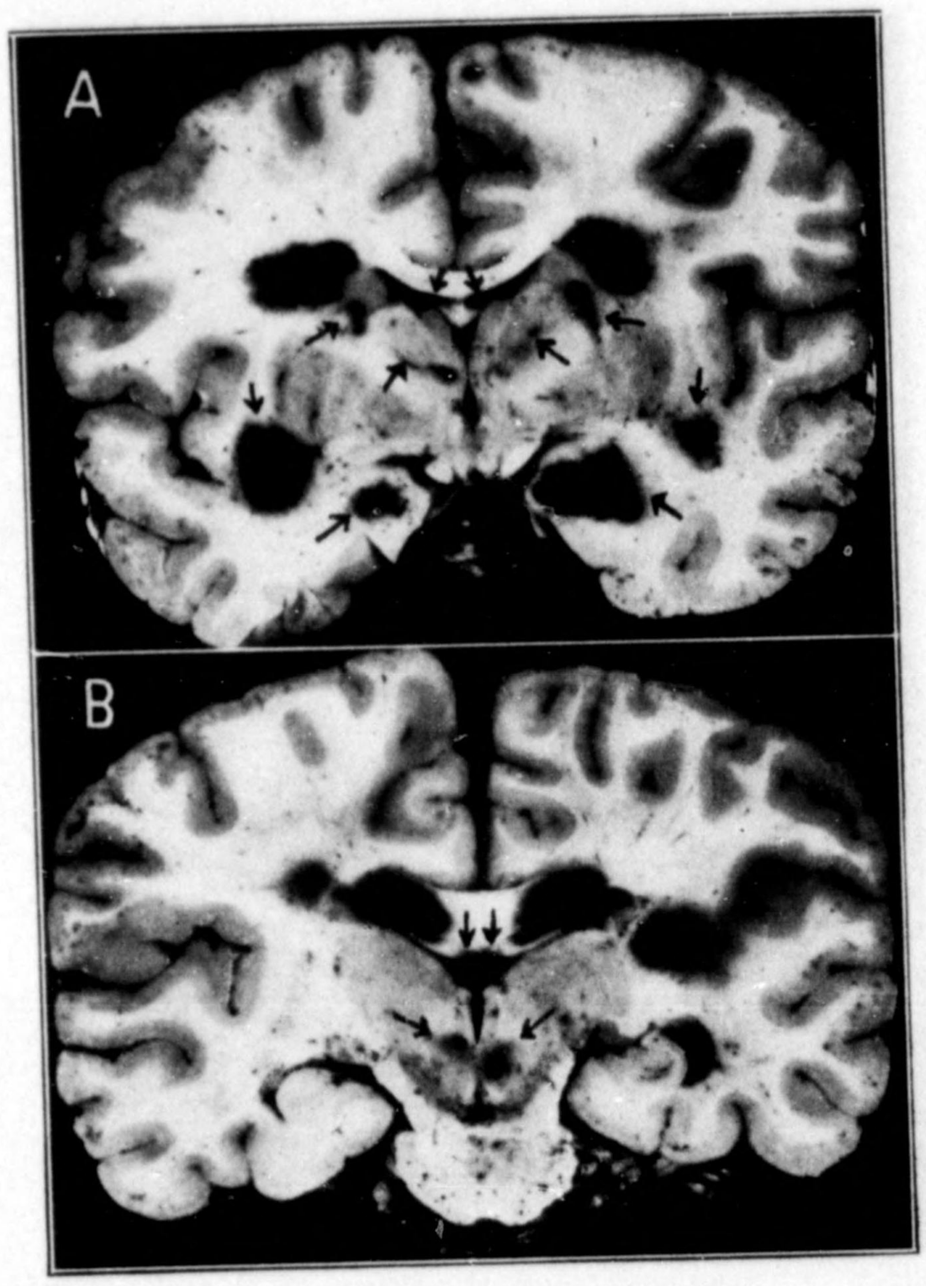

Fig. 2 (case 3).—*A*, cross section through the midbrain showing multiple areas of hemorrhagic necrosis. Note foci in the fornices and red nuclei (arrows). All areas are not symmetrically placed. *B*, cross section of the brain showing symmetric areas of hemorrhagic softening in the splenium of the corpus callosum, fornices and hypothalami.

vomited once and refused her evening meal. On the morning of April 30 she could not be aroused. Soon after she was found in this state she had a generalized convulsion. She was admitted on this day to the hospital.

Examination of the now stuporous patient showed that her pupils were dilated and failed to react to light, the upper extremities were spastic in flexion and all deep reflexes were hyperactive.

A lumbar puncture showed a pressure of 125 mm.; the fluid was clear and colorless, and there were 11 lymphocytes per cubic millimeter. The globulin was considerably increased; the chlorides amounted to 750 mg. and the sugar to 80 mg. per hundred cubic centimeters. The Wassermann reaction of the spinal fluid was negative. The colloidal benzoin curve was 11221000333321. The Wassermann reaction of the blood was negative.

The patient's progress was rapidly downward. On May 5 her temperature arose to 107.8 F. rectally, all extremities became flaccid and the deep reflexes could not be elicited. A peculiar gray cyanosis of the face and hands was noticed. Death came on the same day.

Autopsy, performed by Dr. W. V. Knoll, showed some acute congestion in the lower lobes of the lungs with small patches of inflammatory reaction. No other significant visceral changes were observed. The convolutions of the brain were generally flattened, suggesting a moderate degree of edema. A small focus of subarachnoid hemorrhage was found over each frontal lobe, but no other external lesions were evident. On coronal sections two small foci of red softening were found in the centrum of the left frontal lobe. Similar areas, symmetric in distribution, were found in the section through the internal capsule; these areas were lateral to and beneath the anterior tip of the lenticular nucleus and measured 2.1 by 1.1 cm. in diameter. A section of tissue just posterior to the optic chiasm disclosed several similar lesions in symmetric locations in the corpus callosum, the corona radiata and the lower portions of the external capsule (fig. 2). Still other lesions occupied almost identical positions in the parieto-occipital centrum.

Microscopically, sections through the edge of these hemorrhagic foci showed the entire area to be pale, necrotic and infiltrated with focal hemorrhages. In some of these foci considerable numbers of leukocytes were in evidence, and in the surrounding tissue in both gray and white matter a considerable increase in the oligodendroglia was evident. No inflammatory reaction was noticed in the meninges or the nerve tissues.

In this case the history is classic with the onset of symptoms. The history of toxemia of pregnancy suggests the possibility of renal damage about forty-eight hours after a second injection of neoarsphenamine. A considerable number of rather small foci were found in this case, all within the white substance of the brain. The focal hemorrhages becoming confluent with necrosis of the intervening tissue indicated the essential nature of these larger lesions.

CASE 4.—*Weekly injections of neoarsphenamine and bismuth for fourteen weeks in a young woman. Development of slight headache, fatigue and weakness. Gradual increase in lethargy progressing to coma. Repeated convulsions before death. Multiple scattered petechial hemorrhages and multiple symmetric foci of hemorrhagic necrosis in the corpus callosum and centrum of both cerebral hemispheres.*

A white woman aged 23 had been well until July 1937, when a dull occipital headache developed accompanied by a feeling of fatigue and weakness. Two weeks after the onset of these symptoms, it was found that she had a positive Wassermann reaction. Shortly thereafter she began to take weekly injections of neoarsphenamine, 0.5 Gm., and bismuth subsalicylate, 1½ grains (0.1 Gm.). She received fourteen such injections, the last one on November 6 at 5:00 p. m. On the following day the patient felt tired and weak and complained of a slight gen-

eralized headache. Toward evening she felt somewhat lethargic. On November 8 she became increasingly drowsy and lapsed into coma. She was admitted to the hospital, service of Dr. Samuel D. Ingham, at 10 p. m. of this day.

On examination, the pupils were found to be irregular and unequal, the left being larger than the right. Occasional nystagmoid movements were also observed. The neck was slightly rigid to flexion and Kernig's sign was positive. Both arms were held in a position of spastic extension; a bilateral extensor toe response was also elicited.

A lumbar puncture revealed a pressure of 180 mm.; the fluid was clear and colorless. The Wassermann and Kahn reactions were negative. There were 100

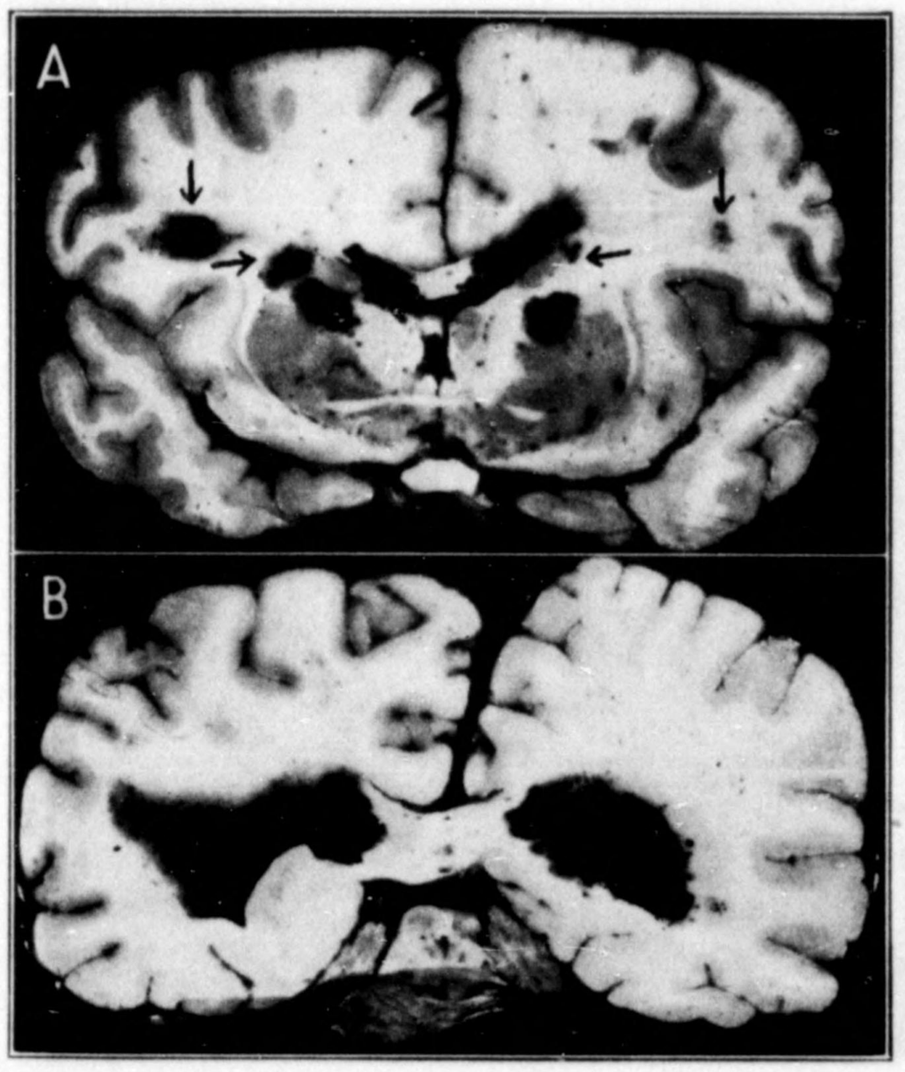

Fig. 3 (case 4).—*A*, cross section of the brain through the anterior commissure, showing symmetric areas of softening. Areas of necrosis are symmetrically located, though not always equal in size. *B*, hemorrhagic foci in the proximal portion of the forceps major and adjacent to the lateral ventricle.

red cells per cubic millimeter. The total protein content was 0.26 Gm. per hundred cubic centimeters. The Wassermann reaction of the blood was strongly positive.

During the evening of November 9 the patient had several generalized convulsions, which were controlled only with difficulty by heavy doses of sodium phenobarbital. Death came at 9:30 p. m.

At autopsy, performed by Dr. C. B. Hendricks, evidences of an early pneumonia were evident, with diffuse hemorrhagic infiltration into the parenchyma and areas of grayish consolidation. Small petechial hemorrhages in considerable numbers

were found in the mucosa of the stomach and small intestine. Petechial hemorrhages were also found in the cortex of both kidneys.

A chemical study of the tissues of the various organs gave the following results: kidney: arsenic 0.4 mg. per hundred gram of tissue and bismuth 0.4 mg. per gram of tissue; liver: arsenic 0.6 mg. and bismuth 0.65 mg.; brain: arsenic 0 and bismuth 0.4 mg.

The convolutions of the brain were slightly flattened, suggestive of a mild edema, but no gross lesions of the exterior were evident. Coronal section through the genu of the corpus callosum showed a number of scattered petechial hemorrhages throughout this structure and in addition patches of hemorrhagic necrosis in the corona radiata and the frontal centrum. Section through the anterior limb of the internal capsule showed foci of softening in the outer limits of the corpus callosum, the internal capsule and the centrum. These hemorrhagic foci tended to assume symmetric situations in the hemispheres, although this was not invariably the case. Section through the posterior limb of the internal capsule disclosed almost complete destruction of the corpus callosum and corona radiata as well as numerous spotlike hemorrhages in the internal capsule on the left side. There was an extensive focus of hemorrhagic necrosis in the proximal portion of each forceps major and adjacent cerebral centrum about the lateral ventricles (fig. 3).

Microscopically, sections through the margins of the foci of hemorrhagic necrosis demonstrated the nerve tissue to be completely necrotic and infiltrated with many small focal hemorrhages. The nerve tissue in the region of these foci appeared pale. The adjoining tissues were vacuolated and broken up by scattered hemorrhages. About some of the blood vessels the polymorphonuclear cells were increased in number, possibly the result of regional hemorrhage. A few pigment-laden phagocytic cells were found in the perivascular spaces of some of the regional blood vessels. Some of these vessels appeared to be occluded with some sort of hyaline material. The oligodendroglia presented evidence of increased proliferation and had undergone some degree of acute swelling.

This is an important case in that it indicates the essential relationship of the petechial hemorrhages which characterize the pathologic picture in hemorrhagic encephalitis and the lesion under consideration. Both were present in this case. The rather long period of treatment before the onset of the encephalitic manifestations is somewhat unusual. It is significant that in the presence of severe cerebral lesions no arsenic could be found in the brain, suggesting some organic combination as the actual cause of the vascular lesions.

CASE 5.—*Weekly injections of neoarsphenamine given in series of ten for one year to a young woman. Clinical evidences of progressive encephalitis. Death six days after last injection. Foci of hemorrhagic necrosis in the corpus callosum, internal capsule and forceps major of both cerebral hemispheres and in the midbrain and cerebellar peduncles.*

A white woman 25 years of age had been receiving antisyphilitic treatment for a year, consisting of alternating series (ten each) of injections of neoarsphenamine and of bismuth subsalicylate. As the seventh injection of neoarsphenamine in this particular course, 0.6 Gm. of the drug was given on June 24, 1938. On June 27 the patient complained of slight dizziness and headache (as though she had a "cold"), which symptoms became exaggerated on the following day. On June 29 she

vomited several times and gradually lapsed into coma. In this condition, she was brought to the Los Angeles General Hospital, where she was admitted to the service of Dr. Harold P. Hamilton.

On examination it was found that the patient was deeply comatose and cyanotic. The head and eyes were deviated to the right. A wide coarse horizontal nystagmus was also evident. The left arm was spastic, and the Babinski sign was present on the left.

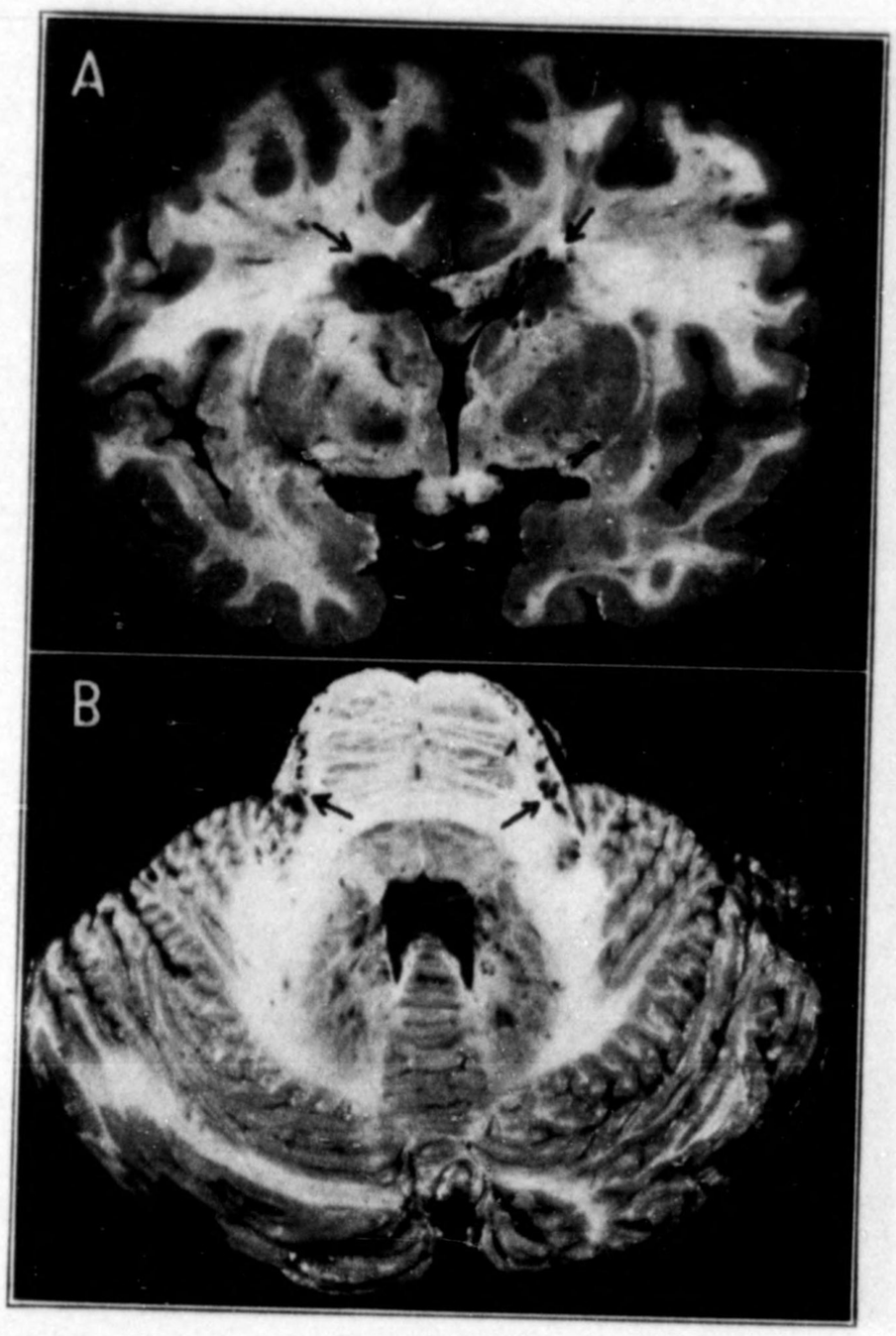

Fig. 4 (case 5).—*A*, section through the optic chiasm showing symmetric lesions in the corpus callosum. *B*, horizontal section through the pons and cerebellum showing numerous small symmetric hemorrhages in the outer fibers of the brachium pontis (arrows).

A lumbar puncture made on the day of admission disclosed the spinal fluid to be under an increased pressure of 240 mm. The fluid was clear and colorless and was otherwise (cytologically, chemically and serologically) normal. The Wassermann reaction of the blood was strongly positive.

The patient died on June 30.

At autopsy, performed by Dr. S. M. Soll, the essential lesions were found to be in the brain. The leptomeningeal blood vessels were definitely congested. A few small focal extravasations of hemorrhage were found in the meninges over the right occipital lobe. On coronal section, bilateral foci of necrosis were discovered in the ventral aspect of the body of the corpus callosum at the level of the anterior limb of the internal capsule. The extent of this bilateral necrosis was even greater in further sections. Hemorrhagic necrosis also involved the posterior limbs of both internal capsules, both parietal centrums, both forcipes majores, both sides of the midbrain and both middle cerebellar peduncles (fig. 4).

Histologically, the typical areas of necrosis infiltrated with hemorrhage and surrounding foci of infarction with satellite hemorrhages were present in the sections studied.

In this case is presented another history of many courses of neoarsphenamine without untoward effects. Then suddenly and without warning or reason, the blow fell. After a therapeutic dose of neoarsphenamine, the patient began to show the typical signs of hemorrhagic encephalitis, in the course of three days after the onset of symptoms of encephalitis and six days after the last injection. The numerous, large and unusually widespread lesions were of particular interest.

CASE 6.—*Frequent untoward reactions, consisting of nausea, vomiting and dyspnea, after injections of neoarsphenamine in a young woman over a course of eighteen months' antisyphilitic therapy. Symptoms of myelitis two days after last injection of drug. Death in six days. Multiple symmetric foci of hemorrhagic softening with hemorrhages into spinal cord.*

A white woman 27 years of age had been receiving weekly injections of neoarsphenamine and bismuth subsalicylate in alternate periods for eighteen months. It was learned that on several occasions after the injections of neoarsphenamine she had become ill, with pain in her extremities, nausea, vomiting and difficulty in breathing. The last injection of the drug was on Feb. 20, 1940. On February 22 fever, malaise and headache developed. The patient remained in bed at home for the next four days, thinking that she had the "flu." On February 26 she became somewhat irrational and paralysis of both legs developed; she was therefore admitted to the hospital, service of Dr. Harold P. Hamilton.

On examination, the patient was found to be restless and somewhat irrational, although she had sufficient possession of her faculties to complain that she "hurt all over." The pupils were small and irregular and did not react to light. A complete flaccid paraplegia was found to be present, with abolition of the deep reflexes in the lower extremities and loss of pain, temperature, touch and position sensibilities below the costal margins. There was also loss of sphincter control.

The spinal fluid pressure was found to be 175 mm. The fluid was slightly xanthochromic and contained 13 lymphocytes and 6 polymorphonuclear cells per cubic millimeter. The reaction to a Pandy test for increased globulin was 2 plus. The Kahn reaction of the spinal fluid was positive; the Wassermann reaction of the blood was negative and the Kahn reaction positive.

On February 28 she was noticeably weaker and showed some increasing difficulty in breathing and swallowing. There was also complete loss of the pharyngeal reflex. The clinical findings were those of transverse myelitis with ascending involvement of the spinal cord. The patient died on February 28.

At autopsy, performed by Dr. T. Bonynge, tissue was taken from the various internal organs as well as from the brain, and this was found to contain arsenic in excess of therapeutic amounts, as follows: liver, 470 micrograms per hundred grams of tissue; kidney, 510 micrograms; thyroid, 400 micrograms; pancreas, 128 micrograms; spleen, 206 micrograms; heart, 49 micrograms; muscle, 35 micrograms; sciatic nerve, 84 micrograms, and brain, 25 micrograms. The lungs presented moderately advanced pneumonia with areas of consolidation. The tracheobronchial tree was moderately injected and contained some hemorrhagic edematous

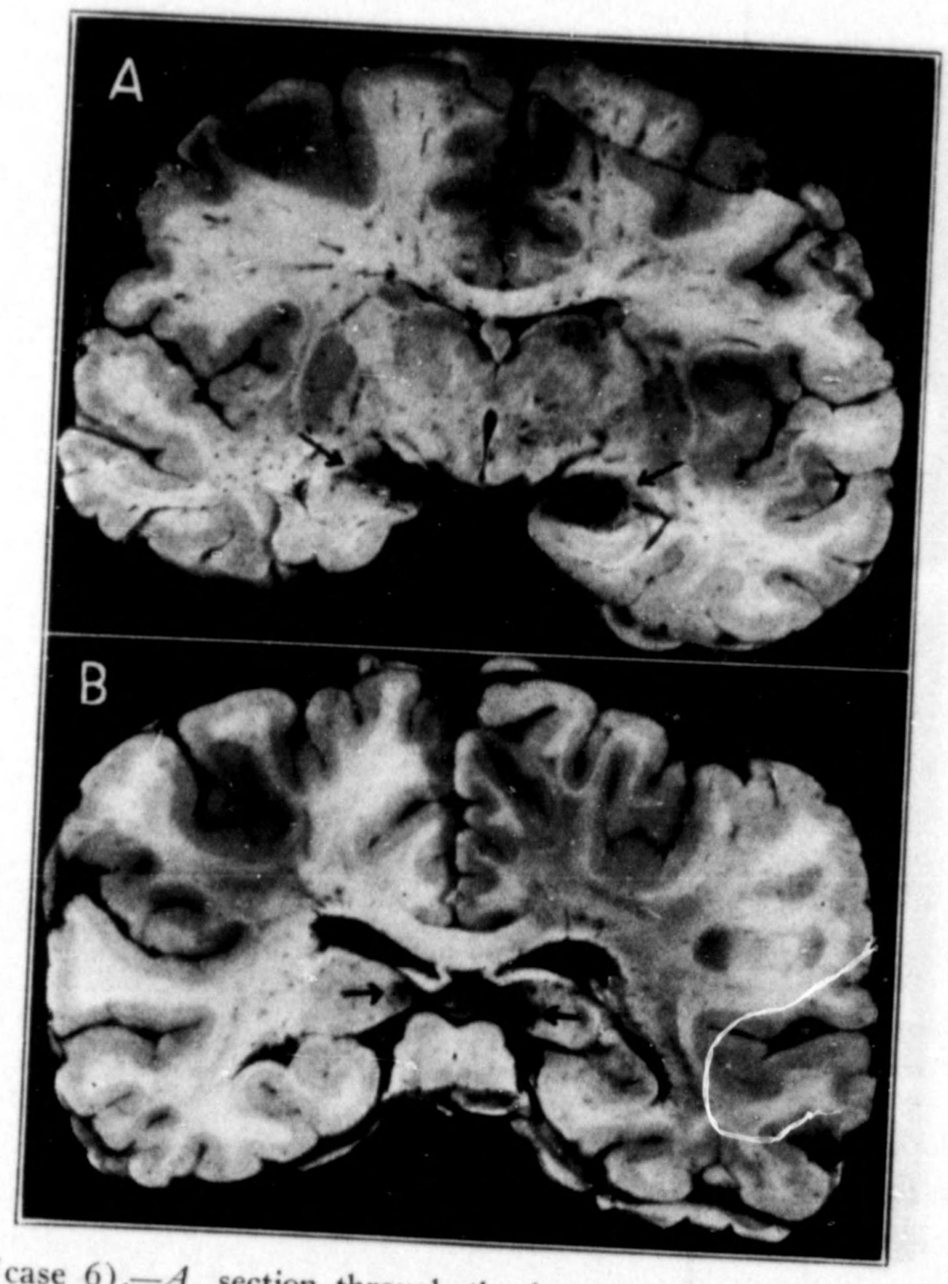

Fig. 5 (case 6).—*A*, section through the basal ganglions showing symmetric areas of hemorrhagic softening in the hippocampal gyri (arrows). *B*, cross section through the posterior thalamus showing symmetric hemorrhagic lesions in the right and left pulvinars.

fluid. The liver was slightly enlarged but was essentially normal on microscopic examination.

The brain presented evidences of advanced congestion. The arachnoid was chronically thickened in the vicinity of the pacchionian granulations. Coronal sections of the brain presented a number of foci of hemorrhagic softening, frequently occupying symmetric positions in the two cerebral hemispheres. The first pair of these lesions was located in the section through the anterior commissure and

found in the white matter below and lateral to the putamen, the right focus measuring 1.2 by 0.7 cm. and the left 0.9 by 0.7 cm. Section through the anterior portions of the temporal lobes presented smaller areas of necrosis in the hippocampus of each cerebral hemisphere. The area on the right measured 1.2 by 0.7 cm. and that on the left 1.5 by 0.9 cm. Section through the pulvinar of the thalami showed small hemorrhagic foci on the medial and posterior aspects of these structures, the lesion being slightly larger on the right (fig. 5). Other smaller foci, composed of several isolated petechial hemorrhages, were seen in the right side of the splenium of the corpus callosum and in the left internal capsule. Scattered hemorrhages were found in sections through the spinal cord.

Sections from blocks taken through the lesions showed areas of infarction as clear pale foci in the white substance of the brain. The tissue in these areas appeared to be friable. Foci of hemorrhage were scattered throughout the area. Myelin sheath preparations showed more or less complete loss of these structures in the infarcted area. Hemorrhages within pale foci were also found in different levels of the spinal cord.

This case is somewhat unusual in that there were a definite hemorrhagic myelitis as well as encephalitis present, evidently not a common situation, judging from our observations and the silence of the literature on the subject. The development of paraplegia and a sensory level suggested the localization of a lesion at about the eighth dorsal segment, although the subsequent development of difficulties in swallowing and breathing indicated subsequent involvement of higher levels. Microscopic as well as gross evidence of small hemorrhages into the cord verified this clinical supposition. Once again the symptoms came on after a long period of antisyphilitic therapy, although it would seem as though the repeated episodes of nausea and vomiting, diffuse pains and respiratory difficulties should have made some one suspect that the patient was susceptible to the drug.

CASE 7.—*Young woman with history of idiopathic grand mal, prior treatment of bartholinian abscess and secondary syphilitic lesions. Symptoms of encephalitis after second injection of neoarsphenamine. Progressive course with intermittent convulsions and residual left hemiplegia. Death three days after onset of encephalitic manifestations and six days after last injection.*

A Mexican woman of 21 years was first admitted to the hospital on Feb. 3, 1934, service of Dr. Harold P. Hamilton, with a history of frequent convulsive seizures for six months; a diagnosis of idiopathic grand mal was made. She was readmitted to the hospital on Nov. 14, 1939 for treatment of a bartholinian abscess, which ruptured spontaneously soon after her admission. Her third admission was on June 21, 1940, with secondary syphilitic lesions of the mouth and vulva and ulcerating perianal condylomas which had been present for two months. The patient was also in her eighth month of pregnancy.

The Wassermann reaction of the blood and of the spinal fluid was reported as strongly positive.

The patient received an intravenous injection of 0.3 Gm. of neoarsphenamine on June 27 and 0.45 Gm. of the same drug on July 1.

On the morning of July 4 the patient complained of generalized headache; later in the day she became somewhat confused and urinary incontinence developed.

A Babinski sign on the left side was the only abnormal neurologic finding at this time. The next day the patient had two generalized convulsions, following which there was a residual left hemiplegia. On the morning of July 7 she was found to be deeply comatose, and she died at 2 p. m. that day, three days after the onset of signs of encephalitis and six days after the second injection of neoarsphenamine.

Autopsy, performed by Dr. E. M. Butt, staff pathologist, revealed an enlargement of the liver, in which the lobular markings were indistinct. The uterus contained a normal fetus 40 cm. long. No other visceral alterations were present. A study of the various organs for arsenic disclosed the following values: kidney,

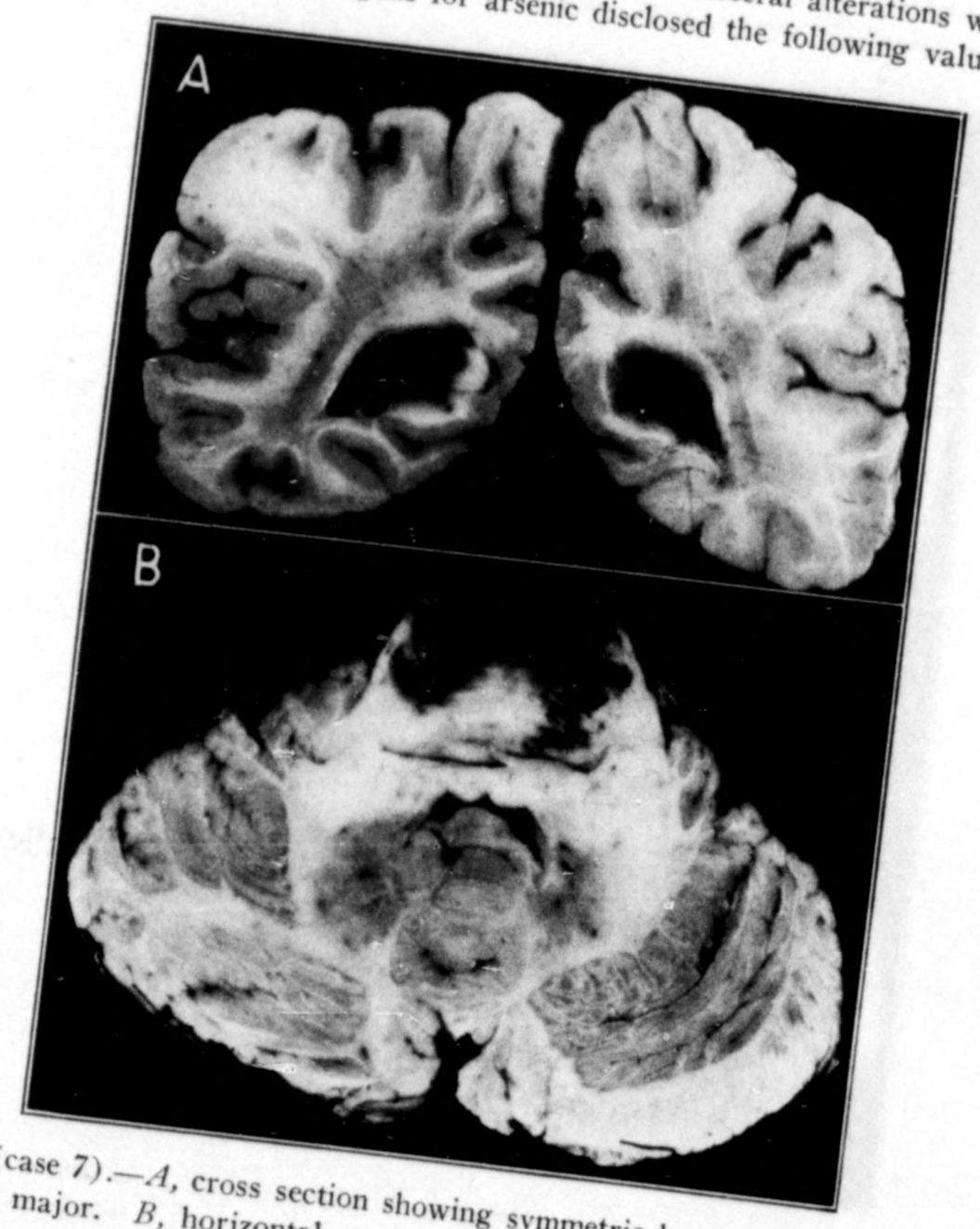

Fig. 6 (case 7).—*A*, cross section showing symmetric hemorrhagic softening in the forceps major. *B*, horizontal section through the brain stem and cerebellum showing symmetric hemorrhages in the basilar pons.

2,880 micrograms (2.8 mg.) per hundred grams of tissue; liver, 1,830 micrograms (1.8 mg.), and brain, 31 micrograms (0.031 mg.).

The external surface of the brain showed small foci of leptomeningeal hemorrhages, probably preterminal. The veins showed evidence of severe congestion. The basilar pons showed swelling and discoloration. On coronal section, a number of petechial hemorrhages were found in the left frontal lobe in the outer portion of the cerebral centrum. A few hemorrhages were also found in the inferior portion of the corpus callosum at the level of the tuber cinereum. These were in approxi-

mately symmetric positions on the two sides. Another section, through the mamillary bodies, showed hemorrhagic areas, somewhat larger but in about the same location. Section through the brain stem at the level of the red nucleus again showed these areas involving the region symmetrically. These areas, composed of a confluence of petechial hemorrhages, extended well back into the splenium of the corpus callosum and on into the forceps major still in the same symmetric position (fig. 6). There was extensive bilateral softening of practically the entire basilar pons, but the medulla was not affected.

Sections studied from blocks taken from the lesion in the left frontal lobe, the corpus callosum and the pons disclosed pale areas, evidently the result of focal infarctions or small hemorrhages. In the subcortical area the small blood vessels seemed to be thickened, and some of them were occluded by thrombi or emboli. In the lesion of the corpus callosum there was a diffuse infiltration of this structure with red blood cells. There was also an accumulation of round cells about the regional blood vessels. The tissue in this region was pale and less well stained than normal, presumably because of anemia incident to hemorrhage and pressure. Section through the basilar pons revealed a diffuse hemorrhage throughout this structure with focal softening and degeneration of the cell groups (pontile nuclei) in this region. There was much free hemorrhagic pigment in the region. The involved tissue was loose and friable. About some of the blood vessels there appeared to be many leukocytes, probably the result of the hemorrhage.

One can almost certainly trace the whole tragic history of syphilis and its unforeseen results in this case. The primary infection, evidently complicated by gonorrhea, took place in the fall of 1939, the primary syphilitic lesion evidently being masked by the development of the bartholinian abscess, with pregnancy very likely the result of the same sexual contact. The serologic reactions, both blood and spinal, were found to be strongly positive, and an intensive program of treatment was planned to spare the child from congenital syphilis. After the second injection of neoarsphenamine the unfortunate complication of encephalitis developed, which proved fatal.

COMMENT

A review of the reported cases of hemorrhagic encephalitis in which mention is made of larger foci of hemorrhagic necrosis, as well as of the cases which have come to our attention, clearly indicates that in addition to widely scattered "flea bite" hemorrhages which occur in the brain, areas of hemorrhagic necrosis may be found either associated with the smaller discrete hemorrhages or occurring as separate and distinct lesions. Since this is true, a larger view of the causation and mechanism of these lesions will have to be taken. That it is primarily a problem of pathogenesis and pathology is suggested by the fact that the clinical factors in both types of cases seem to be very much the same, with the same tendency to occur in young women with onset of symptoms within a few days after an ordinary therapeutic dose of neoarsphenamine has been given. This unfortunate accident usually occurs after two or three

injections of the drug, although in some instances it may develop only after many injections have been given. Perhaps the most outstanding difference in clinical manifestations in the two groups of cases (of scattered petechial hemorrhages versus larger symmetric foci of necrosis) was the greater tendency for the occurrence of focal neurologic signs in the latter group, particularly in the form of motor phenomena.

Directing attention, therefore, to the problems of mechanism and the characteristics of the resultant lesion, a number of questions present themselves. Why should the lesions produced by neoarsphenamine occur as discrete petechial hemorrhages in one case and larger foci of hemorrhagic softening in another? Why in the latter instance should the lesions tend to assume symmetric situations in the two sides of the brain? Do the lesions show a predilection for any particular areas of the brain, and if so why?

VARIATION IN TYPE OF LESIONS OF NEOARSPHENAMINE ENCEPHALITIS

In the 12 cases of cerebral lesions following neoarsphenamine (or some allied type of arsenical) therapy, reports of which are in the files of the pathologic laboratory of the hospital and are now available to us for study, it seems evident that four general types of lesion may be found: (1) petechial hemorrhages scattered generally throughout the white matter of the brain, typical hemorrhagic encephalitis, (2) gross cerebral hemorrhage, (3) multiple and usually symmetric foci of red softening involving both the gray and white matter of the brain and (4) a combination of any two (or possible three) of these lesions. The observations in these cases are indicated in the accompanying table. In this group of 12 cases, there are 4 cases of multiple petechial hemorrhages, 1 case of gross cerebral hemorrhage, 6 cases of multiple symmetric foci of red softening and 1 case of both disseminated hemorrhages and symmetric foci of red softening. If these few cases are typical of the group of cases at large, then multiple foci of red softening is the most common cerebral lesion after arsphenamine intoxication. If this is true, the real nature of some of these lesions must have been misunderstood in the past.

Disseminated Petechial Hemorrhages.—It is this lesion which has been commonly described as hemorrhagic encephalitis following injection of drugs of the arsphenamine group. These small lesions vary considerably in number. In some cases the white matter of the entire brain (and at times the spinal cord as well) has been literally "peppered" with these discrete ring or ball hemorrhages. The hemorrhages are usually limited sharply to the white matter, but occasionally the gray matter may be the seat of some of them. This is well illustrated in one of our cases (case 8).

CASE 8.—An anemic white woman aged 42 died with symptoms of encephalitis twenty-one days after the last known injection of neoarsphenamine (the third injection of a third series given over a period of two years). Scattered ecchymotic spots were observed in the skin before death and were found in the heart muscle and mucosa of the bladder at autopsy. The white matter of the entire brain was "peppered" with petechial hemorrhages up to 1 mm. in size. A few spots were found in the cerebellar cortex and in both lenticular nuclei. The advanced anemia

Lesions of the Brain Following Intoxication with Drugs of the Arsphenamine Group

Case	Age	Sex	Drug Used	General Lesions	Cerebral Lesions
1	20	F	Arsphenamine	None	Multiple symmetric foci of red softening
2	32	F	Neoarsphenamine	Bronchopneumonia	Multiple symmetric foci of hemorrhagic necrosis
3	24	F	Neoarsphenamine	Bronchopneumonia	Multiple symmetric foci of hemorrhagic necrosis
4	23	F	Neoarsphenamine	Hemorrhagic pneumonia; petechial hemorrhages in mucosa of gastro-intestinal tract and cortex of kidneys	Disseminated petechial hemorrhages; multiple symmetric foci of hemorrhagic necrosis
5	25	F	Neoarsphenamine	None	Multiple symmetric foci of hemorrhagic necrosis
6	27	F	Neoarsphenamine	Bronchopneumonia and enlarged liver	Multiple symmetric foci of hemorrhagic necrosis
7	21	F	Neoarsphenamine	Pregnant uterus and enlarged liver	Multiple symmetric foci of hemorrhagic necrosis
8	42	F	Neoarsphenamine	Petechial hemorrhages in heart muscle and mucosa of bladder; fatty changes in liver	Disseminated petechial hemorrhages
9	29	F	Sulfarsphenamine	Petechial hemorrhages throughout visceral mucosa and lining of pericardial, pleural, and peritoneal cavities	Gross cerebral hemorrhage (left insula and temporal lobe)
10*	38	F	Arsphenamine	None	Disseminated petechial hemorrhages
11	19	M	Neoarsphenamine	Bronchopneumonia; petechial hemorrhages in mucosa of gastrointestinal and urinary tracts	Disseminated petechial hemorrhages throughout white matter of brain
12	40	M	Neoarsphenamine	Multiple petechiae of skin, heart, pleura, stomach and kidneys	Disseminated petechial hemorrhages of cerebrum and cerebellum

* This case has been reported under another title by Dr. Elinor Ives, then resident in the neurologic service (Disseminated Areas of Necrosis in the Brain Following Intravenous Injection of Neoarsphenamine, Bull. Los Angeles Neurol. Soc. **2**: 140-143 [Sept.] 1937).

and terminal pneumonia as well as the neoarsphenamine may all have played a part in the production of this unusually brilliant pathologic picture.

In this group of cases, the terminal cerebral lesion has long been known and is not likely to be mistaken for any other.

Gross Cerebral Hemorrhage.—The occurrence of gross bleeding into the substance of the brain after administration of neoarsphenamine must be of rare occurrence. While we know of no other such case reported in the literature, other instances must certainly have occurred. Nevertheless, changes in the wall of some large anomalous vessels are always

a possibility, and under such circumstances gross bleeding might occur. It is also possible that vascular syphilis might predispose to such a lesion. The following case exemplifies the situation.

CASE 9.—A Mexican woman of 29 years gave a history of previous untoward reactions to injections of arsenicals in the form of bleeding gums, ecchymosis and blood-streaked vomitus. The day following an injection of sulfarsphenamine severe headaches developed and the patient had a "stroke" followed by vomiting of blood-stained material. A generalized purpuric eruption of the skin was found on admission to the hospital. Death occurred about twenty hours after the injection and three hours after the "stroke." Gross hemorrhage into the external capsule and left temporal lobe with destruction of the posterior limb of the internal capsule was the only cerebral lesion found at autopsy. There was no gross evidence of cerebral syphilis. Petechial hemorrhages were found beneath the epicardium and endocardium and in the pleura, the peritoneum and the mucosa of the gastro-intestinal tract.

Why in this case a single large vessel of the brain should be affected by the toxic process is unknown, but in the presence of such widespread evidence of vascular changes after treatment with sulfarsphenamine and the absence of other recognized causes, it may be presumed that the cerebral hemorrhage was an ultimate consequence of the arsenical injection.

Multiple Symmetric Foci of Hemorrhagic Necrosis.—As shown previously, this lesion seems to be a common, if not the most common, lesion after arsenical administration. It may be associated with disseminated petechial hemorrhages and possibly with gross hemorrhage as well, as the case of Black[7] seems to suggest (in this case sulfarsphenamine was also used). These foci are found in both the gray and the white matter of the brain, with special predilections for the corpus callosum, the optic thalami, the external capsule and the frontal and parieto-occipital centrums, especially the forceps minor and forceps major. The caudate nuclei, the hippocampal gyri and the brain stem are also affected. The lesions are made up of sharply circumscribed groups of small perivascular hemorrhages, whose close proximity evidently results in necrosis of the intervening tissues, at times to the extent of softening of the affected area. This necrosis may result in the complete disintegration of the affected areas, as was so well shown in case 2.

Perhaps the most striking and unusual feature of the lesion is its decided tendency to occur in symmetric positions in the two sides of the brain. While the lesions are not always identical in size or situation, this factor is so often striking as to call for special comment. Aside from the symmetric lenticular lesions in progressive lenticular degeneration and after asphyxia, there is no known counterpart of this phenomenon in the whole realm of neuropathology.

THE POSSIBLE CAUSES OF SYMMETRY IN HEMORRHAGIC NECROSIS

It has long been recognized that the essential cause of the small perivascular (ring or ball) hemorrhages which constitute the lesion in hemorrhagic encephalitis is a toxic effect on the endothelium of the small blood vessels of the brain, an effect which apparently has a predilection for the place of branching of these vessels. Since there is often no great excess of free arsenic in the brain, it is believed that this toxic effect is due to a combination of the arsenic from the broken-down molecule of the arsphenamine complex with some other substance, perhaps a protein.

Since Ehrlich [2] first postulated the etiologic factors in the causation of this condition, it has been believed that some additional factor is also present. Lack of epinephrine was considered as this other factor by Ehrlich and some others. This conclusion was made on the basis of the clinical observation that patients with impending coma after injections of arsphenamine promptly recovered after epinephrine was administered. While this observation does not necessarily prove that there was a deficiency of this drug in the circulation of blood at the time, it does suggest that dilatation of the affected blood vessels does play some part in the production of the pathologic picture.

The recognition of the occurrence of multiple symmetric foci of hemorrhagic necrosis as a part of this situation demands the consideration of other possible anatomic and physiologic concepts to account for the complete picture. The tendency for these foci of confluent petechiae to occur in certain circumscribed anatomic locations, such as the corpus callosum (including the forceps major and forceps minor as well as the body of this structure), the thalamus (chiefly its lateral nuclei), the caudate nucleus (chiefly its tail), the external capsule, the hippocampus and the basilar pons, compels one to conclude that the blood vessels in these areas, for some reason or other, are particularly sensitive to the effect of the drug. Whether this sensitiveness is due to a difference in the essential structure of their walls, in the frequency of their branching or in the number or peculiar distribution of the vessels in these particular zones is of course uncertain.

The unusual tendency for the lesion to develop in closely approximately symmetric locations in the same brain (although the location of the lesions may vary somewhat from one case to another) suggests that a physiologic factor is also to be reckoned with. The blood vessels in the anatomic regions predisposed to damage by the toxic process evidently show a simultaneous (and very likely fluctuating) sensitivity on both sides of the brain. This fluctuation of predisposition is shown by the fact that identical areas, even in commonly involved regions of the brain, are not affected in all cases.

We suggest the concept that this variability in susceptibility to vascular damage in these regions is due to changes in degree of physiologic activity of the affected vessels from time to time. This variability must of necessity consist of the degree of contractibility of these vessels at the time damage is sustained. The symmetric disposition of the lesion further suggests that there is some symmetry in the vasomotor control of the vessels in these regions. If Ehrlich's original premise about epinephrine is correct, then another step can be taken, and it can be assumed that these vessels are most sensitive to the toxic process during episodes of vasodilatation.

By assuming, then, that there is a recurrent (and probably rhythmic) alternation in constriction and dilatation of the groups of arterioles, more evident in certain parts of the brain, those vessels which are most dilated at the time of action of the toxin are most apt to be affected. The area of brain supplied by the cluster or group of vessels so altered will then be the seat of numerous confluent hemorrhages, which collectively make up the gross areas of hemorrhagic infiltration. Necrosis of the intervening tissue is a result of advanced degrees of asphyxia incident to a serious disruption of regional circulation and therefore of tissue respiration.

One final question remains to be considered. Why in some cases do these areas of symmetric necrosis develop while in others they occur only as widely spread petechial hemorrhages? On the basis of this postulate, it is to be assumed that for physiologic reasons the alternating constriction and dilatation of the vessels in or near the central or ganglionic portions of the brain is for the time being quiescent. The individual vessels throughout the brain which happen to be in a state of dilatation are alone affected by the toxin, and typical hemorrhagic encephalitis then results. A transitional situation would result, as it does in rare cases, in transitional conditions or a combination of both types of lesions.

SUMMARY AND CONCLUSIONS

This study is concerned with an unusual and hitherto unstudied lesion of the brain, which we have come to designate as multiple symmetric foci of hemorrhagic necrosis, which constitutes an integral part of the encephalitis syndrome following intoxication with neoarsphenamine.

The lesion is closely allied with pericapillary encephalorrhagia, which has often been described, in that it is composed of many perivascular (ring) hemorrhages, which in this case are grouped into circumscribed areas in contrast to their otherwise diffuse spread throughout the white matter of the brain.

The basis for this study was a series of 12 cases of encephalitis due to arsphenamine in which the cerebral lesions were observed at autopsy.

In 7 cases multiple symmetric foci of hemorrhagic necrosis were found (in 1 case, both grouped and scattered petechial hemorrhages were present); in 4 other cases, typical petechiae scattered throughout the white matter were found, while in 1 case gross hemorrhage into the brain had taken place. Any combination of these three lesions may possibly exist.

One feature of special interest was the tendency of these hemorrhagic foci to localize in regions of both the gray and the white matter of the brain. The corpus callosum, the optic thalami, the external capsule and the frontal and parieto-occipital centrums (forceps minor and forceps major) seem to be sites of special predilection.

The further tendency for the lesion to occur in symmetric areas of the brain suggests some functional vascular basis for its occurrence. The focal blood vessels supplying these areas are evidently susceptible to the toxic agent to the same degree at the same time. While the lack of epinephrine may enter into this situation, as Ehrlich originally postulated, one can be more sure that dilatation of the blood vessels (arterioles) predisposes them to involvement by the toxic process.

As in the case of disseminated petechial hemorrhages, this lesion is not necessarily fatal, as a case in which there was a rather long survival period indicates, although it must produce serious clinical residuals if at all widespread or severe.

This lesion should be considered a pathologic entity which with disseminated petechial hemorrhages and the rare gross cerebral hemorrhage (with its uncertain relation to sulfarsphenamine) constitutes one of the essential pathologic elements resulting in the clinical syndrome of postarsphenamine hemorrhagic encephalitis. The occurrence of localizing or lateralizing clinical phenomena in a clinical case should suggest the occurrence of this particular lesion.

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NEONATAL ASPHYXIA*

ITS ENCEPHALIC RESIDUALS AND THE MECHANISM OF THEIR PRODUCTION

CYRIL B. COURVILLE, M.D., AND CLEMSON MARSH, M.D.

One of the apparently simple yet actually complex problems of neuropathology is that concerned with the effects of neonatal asphyxia on the central nervous tissues. The etiologic factors are now fairly well understood, the clinical syndromes produced thereby are quite easily recognized by their manifestations, and the correct diagnosis can be made in most cases with reasonable assurance. In spite of all this, there is no uniformity of opinion as to the exact nature of the resultant cerebral lesion or lesions produced by this type of asphyxia. It is the object of this contribution to describe briefly the structural effects of neonatal asphyxia on the brain, approaching this subject from the viewpoint of the clinical manifestations, the pneumoencephalographic picture, and the postmortem findings. Attention will be directed in particular to a poorly-understood group of cerebral lesions of early life thus far variously designated as congenital agenesis, degenerative lesions of the cerebral gray matter, or as diseases of unknown etiology which seem to the writers to be the consequence of asphyxia at birth. To give a third dimension to the picture, a brief historical survey of the problem will be made.

HISTORICAL BACKGROUND

Almost exactly one hundred years ago (1843), W. J. Little delivered a course of lectures at the Royal Orthopedic Hospital in London "On the Nature and Treatment of the Deformities of the Human Frame."[1] In the seventh lecture dealing with deformities due to diseases of the brain and spinal cord he said:

> "In many instances the spasmodic affection is produced at the moment of birth, or within a few hours or days of that event. . . . In two cases the birth occurred at the full period of gestation, but owing to the difficulty and slowness of parturition the individuals were born in a state of asphyxia (asphyxia neonatorum), resuscitation having been obtained at the expiration of two and four hours, through the persevering efforts of the accoucheurs."

After a decade had passed (1853), when Little published these lectures as a monograph, he was able to append short case histories of two additional cases of asphyxia neonatorum with residual spasticity which had meanwhile come to

* From the Cajal Laboratory of Neuropathology, Los Angeles County Hospital and the Department of Nervous Diseases, College of Medical Evangelists, Los Angeles, California.

his attention. While the clinical picture had been described by Andry[2] a century before Little gave his now-famous course of lectures, and while Delpech[2] had described a case in 1828, no one had previously ascribed asphyxia, or any other specific cause, for the condition which came to bear the eponymic title of "Little's Disease." Both Erb and Charcot[2] independently attributed the spasticity in these cases to disease of the spinal cord and designated the condition as "spastic tabes of childhood." Dr. Sarah McNutt[3], in her thesis on cerebral palsies of childhood (1885), concluded that the cause of the condition was meningeal hemorrhage. Supported by such authorities as Osler[4] and Gowers[5], this assumption was seized upon by the profession at large and is still held by many students of the problem to this day. In this same year Strümpell[2] (1885) suggested that polioencephalitis was a cause for the cerebral lesion. Osler's study (1889) was based upon a series of 17 cases verified at autopsy in which porencephalic cavities, diffuse atrophy and sclerosis were found as the essential change in the brain. Brissaud[6] (1894) was of the opinion that incomplete development of the brain incident to prematurity accounted for the physical changes in the nervous system. Freud[7] (1897) advanced the idea that intrauterine disease of some sort was the etiologic factor. In summarizing the literature up to 1899, Collier[8] concluded that there was not one but many causes. McCarrison[2] (1908) decided that thyroid deficiency might be at the root of the trouble since in some cretins ('nervous cretins') generalized spastic paralysis was present in addition to idiocy. On the basis of one autopsied case, Anglade and Jacquin[2] (1909) concluded that neuronic degeneration of some cause was responsible for the gross cerebral changes. In a second paper on the subject, Collier[8] (1924) wrote that the "essential anatomic cause of diplegia is a primary degeneration of cerebral neurons from causes which are at present elusive." In his scholarly treatise on birth injuries of the central nervous system, F. R. Ford[9] (1927) reviewed the pathology of the group of motor lesions which develop progressively after birth and concluded that "the anatomic evidence lends no support to the possibility that either meningeal hemorrhage or thrombosis of the superior longitudinal sinus is a frequent cause of congenital diplegia." The clinical picture was due, in his opinion, to "atrophic lobar sclerosis," developmental defects, and to some less extent, to birth injury.

In recent years a more comprehensive understanding of the effects of asphyxia on the brain has made possible a somewhat different approach to the problem. In 1936[10], on the basis of a series of cases of asphyxia consequent to nitrous oxide anesthesia, the senior author was able to make a number of clinical and pathologic observations pertinent to the problem.

1. Asphyxia with lethal brain damage may occur without recognized clinical manifestations (cyanosis, circulatory and/or respiratory failure).
2. Apparent recovery from asphyxia may be followed by clinical signs of progressive cerebral damage.
3. The most characteristic acute manifestations of asphyxia with brain damage are motor symptoms (muscular twitchings, convulsions, decerebrate or generalized rigidity, athetosis, ataxia and tremor) and psychic changes.

4. As suggested by both clinical symptoms and pathologic changes, the cerebral lesions resulting from asphyxia are progressive in development.
5. Residual postasphyxial changes in the brain may be diffuse or focal, mild or severe.
6. Areas of softening, at times of considerable size, are sometimes found and are due to primary selective action of asphyxia on nervous tissue or to secondary vascular changes.
7. The characteristic microscopic alteration is selective and usually focal necrosis of the nerve cells. Confluence of such focal areas leads to laminar or subtotal cortical necrosis.

In 1938 Schreiber[11] called attention to the possibility that excessive sedation of the mother during labor might well be the cause of neonatal asphyxia in some cases, and suggested that some of the cerebral lesions now considered as congenital deformities might actually be the result of asphyxia. In their important contribution to the study of epilepsy, Penfield and Erickson[12] (1941) pointed out that certain lesions of birth and early infancy which are capable of producing seizures occur (1) in the form of local microgyria considered to be due to birth ischemia, and/or (2) as "brain cysts" (which often have atrophic gyri at their margins) thought to be due to arterial occlusion. It was shown that the characteristic histologic change in the cortex of these atrophic gyri was focal necrosis.

In this same year (1941) Friedman and Courville[13] demonstrated that the essential histologic characteristic of "atrophic lobar sclerosis" and "partial cerebral agenesis," hitherto considered to be some type of degenerative disease, was in fact a focal or diffuse necrosis of the cerebral cortex, and that these conditions were very evidently a residual of neonatal asphyxia. Unpublished studies from the Cajal laboratory on the cerebral effects of asphyxia due to carbon monoxide further indicate that large areas of cortical necrosis may be a direct result of this process, areas sufficiently large to account for the formation of "brain cysts" described by Penfield and Erickson, or for that matter, for the ultimate production of the larger porencephalic cysts so often attributed to "birth injury."

The progressive accumulation of evidence now seems to indicate the probability that the variety of lesions responsible for the idiopathic infantile diplegias, idiocies and epilepsies whose etiology has heretofore not been definitely established, are caused, at least to a considerable extent, by neonatal asphyxia. It is the object of this study to show that such is the case. A brief review of the clinical and roentgenologic evidence is, however, first in order.

THE CLINICAL PICTURE

If one can obtain a clear impression of the various symptoms or symptom-complexes which ultimately result from asphyxia neonatorum, he will be better prepared to evaluate the residual changes in the brain when opportunity for pathologic study of a specimen offers itself. The following clinical pictures have been observed as unquestioned late effects of asphyxia at birth, two or more of them usually being present in a single case: (1) mental deficiency, often asso-

ciated with varying degrees of microcephaly, (2) the striatal syndromes ("congenital chorea," athetosis or choreoathetosis), (3) motor deficit syndromes (decerebrate rigidity, diplegia, hemiplegia, or double hemiplegia), (4) convulsive disorders (generalized seizures with or without focal signs), (5) speech defects (impaired development of the function of speech or dysarthria), (6) visual symptoms (either optic or oculomotor), and (7) cerebellar syndromes (usually bilateral and general in effect).

Mental deficiency alone or in combination with one of the other symptom-complexes is perhaps the most common of the clinical pictures. In fact, most of the patients who survive for a sufficiently long interval will show some mental deficit, varying in degree from complete amentia to minor cuts in the realms of judgment, initiative, intellectual capacity, etc. The memory is often retained to a remarkable degree.

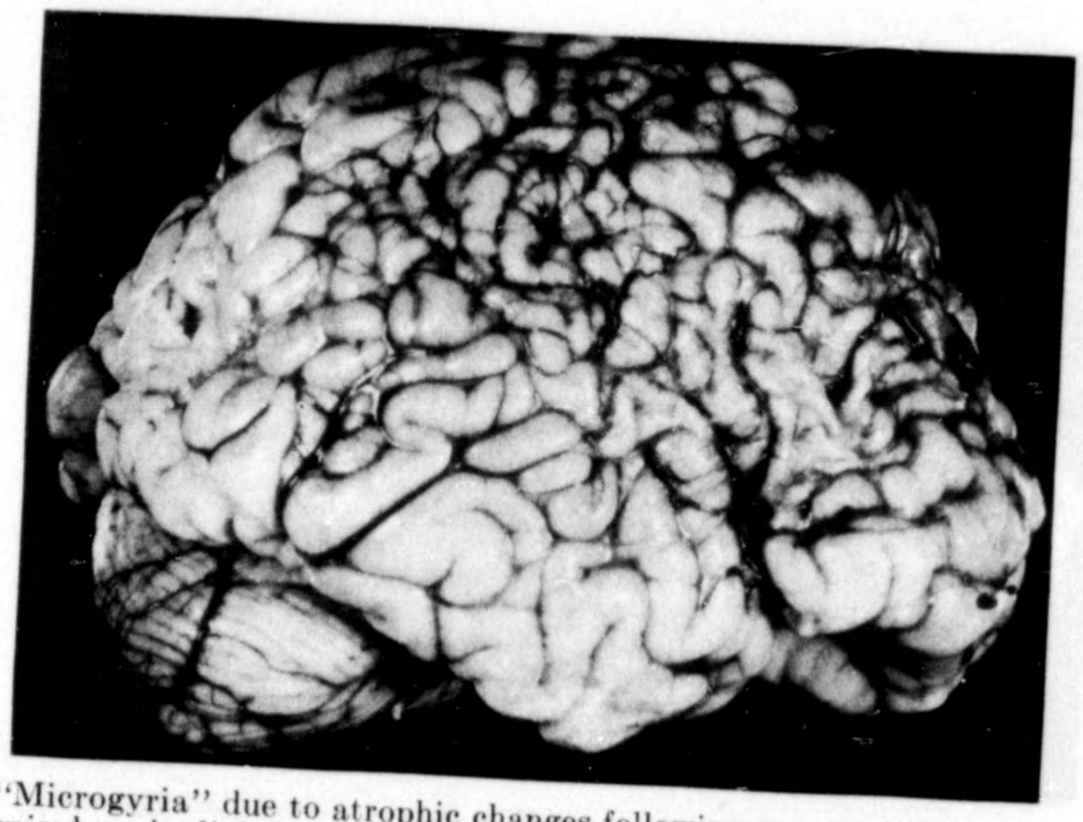

FIG. 1. "Microgyria" due to atrophic changes following neonatal asphyxia. The right cerebral hemisphere is slightly smaller than the left. Survival 17 months.

In cases of *chorea*, *athetosis* or *choreoathetosis* it has long been assumed that the seat of the lesion is the corpus striatum, this organ being diffusely but not totally affected. While not conclusively verified, this assumption is not difficult to believe when it is realized that the lenticular nucleus is especially susceptible to the effects of oxygen want[14] and that this syndrome is at times found in adults who have survived an asphyxial episode of other etiology. The clinical signs of either chorea or athetosis may be predominant, but often a fusion of the two syndromes is observed, the quick, purposeless, arrhythmic, choreiform muscular jerks being interspersed with the slow, more or less continuous, writhing movements of athetosis.

The easily recognized motor defect or "spastic" syndromes of *decerebrate rigidity*, *diplegia*, *hemiplegia*, or *double hemiplegia* have long been described as the effects of "birth injury." Such developments suggest some predominant focal damage which has been generally presumed to be the effect of physical violence

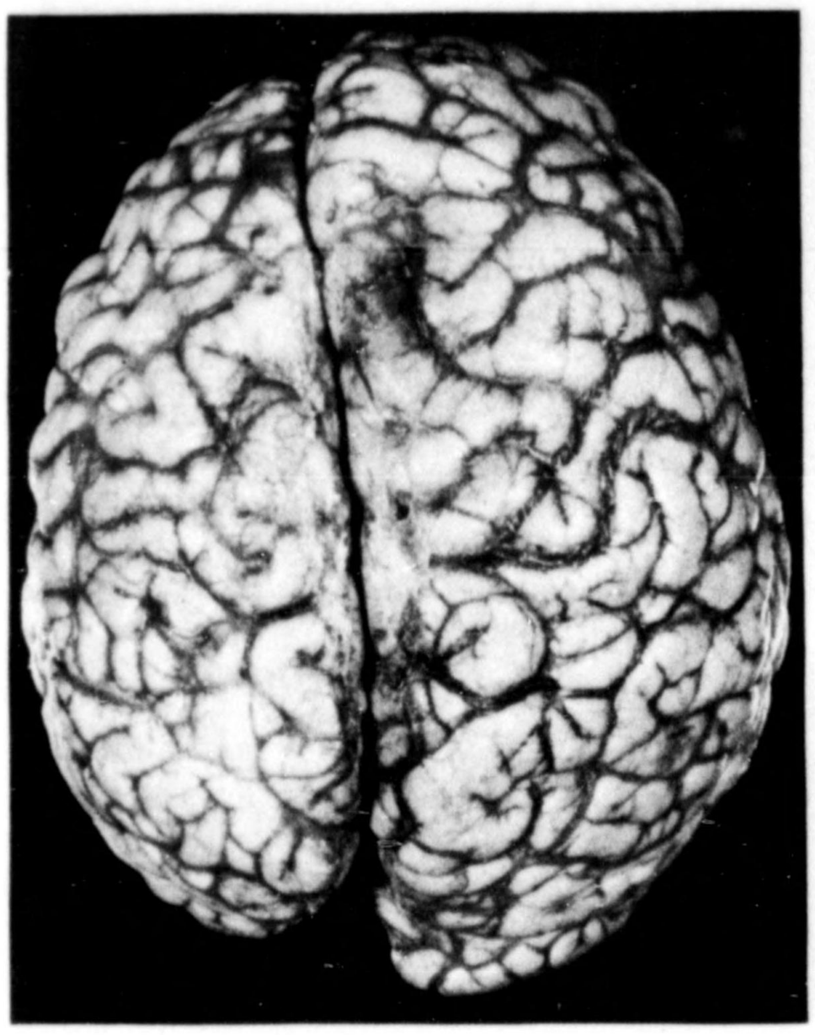

FIG. 2. Hemiatrophy following neonatal asphyxia. The left cerebral hemisphere is diffusely affected

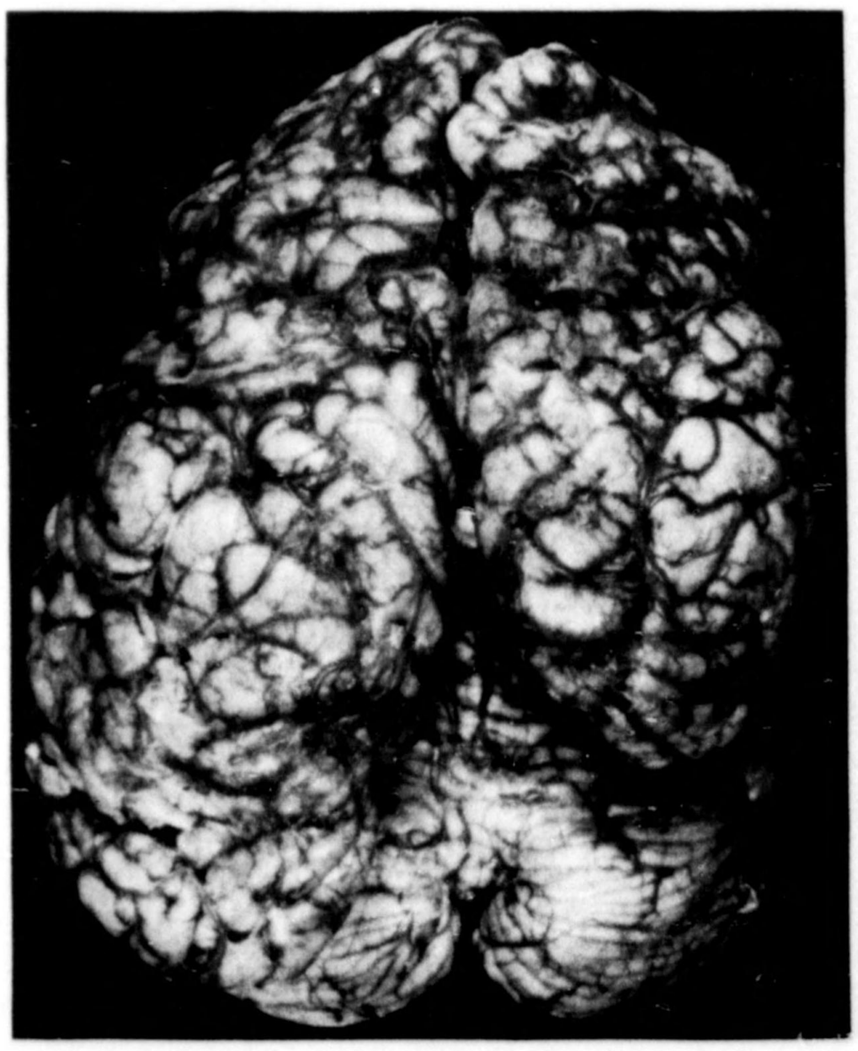

FIG. 3. Combination of microgyria and hemiatrophy of right cerebral hemisphere, a residual of neonatal asphyxia after forceps delivery. Survival 13 months.

rather than asphyxia. To make clear that focal effects of asphyxia can and do occur is one of the primary objectives of this study. Hence the occurrence of such focalizing or lateralizing symptoms does not exclude asphyxia as their cause.

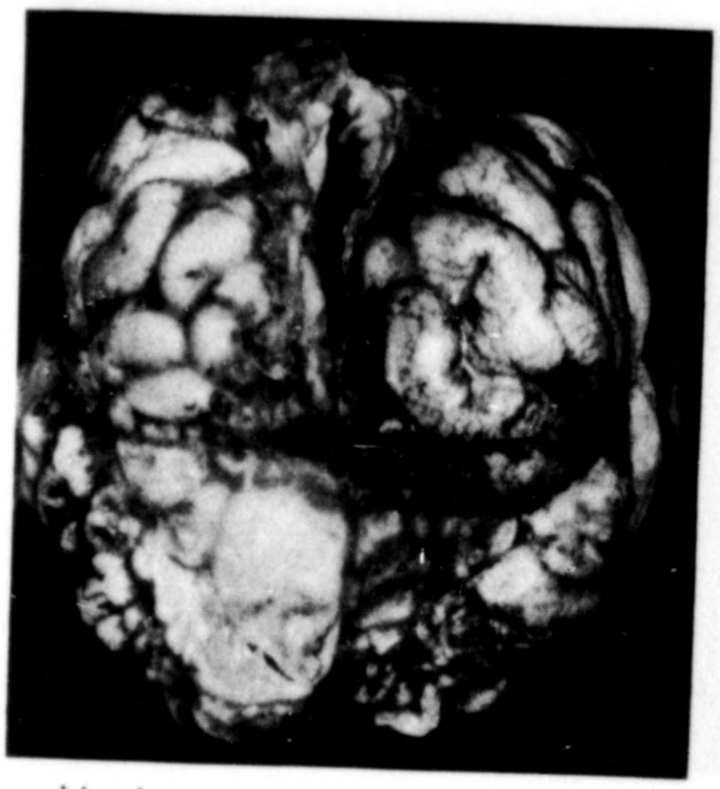

FIG. 4. Advanced atrophic changes, both generalized and localized, in the brain of an epileptic idiot, the consequence of a "birth incident". Note porencephalic cyst in the left parieto-occipital region. Survival 3½ years.

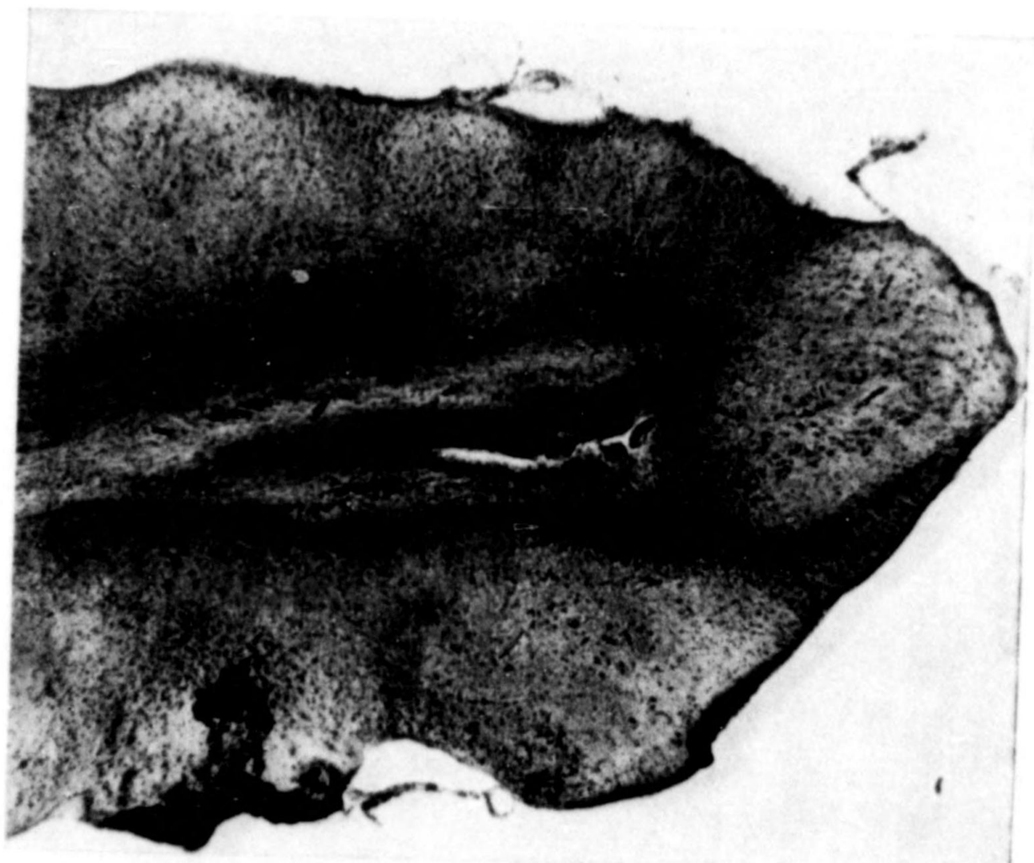

FIG. 5. Irregular decellularization of the cerebral cortex as a consequence of neonatal asphyxia. The child had survived 17 months. H. & E. × 32.

Moreover, patients afflicted with a convulsive disorder, often associated with mental deficiency or one of the motor defect syndromes, are often found to have focal cortical lesions which are strongly reminiscent of those of asphyxial etiology.

Speech defects are due either to incomplete development of the cortical speech areas or to interference with the terminal speech mechanism due to cerebellar involvement. Speech disorders of cortical origin are associated as a rule with

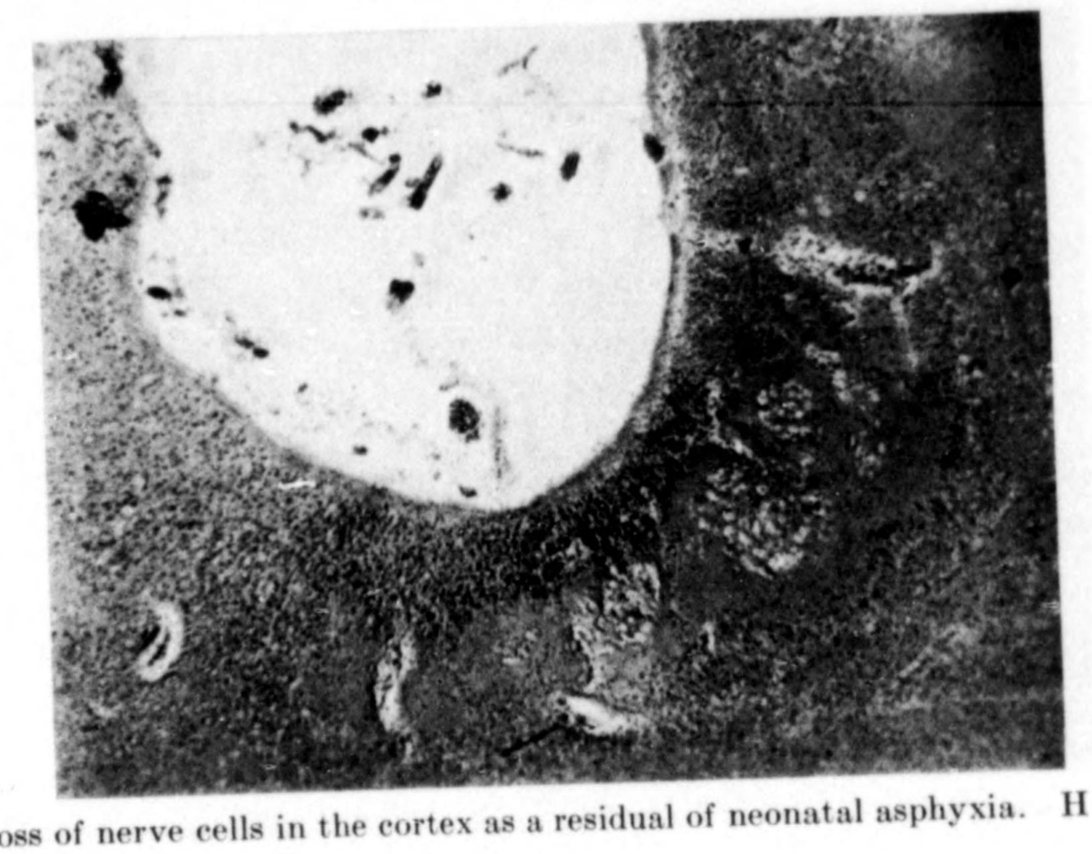

FIG. 6. Loss of nerve cells in the cortex as a residual of neonatal asphyxia. H. & E. × 43

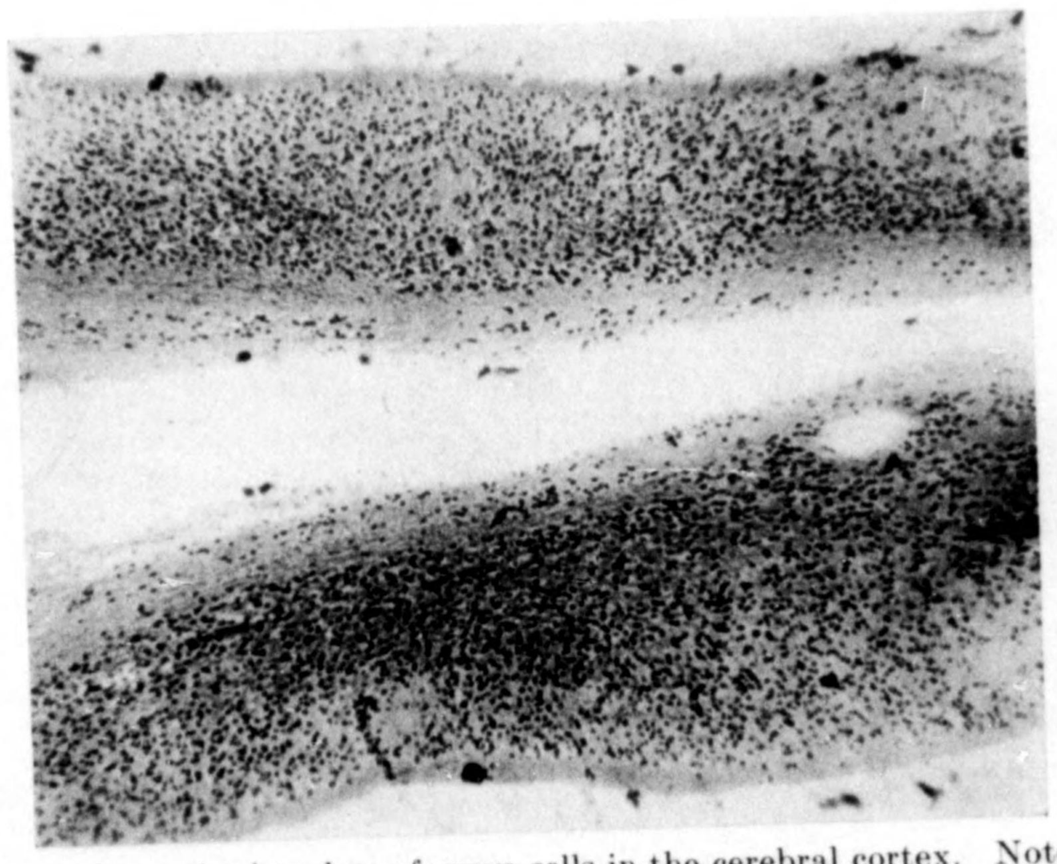

FIG. 7. Irregular and minor loss of nerve cells in the cerebral cortex. Note absence of underlying white fibers, due to secondary degenerative change. H. & E. × 60.

definite mental impairment. Peculiarities of speech may also occur with the choreoathetoses.

Visual symptoms may be due either to optic or oculomotor involvement. They are most commonly due to destruction of the visual cortex (porencephalic cysts), but in some rare instances the optic nerve may be primarily affected (optic

atrophy). The mechanism producing paresis of the extraocular nerves is not understood.

The *ataxic syndrome* is likewise seldom observed as an isolated symptom-complex, but is rather only one symptom of the entire clinical picture. It is less commonly observed than the other symptom groups. It is due to diffuse changes in the cerebellar cortex, and the entire organ is found to be reduced in size, suggestive of agenesis.

PNEUMOENCEPHALOGRAPHIC PICTURES

The introduction of air into the spinal subarachnoid space with consequent filling of the cranial subarachnoid and ventricular systems in cases with clear-cut pictures of neonatal asphyxia discloses three fairly typical groups of radiologic syndromes. Those most commonly seen are (1) a generally and more or less symmetrically dilated ventricular system, with or without enlargement of the subarachnoid space, either pericerebral or pericerebellar, (2) an exaggerated dilatation of one lateral ventricle, in whole or in part, and (3) gross cerebral defects, resulting in lobar sclerosis, "brain cysts" or porencephaly. When viewed in the light of the various clinical syndromes, it becomes clear that in general we have to do with asphyxial effects which, on the one hand, are predominantly general and of equal distribution on both sides of the brain, and, on the other, are predominantly asymmetric and even local in their effects ("brain cysts," porencephaly). It is in this latter group in which the one-sided motor manifestations, either in the form of lateralized convulsions or spastic hemiplegia or hemianopias, are apt to be present.

With these clinical and pneumoencephalographic pictures in mind, we are in a position to better understand the pathologic picture which has thus far been the cause of so much misunderstanding.

THE PATHOLOGIC PICTURE

Paradoxical as it may seem, it is the attempt to analyze the possible effects of neonatal asphyxia which has contributed most to the existing confusion of opinion. The clinical and pneumoencephalographic pictures of neonatal asphyxia are seemingly clear, while the pathologic residuals of this condition are not well understood. There are some logical reasons for this situation. In the first place, the relatively long survivals of many of the unfortunates tends to obscure the original cause of cerebral lesion, the history of a "birth injury" tending to be forgotten. This situation is exaggerated by the fact that birth records are still too often incomplete and inexact on points pertaining to the unfortunate details of parturition. Finally, the disastrous ultimate effects of minor and undetected asphyxia have never before been fully appreciated.

A study of a series of brain specmens removed at autopsy from the bodies of young individuals having suggestive symptoms indicates that it is not always a simple matter to account for the mechanism of evident alterations even when asphyxia has been suspected. But before an effort is made to understand the late effects of this pathologic state, it is advisable to study the immediate ones.

Immediate Effects. In evaluating the findings in the brain of an infant who has succumbed to the effects of recent neonatal asphyxia (perhaps due in part to the traumatizing force which accompanied or produced it) or perhaps to an intercurrent disease which may follow "birth injury," one must separate the asphyxial lesions from the traumatic ones. This is not always easy, as will be shown. Nevertheless, gross subdural hemorrhages due to tears in the falx cerebri and tentorium, or lacerations of the brain substance incident to depressed fragments of the skull caused by compression by forceps are not likely to be confused with the various lesions of asphyxia.

In the brain of an infant who survived for only one and a third hours a disastrous asphyxial episode, foci of subarachnoid hemorrhage were found to be scattered over the dorsolateral surfaces of the cerebral hemispheres. An area of red softening about the size of a quarter was found (on section of the brain) in the cortex of the right occipital lobe. Histologically nothing unusual was discovered save for congestion of the small blood vessels and a few scattered petechial hemorrhages. If the infant should survive for a day or two, minor alterations may be found in some of the cortical nerve cells.* In case of more severe lesions, especially when red softening has occurred, focal or zonal necrosis or more or less complete destruction of the involved cortex becomes evident. Interesting as these acute lesions may be, they can do little more than provide a basis for a better understanding of the late residuals.

Late Residual Effects. It is generally agreed that these late effects are not well understood. No satisfactory classification of these residuals has been found. In order to have a basis for discussion, the following tabulation of lesions is suggested.

1. *General Alterations.*
   a. Grossly normal brain but with scattered patches of cellular degeneration in the cortex or corpus striatum.
   b. Cerebral and/or cerebellar atrophy, with more or less uniform, minor, moderate or severe ("walnut kernel brain") alterations in the cortex.
   c. Marked irregular widespread cortical change usually associated with "brain cysts" or porencephaly.
2. *Local Changes.*
   a. Focal cortical and subcortical lesions (microgyria, "brain cysts").
   b. Lobar lesions (lobar sclerosis [ulegyria], porencephaly).
   c. Hemispheral changes ("agenesis").

It has been appreciated for some time that "idiopathic" motor syndromes of infancy and childhood may occur without any grossly evident changes in the brain (Ford, 1927). It has also been recognized for many years (Cotard, 1868)

* Perhaps no other detail of the effects of asphyxia has been so misunderstood as this absence of characteristic histologic change in patients who have survived the episode for only a short interval of time. One must remember that cell change, like postmortem somatic change, takes time to become apparent. In the senior author's studies on changes in the brain following asphyxia incident to nitrous oxide anesthesia, it has been pointed out that approximately thirty-six hours of survival must elapse before such changes are sufficiently advanced to become evident under the microscope.

that the most uniform histologic alteration in all these cases is the selective and scattered destruction of individual cortical nerve cells or groups of such cells. This well established observation led Collier (1924) to conclude that these spastic conditions were due to a "primary degeneration of the cerebral neurons from causes which are at present elusive." When it is realized that the characteristic effect of asphyxia of any cause is the selective destruction of individual neurons or groups of neurons (Courville, 1936), the relation of such minor alterations of the cortex to neonatal asphyxia becomes clear.

Generalized atrophy of the brain results from this diffuse loss of cortical nerve cells, a process which has proceeded to a more advanced degree. The cell loss has reached such proportions as to result in grossly evident atrophic cortical changes. These changes may affect one hemisphere more than the other which often appears definitely smaller than its fellow. Purely focal changes may also be present, more often in the smaller hemisphere.

Predominantly focal changes are the most interesting and evidently the most misunderstood group of lesions. The presence of small atrophic convolutions (microgyria) in circumscribed areas of the brain has long been recognized, but one is usually left with the impression that such lesions are imperfectly developed gyri, a congenital lesion. Penfield and Erickson pointed out that such lesions were not infrequently the cause of eileptiform seizures. These investigators concluded that such lesions were the consequence of 'ischemic' or anoxial changes in the brain suffered at birth, but were unable to satisfy themselves as to the mechanism of their production. That they are actually the result of anoxemia should be made clear in an illustration of a typical lesion presented in their monograph, in which the areas of focal and zonal necrosis, so characteristic of the asphyxial process, are plainly evident. It is not only that "these small gyri fail to grow during the first year or two of life because of severe anoxia to which they were subjected during the process of birth," but also that these small gyri are the ultimate focal effect of a severe anoxemia which left them seriously and permanently damaged.

Another of these focal lesions, one obviously due to more severe change, is that which Penfield and Erickson describe as a "brain cyst" and attributed by them to an occlusion of a larger arterial channel. Such lesions consist of an area more or less completely devoid of nervous tissue in which the thickened leptomeninges are more or less closely approximated to the ependymal lining of the subjacent ventricle. They are simply miniature porencephalic cavities. The borders of these "cysts" are often marked by atrophic gyri which have been referred to above.

The determination of the exact etiology of these lesions is of paramount importance in this connection. One must agree that they may be due, as Penfield and Erickson postulate, to some local and profound interference with tissue metabolism. Their close resemblance to old cerebral lesions which are the end result of infarction produced by occlusion of a major branch of one of the cerebral arteries suggests that arterial thrombosis is their ultimate cause. Similar lesions, not so far advanced, are found in the brains of individuals who survive asphyxiation by carbon monoxide for a number of days. Whether this lesion is the result of highly selective asphyxia with complete local cortical destruction, or a consequent

thrombosis of arteries (or perhaps of the regional veins) incident to such asphyxia, has not yet been decided. The presence of serious alterations in the blood vessels in cortical regions seriously damaged by asphyxia suggests that the mechanism of thrombotic process may also be asphyxial. The fact that such lesions *are* the result of asphyxia of other etiology demands consideration as the cause or one of the causes of this lesion in cases of asphyxia neonatorum.

A study of one of the next larger lesions described by neuropathologists as 'atrophic lobar sclerosis of childhood' or 'ulegyria,' hitherto described as a lesion of unknown etiology, will make this situation clear. A study emanating from the Cajal Laboratory of two such cases, obviously the result of neonatal asphyxia, made evident the true etiology of these lesions. To note the striking similarity of the cortical changes in ulegyria to those of Penfield's epileptogenic microgyria one needs but to compare illustrations. It was concluded, on the basis of the history and histologic findings, that these larger expanses of atrophic gyri were the direct result of neonatal asphyxia.

The so-called "porencephalic cysts," occasionally found in cases of "birth injury," are simply a lesion of greater extent than a "brain cyst," as described by Penfield and Erickson. It very likely has a similar genesis. The occurrence of porencephalic cysts in epileptics and mental defectives whose trouble can be traced unequivocally to neonatal asphyxia or to a less well-defined birth injury, and their association with diffuse cerebral or hemispheral atrophy and atrophic gyri suggestively asphyxial in etiology demands a reconsideration of their possible cause other than the unproven and less tenable concept of cerebral hemorrhage. As explained above, the larger area of cerebral destruction may be due to more advanced degrees of degeneration or to thrombosis of larger arterial channels also initiated by asphyxia.

The next most prominent lesion in the series is atrophy of an entire cerebral hemisphere, found at autopsy to be smaller than its fellow. The etiologic relationship of this lesion to the ones already described is suggested by the occurrence of clusters of small gyri (microgyria) of "lobar sclerosis" or of "brain cysts," or even of porencephalic cysts in such atrophic hemispheres.

Likewise one cerebellar hemisphere may be atrophic, although when the cerebellum is thus affected both hemispheres are more apt to be symmetrically involved.*

It is only an advanced step from this stage to the more generalized but irregularly spotty changes as observed in the more seriously altered specimens which sometimes become available for study. In such instances, islands of normal or

* The designation of these atrophic portions of the brain as of asphyxial origin demands a reconsideration of the entire group of lesions described as agenetic in the sense of a congenital abnormality. That retarded development, particularly of the cerebellar hemispheres, does occur as a congenital lesion must be admitted, since in extreme examples no other logical conclusion can be drawn. Nevertheless, the association of a small cerebellum with focal or hemispheral cerebral changes makes the assumption of the asphyxial etiology of the entire change in the brain at least reasonable. The finding of the residuals of focal necrosis microscopically, evidenced either by clear areas devoid of nerve cells or of isolated islands of nerve cells *in a cortex of normal anatomic markings* should further tend to confirm this supposition.

even hypertrophic gyri stand out in a sea of small atrophic gyri or from smoother expanses of leptomeninges which mark the location of brain cysts or porencephalic cavities. It is obvious that, regardless of the exact mechanism of production, these profound alterations are to be accounted for largely if not entirely by a severe degree of asphyxia neonatorum.

The one important and basic alteration which ties all of these lesions in one group is the characteristic type of cellular necrosis which is discovered on microscopic study of the altered cortex. Destruction of the cortical nerve cells has also been shown to be present as a late residual of experimental neonatal asphyxia as disclosed by the recent investigations of Windle and Becker.[15] Absence of groups of cells, focal circumscribed areas devoid of nerve cells, laminar degeneration or subtotal destruction of all parenchymatous elements with subsequent reduction of the cortex to a thin stratum of fibrous astrocytes, all bespeak the effect of anoxia. Such lesions have been definitely established as characteristic effects of asphyxia of other etiology, and when discovered after neonatal asphyxia, their true significance should no longer be in serious doubt.

THE MECHANISM OF CORTICAL DAMAGE[16]

From a study of the residual effects of neonatal asphyxia as observed in the brains of the victims of this condition who have survived for a period of months or years, it is suggested that two possibly separate processes are at work in the production of these lesions. The more or less generalized, rather uniform, diffuse change, characterized by widespread atrophic alterations affecting the entire brain, the cerebellum alone, or perhaps a cerebral hemisphere alone, can be explained only on the basis of some generalized process. Such effects are best understood as incident to the decrease of oxygen tension in the circulating blood, a direct consequence of the failure of respiration and sometimes of the circulation as well. Whether this reduction of oxygen tension (probably associated with an excessive accumulation of carbon dioxide) is the result of serious depression of the vital centers as an effect of drugs or intracranial tension, or of an interference with fetal circulation incident to premature placental separation or compression of the cord, or whether there has occurred some mechanical interference of the respiratory functions of the child in the process of delivery, is of no great concern to us in this connection. The fact remains that anoxemia har occurred for a sufficiently long interval of time as to be effective in the destruction of susceptible nerve cells throughout the affected portion of the brain.

The actual mechanism of production of the more localized effects such as microgyria, lobar sclerosis, "brain cysts" or porencephalic cavities, as already stated, is not so obvious. It has been learned, however, that for some reason or other asphyxia can and does produce localized changes apparently due to greater predisposition to the effects of oxygen want by those portions of the brain. This has been shown by the occurrence of scattered and often isolated areas of cortical necrosis and apparently by specific susceptibility of the globus pallidus and calcarine cortex to the fatal anoxemias which sometimes accompany nitrous oxide anesthesia. In cases of asphyxia due to carbon monoxide (illuminating gas),

the usually sharply delineated areas of destruction are even more conspicuous because they are often extensive and profound. The size and depth of some of these areas strongly suggest that some vascular change, perhaps in the form of endothelial proliferation, has resulted in thrombotic occlusion of some of the larger arterial branches supplying the affected cortex. In addition to these apparent effects of arterial occlusion, certain venous effects, possibly also thrombotic, must also be considered as potential causes of such focal damage.[17] As has already been described in the section dealing with the immediate effects of neonatal asphyxia, areas of red softening strongly suggest that venous occlusion, either permanent or transitory, may play a part in their production. It must be recognized that asphyxia may be only an indirect cause of damage. Deformations of the cranial vault with overlapping of the parietal bones can possibly result in occlusion of the terminal portions of the superior cerebral veins. If this occlusion is prolonged, or if permanent thrombosis occurs, the area of the cortex supplied by the affected vein or veins will undergo red softening. Such a lesion could also result in the localized atrophic areas observed as late residuals of "birth injury."

Thus, it should be clear that in neonatal asphyxia, with or without venous complications incident to cranial deformation, we have potentialities capable of producing both the generalized and localized lesions which are so characteristically found in children who present the complex residual syndromes commonly grouped as mentally defectives, epileptics, and spastics.

SUMMARY AND CONCLUSIONS

Because the problem of the immediate and remote effects of neonatal asphyxia has not been adequately solved, an effort has been made in this study to clarify certain points in the pathogenesis and pathology of this condition. The material upon which this study is based is a series of clinical cases presenting the effects of neonatal asphyxia together with air encephalograms which were taken in each case, compared with a series of specimens of brains removed from individuals who survived this sort of episode for a period of months or years. From a clinical viewpoint this group of patients presents the well-known symptom-complexes of mental deficiency, hemiplegias or diplegias, athetosis, convulsions or ataxias, or various combinations of these syndromes. By deduction one would suspect in these cases either more or less generalized atrophy on one hand, or unilateral or bilateral focal atrophies of the cerebrum and cerebellum on the other. This presumption was sustained by the pneumoencephalographic studies made in these cases.

From a study of the series of brains which show structural alteration due to asphyxia, these generalized and focal changes were also evident. The focal changes in the brain have hitherto often been described as congenital malformations (microgyria, porencephaly or agenesis) or the effect of some degenerative disease (atrophic lobar sclerosis). Their status as an effect of asphyxia now seems to be established by the presence in these atrophic gyri of areas of focal, zonal or subtotal cortical necrosis, lesions which are classically present in cerebral

cortex and lenticular nucleus after other types of asphyxia. There is evidence from the same source to indicate that asphyxial mechanisms are capable of producing such lesions either by themselves, or perhaps in some instances assisted by the more mechanical defects of cranial deformation.

REFERENCES

[1] Little, W. J.: On the Nature and Treatment of the Deformities of the Human Frame, London, Longman, Brown, Green, and Longmans, 1853, pp. 114–118.

[2] Cited by Collier (1927).[8]

[3] McNutt, Sarah J.: Double Infantile Spastic Hemiplegia, Am. J. M. Sc. 89:58–79, 1885.

[4] Osler, W.: The Cerebral Palsies of Children, Philadelphia, P. Blakiston, Son & Co., 1889, 103 pp.

[5] Gowers, W.: Birth Palsies, Lancet, 1:709 (Apr. 14) and 759 (Apr. 21) 1888.

[6] Brissaud: Maladie du Little et tabes spasmodique, Sem. Med. 14:89–92 (Feb. 24) 1894.

[7] Freud, S.: Die infantile Cerebrallähmung, Wien, A. Holder, 1897, 327 pp.

[8] Collier, J. S.: Cerebral Diplegia, Brain. 22:373, 1899. Ibid: The Pathogenesis of Cerebral Diplegia, 47:1, 1924.

[9] Ford, F. R.: Cerebral Birth Injuries, in Birth Injuries of the Central Nervous System, Baltimore, Williams & Wilkins Co. 1927.

[10] Courville, Cyril B.: Asphyxia as a Consequence of Nitrous Oxide Anesthesia, Medicine 15:129 (May) 1936.

[11] Schreiber, F.: Apnea of the Newborn and Associated Cerebral Injury. A Clinical and Statistical Study, J. A. M. A. 111:1263 (Oct. 1) 1938.

[12] Penfield, W. and Erickson, T. C.: Epilepsy and Cerebral Localization, Springfield and Baltimore, Charles C. Thomas, 1941, pp. 274–278.

[13] Friedman, A. P. and Courville, C. B.: Atrophic Lobar Sclerosis of Early Childhood (Ulegyria). Report of Two Verified Cases with Particular Reference to Their Asphyxial Etiology, Bull. Los Angeles Neurol. Soc. 6:32 (Mar.) 1941.

[14] Courville, Cyril B.: Untoward Effects of Nitrous Oxide Anesthesia, Mountain View (California) Pacific Press, p. 131, 1939.

[15] Windle, W. F. and Becker, R. F.: Asphyxia Neonatorum. An Experimental Study in the Guinea Pig, Am. J. Obst. & Gynec. 45:183 (Feb.) 1943.

[16] Courville, Cyril B.: The Pathogenesis of Necrosis of the Cerebral Gray Matter following Nitrous Oxide Anesthesia, Ann. Surg. 107:371 (Mar.) 1938.

[17] Courville, Cyril B.: Pathology of the Central Nervous System, Mountain View (California), Pacific Press, 1937, p. 187.