VIRAL ENCEPHALITIS

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A Symposium

Fifth Annual Scientific Meeting of the
Houston Neurological Society
Texas Medical Center, Houston, Texas

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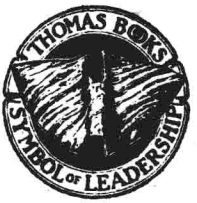

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A Symposium — March 1, 1957

FOREWORD

THIS VOLUME, composed of presentations given by invitation to the symposium on *Viral Encephalitis* at the Fifth Annual Meeting of the Houston Neurological Society, is the third of a series begun in 1955.

The organization of the symposium and publication of the material herewith presented could not have been accomplished without the contributions of:

Ayerst Laboratories
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To them the society expresses its gratitude.

The symposium was moderated by Dr. Russell J. Blattner, whose experience and acuity in the field of viral agents contributed significantly to the merit of the discussions.

As with its predecessors, *Hypothalamic-Hypophyseal Inter-relationships* (1955) and *Brain Mechanisms and Drug Action* (1956), this symposium and its published record is testimony to the breadth of view, energy and organizational skills of Dr. William S. Fields, who was chiefly responsible for arrangement of the symposium and discharge of the numerous duties incident to its present publication. To him, as well as to the participants, the society expresses its admiration and thanks.

GEORGE EHNI, M.D.
President, Houston Neurological Society

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INTRODUCTORY REMARKS

RUSSELL J. BLATTNER, M.D.
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DURING the past twenty-five years, outstanding advances have been made in our understanding of the viral group of infectious agents. An important segment of this field of scientific endeavor includes the great volume of highly significant contributions which deal with virus invasion of the central nervous system. Nineteen hundred thirty three marked the beginning of this productive investigative era with the definitive isolation of a viral agent from brain tissue recovered from a patient who died with acute encephalitis. Since that time numerous fundamental investigations on "encephalitis" have been carried out and recorded. (Muckenfuss, R.S., Armstrong, C., and McCordock, H.A.: *Public Health Rep.*, U.S.P.H.S., *48*:1341, 1933.)

Along with the rapid development of techniques for study of viruses, many aspects of pathogenesis have been clarified, problems of epidemiology solved, etiologic diagnosis of clinical syndromes established, and certain aspects of control, prevention and treatment delineated.

This field is an active one and current endeavor in many laboratories promises new contributions. It was the purpose of the symposium, which is summarized in this volume, to provide a recapitulation of important aspects of knowledge in this dynamic field, and to supply information concerning recent advances. The participants are eminently qualified to do so, and it is hoped that the compilation of the material presented at the Symposium will

prove useful to practicing physicians and other workers in this field.

VIRAL ENCEPHALITIS

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THE expression "viral encephalitis," employed in a general sense, means an inflammation of the brain caused by a virus. Often the spinal cord can be involved, either primarily or secondarily, in which case the expression "viral encephalomyelitis" is used. These designations are based on clinical observation and, when available, on pathological studies; consequently, they indicate more or less extensive localization of damage in the central nervous system (CNS), with no presupposition as to the virus responsible.

Used in this same general sense, the heading "viral encephalitides" can be said to include not only the diseases caused by viruses that are customarily considered to affect primarily the nervous tissue of the CNS, but also those in which the involvement of the brain membranes is perhaps primary, although the nervous tissue is affected as well. As an extension of this, it can also include encephalitides that are caused by viruses not ordinarily considered as invading the CNS. Finally, certain diseases of the CNS may be mentioned here which are essentially of unknown etiology but, owing to their general aspect, might be of a viral nature.

It is not intended to take up all the different diseases that would fall in a chapter of viral encephalitides, as that expression is generally understood, but rather to confine the discussion to a special group of these diseases. It might be helpful, however, for a better understanding of the problems involved, to enumerate the more outstanding disease entities that can be or have been included in a general study of the viral encephalitides. For the purposes of this presentation, the viral encephalitides can be divided

into two groups: those of known viral etiology, and those in which viral etiology has not been proved. The first group can, in turn, be subdivided. Subdivision (a) includes the arthropod-borne viral encephalitides: Eastern equine encephalitis (EEE), Venezuelan equine encephalitis (VEE), Western equine encephalitis (WEE), Japanese B encephalitis, louping ill, Murray Valley encephalitis (MVE), Russian spring-summer or Far East encephalitis (Russian SS) and St. Louis encephalitis. Several encephalitides (other than spring-summer) known to exist in the Soviet Union should perhaps be included here, but information concerning them was not available at the time of writing this article. Subdivision (b) consists of encephalitides and other CNS infections caused by viruses not arthropod-borne. In this heterogeneous aggregate can be placed the following diseases or viruses: Coxsackie virus, some of the Echo viruses, encephalomyocarditis, herpes simplex, herpes zoster, infectious mononucleosis (viral?), Lymphocytic choriomeningitis, Lymphogranuloma venereum, measles, mumps, poliomyelitis, rabies and Sabin's B virus. Many of these viruses are not considered to be ordinarily encephalitogenic, and some are associated with characteristic clinical entities other than encephalitis.

The second main group of viral encephalitides includes diseases for which a viral etiology has, at some time or other, been proposed but that etiology lacks confirmation and is only one of the several advanced for these diseases. This is the group of the demyelinating encephalitides, among which are: acute primary hemorrhagic encephalitis, multiple sclerosis, postinfection and postvaccination encephalitides.

Finally, von Economo's disease and Guillain-Barré syndrome can be mentioned; these diseases are neither of proved viral etiology nor of the demyelinating type.

Of all these different varieties of encephalitis, we would like to discuss the group with which we are most familiar, namely, the arthropod-borne viral encephalitides. The encephalitic syndrome given by the different viruses in the group is essentially the same with all these viruses when allowance is made for localization and degree of intensity. The pathological picture, again in general

terms, is fairly uniform within the group as a whole and is characterized by diffuse rather than localized involvement of brain and cerebellum; the lesions show a degree of neuronotropism but also marked involvement of the supporting elements. The meningeal layers present a diffuse cellular infiltration chiefly of lymphocytes and engorgement of blood vessels. In the brain tissue itself there is a diffuse infiltration predominantly of the cortical gray matter with lymphocytes and polymorphonuclear leucocytes; perivascular infiltration, small hemorrhages and foci of neuroglial proliferation are conspicuous along with necrosis of neurons and neuronophagia; perivascular demyelination is not seen.

Because of this general uniformity, clinical and especially pathological observation can, at best, indicate only that a particular brain infection may be the result of an arthropod-borne virus. The specific diagnosis, if one is possible at all, is to be achieved through laboratory studies, leading either to isolation and identification of the virus or to the detection of antibodies against a given virus in the serum of the patient.

The name arthropod-borne virus encephalitides was first suggested by Hammon (1943) to describe a number of endemic and epidemic virus infections including EEE, VEE, WEE, Japanese B, louping ill, Russian SS and St. Louis encephalitis; subsequently, MVE was added to the group. Notable advances have been made of recent years in the understanding not only of these diseases and of the viruses that cause them, but also of viruses shown to be related to them but not associated with clinical encephalitis. It has, furthermore, become apparent that encephalitis is only one of the forms that infection by the arthropod-borne encephalitis viruses can take; with some of these agents there is evidence that encephalitis is an infrequent occurrence in proportion to the number of persons who have suffered an inapparent infection or perhaps a nonencephalitic type of illness.

As an extension of the above concepts, it was not surprising to find that the agents causing arthropod-borne viral encephalitides are, in fact, selected members of a much larger aggregation or family of viruses which we have called arthropod-borne animal viruses (arbor viruses), many of which have no natural capacity

or tendency to invade the CNS. Under the circumstances, it would seem advisable to broaden the subject of this discussion to include the entire family, rather than restrict it to the more limited encephalitic group.

Arbor viruses are defined as viruses which in nature multiply in the body of arthropods without exerting detectable damage to their tissues or causing other ill effects. It is known for some of these viruses and postulated for others that transmission of the virus to man or other hosts takes place through an arthropod bite; the vector, in turn, becomes infected by ingestion of blood from a host at the time when virus is present in the latter's peripheral circulation.

Antigenic relationships among these viruses, leading eventually to a grouping or classification, have been the subject of study for some time. Thus, cross-reactions were shown by Smithburn (1942) between Japanese B, St. Louis and West Nile viruses; by Casals (1943) between louping ill and Russian SS viruses; by Havens and associates (1943) between EEE and WEE viruses; and by Sabin (1948) between some of the viruses causing encephalitides and those of dengue and yellow fever.

A systematic study of the interrelationships among arbor viruses, by Casals and Brown (1954) and Casals (1956), showed that there were at least three sharply defined groups of arbor viruses, designated A, B and C. This conclusion resulted from the study of forty-seven distinct arbor viruses and was based exclusively on the detection of immunological cross-reactions. These cross-reactions were investigated by different methods; complement-fixation (CF), hemagglutination-inhibition (HI) and neutralization (NT) tests. It is not intended to describe these methods in detail here, but only to report some of the results obtained.

One fact that soon became apparent, particularly with Groups A and B, was that the HI test showed a wider range of serological overlaps than the CF test, which in turn was more cross-reacting than the intracerebral NT test. Hence, the present grouping of the arbor viruses is based essentially on the behavior of these viruses and their hyperimmune sera in the HI test; with the understanding that whatever cross-reactions were detected by NT

or CF tests could, in all cases, be demonstrated also by HI tests.

Reduced to its essentials, the plan used consisted in preparing by a constant technique hyperimmune sera in animals usually mice, for each virus under study and testing these sera against as many agglutinating antigens as were available. The result of these studies clearly showed, on the basis of inhibition of hemagglutination, that there was a sharp division of the arbor viruses into groups, as illustrated in Table I.

All viruses in Groups A and B developed hemagglutinating (HA) antigens. In Group C, however, some viruses were apparently too "weak" to produce utilizable HA antigens, although the immune sera prepared against them reacted well with the available antigens of the same group. Failure to produce antigens with the majority of the ungrouped viruses may thus be more a matter of quantity—or technique—than of inherent absence of hemagglutinin; this point is, naturally, of importance and is currently receiving attention. Hyperimmune sera against any of the viruses of Group A reacted not only against the homologous antigen but also, to a greater or lesser extent, with all the remaining viruses in the group, while in no instance was a reaction detected against any virus not of Group A. A similar thing occurred with Groups B and C. Concerning the ungrouped viruses, less work could be done since few antigens are, at present, available; however, none of the hyperimmune sera against these viruses reacted with antigens of either Groups A, B or C.

Table I also shows that the encephalitic viruses appear some in Group A—EEE, VEE and WEE, and others in Group B—Japanese B, louping ill, MVE, Russian SS and St. Louis. A virus such as WEE, which can cause an encephalitis in man not unlike the one due to St. Louis virus, is in its antigenic behavior much closer to Chikungunya virus (which in its known clinical manifestations is similar to dengue) than it is to St. Louis virus.

The HI reaction with hyperimmune sera has definite advantages for grouping arbor viruses; the cross-reactions detected within Group B, however, are so marked that it is often impossible to arrive at a specific diagnosis with this method. In that case, the use of simple immune sera—obtained from experimental ani-

TABLE I

CLASSIFICATION OF THE ARTHROPOD-BORNE ANIMAL VIRUSES

Group A	*Group B*		*Group C*	*Ungrouped*	
Chikungunya	Bat salivary gl.	SA H 177	BeAn 15	Anopheles A	Eg AR 1152
Eastern EE	Dengue, type 1	SA H 336	BeAn 17	BeAn 73	LEN 731-19
Mayaro	Dengue, type 2	*St. Louis*	BeAn 848	BeAn 277	Rift Valley Fever
Semliki Forest	Ilheus	Uganda S		Be H 151	Sandfly Fever, Naples
Sindbis	*Japanese B*	West Nile		Bunyamwera	Sandfly Fever, Sicilian
Venezuelan EE	*Louping Ill*	Yellow Fever		Bwamba	SA TAR 53
Western EE	*Murray Valley E.*	Zika		California, Hammon-Reeves	Tr 3587
	Ntaya			Colorado Tick Fever	TR 8900
	Russian S-S			Eg AR 492	TR 9760
	SA TAR 94			Eg AR 1095	Wyeomyia