IMMUNOLOGICAL ASPECTS OF MULTIPLE SCLEROSIS

ESSAY

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by

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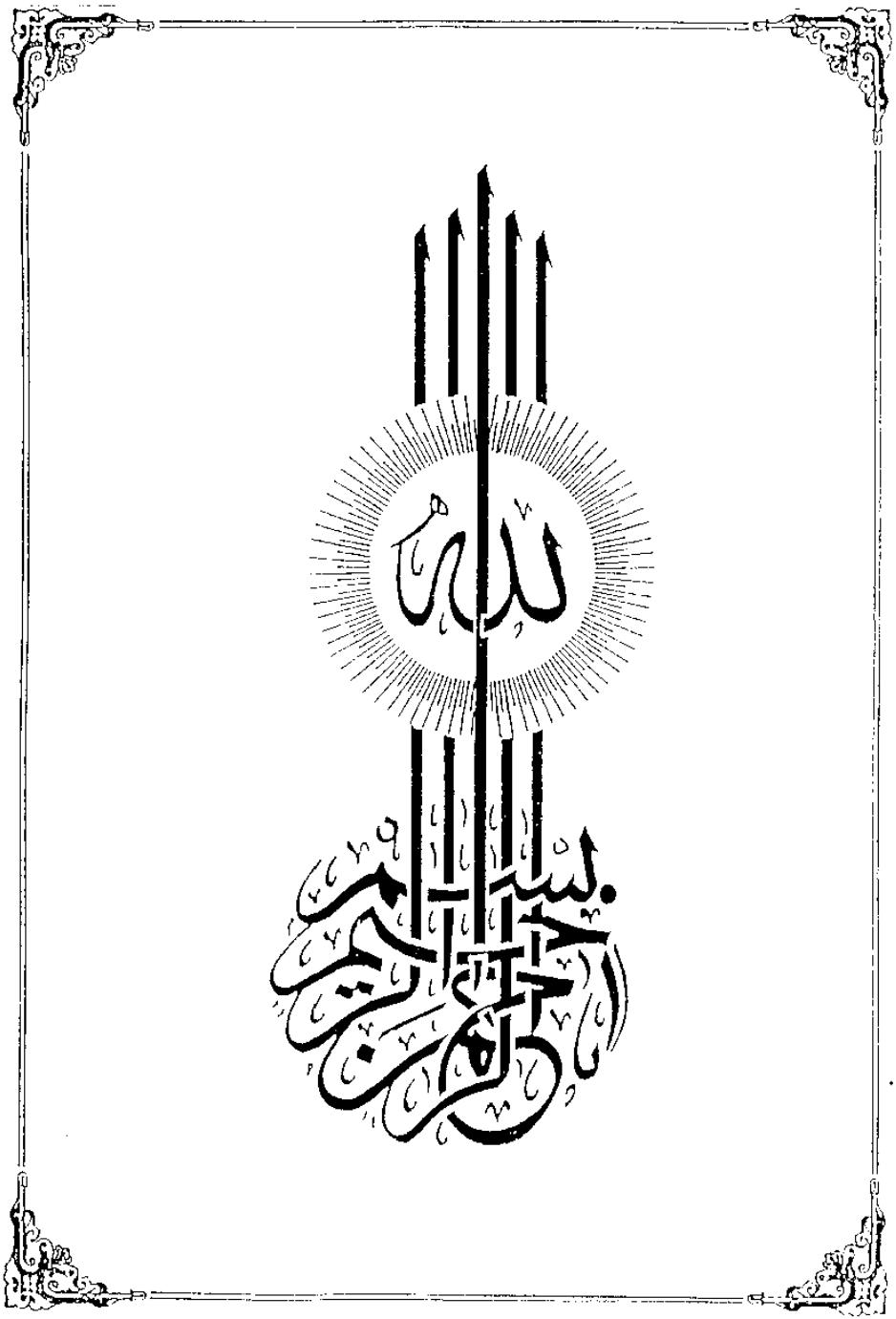

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LIST OF ABBREVIATIONS

AGA	Antiganglioside antibody
CPMS	Chronic progressive multiple sclerosis
DZ	Dizygotic
EAE	Experimental allergic encephalomyelitis
EDSS	Expanded disability status scale
GD	Gadolinium
ICAM	Intercellular adhesion molecule
IFN	Interferon
IL	Interleukin
IL-2R	Interleukin-2 receptor
IVIg	Intravenous immunoglobulin
LT	Lymphotoxin
MAG	Myelin associated glycoprotein
MBP	Myelin basic protein
MBPLM	Myelin basic protein like material
MHC	Major histocompatibility complex
MOG	Myelin oligodendrocyte glycoprotein
MP	Methyl prednisolone
MS	Multiple sclerosis
MZ	Monozygotic
NK cell	Natural killer cell
OCBs	Oligoclonal bands
OND	Other neurological diseases
PLP	Proteolipid protein
PPMS	Primary progressive multiple sclerosis
RRMS	Relapsing remitting multiple sclerosis
sE-selectin	Soluble E-selectin
sICAM	Soluble intercellular adhesion molecule
sIL-2R	Soluble interleukin-2 receptor
SPMS	Secondary progressive multiple sclerosis
sVCAM	Soluble vascular cell adhesion molecule
TCR	T-cell receptor
TGF	Transforming growth factor
TNF	Tumor necrosis factor
VCAM	vascular cell adhesion molecule

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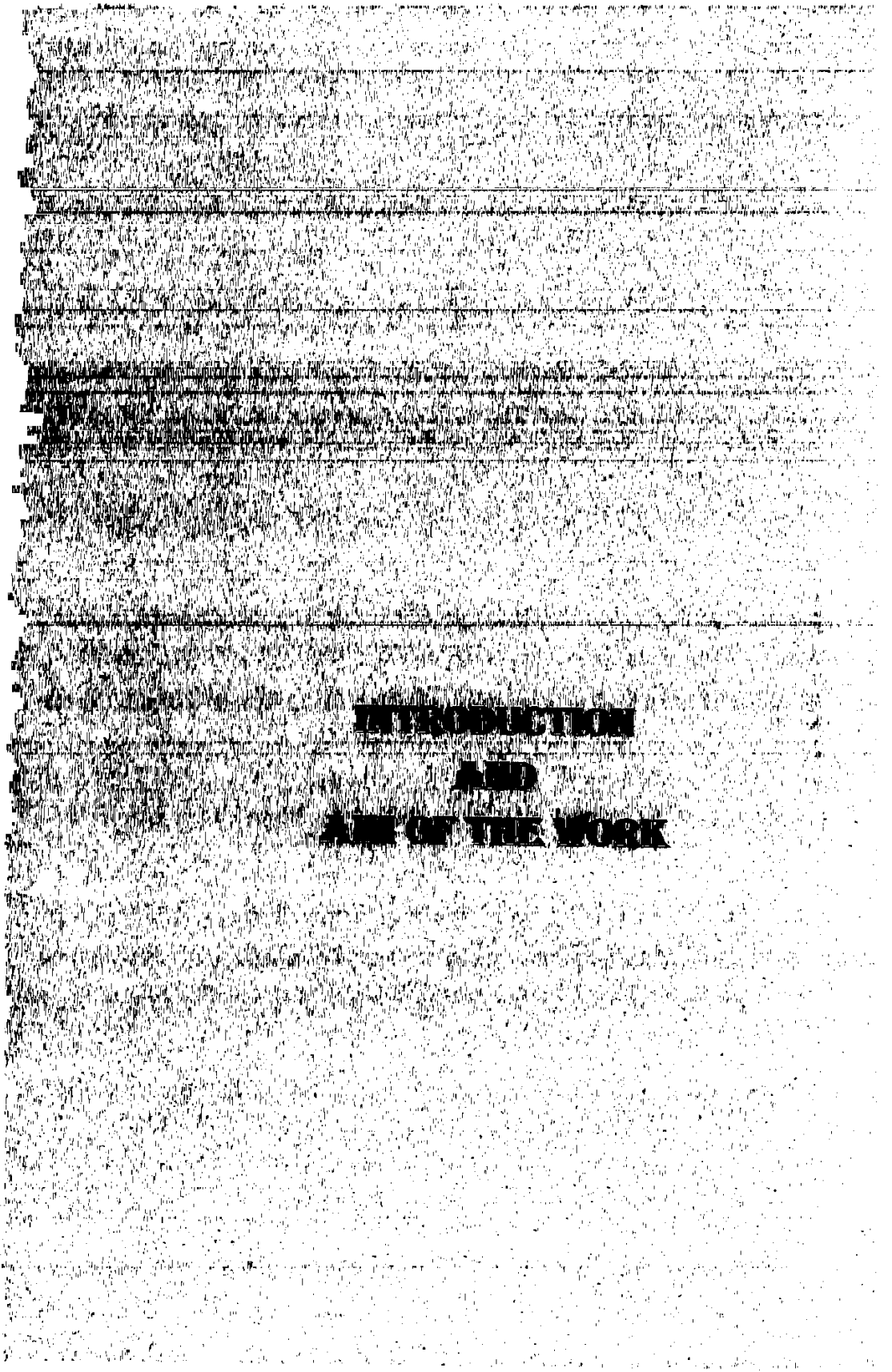

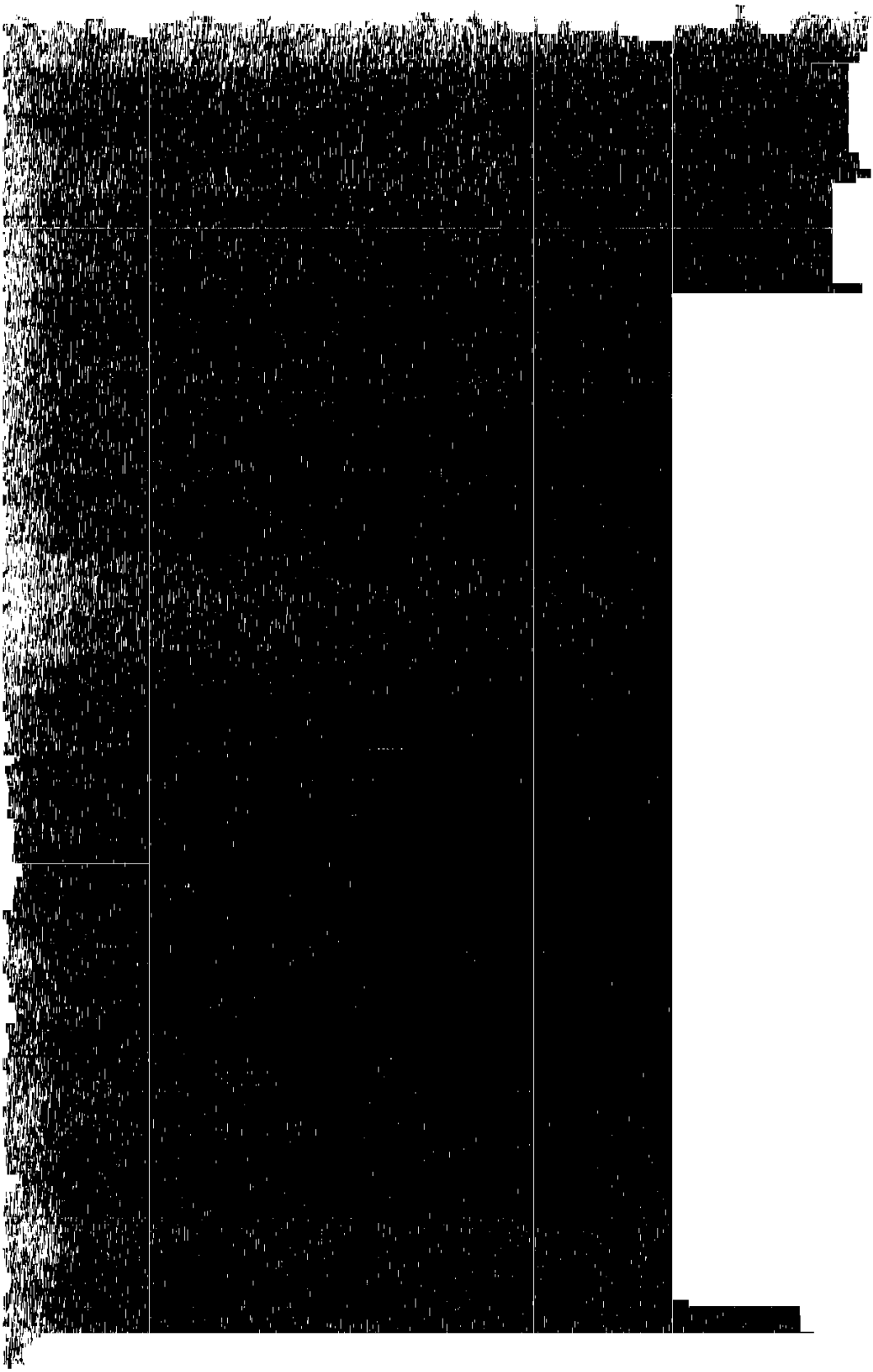

INTRODUCTION AND AIM OF THE WORK

Multiple sclerosis (MS) is a difficult and depressing disease. Patients face not only the prospect and reality of increasing disability, but also the uncertainty of when new relapses will occur or when established disability will set in.

MS is an inflammatory, primary demyelinating disease of the central nervous system. It affects mostly young adults and results in considerable disability and suffering. MS is unevenly distributed over the world, and in areas of high prevalence, it is the commonest crippling neurological disorder of young adults (*Waksman, 1993*).

Although the etiology and pathogenesis remain unknown, accumulating evidence supports the hypothesis that exposure to an as-yet-unidentified infectious agent(s) triggers an aberrant immune response against self nervous tissue in genetically susceptible individuals. The tenfold higher concordance rate for MS in monozygotic twins compared to dizygotic twins, the increased incidence of MS in women compared to men (2:1), and the familial and racial occurrence of MS provide strong evidence that genetic factors influence susceptibility to MS (*Bansil et al., 1995*).

Immunological abnormalities have been repeatedly documented but the relative role of each component of the immune response in mediating tissue damage, and the extent to which these changes are the cause or consequences of myelin injury, remain to be established. Major immunologic features include:

-There is inflammatory demyelination in the CNS white matter.
-There are alterations in immunoregulatory T cell function and cytokines.

-There are oligoclonal immunoglobulins in the CSF.
-It responds to immunosuppressive and immunomodulating agents.

MS is typified by a chronic and unpredictable course. The natural history of MS has been studied extensively for clinical features or laboratory measurements that might predict, anticipate, or parallel the future course of the disease. There are certain clinical characteristics that appear to predict a future progressive course, but such clinical scales have limitations in themselves (*Paty et al., 1992*). This imprecision in clinical patterns and natural history requires markers for signaling progression (*Weinshenker and Ebers, 1987*).

Several laboratory methods have been reported to predict or parallel subsequent disease course in MS. Confirmation of these reported relationships has been conflicting. Serial cranial MRI, with or without gadolinium, represents another measure of clinical disease activity in MS (*Paty et al., 1992; Paty et al., 1993*). Cranial MRI may predict the development of MS after initial signs, serve as a presumed surrogate marker in early MS, and demonstrate increasing lesion burden with longer duration of disease. The cranial MRI findings that are indicative of a CP course or that mark the transition from RR to CP disease are uncertain (*Thompson et al., 1990*). Newer MRI techniques, such as magnetization transfer (*Gass et al., 1994*), may demonstrate the changes of CPMS more accurately. Whatever the technique, cranial MRI may furnish an incomplete record about the change to a CP course, which often results from involvement of the spinal cord (*Whitaker et al., 1995a*).

Since MS is believed to be an autoimmune disease, research efforts have been directed primarily toward the development of safe immunomodulatory therapies. In July

1993, MS care entered a new era with the decision by the Food and Drug Administration (FDA) to license interferon beta-1b. Since then there has been enormous activity and energy in the pharmacological arena. After many years without effective treatments, it appears that we are on the threshold of seeing an exponential increase in new therapies. Treatments are now available for hastening remissions, decreasing exacerbations rate, and probably slowing the rate of progression. Newer therapies can be expected, perhaps used in combinations, which will also alter the long-term prognosis (*Bansil et al., 1995*).

Aim of the work

There has recently been an explosive development of new concepts and methods in immunology, which have been quickly applied to multiple sclerosis.

In this essay, we will review the following :

I. Current theories on immune mechanisms:

- Genes and susceptibility to MS
- The different immune abnormalities.

II. Possible markers to monitor the immunological status of patients and/or predict the course of the illness:

- Differentiating the types of MS
- Monitoring disease activity

III. Update on immunotherapies.

NEUROBIOLOGY

The CNS contains about 100 billion neurons. It also contains 10-50 times this number of glial cells. The neuron (or the nerve cell) is the structural and functional unit of nervous tissue and hence of the nervous system. The cell body or soma consists of a mass of cytoplasm in which a nucleus is embedded, and is surrounded by a plasma membrane. Dendrites are short processes of the nerve cell body. They are usually short and always branched and are not myelinated. A typical neuron also has a long fibrous axon. Close to their termination, axons usually divide into fine terminal twigs which make a synaptic contact with cell bodies or dendrites of other neurons (*Walton, 1993*).

In the peripheral nervous system (PNS), all dendrites and axons are surrounded by specialized cellular sheaths, but in the CNS dendrites are not so enclosed. In peripheral nerves, axons more than 1-2 μm in diameter are ensheathed by neurolemmal cells (Schwan cells) whose cytoplasmic processes form a spiral enclosing a complex lipoprotein containing sphingomyelin, cerebroside, and cholesterol, called myelin (*Hirano and Dembitzer, 1967*). Unmyelinated axons are also surrounded by neurilemmal cells. In the CNS, both myelinated and unmyelinated fibers also occur. Here, myelin is formed by oligodendrocytes. In myelinated fibers, the investing myelin is interrupted at regular intervals by short gaps, the nodes of Ranvier. The speed of conduction in myelinated fibers is much faster than in unmyelinated axons, and is indeed faster the greater the diameter of the myelin sheath. This may be related to the insulating quality of the myelin which decreases membrane capacitance and reduces the number of charges held across the membrane allowing rapid conduction by the fact that conduction "jumps" from one node of Ranvier to the next, a