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CHAPTER 13

The Major Vascular Syndromes of the Brain Stem are Reviewed in the following Table 13-2 modified from Adams, Victor & Ropper 1997

PARAMEDIAN PENETRATING, BRANCH SYNDROMES

	EPONYM	SITE& ARTERY	CRANIAL NERVE	TRACTS & OTHER NUCLEI	SIGNS/ SYMPTOMS
	1. Weber's	Upper midbrain Posterior cerebral artery	III	Corticospinal tract	Ipsilateral CNIII Contralateral (crossed) Hemiplegia
	2. Benedikt's	Upper midbrain Posterior cerebral artery	III	Red nucleus (superior cerebellar peduncle after decussation)	Ipsilateral CNIII and contralateral, cerebellar ataxia & tremor
	3. Millard- Gubler and Raymond Foville	Lower pons basilar artery	VII & VI	Corticospinal tract	Ipsilateral peripheral facial paralysis and abducens paralysis (+ gaze paralysis) and Contralateral (crossed) hemiplegia

4. H.Jackson	Upper medulla vertebral artery	XII	Corticospinal tract + medial lemniscus	Ipsilateral lower motor paralysis of tongue plus Contralateral (crossed) hemiplegia + crossed hemianesthesia
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* These are predominantly vascular - although occasionally other etiologic factors may be operational

B. CIRCUMFERENTIAL BRANCH SYNDROMES

EPONYM	SITE	CRANIAL NERVE	TRACTS & NUCLEI	SIGNS/ SYMPTOMS
1. Lateral superior pontine syndrome Superior cerebellar artery syndrome (from basilar)	Upper pontine tegmentum	Vestibular nuclei	Superior cerebellar peduncle Spinothalamic Medial lemniscus Descending sympathetic Pathway	Dizziness, vomiting, Ipsilateral limb ataxia Contralateral decreased pain and temperature Contralateral decreased position & vibration Ipsilateral Horner's
2. Lateral mid pontine syndrome Short circumferential artery (from basilar)	Mid pontine tegmentum	Trigeminal nerve and main sensory & motor nucleus	Middle cerebellar peduncle	Impaired sensation over face all modalities. Ipsilateral weakness mandibular Ataxia of limbs ipsilateral

3. Lateral lower pontine syndrome Anterior inferior cerebellar artery syndrome (from basilar)	Lower pontine tegmentum	VII VIII auditory VIII vestibular V descending spinal	Spinothalamic Descending sympathetic pathway; middle cerebellum peduncle + cerebellum + lateral gaze center	Vertigo, nystagmus, acute ipsilateral, deafness ipsilateral peripheral facial weakness. Ipsilateral impaired pain & temperature over face Ipsilateral Horner's Contralateral impairment of pain & temperature over limbs & body; Ipsilateral ataxia arm & leg, + gaze paralysis
4. Dorsolateral medullary syndrome (Wallenberg) posteroinferior cerebellar artery OR vertebral	Lateral upper medulla tegmentum	IX, X Nerve ambiguus V descending tract & nucleus, VIII vestibular nucleus	Spinothalamic, Inferior cerebellar peduncle. Olivocerebellar fibers, spinocerebellar tract Descending sympathetic Pathway	Ipsilateral vocal cord paralysis Ipsilateral impairment of gag Ipsilateral weakness of uvula Ipsilateral loss of pain & temperature over face Vertigo & nystagmus Ipsilateral ataxia of arm & leg Ipsilateral Horner's Syndrome Contralateral impairment of pain With temperature
5. Parinaud's* Syndrome Aqueduct of Sylvius	Dorsal mid-brain and pretectal		Conjugate vertical gaze centers Interstitial nucleus at upper end of MLF	Impairment of conjugate up gaze Impairment of pupillary response to light

syndrome			(pretectal)	Lid retraction
Pretectal			Pretectal nucleus	
syndrome				

*Note - usually due to pinealoma ,hydrocephalus or hemorrhage into pulvinar

CHAPTER 18 MOTOR SYSTEM

TABLE 18-3 Pattern Of Recovery In The Monkey After Complete Area 4 Ablation

TIME AFTER ABLATION	<i>MOTOR FUNCTION</i>
Immediate	Crossed flaccid hemiplegia with absent or depressed DTR's
Within hours	Begins to use proximal muscles of lower extremity
2-3 days	If frightened, affected arm used in climbing. DTR's ,active
7-10 days	Spasticity in flexors of upper and extensors of lower limb
17-24 days	Synergistic flexion in upper limb as part of traction grasp. Typical hemiplegic posture:in upper flexion; in lower extension with external rotation and positive support reaction
After several additional weeks	Wrist and fingers to move independent of proximal joint.
After several additional days	Gross movements of limb to bring food to mouth facilitated by passive and then active use of tonic neck reflexes
After several additional weeks	Whole hand grasp reflex triggered by moving tactile stimulus
In a complete lesion	No return of the complete instinctive grasp reflex ,no orienting response. Eventually thumb may be crudely opposed.

CHAPTER 22 LIMBIC SYSTEM

Temporal Lobe: Stimulation. Seizures involving the temporal lobe are frequent and produce a variety of symptoms:

- autonomic phenomena –
- fear
- simple auditory sensations , and simple auditory and visual distortions
- vestibular sensations (dizziness)
- alterations in perception
- arrest of speech
- hallucinations in the auditory, visual or olfactory spheres
- repetitive movements of a complex type (automatisms)
- complex emotional behavior
- confusion with defects in memory recording.

Correlations of symptoms in simple and complex partial epilepsy with temporal

structures: The correlations to be presented here represent the preferential effects of limited stimulation. Seizure discharges however spread rapidly within a system that has been viewed as a widely distributed neuronal matrix. It is also important to take into consideration that the stimulation is performed in patients who are already subject to simple and complex partial seizures of temporal lobe origin. The brain being stimulated has already been the subject of various pathological processes. When limited symptoms occur with full awareness and without amnesia, confusion or automatisms, the seizure is termed simple partial. When consciousness is altered in the sense that confusion, amnesia and automatisms occur, the seizure is termed complex partial. Obviously, a seizure of temporal lobe origin may begin as a simple partial seizure and then evolve into a complex partial seizure. Secondary generalization into a generalized tonic/clonic seizure may occur in both instances.

1. **Autonomic phenomena** result most commonly from stimulation of the amygdala. As discussed above, autonomic phenomena may also occur on stimulation of cingulate or orbital frontal areas.

2. **Fear**, the most common emotion, occurring during a temporal lobe seizure is most readily reproduced by stimulation of the amygdala. Less often fear is produced by stimulation of the hippocampus. Less often other emotions such as anger may occur on stimulation of the amygdala in the human patient.

3. Auditory and visual illusions, the distortion or alteration in the quality of perception in these modalities is most readily produced by stimulation in the higher order auditory and visual association cortex. Note that the tertiary visual association cortex (V 5) is actually located in the temporal lobe. Crude auditory sensation, such as tinnitus (a tone, buzzing, or knocking in the ear), is best produced by stimulation of the primary auditory projection area, Heschl's (anterior) transverse gyrus (**Fig. 22-13**). At times, an auditory sensation is produced by stimulating the adjacent superior temporal gyrus, but this is considered to represent an alteration in the interpretation of sound rather than an actual auditory sensation. In Penfield's studies, auditory illusions (sounds seem louder, fainter, more distant, or nearer) occurred on stimulation of the superior temporal gyrus in either hemisphere. In contrast, visual illusions (objects seem nearer, farther, larger, or smaller) occurred predominantly but not exclusively on stimulation in the nondominant temporal lobe. (**Fig. 22-15**).

4. Vestibular sensations (vertigo, or dizziness) can sometimes be produced by stimulation of the superior temporal gyrus adjacent and posterior to the auditory cortex (**Fig. 22-14**). The studies of Friberg and coworkers (1985) indicate a focal increase in cerebral blood flow in this region with contralateral vestibular caloric stimulation.

5. Arrest of speech is produced by stimulation of area 22 of the superior and adjacent middle temporal gyri of the dominant hemisphere (Wernicke's receptive aphasia area). In addition, arrest of speech also occurs on stimulation of the posterior temporal region of the dominant region, which extends into the angular and supramarginal inferior parietal areas. Arrest of speech is not specific to these areas, since it also occurs on stimulation of Broca's area (the inferior frontal gyrus) and of the supplementary motor areas of the dominant hemisphere (**Fig. 24-2**).

6. Experiential Phenomena/Dreamy States: More complex visual and auditory illusions, déjà vu, déjà vécu, jamais vu and other illusions of recognition, visual and auditory hallucinations :

The localization of these several phenomena has been the subject of considerable controversy.

Complex illusions consist of an alteration in perception the sensation that time or one's own thinking is slowing down or speeding up or that a visual scene or voices have become distant. Also in this category are illusions of recognition. **Jamais vu** is the sensation that the perception or scene is dream like. **Déjà vu** is the sensation of reminiscence, that perceptions have a familiarity. **Déjà vécu** is the sensation of a strangeness associated with the perception.

Visual and auditory hallucinations represent in this context the sensation, that a scene from memory has been reproduced.

It should be evident that all of these phenomena are interrelated and therefore will be discussed together.

Jackson & Beevor (1889) Jackson & Coleman in 1898 observed that the dreamy state characterized by vivid memory like hallucinations and /or the sensation of having previously lived through the same experience (*déjà vu*) was associated with pathology involving the mesial temporal structures.

However Penfield and Perot(1963) reproduced the phenomena by stimulation of the neocortex of the lateral temporal lobe,-particularly the superior temporal gyrus. In general deeper mesial temporal structures were not stimulated .**Auditory hallucinations** (hearing a familiar voice or music) occurred predominantly in relation to stimulation of the superior temporal gyrus of either hemisphere. **Visual hallucinations** (seeing a familiar scene or people, such as a parent) occurred predominantly but not exclusively when stimulating the superior temporal gyrus on the lateral surface of the nondominant temporal lobe. There was some tendency for the visual phenomena to be produced from the posterior temporal areas extending into the bordering area 19 of the occipital cortex. (**Fig. 22-16**). For all of these phenomena, the patient often uses the descriptive term “dream like”. In the studies of Penfield and Perot (1963) the illusions of recognition occurred predominantly when the nondominant temporal lobe was stimulated. Usually, both the auditory and visual hallucinations were identified by the patient as past experiences. As Gloor and colleagues (1982) demonstrated, often the patient may be describing an inner or past experience within an emotional context that the patient relates in visual terms.

Halgren et al (1978) reproduced these same phenomena by stimulation of mesial temporal structures (hippocampus and amygdala)-however a wide spread evoked response or afterdischarge was required. The content of the mental phenomena evoked was variable and related to the personality and past experience of the individual patient. The subsequent studies of Gloor et al (1982)[38]suggested that mesial temporal discharge was critical for the occurrence of the mental phenomena-with stimulation of the amygdala being most effective.. Less often stimulation of hippocampus or parahippocampal gyrus which resulted in an afterdischarge involving limbic and neocortical structures also produced the phenomena. The trajectories of the depth electrodes employed in these studies ,however did not sample adequately the neocortex of the superior temporal gyrus ,that area found to be critical in the earlier studies of Penfield and Perot.

The studies of Bancaud et al (1994) resolved many of the issues of the stimulation studies. In 85%of dreamy states evoked by mesial temporal stimulation,the discharges spread to the temporal neocortex. In 53% of dreamy states evoked by stimulation of lateral neocortex, the discharge spread to mesial temporal structures. However in every spontaneous seizure in which a

dreamy state was observed ,the amygdala, anterior hippocampus and the temporal neocortex were all involved. This suggests a network with the anterior hippocampus ,the amygdala and the superior temporal gyrus having privileged access to this system. (see also Burgerman et al –1995 and Walczak – 1995)

More definitive are the reports of Blume et al (1993) and Mullan & Penfield (1959) in which ictal experiential illusions or hallucinations were abolished by ablations limited to the lateral temporal neocortex but ictal automatisms, autonomic phenomena and ictal fear persisted until the previously spared amygdala and hippocampus were ablated.

In interpreting all of this data, from the standpoint of the localization of memory traces a certain degree of caution is essential. One should not jump to the conclusion that specific memory traces are localized to the areas stimulated during surgery. Certain points should be kept in mind:

1. The memory remains after ablation of the area that has been stimulated.
2. Moreover, these experiential responses are not obtained on stimulation of the "normal" temporal lobe during surgery directed at disease of the temporal lobe. However, in the studies of Sem-Jacobson and Torkildsen (1960) and Ishihashi (1964), experiential responses were obtained on stimulation of the temporal lobe in patients with schizophrenia (see below).
3. Although some of the patients with temporal-lobe seizures have disease involving the neocortex on the lateral surface, most have pathology involving the mesial temporal areas, that is, the amygdala, hippocampus, and parahippocampal gyri.

As we will see in the chapter on memory the hippocampal areas are involved in the recording of new memories.

7.Olfactory hallucinations . The olfactory hallucination is usually termed an unfamiliar , unpleasant odor. Rarely, during surgery, these olfactory hallucinations are produced by direct stimulation in or near the cortex of the uncus. (Note that the lateral olfactory stria projects to the uncus.) In the early reports of Jackson & Beevor, and of Penfield ,olfactory hallucinations were related to pathology involving the uncus (uncinate seizures). The more recent studies of Bancaud (1987)[42] suggest that this symptom also follows stimulation of the posterior orbital frontal cortex, as would be predicted from **Figure 28**. Gloor[33] reviews studies indicating elicitation of this symptom at times on stimulation of the amygdala.

8. Pure amnesic seizure with anterograde memory deficit but without confusion or unresponsiveness has been related by Gloor (1997) to selective bilateral functional inactivation of the mesial temporal structures but without involvement of the neocortical structures. Gloor suggests that when unresponsiveness and confusion occur in the temporal lobe seizure, spread to neocortical areas has occurred. A stronger alternative explanation, when seizures arise in the lateral temporal neocortex is that spread to the mesial temporal structures has occurred. Confusion with amnesia reflects then the interference effect of hippocampal stimulation on the capacity for recording new memories. During this time, relatively complex but familiar activities, such as the driving of an automobile, may be continued. The problem of memory recording will be discussed further in Chapter 30. For perhaps the best illustration of the phenomenon, refer to the case reports of Hughlings Jackson concerning "dreamy states" (in Taylor, 1931). For example, a physician with temporal-lobe seizures was able to perform a relatively complete physical examination and to begin appropriate treatment during such an episode but had no memory of anything he did.

9. Automatisms-simple or complex stereotyped repetitive motor behavior occurs during a time when the patient is otherwise unresponsive to stimuli and confused. In general automatisms represent the primary or secondary bilateral involvement of the amygdaloid/hippocampal areas by seizure discharge. The automatisms are invariably accompanied by some degree of confusion; the patient is always amnesic for the behavior and other events. The testimony of witnesses must be obtained. The most common form are the repetitive oral movements involving mouth lips and throat such as chewing, licking swallowing. It is uncertain whether these oral automatisms represent the spread of discharge from amygdala to brain stem motor nuclei or the effects of release of the brain stem structures from higher control. Other automatisms consist of other repetitive complex movements, such as constantly rubbing an ear, or smoothing of bedding or clothing. Ictal automatisms otherwise represent the effects by the discharge of a wide spread interference in function of the mesial temporal and the temporal and frontal neocortical association areas. Similar automatisms may also occur in the absence seizure as a result of the interference effects of a wide spread discharge. Automatisms may also occur during the post ictal stage of a seizure, when neocortical and mesial temporal functions are also depressed in a widespread manner. Although automatisms are usually defined as occurring without reference to prevailing circumstances, it is often evident that environmental stimuli may trigger some of the more complex automatisms. Thus automatisms are often modified by or appropriate to a specific stimulus that has been introduced into the environment. Thus, patients may continue

actions that were being performed at the onset of the seizure but in an imperfect, repetitive manner. If an object touches the back of the neck or ear, patients may brush this away repetitively. If attempts are made to restrain, patients may resist, assault those attempting to restrain them, or attempt to flee. Sometimes automatisms have a strong emotional flavor, such as those accompanied by laughter, crying, or anger. Automatisms or perseveration of speech may occur particularly in response to questions .

Prefrontal cortex: stimulation. Frontal lobe epilepsy: The threshold of the prefrontal areas is relatively high. Thus, tumors originating in this area may produce seizures only as they expand to compromise adjacent low threshold areas. In seizures beginning in this area, loss of consciousness may be the initial symptom with subsequent progression to adverse head and eye deviation or to focal motor seizure and then to a generalized convulsive seizure. Spread into limbic areas may occur related to the significant interconnections with resultant complex partial seizures (see below). At times, in the experimental animal (the monkey), it has been possible to produce a prolonged, bilateral, electrical seizure discharge in the prefrontal areas (which remain limited to these areas) (Marcus et al., 1968). Such animals do not show any gross impairment or alteration of behavior. They are able to reach for and grasp objects introduced into the visual field. They are able to respond appropriately to a beaker of water. More detailed testing of such animals as indicated by Weiskrantz et al., (1962) however, does reveal deficits in such tests as delayed response and delayed alternation. These deficits are similar to those noted following bilateral ablative lesions in the prefrontal areas.

Stimulation of the orbital frontal area (area 13) and the adjacent anterior cingulate gyrus (area 24) in the monkey and the human has produced various autonomic effects (both sympathetic and parasympathetic). In addition, arrest of respiration and alteration in blood pressure have occurred. In the understanding of these autonomic effects and of the effects on emotional behavior, the connections of these prefrontal and anterior cingulate orbital areas to the hypothalamic, anterior thalamic, dorsomedial thalamic nuclei and mesolimbic areas of the temporal lobe assume considerable importance.

It is clear that increasing attention is being centered on the frontal lobe.

Complex partial seizures (partial seizures with impairment of consciousness) were formerly considered to be entirely temporal lobe in origin. It is now recognized that 20-30% of such seizures are extratemporal in origin - predominantly frontal lobe (Schwartz et al 1989, Williamson et al 1988). Compared to complex partial seizures of temporal lobe origin, complex partial seizures of frontal lobe origin are usually briefer, occur more frequently and tend to have a much shorter post ictal period of confusion. Recent studies of St.Hilaire et al; Wada and Weiser (see Chauvel et al 1992) suggest that these

automatisms of orbital or medial parasagittal origin are often complex involving both arms or both legs or trunk or pelvis, at times in organized kicking, struggling, running or screaming. In contrast, automatisms of temporal lobe origin more often were oral or alimentary (licking, chewing, swallowing, etc). Such frontal lobe seizures must also be differentiated from seizures of psychogenic origin and from the absence seizures of generalized epilepsy (see Chapter 29). Thus, orbital frontal seizures present many features previously associated with pseudo or psychogenic seizures. Frontal polar seizures or dorsolateral convexity may present as forced thinking or apparent petit absence seizures. Quesney et al, 1990 make a distinction between discharges originating in the dorsolateral convexity which are more likely to present with automatisms and affective components compared to parasagittal discharges which are more likely to present with motor or somatosensory components.

The present International Classification (see Commission - 1989) provides a summary of the localization types of frontal epilepsy. The term "frontal lobe epilepsy" includes more than the prefrontal areas : (a) supplementary motor: tonic, postural and speech arrest; (b) cingulate: complex partial; (c) anterior frontal polar: forced thinking or initial loss of consciousness plus adverse components; (d) orbital frontal: complex partial plus olfactory hallucinations plus illusions; (e) dorsolateral: tonic plus or minus adversion; (f) opercular: (mastication, salivation, swallowing) plus speech arrest plus or minus epigastric and gustatory symptoms (see under parietal) plus or minus secondary spread to other simple partial. However, other authors for example Quesney et al, 1990, Geier et al, 1977 have reached different correlations

Geier et al (1977) analyzed several hundred seizures in 22 patients with frequent frontal lobe seizures. At some point in one or more seizure each patient had an interruption of contact, usually brief, related to discharge in speech area or frontal pole or spread of discharge. Bilateral frontal discharge (probably reflecting callosal spread of discharge) always resulted in a complete break off of contact. Memory disturbances (often accompanying the contact break) also occurred at some point in 100% of patients - (possibly signifying spread to the hippocampal areas concerned with memory recording). In 86% of patients contralateral or ipsilateral deviation of head and/or eyes occurred correlated with discharge on the mesial surface anterior to the supplementary motor cortex or lateral surface (midportion of the superior and mid frontal gyri). The more anterior the discharge, the more isolated and ipsilateral were the movements.

The more posterior the discharges, the more likely contralateral.

Disturbances of speech occurred in 86% of patients usually related to discharge of dominant hemisphere inferior, frontal or adjacent midfrontal gyri. Brief falls - 5-10 seconds - occurred in 82% of patients

related to loss of postural tone or sudden jerks of head or body. Partial clonic movements of face (intermediate frontal gyrus - lateral surface), hemibody or both arms (mesial surface) occurred in 77% of patients as an initial phenomena; always accompanied by a loss of contact and usually indicating extensive spread through the frontal area. Disorganization of motor sequences occurred in 36% of patients usually correlated with a mesial discharge. Motor automatisms (see below under temporal lobe seizures) usually involving the arms occurred in 73% of patients; complex motor automatisms occurred in 32% of patients. Autonomic disturbances occurred in 59% of patients. Geier et al indicates that frontal lobe seizures are particularly motor and not psychic, i.e., emotional or affective signs are absent or minimal compared to complex partial seizures of temporal lobe origin. Quesney et al, 1990, made a distinction between discharge originating dorsolateral convexity (more likely to present with automatism and affective components) and parasagittal (more likely to present motor or somatosensory components).

The study of Tharp (1972) suggested that automatisms were more likely to occur with discharges originating in the orbital areas.

Whether seizure discharges in the prefrontal area may have long term effects remains unclear.

In a human patient with seizures, whom we have observed with electroencephalographic discharge predominantly in both prefrontal areas, a transient alteration in personality with a compulsiveness of behavior and a release of inhibitions persisted for a period of several weeks into the postictal period. A similar interference effect of seizure discharge in this area has been described by Penfield and Jasper (1954).

NEUROLOGICAL ASPECTS OF PSYCHIATRIC DISORDERS

It is not possible to discuss the full range of psychiatric disorders. What follows is an outline with emphasis on major neurological and neuropathological aspects.(An excellent review of psychiatric disorders is provided by Adams et al 1997. A more detailed neurobiologic perspective is provided by Kandel (2000a and 2000b).DSM III and DSM IV of the American Psychiatric Association provide a detailed monographic approach to definitions and classification) .

Psychiatric disorders are essentially divided into those disorders characterized by psychotic disturbances of mental function and emotion (or to use the legal term - insanity) and the non-psychotic disturbances of mental function and emotion: the anxiety disorders/neurosis and the personality disorders. A psychotic disorder is defined

(DSMIII) by "a gross impairment in reality testing. The individual incorrectly evaluates the accuracy of his or her perceptions and thought and makes incorrect inferences about external reality." "Direct evidence of psychotic behavior would be the presence of either delusions or hallucinations without insight into their pathological nature." "Behavior is grossly disoriented."

Psychotic Disorders: In terms of the traditional classification of psychotic disorders the following major categories may be listed:

1)Those disorders secondary to a general medical condition ,or diffuse neurological disorder or focal neurological disorder. These were formally called "organic". A better term would be secondary psychosis .The disorders would include a. The acute confusional /delirious states associated with fever, or various metabolic disorders or the psychosis which may occur in severe disorders of the thyroid . b. Focal or multifocal disorders of cortical function particularly involving the frontal and temporal areas such as tumors or Pick's disease c. more diffuse neurological disorders – of an acute nature as in encephalitis or of a more chronic nature as in general paresis of neurosyphilis or Huntington's, or Alzheimer's diseases.

2)Those disorders in which no underlying neurological or medical condition could be established. The term formerly employed was "functional psychosis" .Using the terminology usually employed in medicine and neurology, better labels would be primary or idiopathic or essential. As will be discussed below, it is now evident that modern research suggests that there is an underlying genetic, structural or biochemical neurologic basis .

Essentially two disorders are considered within this category :the schizophrenias and the major affective or mood disorders.

The modern classification of the "functional disorders" should be attributed to Kraepelin, who made the clear-cut separation of "dementia praecox (now called schizophrenia¹) and the affective disorders. He recognized that "dementia praecox" (schizophrenia) began in adolescence and early adult life, progressed as a chronic disorder and almost always ended with a marked deterioration of personality. It was recognized that exacerbations and remissions occurred but that the individual never returned to the pre-morbid level of personality and function. In contrast affective disorders were not characterized by this deterioration. One could hypothesize that a structural basis probably would be found in schizophrenia but not in affective disorders.

SCHIZOPHRENIA:

The diagnosis of schizophrenia is based on the following criteria: (1) there are psychotic features during the active phase .(2) There is a deterioration from previous level of function (3) there are characteristic symptoms and signs

¹ The term schizophrenia was proposed by Bleuler to describe not the splitting of personality (into multiple personalities) but rather the divorce of one's self from reality (Autism) and the dissociation of thought processes, emotion and perception from the reality of the external world.

that involve multiple psychological processes that have been present for at least 1 month but with some symptoms of a premorbid or residual nature present for at least 6 months. These are as follows:

- a. content of thought: delusions (of persecution and reference) and hallucinations (predominantly auditory or somatic less often olfactory or visual)
- b. form of thought: loosening of associations
- c. affect: blunting, flattening, and inappropriate
- d. sense of self: loss of ego boundaries (depersonalization and derealization)
- e. volition: disturbance in self-initiated goal directed activity. This impacts work and academic performance
- f. relation to external world: is restricted .This impacts interpersonal relations.
- g. psychomotor behavior: reduced: (catatonia - waxy flexibility) or excessive stereotyped movements.

Overall symptoms are often described as positive (thought disorders, delusions and hallucinations)or negative (poverty of speech, decreased movements, poverty of affect and withdrawal). In a sense ,many of the positive symptoms are suggestive of temporal lobe dysfunction as in seizures of temporal lobe origin .Heath (1982) did find electrical seizure discharges on depth electrode recordings from the septal region ,hippocampus and amygdala. Many of the negative symptoms suggest the syndromes produced by prefrontal pathology (Mesulum –1990).

Various subtypes are defined by the predominant symptomatology at the time of evaluation : (1)**Paranoid** (the least severe) with prominence of delusions and auditory hallucinations but with relative preservation of cognitive function and affect .(2)**Disorganized** (the most severe) with disorganized speech and behavior and flat or inappropriate affect.(3) **Catatonic**(also in the most severe category) .This type was once seen frequently in chronic hospitals but is now rare.The characteristic features are motor immobility with retention of postures which have been set by the examiner (cataplexy) or stupor or excessive motor activity which is unrelated to external stimuli. Extreme negativism ,mitism and gegenhalten similar to frontal lobe disease may be present. Posturing ,mannerisms and grimacing may be present suggesting dystonia, or dyskinesias of basal ganglia disease.(4) **Undifferentiated** which does not clearly fall into the more specific subtypes noted above. (5) **Residual** in which positive symptoms are attenuated but negative symptoms are still present

Etiology of schizophrenia:

Neuropathology and Neuroimaging Studies: Many of these studies have been reviewed by Roberts et al (1997) .The study of the underlying cellular neuropathology of schizophrenia involved those early leaders in the study of the cytoarchitecture of the cerebral cortex such as Alzheimer, Oscar Vogt, Spielmeyer and Schotz.

Essentially, early findings as regards frontal cortex, could not be confirmed when quantitative studies with age matched controls were utilized. More recent careful morphometric studies have demonstrated reductions in volume of medial temporal limbic structures and abnormalities in the pattern of the temporal lobe gyri. See Shenton, et al, 1992.

The development of modern neuroimaging techniques has allowed a fresh approach to the problem, in vivo changes can be clearly delineated. CT scans demonstrated enlarged ventricles and widened sulci. More specific findings have been noted in MRI studies. Suddath et al, 1990, studied monozygotic twins who were discordant for schizophrenia - the hippocampus was smaller bilaterally with secondary enlargement of the ventricles in the twin affected by the schizophrenia, as opposed to the normal twin. Sets of twins without schizophrenia did not manifest such differences. The very careful quantitative MRI studies of Shenton, et al, 1992; demonstrated reductions of volume of gray matter in the left anterior hippocampus - amygdala - by 19%, the left parahippocampal gyrus by 13%, and the left superior temporal gyrus by 15%. The reduction in volume of the left posterior superior temporal gyrus, correlated with the degree of thought disorder. In other studies, these MRI findings have been noted early in the disease, prior to the introduction of any neuroleptic agents and prior to any process of deterioration. Other MRI studies reviewed by Foong et al (2001) have reported regional reductions in grey matter of the frontal or temporal lobes or hippocampus or amygdala, with the frontal lobe findings particularly associated with a predominance of negative symptoms. The specialized quantitative MRI studies by Foong et al (2001) indicated diffuse bilateral cortical abnormalities most prominent in the frontal and temporal areas. In patients with severe negative symptoms, there was as well significant reduction in the left parietal and bilateral temporal - occipital cortex and the genu of the corpus callosum. Studies of regional cerebral blood flow (RCBF) reviewed by Friston, et al, 1992 - suggested correlated decreases in RCBF in prefrontal and left parietal association areas when psychomotor poverty was present. Reality distortion was associated with increased RCBF in the left parahippocampal regions.

Dopamine hypothesis :The significant improvement in the symptoms of schizophrenia following the administration of dopamine receptor antagonists has led to the dopamine hypothesis regarding the underlying etiology of schizophrenia which suggests abnormal function in the dopaminergic meso frontal and mesolimbic circuits (refer to Kandel –2000)

Epidemiology - The overall prevalence of schizophrenia in the population is at least 0.5 cases per 100. Some estimates suggest overall cases, at home, in hospitals, in remission, or exacerbation may be close to 1.0 per 100. In terms of the population in mental hospitals prior to the introduction of the neuroleptics, patients with the diagnosis of schizophrenia, constituted 20-30% of admission and occupied 50% of the beds.

Genetics - The studies of Kallman in the 1940's indicated incidence in parents or siblings or fraternal twins to each be 11%. Monozygotic twins of an affected twin demonstrated a 68% incidence of schizophrenia. If both parents were affected, the incidence in the offspring was 50%. Other studies have reported statistics for identical twin pairs which were less than those found by Kallman, but still greater (e.g., 25-50%) than the 11% of siblings and fraternal twins affected.

Children of schizophrenic parents, removed from the home at an early age, into homes of normal adoptive parents, also developed schizophrenia at the same rate. Similar studies in monozygotic twins separated at any early age also confirmed these genetic factors. These studies suggest the importance of nature (genetics) over nurture. (cultural and learned factors). The precise type of inheritance remains uncertain. An autosomal dominant pattern with variable penetrance has been suggested.

AFFECTIVE OR MOOD DISORDERS

This large group of patients includes not only those patients with a psychosis but the much larger category of non psychotic mood disorders particularly depression. Depression is common occurring frequently not only among psychiatric admissions but also among general medical admissions.

Depression is the most common reason for psychiatric liaison consultation for patients on a medical service. The major categories of depressive illness include (1) grief reaction (2) reactive or secondary depression in medical and neurological disorders (3) endogenous or primary depression +/- anxiety and agitation, and bipolar manic depressive disorder (4) depression as part of a neurosis or or personality disorder.

Among the endogenous affective disorders, the following subcategories are recognized (1) Unipolar disorders, usually referring to a depression of mood and less often to a manic (severe) or hypomanic (less severe) state. (2) bipolar disorder in which both manic and depressive episodes occur.

Neurological basis (Brumback-1993) : In patients with cerebral infarcts, depression is most likely in those with infarcts of the left hemisphere involving the lateral frontal cortex or basal ganglia. Other studies, however, have implicated the right frontal area in patients with traumatic penetrating injuries particularly as regards the affective aspects of language (prosody) and gesture. Psychotic depression with hallucinations and delusions have been reported in patients with right temporal parietal infarcts.

As regards patients with endogenous depression, no clear cut neuropathological findings have been reported. However, Tebartz van Elst et al (1999, 2000) have reported an increased volume of the amygdala on quantitative MRI studies in patients with depression or bipolar disorder. Moreover PET

scan and functional MRI studies by Drevets et al (1997) have demonstrated an area of decreased activity in the medial inferior prefrontal cortex (and anterior cingulate gyrus) below the genu of the corpus callosum during depression. During the manic phase of manic depressive disorder activity in this area is increased.

Epidemiology and genetic basis of affective disorders :*Manic - depressive disease may be seen at any age. Depression is common in the elderly and often accompanies loss of spouse, ,many of the degenerative diseases of the nervous system and the various chronic medical disorders. The overall lifetime risk for a major depression is 8-12 % in males and 16-24 % in females. Patients with affective disorder have a high frequency of relatives with the same disorder .Among first degree relatives, 14-25% will be affected.. Adoptees have the same risk as the original biologic family as opposed to the adoptive family.*

Bipolar disorder constitutes 10 % of all affective disorders and has a characteristic onset in younger/ middle aged adults with some cases already evident in adolescence. The overall frequency of bipolar disorder in the general population is 1-2 %. In contrast ,first degree relatives have a 15 % risk for bipolar disorder. Among twins 72 % of monozygotic twins are concordant for bipolar disease compared to 14 % of same sex dizygotic twins. In contrast , in monozygotic twins with unipolar endogenous disorder the concordance rate is 40% whereas the rate for dizygotic same sex twins is 11%.

Biochemical correlates :In patients with endogenous depression, metabolites of norepinephrine and serotonin are decreased in the CSF. In patients with endogenous mania ,metabolites of norepinephrine .are increased in the CSF. The tricyclic antidepressants (general nonspecific reuptake inhibitors of biogenic amines)and the monoamine oxidase inhibitors which are effective in treating depression increase norepinephrine and serotonin at selective receptor sites in the hypothalamus and limbic system. The tricyclic antidepressants also have anticholinergic side effects. The selective serotonin reuptake inhibitors (SSRI's) which have greater action on serotonin receptors than on norepinephrine sites ,overall are less effective than the tricyclic antidepressants in severe cases but also have less anticholinergic side effects .

In patients with depression, a hypothalamic dysfunction also occurs with increased secretion of ACTH and a secondary increase in secretion of cortisol from the adrenal cortex.

Patients with manic symptoms are treated with lithium carbonate ,but since time is required to achieve a therapeutic effect, neuroleptics (dopamine antagonists) are employed to decrease agitation .

Electroconvulsive therapy may be used for severe episodes of severe endogenous depression or of mania.

Suicide is a major risk in all types of affective disorders . If suspected to any degree immediate psychiatric consultation must be obtained , and immediate hospitalization arranged.

ANXIETY DISORDERS (NEUROSES)

A variety of syndromes are include under this category of disease (1) generalized anxiety (2) acute panic attacks (or acute anxiety attacks and hyperventilation syndrome),(3) post traumatic stress disorder ,(4)phobic disorders,(5)obsessive compulsive disorder,(6)Hysteria with conversion symptoms and (7) Hypochondriasis.

In general , there are no clear cut structural abnormalities in these disorders ,although obsessive compulsive disorder (OCD) may also be seen in diseases of the basal ganglia .

Panic attacks :The autonomic activation that occurs with acute panic attacks is similar to that which occurs with fear .Attacks can be induced by intravenous administration of or inhalation of carbon dioxide .The adrenergic locus ceruleus and the serotonergic centers have been implicated in anxiety. In addition in patients with panic attacks , blood flow to the right limbic system and parahippocampal gyrus are increased between attacks .Attacks may be decreased with the use of the antidepressants described above or with the use of benzodiazepines (the latter however have possible substance abuse potential). Note that anxiety and hyperventilation may certainly occur in a number of systemic metabolic disorders such as hypoglycemia, hyperthyroidism, pulmonary disease, etc.

Hysteria: Patients with the conversion symptoms of hysteria are usually referred for neurological consultation prior to any psychiatric referral because the patient presents with apparent paralysis, or sensory deficits or blindness, or amnesia (dissociative state) . Related disorders include dissociative reaction, fugue state, multiple personality (dissociative identity disorder) and compensation neurosis. This diagnosis accounts for 1-3% of all general hospital admissions. The term hysteria refers to the ancient concept among the classical Greek physicians that the symptoms represented the effects of a wandering uterus. The term conversion refers to the psychoanalytic concept that ego defense mechanisms in response to unconscious psychological conflicts convert the anxiety generated into physical symptoms. Most patients are female although conversion symptoms may occur in males. It is of importance to recognize that the initial modern studies on hysteria were undertaken by physicians who dealt with neurological disorders such as Charcot, Janet ,Breuer and Freud (see Breuer & Freud –1957). In hysteria, the symptoms are not feigned ,they are not the result of malingering. Vuilleumier et al, (2001) have

recently reported that in patients with unilateral motor +/-sensory hysterical symptoms ,there are significant focal contralateral deficits on SPECT scan during passive vibratory stimulation of both hands. These decreases in regional cerebral blood flow occurred in the contralateral thalamus, caudate and putamen. These focal deficits resolved on recovery from the focal neurological deficits. The authors suggest that limbic inputs from the amygdala and orbital frontal areas as a result of emotional stresses might modulate the activity of specific basal ganglia and thalamo cortical circuits . In addition, actual lesions in these areas may result in akinesia and motor/sensory neglect syndromes . Thalamic lesions may result in the useless limb which the patient fails to move despite an absence of motor lesion. They also hypothesize that the failure to move the limb might derive from the more primitive reaction seen in some animals such as the rabbit etc of instinctive freezing or immobilization in response to perceived life threatening stimuli(the appearance of a dog).

Obsessive/compulsive disorder: obsessions are thoughts which keep recurring despite the patient's desire to get rid of the idea for example the constant preoccupation that one is going to be contaminated by dirt or germs. The compulsions are the motor acts (rituals) that are performed to deal with the obsession, for example a constant hand washing routine. On PET scans, patients with this disorder are found to have increased metabolic activity in the dorsolateral prefrontal, and anterior cingulate cortex and the caudate nuclei (Buchsbaum et al 1997).Treatment with tricyclic antidepressants or SSRI'S produces a significant improvement in symptoms and a return to normal levels of metabolic activity in the caudate.

PERSONALITY DISORDERS

A variety of disorders are included within this category. Unfortunately , the terminology overlaps with some of the anxiety disorders listed above. In order of frequency in a large series (Winokur& Crowe-1976) the more common may be listed as follows : (1)hysterical or histrionic, (2)passive aggressive,(3)antisocial which overlaps with criminal behavior, (4)passive dependent,(5) schizoid – possibly a premorbid or less marked variant of schizophrenia (6) obsessive –compulsive personality – perfectionistic with excessive concern with details ,standards and with a possible predisposition to OCD,(7) inadequate personality ,(8) paranoid personality –possibly premorbid condition predisposition for paranoid schizophrenia.

We have already discussed above the effects of prefrontal lesions in producing alterations in personality ,in some cases resulting in a loss of inhibitions and antisocial behavior .The “ pseudopsychopathic” syndrome may follow damage to the prefrontal areas. Psychopathic is a term formerly employed instead of the more recent terms of antisocial or sociopathic personality disorder. Prefrontal damage early in life

may result in antisocial behavior with problems in the control of anger and aggression. Studies of violent antisocial individuals have indicated smaller prefrontal areas. As discussed above, the orbital prefrontal areas are involved in a circuit that includes the amygdala and the anterior cingulate cortex and violent behavior may reflect dysfunction in other parts of this circuit (Davidson et al –2000).

DEVELOPMENTAL DISORDERS WITH ALTERATION IN SOCIAL BEHAVIOR

Autism and Asperger's syndrome are the two entities included here. We have already defined the term autism in relation to schizophrenia (the divorce of one's self from reality) and have discussed the role of the amygdala in the recognition of the emotional facial expression of others. In children with autism there is a discrepancy between (a) the development of motor skills (which are not entirely normal with findings relevant to gait and coordination) and at times types of retentive memory and (b) the poor development of social /emotional interactions. Eye contact is avoided. Stereotyped motor automatisms may develop. Some patients can achieve a high level of intellectual function (Grandin-1997) although 78% are classified as mentally deficient. In some cases, the child appears to develop normally until 18-24 months of age and then regression occurs. In other cases, abnormalities of behavior are noted earlier in life and no speech develops. The overall incidence is 4.5 –20 per 10,000 with a 4 or 5: 1 male predominance. There is an increased risk of the disease in siblings and identical twins. MRI studies have demonstrated cerebellar hypoplasia, which may affect some aspects of motor learning and cognitive function and attention shifting capacity (refer to cerebellar chapter). The careful neuropathologic studies of Kemper & Bauman (1993) have found alterations in hippocampus, amygdala, entorhinal cortex, septal nuclei, mammillary bodies as well as the cerebellum.

Some authors have considered Asperger's disorder a less severe form of autism. However the location and type of pathology differ from the findings in autism (Aronowitz et al ,1997). Neocortical abnormalities are present with areas of polymicrogyria and other aspects of a neuronal migration disorder. This has suggested etiologic events prior to the end of the fifth prenatal month. Verbal IQ is usually higher than performance IQ. Recognition of emotion in the facial expression of others is usually normal.

CHAPTER 27: NEUROPATHOLOGY NON VASCULAR DISEASE Parts III,IV,V DIFFUSE AND MULTIFOCAL DISORDERS

CHAPTER 27 PARTS III,IV,V

PART III PART B .GENERALIZED INFECTIONS:

This category of diseases is usually considered in more detail in microbiology courses and in the infectious disease sections of internal medicine. We will, however, outline several common syndromes.

In a broad sense such infections may be subdivided into

- a. Those involving primarily the leptomeninges (pia and arachnoid) producing *leptomeningitis*. Generalized infection of the dura (*pachymeningitis*) is uncommon.
- b. Those involving primarily the parenchyma of the brain, producing *encephalitis*.

There are some infections, often viral, that involve both structures producing, a meningoencephalitis.

MENINGITIS (Leptomeningitis)

This is the most common form of infection of the nervous system. The manifestations of meningitis depend on the organism involved, the age of the patient, and the underlying physical status of the patient. Acute, subacute and chronic forms may be considered.

Acute Purulent (Bacterial or Septic) Meningitis: This is the most common form of infection of the central nervous system among patients requiring hospitalization². In each case, a specific bacterial organism may be isolated from the cerebrospinal fluid (CSF) in the subarachnoid space. In addition, the spinal fluid shows evidence of an acute inflammatory reaction. The fluid is cloudy and under increased pressure with large numbers of white blood cells, predominantly polymorphonuclear leukocytes, e.g., 90 to 98 percent of 500 to 40,000 white blood cells per cubic mm. The CSF sugar content is markedly reduced, relative to the blood sugar. (Normally spinal fluid sugar is >50% of the blood sugar). Gram stain of the spinal fluid, latex agglutination tests of CSF and cultures will allow identification of the specific organism.

The specific responsible organism will depend on the age of the patient (Schuchat et al,1997). During the first month of life *group B streptococcus* (a gram positive coccus) is the predominant pathogen. Before the development of conjugate vaccines, *Haemophilus influenza type b* (a small gram negative bacillus occurring in rod or coccoid form) was responsible for meningitis or invasive disease in one of 200 children under the age of 5 years and accounted for 70% of all cases of meningitis in this age

² Many cases of viral meningitis are mild and self limited .They may not necessarily come to medical attention and often do not require hospitalization.

group in the United States. Prior to the licensure of this vaccine, in 1990, two thirds of patients with bacterial meningitis were between one month and 5 years of age. By 1995, the cases in this age group had declined by 87%. As a result the median age for all cases of bacterial meningitis shifted from 15 months to 25 years. In the age range of 1-23 months, *Streptococcus pneumoniae* is responsible for 45% and *Neisseria meningitidis* for 31% of cases.

In the age group, 2-18 years, *Neisseria meningitidis* (meningococcus), an intracellular gram-negative diplococcus, predominates. Sporadic cases occur but the majority of cases probably occur during epidemics when overcrowded conditions exist. Such conditions are likely to exist in school dormitories or in military barracks. In addition in the sub-Saharan “meningitis belt” extending from Ethiopia to Senegal outbreaks of serogroup A meningococcal disease occur every 8-12 years with attack rates of 500-1000 cases per 100,000 population.

The agent is present in the nasopharyngeal secretions, and spread probably occurs through droplet contamination.

In this age group, those cases not due to the meningococcus are invariably due to the *Streptococcus pneumoniae*: (pneumococcus), a lancet-shaped, gram-positive diplococcus.

In the age group 19-59 years, 60% of cases are due to *streptococcus pneumoniae* an agent more commonly responsible for infections in the respiratory tract (lung, middle ear, and paranasal sinuses) and 20% to *n.meningitidis* the latter still affecting those in the young adult range.

Over the age of 60 years *streptococcus pneumoniae* is the most common cause of meningitis. In patients with CSF fistulas, sickle cell anemia, post splenectomy and in the immune suppressed state *S. pneumoniae* predominates.

At all ages, acute meningitis due to trauma (associated with compound skull fractures) or as a neurosurgical complication is often due to gram-negative organisms or the *Staphylococcus*. Dural/arachnoid tears allowing communication of the subarachnoid space with the paranasal sinuses, may also be complicated by meningitis due to the pneumococcus, or less often to the staphylococcus. The method of invasion of the central nervous system in other cases may involve the direct extension of a purulent infection involving the middle ear or paranasal sinuses or bone of the skull (osteomyelitis). Rarely, retrograde infection from these areas may involve the dural venous sinuses in a thrombophlebitis and, then, in a retrograde manner, may spread to involve the leptomeninges. On rare occasions, a congenital dermal sinus tract is present. In such cases, anaerobic bacteria or the staphylococcus may be involved permitting skin bacteria to invade the meninges.³ Meningococcal

³ The relative frequency of bacterial pathogens in adult case of meningitis may vary depending on the type of hospital and era under analysis. At the Massachusetts General Hospital 1962-1970, *S. pneumoniae* accounted for 36% of cases, gram negative bacilli for 11%, and *N meningitidis* for

conjugate vaccines are under development, quadrivalent polysaccharide vaccines are available but do not cover all serological subtypes and have a limited duration of action. Pneumococcal vaccines are also available and are routinely administered to the population over 65 years. *In the large majority of cases of bacterial meningitis, the organism has infected the meninges after entering the blood stream from a primary focus in the respiratory tract or gastrointestinal tract.* The circumstances that allow such blood borne infection to involve the meninges only in particular cases are not certain. Thus, most patients with a bacteremia do not develop a meningitis. Quagliarello and Scheld (1992) and Rosenstein et al (2001) provide reviews of pathogenesis.

The pathological features on post-mortem examination of the brain reflect the cerebrospinal fluid findings. Grossly, the pia-arachnoid is congested and cloudy (Fig. 27-24). Creamy colored, purulent material may be visualized in the subarachnoid space particularly within the sulci and subarachnoid cisterns. Microscopic examination reveals that the subarachnoid space is filled with an exudate of polymorphonuclear leukocytes with infiltration of the pia and arachnoid (Fig. 27-25). Within the exudate, bacteria may be present in an intracellular or extracellular manner. The exudate is also noted within the Virchow Robin spaces - that extension of the subarachnoid space about the blood vessels as they pass into the substance of the brain. The subpial areas of the cortex usually appear otherwise quite normal. Infiltration of the outer adventitial sheath of the blood vessels within the subarachnoid space may be noted. If the inflammatory process continues as when treatment has been delayed, these vessels may be occluded with infarction of the cerebral cortex. Also, with time, the character of the exudate changes: mononuclear cells appear, fibrin is deposited, and eventually (after 3 or 4 weeks) fibroblastic proliferation occurs. This latter process may result in compression of the cranial nerves at the base of the brain and obliteration of the subarachnoid cisterns. A secondary arteritis may also occur resulting in cerebral infarcts.

The clinical picture of acute purulent meningitis depends on the age of the patient. An infant under 6 months of age may be febrile, listless and drowsy and may vomit and fail to take feedings. The anterior fontanelle of an infant will be under increased pressure and bulging. An older infant or a child is likely to have nuchal rigidity (resistance to passive flexion of the neck) in addition to fever,

13 %. For the period 1980-88, *S. pneumoniae* accounted for 21%, gram negative bacilli for 25% and *N. meningitidis* for only 4%. It is also important to distinguish community vs hospital infections, with *S. Pneumoniae* the most common organism in community acquired infection; gram negative bacilli the most common in hospital acquired (Nosocomial) (See Durand et al 1993). Some authors (Rosenstein et al ,2001) consider meningococcal disease of all types to be most common in infants .

convulsions, and coma. A posture of opisthotonos may be present (extreme extension of head, neck, trunk and limbs).

The older child and adult with meningococcal meningitis will usually have a prodromal period characterized by symptoms of an upper respiratory infection, low-grade fever, and various body aches. With septicemia and, then, the subsequent involvement of the meninges, the symptoms of chills, vomiting, severe headache, and neck stiffness occur, often followed by an alteration in consciousness. The signs of central nervous system involvement often appear relatively abruptly. A skin rash is common in the stage of bacteremia. Small or large areas of skin hemorrhage (petechiae and purpura) due to involvement and occlusion of the skin capillaries occur during the process of septicemia and are caused either directly by the organism or indirectly as a result of disseminated aggregation of platelets into small thrombi.

The early recognition of acute purulent meningitis is of importance. If it is untreated, serious intracranial complications develop and death is the usual outcome. Prior to the era of specific antimicrobial therapy, the mortality was close to 90%. With specific therapy, this figure has been markedly reduced so that the actual mortality in meningococcal meningitis is now 3%, although the mortality in patients with overwhelming meningococcemia may still approach 40%. For *S. pneumoniae* the case fatality rate remains high at 21% due to the age of the patients. The case fatality rate for *H. influenzae* is 6 % and for group B streptococcus 7% percent. Eleven to 19% of survivors of meningococcal disease have sequelae at times minor ,at times major: peripheral facial weakness, hearing loss, focal neurological deficit or focal seizures or loss of a limb. There are several other possible complications of meningitis. While these are more likely to occur in delayed or untreated cases, some may occur in those patients receiving adequate treatment. With a marked increase in intracranial pressure (at times, lumbar subarachnoid cerebrospinal fluid pressure at lumbar puncture may be 600 mm. of CSF compared to a normal pressure of 150 mm.) herniation of medial temporal areas through the tentorium may occur with compression of the third cranial nerve and midbrain. With involvement of blood vessel walls, occlusion of cortical arteries and veins may lead to dural sinus occlusion. The occlusion of cortical veins and superior sagittal sinus may lead to hemorrhagic infarction of the parasagittal frontal parietal areas with a resultant weakness of the lower extremities and focal seizures. In addition, a further increase in intracranial pressure may occur.

As we have already indicated, a thick exudate at the base of the brain (somewhat more likely to occur in pneumococcal meningitis) may damage cranial nerves and also obliterate the subarachnoid cisterns. The end result may be a significant degree of hydrocephalus since cerebrospinal fluid will be unable to pass up over the hemispheres to the areas of absorption. In the child, a progressive enlargement of the head occurs.

Another complication in the infant (usually in relation to *H.influenzae* meningitis) may also result in progressive drowsiness and a progressive enlargement of the head: subdural effusions. This complication can be ascertained through the use of the translumination of the skull, and, more specifically, the CT scan. Subdural taps through the lateral corners of the anterior fontanelle, will confirm the presence of fluid collections and allow for removal. Overall, in the recent series of Pomeroy et al (1990), 14% of children had neurological deficits that persisted beyond a year after bacterial meningitis, of these 10% had only sensori-neural hearing deficits and 4% had multiple neurologic deficits. Seven percent had late, non-febrile seizures. (see also Taylor et al 1990 and Smith 1990).

Treatment: The present recommendations (Quagliarello 7Scheld,1997,Rosenstein et al,2001) as to choice of intravenous antibiotics which are to be started based on the Gram's stain of the CSF when the patient is first seen but before csf or blood cultures are available are as follows :

Gram positive cocci: Vancomycin plus a broad spectrum antibiotic

Gram negative cocci: Penicillin G

Gram-positive bacilli: Ampicillin (or penicillin G) plus aminoglycoside

Gram negative bacillus: Broad spectrum cephalosporin plus aminoglycoside

An empirical approach to management of all children older than one month is the use of vancomycin plus cefotaxime or ceftriaxone. For children less than one month, ampicillin plus a broad spectrum cephalosporin plus vancomycin.

Once the organism has been identified on culture, the recommendations are as follows:

S. Pneumoniae: Vancomycin plus a broad-spectrum cephalosporin

H.influenzae: Ceftriaxone

N.meningitidis: Penicillin G

Group B streptococcus: Penicillin G (plus in neonates initially gentamicin for 72 hours)

Less common agents

L. monocytogenes: Ampicillin plus gentamicin

Enterobacteriaceae: Broad spectrum cephalosporin plus aminoglycoside

For epidemics of meningococcal meningitis in developing countries a single intramuscular injection of a suspension of chloramphenicol in oil has proven to be effective.

Patients with meningococcemia may have adrenal collapse requiring glucocorticoids. The value of such steroids in reducing neurological complications in *H.influenzae* has also been demonstrated.

Contacts of patients with bacterial meningitis, particularly meningococcal meningitis should receive prophylactic treatment with rifampin. Contacts or in the midst of an epidemic all potential cases may be immunized with polysaccharide vaccines against the meningococcus (Lepow 1983). The student should consult appropriate references as regards all dosage and duration of treatment with the various agents.

Acute Aseptic Meningitis: In these cases, the clinical signs and symptoms of meningitis are present in the sense that the patient complains of headache and stiffness of the neck. Vomiting and nuchal rigidity are present. However these findings are usually less fulminating than those in acute purulent meningitis, e.g., sudden coma and purpura in the adult is unlikely; consciousness is usually well-preserved. The spinal fluid, moreover, is often clear or only minimally cloudy (often described as opalescent). A relatively small number of white blood cells is present (5 to 2000 per cubic mm. and usually less than 500 per cubic mm.) in comparison to acute purulent meningitis. Moreover, the white blood cells are predominantly mononuclear (lymphocytes and monocytes). The sugar content of the spinal fluid is normal. Moreover, smears, agglutination studies and bacteriological cultures of the spinal fluid fail to reveal a responsible organism. In general, the causative organism is a virus: ECHO, Coxsackie, non-paralytic poliomyelitis, mumps and lymphocytic choriomeningitis.

The student should note, however, that a similar cerebrospinal fluid reaction may also characterize certain diseases where a secondary meningeal reaction occurs: subdural empyema, brain abscess, and venous sinus thrombosis. At times, a similar spinal fluid formula may be noted in a viral encephalitis. The aforementioned viral agents may, of course, at times present a combined syndrome of meningoencephalitis.

Moreover, at times several more significant subacute infections in their early stages may present a predominately mononuclear reaction in the spinal fluid: tuberculous and cryptococcal (fungal) meningitis. Bacterial organisms will be absent on routine smears and cultures of the cerebrospinal fluid. However, both of these infections are characterized by a low spinal fluid sugar, and appropriate stains and cultures (and in the case of cryptococcal infection specific antigen studies) will eventually disclose the organism. These infections, although not common at the present time, in the non-immunosuppressed population, are of importance because a) specific therapy is required, b) with the increase in cases of acquired immune deficiency syndrome; the incidence of these diseases has increased.

Differentiation of the various types of viral meningitis may be made by specialized immunological techniques for the measurement of neutralizing antibodies. Viral meningitis is a self-limited disease. No specific treatment is available (see below, however, under H.simplex). Recovery is in general complete - unless, the meningitis is an epiphenomenon in the midst of an encephalitis.

Subacute and Chronic Forms of Meningitis: Within this group the following may be included: tuberculous meningitis (*Mycobacterium tuberculosis*), fungal meningitis, (usually *Cryptococcus neoformans*), and the meningovascular form of neurosyphilis (*Treponema pallidum*). Chronic meningitis may also occur on a non-infectious basis when a metastatic carcinoma, a sarcoma, or a glioblastoma involves the meninges. Each of these infections is associated with a mononuclear reaction

in the cerebrospinal fluid. The protein content is increased. The sugar content is low in the tuberculous and fungal forms, but usually normal in the meningitis-complicating neurosyphilis. The chloride content is often low in the tuberculous and fungal varieties.

Each of these diseases is characterized from the pathological standpoint by a more chronic type of inflammatory reaction with infiltration of the meninges by mononuclear cells including lymphocytes and plasma cells. In tuberculous meningitis a reaction occurs which is designated as granulomatous and is characterized by aggregates of mononuclear cells, altered elongated mononuclear cells (epithelioid cells), multi-nucleated giant cells, and fibroblasts. Granulomas may also be found in cryptococcal infection and occasionally in the syphilitic variety. In both the tuberculous and syphilitic varieties, inflammatory involvement of blood vessel walls is prominent.

Tuberculous meningitis: In general, tuberculous meningitis occurs in young children or young adults, and is usually indicative of miliary dissemination from a primary focus in the lung (less often the primary focus is gastrointestinal). It is still uncertain whether direct hematogenous spread to the meninges occurs or whether there is a prodromal stage of hematogenous spread resulting in tubercles (chronic granulomatous infection) involving the meninges or the surface of the cortex, with secondary meningeal dissemination then occurring from these areas.

The picture on pathological examination is that of a thick, gray, fibrous, gelatinous, and necrotic exudate at the base of the brain. Areas of caseation (cheese-like necrosis) may be found in addition to small firm yellow-white nodules (tubercles). Microscopic examination reveals a dense exudate composed of lymphocytes, histocytes, fibrin, local areas of necrosis and surrounding epithelioid cells. Infrequent giant cells are noted. The acid-fast tubercle bacillus may be demonstrated with special stains. Involvement of the walls of an artery by this inflammatory reaction is common, producing an arteritis with a resultant occlusion of the vessel and infarction of the areas supplied by the vessel. The pathophysiology involves, however, not only this vascular process but also the local compression and invasion of cranial nerves at the base of the brain. Thus, extraocular palsies may be frequent and persistent. This thick exudate at the base of the brain also serves to obliterate the subarachnoid cisterns; hydrocephalus then is a possible complication in cases which survive.

The diagnosis is made on the basis of the clinical picture of subacute ill health, weight loss, vomiting, headache, confusion, and extraocular palsies, plus chest X-ray findings, plus spinal fluid findings (increased WBC of 50-500/cumm - predominantly lymphocytes, increased protein and decreased sugar) plus or minus a positive tuberculin skin test in a young child or young adult. The organism may be demonstrated in acid-fast (Ziehl-Neelsen) stains of smears of the fibrin clot, which often forms in a test tube of cerebrospinal fluid. The results of the smear may be confirmed by special cultures and guinea pig inoculation. Untreated, the disease, in the past, was usually fatal in 3 to 8 weeks. Modern

treatment utilizes triple therapy :isoniazid, and rifampin and ethambutol or pyrazinamide. Streptomycin may also be added to this regimen. Steroids (dexamethasone or prednisone) may be utilized to reduce the inflammatory response. The mortality rate in young children has now been reduced to 25 percent. If early treatment is undertaken, significant permanent morbidity may often be avoided. If treatment is delayed, the patient may survive but with significant residual deficits of the types previously indicated.

Fungal meningitis: The most common form of fungal meningitis is that caused by *Cryptococcus neoformans*. This is a relatively uncommon disease, in an otherwise intact individual. Most of the cases have occurred in patients with alterations in immunological defenses, e.g. (AIDS) acquired immune deficiency state or patients with leukemia or lymphomas, particularly those treated with immunosuppressive drugs or with high dosages of corticosteroids. Cases have also been reported in patients under treatment for pulmonary tuberculosis or for sarcoid, the latter a chronic granulomatous disease often treated with corticosteroids. Note that 10% of patients with AIDS are estimated to have this CNS complication. The clinical picture is that of a chronic headache, with signs of meningeal irritation and increased intracranial pressure. The process is often present for weeks to months prior to the establishment of a diagnosis. From a gross pathological standpoint, a chronic granulomatous exudate is found at the base of the brain. This often contains nodules and foamy gelatinous cysts which may involve the superficial layers of the cortex and ventricular system as well. The exudate contains mononuclear cells, giant cells and the thick encapsulated organism. With ventricular involvement ,hydrocephalus may result..

The diagnosis is made on the basis of the clinical picture of chronic meningitis occurring in special-risk patients (patients with AIDS or with immunosuppression or with diseases of the reticuloendothelial systems), plus the characteristic cerebrospinal fluid findings, plus or minus the demonstration of the thickly encapsulated organisms on India Ink stains of the spinal fluid, and with the isolation of the organism by culture of the cerebrospinal fluid on Sabouraud's medium or after animal inoculation of the spinal fluid. A more rapid diagnosis may be made by the detection of cryptococcal antigen in CSF.

The untreated disease is often fatal within months; however, it is not unusual to find cases where the disease has been present for several years. A significant improvement will occur following treatment with the high dose amphotericin B alone in combination with flucytosine (Van der Horst et al 1997). These agents must be administered intravenously; various side effects commonly occur, most commonly renal tubular acidosis or leukocytosis. Other fungi may invade the nervous system as opportunistic agents. This includes candidiasis, mucormycosis, aspergillosis, coccidiomycosis.

Meningovascular syphilis: The nervous system may be involved by syphilis (*Treponema pallidum*) in a variety of syndromes grouped under the term neurosyphilis. Invasion of the central nervous system by *Treponema pallidum* may occur within a few weeks or months of the original infection. Rarely, abnormalities may be noted in the cerebrospinal fluid during the primary (local) stage of the infection (the stage of the primary cutaneous or mucus membrane chancre). Abnormalities do occur in the spinal fluid in one-third of the patients during the secondary state (a stage of a generalized rash when generalized dissemination of the disease has occurred. Some patients will present clinical evidence of an acute meningitis at this time, but more often the onset of neurological symptoms is delayed for a number of years until the tertiary stage. These later forms are the eventual result of the chronic meningeal infection.

It should be pointed out that the majority of patients who have had syphilis do not have actual invasion of the central nervous system. Thus, in the era before the use of specific antibiotic therapy (penicillin), Merritt, Adams, and Solomon (1946) found clinical or serological evidence of involvement of the nervous system in only 29 percent of 2263 cases examined after the secondary stage infection. At the present time, adequate treatment with penicillin during the primary or secondary state will prevent the development of significant central nervous system involvement.

In the neurosyphilis series of Merritt, Adams, and Solomon, 31 percent of the cases were asymptomatic, 16 percent were meningovascular (10% vascular and 5% meningeal), 30 percent were tabetic, and 12 percent were parietic.

Tabes dorsalis (which usually has a prolonged latency of 15-20 years) has been considered in Chapter 9, p. . *General paresis* which has an average latency of 10-15 years will be considered and illustrated in the chapter on dementia.

The *asymptomatic cases* represent inadvertent early discovery of instances where tertiary symptomatic involvement of the cardiovascular or central nervous system may occur at a later point in time. The spinal fluid changes - a positive serological test and a minor cellular response - probably indicate subclinical meningeal inflammation. The blood serological tests also are usually positive. These cases are of importance because prompt treatment with penicillin will prevent the development of such late complications.

The *meningovascular form of neurosyphilis* usually appears within the first 2 years of the infection. As noted, however, 10% of the cases of meningitis may occur during the time of the secondary stage of rash. Moreover, the vascular occlusive component of meningovascular syphilis may continue to occur many years after the symptoms of the meningitis have subsided. In the vascular series of Merritt et al, 1946, average latency was 7 years with a range of several months to 12 years. Twenty six of 42 patients had syndromes of the middle cerebral artery.

As with the other forms of chronic meningitis, chronic inflammation of the meninges (mononuclear infiltration, fibrosis, and some granuloma - so-called gumma formation) at the base of the brain results in several complications: (a) obliteration of subarachnoid cerebrospinal fluid pathways with the production of hydrocephalus and increased intracranial pressure (reflected in an increased pressure at the time of lumbar puncture), (b) cranial nerve palsies, or (c) inflammatory involvement of the vessels at the base of the brain and of those smaller vessels present in the pia arachnoid supplying the cortical surface of the cerebral convexity.

The development of focal symptoms such as hemiplegia or aphasia is not unusual. In some patients, the meningeal and vascular pathology appear to involve the spinal cord predominantly with lesser involvement of the cerebral hemispheres.

The diagnosis of meningeal syphilis is made on the basis of subacute meningitis, plus characteristic cerebrospinal fluid findings [increased pressure, cell count of 100 to 1000 lymphocytes per cubic mm., increased protein (with increased gamma globulin and oligoclonal bands) borderline sugar, and positive serology, plus positive blood serology]. In vascular neurosyphilis there will be the history and findings of focal or multifocal infarcts involving the cerebral cortex, brain stem and spinal cord, at times a well-defined history of primary or secondary syphilis in addition to a positive blood and spinal fluid serology, and the CSF findings of 0-100 white blood cells per cubic mm, borderline or increased protein, (particularly gamma globulin) and borderline or normal glucose.

The primary meningeal symptoms of headache, stiff neck, and vomiting usually subside even without treatment within several weeks. These are, however, likely to be residuals reflecting the involvement of cranial nerves and occlusion of multiple vessels. These complications and the later development of the parenchymatous forms of neurosyphilis can be avoided through the prompt administration of penicillin. (see Simon 1990; Houk and Marpa 1992).

Adequate penicillin treatment requires a CSF level of penicillin which is sufficient to kill the treponeme. This CSF concentration has been defined as 0.03 IU/ml (0.18 uG/ml). To obtain this CSF concentration 12 million units given daily in four divided doses, is required. Intravenous treatment should be continued for two to three weeks. At the end of treatment, cell count should have significantly declined. At 6 months after treatment, the CSF cell count should be normal and the CSF protein significantly decreased. The CSF serological test titer may decline but remain positive⁴. Additional discussion of diagnosis and management will be found in the recent review of Marra(1995)

⁴ As discussed in the recent article of Hook and Marra 1992, and McIntosh 1991, there has been a marked increase in cases of syphilis in both adults and infants in the period 1985- 1990's. - compared to the mid 1950's. This reflects factors of promiscuity, poor sexual hygiene, and drug use particularly crack cocaine, and acquired immunity deficiency disease.

Other spirochetal infections: Lyme disease: This disease is caused by the spirochete *Borrelia burgdorferi* which is transmitted by the bite of ticks (*Ixodes scapularis* species of ticks) which have become infected by feeding on infected field mice (or deer). This is now the most common vector transmitted infectious disease in the United States. Human infection usually occurs in the months of May through August. As with syphilis, three stages are recognized.

Stage 1 - Local Infection: Erythema migrans - beginning acutely at the site of the tick bite. At times, regional lymphadenopathy, fever and some minor constitutional symptoms occur. *Stage 2* - Disseminated Infection: Spread occurs to many sites within days or weeks of infection with the development of (a) skin lesions, (b) neurological symptoms (including meningitis, multiple cranial neuropathies and multiple radiculopathies or neuropathies, and (c) joint and other musculoskeletal symptoms and (d) other parenchymal organ symptoms involving heart, liver or eye. All symptoms may wax and wane in episodes that may mimic other disease.

Stage 3 - Persistent Infection: In the second and third year of the disease more persistent arthritis and in a few patients a chronic mild or rarely progressive encephalomyelitis may occur. Such late neurological complications are less common than the arthritic symptoms⁵. Antibiotics; including tetracycline and ampicillin are highly effective in treatment. Specific dosage recommendations can be found in the recent review of Steere (1989).

Leptospirosis: This spirochetal infection may be associated with an aseptic meningitis.

ENCEPHALITIS:

At the present time, significant (encephalitis) diffuse inflammatory involvement of the parenchyma of the brain produced by infectious agents is probably less common as a clinical problem than those diseases considered under the category of meningitis. During particular epidemics certain infectious agents involving the central nervous system have produced a large number of cases with encephalitis. However, subclinical or minor diffuse involvement of the central nervous system probably occurs in the course of a number of common viral diseases, primarily as a mild aseptic meningitis or meningo-encephalitis. Even in epidemics of encephalitis or poliomyelitis, there may be many subclinical cases. For example, for Japanese encephalitis, the ratio of subclinical to overt clinical cases has been estimated at 200 or 300:1 (Monath 1988).

In general, most cases falling into this category reflect viral infection. With the exception of the spirochete, bacteria do not produce a diffuse encephalitis, although bacteria may produce multiple areas

⁵ Polyneuropathy and cranial neuropathies may also occur. At times the disease may appear to mimic other multifocal disorders of the nervous system, e.g. multiple sclerosis, lupus erythematosus and vasculitis.

of abscess formation. Other infectious agents may produce encephalitic involvement of the nervous system. The rickettsiae which are intermediate in size between bacteria and viruses, usually produce signs of a meningoencephalitis in addition to a characteristic skin rash. Examples are typhus, and Rocky Mountain spotted fever). Moreover, certain protozoal parasites may invade the central nervous system producing a subacute encephalitis. Examples include toxoplasmosis and trypanosomiasis (African Sleeping Sickness).

Encephalitis may be acute or chronic. Most cases fall into the acute category; most viral and rickettsial diseases are acute. On the other hand, the spirochetal infection and protozoal infections of the central nervous system are, in general, chronic or subacute processes. Recently, however, several viruses have been implicated in chronic diffuse progressive processes (previously considered to be of an unknown etiology) involving the nervous system.

ACUTE ENCEPHALITIS: ACUTE VIRAL INFECTIONS

The pathology of viral infections the neural parenchyma involves a viral invasion of neurons with the production of intranuclear or intracytoplasmic inclusions and the acute degeneration and destruction of nerve cells. There is a cellular infiltration of neural tissue and an accumulation of inflammatory cells about the degenerating nerve cells, in a perivascular location (Fig. 27-26). The cells are usually mononuclear although in some processes, e.g., acute poliomyelitis or in a severe case of encephalitis, there are often noted a significant number of polymorphonuclear leukocytes at times involved in neuronophagia. A microglia proliferation is often noted in the involved neural parenchyma. To a variable degree adjacent meninges may be infiltrated by inflammatory cells. Depending on the degree of meningeal infiltration and on the severity to which the underlying parenchyma is involved, a variable increase in cells (predominantly lymphocytes) will be noted in the spinal fluid. Occasionally a normal cell count may be present, more often 100 to 500 cells per cubic mm. are present. The protein content is usually increased; the sugar and chloride content are normal.

The differentiation of the particular virus involved depends on:

- a. The specific clinical pattern of the disease: some viruses involve particular areas of the central nervous system; some have associated involvement of other organ systems.
- b. Virus isolation studies: inoculation of blood, nasal washings, excretions, cerebrospinal fluid, or fresh post-mortem brain tissue into susceptible animals. In some specialized centers, tissue culture techniques may be employed.
- c. Application of acute and chronic serological tests to measure antibody levels (complement fixation or antibody neutralization tests).

It had been traditional to divide these viral infections into *neurotropic group* (primary involvement of the central nervous system) and a *non-neurotropic group* (involvement of the central nervous system

in humans is usually secondary to or less prominent than involvement of other organ systems). As we will discuss with the herpes Group of virus infection, the distinction is to some degree artificial.

A more modern classification divides viruses into those containing RNA and those containing DNA.

Examples of RNA containing include: the enteroviruses (polio, Coxsackie, ECHO), the arboviruses (Eastern and Western Equine, Japanese, etc.) rubella, mumps and measles, rabies and HIV.

Examples of DNA containing viruses include Herpesvirus, papovavirus and pox-rus-virus. An overview of viral encephalitis is provided in the review of Whitley (1990).

Neurotropic Group: The neurotropic group is usually subdivided into those viral infections which are epidemic and those which are non-epidemic.

Epidemic group: Within the epidemic group several infections may be grouped together because they share common characteristics: a) Equine encephalomyelitis with Eastern U.S.A., Western U.S.A., and Venezuelan subtypes(Deresiawicz et al,1997). b) Japanese B encephalitis (probably the most common form. World wide in recent years). c) Russian tick encephalitis. d) St. Louis encephalitis. e) West Nile encephalitis a recent problem in the eastern United States (Nash et al 2001, Tyler ,2001) f) LaCrosse virus encephalitis ,probably the most frequent variety in the U.S. in recent years (McJunkin et al,2001).

In each of these infections a relatively diffuse involvement of the cerebral cortex, diencephalon, brain stem and cerebellum occurs. In each, an arthropod, usually a mosquito, has been implicated as a vector of transmission. A species of bird or mammal has often served as a reservoir of infection. For these reasons, cases have occurred predominantly in a seasonal manner. (In northeastern United States, for example, most cases of Eastern equine and West Nile encephalitis have occurred in the late summer or early fall months, a time when mosquitoes are frequent). Vaccines are available for prevention of some of the more common varieties (Hoke et al, 1988).

The clinical syndrome in most cases is characterized by the sudden onset of headache, vomiting, drowsiness, confusion, convulsions, coma, fever, plus or minus, stiffness of the neck. Evidence is often present on examination of the patient of diffuse and, at times, multifocal involvement at multiple levels of the neural axis: coma, confusion, myoclonic jerks, status epilepticus, decorticate or decerebrate rigidity and cerebellar findings. In some cases, cranial nerve findings, aphasia and hemiplegia, will be present. The duration of the disease is a matter of days to several weeks. The state presented by the patient may be described as an encephalopathy. The major differential diagnosis is that of toxic metabolic encephalopathy. A variable mortality occurs related in part related to the age of the affected patients. The mortality of Eastern equine encephalitis, which has affected children predominantly, has approached 75 percent, with significant residuals in those recovering.. *Encephalitis lethargica* (Von Economo's encephalitis) occurred as an epidemic in the period 1916-1926. More

recent case have been described by Howard and Lees(1987). A viral etiology was suspected but never confirmed: the means of transmission remained uncertain.

This infection differed from the previously described varieties of encephalitis in the sense that although diffuse, the pathology tended to be concentrated in a periventricular location with severe involvement of structures bordering the aqueduct and third and fourth ventricles. The periaqueductal region and other structures of the midbrain were particularly affected. Reflecting the significant involvement of the midbrain and of the associated structures of the extrapyramidal system, disorders of eye movement and movement disorders of various types were prominent; in addition to the more general symptoms of lethargy, headache and fever. Since the involvement of the cortex was less severe, seizures and focal cortical deficits were less frequent. The mortality approached 25%. Among those who survived, post encephalitic residuals were common. In contrast to other forms of encephalitis, Parkinson's disease and other disorders of extrapyramidal function were frequently noted; the Parkinson's disease usually appeared to emerge or evolve as a symptom after the clearing of the acute symptoms (see chapter 19).

Acute anterior poliomyelitis, the other member of this epidemic group of neurotropic viruses, has already been discussed in relation to the spinal cord. The portal of entry is the gastrointestinal tract. The central nervous system is involved either by spread along the axis cylinders or via a generalized viremia. The virus involves predominantly the large motor neurons of the anterior horn and of the brain stem with lesser involvement of other neurons in the spinal cord.

Non epidemic neurotropic virus infections

The two most familiar members of this group - Herpes zoster and rabies - do not have their major effects at the level of cerebral cortex.

Herpes Zoster: In herpes zoster, discussed earlier in relation to the spinal cord, the inflammatory changes involve the posterior root ganglion cells with somewhat lesser involvement of the posterior and anterior horns and the anterior and posterior roots, at one or several adjacent segments. On occasion, the corresponding components of cranial nerves, particularly the ophthalmic division of nerve V, may be involved. Rarely, an encephalomyelitis or arteritis may occur, more frequent under condition of an altered immune system. The responsible virus (varicella/zoster) is also responsible for chickenpox. Primary infection with the virus results in chickenpox - which is characterized by a generalized vesicular rash, fever and other systemic infection. During this disease, a life long infection of sensory - posterior post and trigeminal ganglia is established. The H.zoster "shingles" infection is then a reactivation of this latent virus(see Mahalingham et al 1990 and Gilden et al ,1997).

The clinical symptoms of severe radicular pain, which usually lasts for weeks or a month, is clearly related to the segmental involvement of the posterior root ganglion. In some (usually patients, older than

50 years) pain may persist for years after the acute infection as post-herpetic neuralgia). At times, significant segmental weakness is present as well, indicating involvement of the anterior horn and anterior root. In addition, a vesicular eruption similar to that of chickenpox occurs in the skin overlying the involved segments. In patients with immune disorders, the use of the anti-viral drug acyclovir decreases dissemination, new lesion formation and virus shedding. In all patients, acyclovir also decreases acute pain and the formation of new lesions. This agent also decreases the ocular and neurologic complication when ophthalmic (first division) H.zoster is present. Acyclovir does not decrease the eventual occurrence of post herpetic neuralgia. (Strauss et al, 1988 and Wood et al ,1994, Gilden et al ,1994,1997).

Rabies: The virus of rabies is present in the saliva of rabid animals and invades the central nervous system several weeks to months after a bite from an infected animal (dog, cat, wolf, fox, raccoon ,squirrel, or bat). The virus travels to the central nervous system along peripheral nerves. The symptoms relate to the characteristic involvement of nuclei of the brain stem, Purkinje cells of the cerebellum, and pyramidal cells of the hippocampus (Ammon's horn). In addition, there is a significant inflammation and necrosis of the spinal cord or brain stem at the segmental site corresponding to the radicular dermatome involved by the bite. The cerebral cortex is relatively intact and consciousness is preserved. The initial symptoms consist of numbness and tingling in the distribution of the involved peripheral nerve, followed by headache, vomiting and a stage of agitation. This latter stage is characterized by restlessness, generalized convulsions, and at times, visual and auditory hallucinations. Marked alteration in emotions occurs: unreasonable fear, rage and depression. In this stage laryngeal and pharyngeal spasm (with fear of water, "hydrophobia") is prominent. In a later stage of flaccid paralysis, impairment of vocal cords and of respiratory centers develops. In approximately 20 percent of cases, an ascending flaccid paralysis dominates the acute stage (Plotkin 7 Koprowski, 1978).

Death occurs within 2 to 5 days of onset of central nervous system symptoms. At autopsy, the diagnosis may be established in man or other infected animals by the findings of characteristic acidophilic (eosinophilic) inclusions (Negri bodies) within the cytoplasm of hippocampal pyramidal cells (Fig.27-27).

Because of the long incubation between exposure to the virus and the development of neurological symptoms, prophylactic treatment is possible. Thus, the administration of a vaccine containing the attenuated virus(first introduced by Pasteur), induces the production of antibodies, and may prevent the development of neurological symptoms. The combination of this active immunization with passive immunization with antiserum containing antibodies to rabies has been demonstrated to be much more effective. The current vaccine is the human diploid cell vaccine, the current antisera - human rabies immune globulin. Previous treatment protocols involving nervous system derived vaccines resulted in

post vaccinal demyelinating reactions. Once symptoms have developed, no effective treatment is available. In under developed areas of the world a high mortality occurs. (see Baer & Fishbein 1987 and Fishbein & Robins, 1993 for a review of epidemiology and current concepts of treatment.).

Non-Neurotropic Viral Infections:

These viruses were traditionally considered as not producing significant symptoms of central nervous system involvement. Indirect evidence suggests that some of these viruses (mumps, measles, enterovirus) do invade the central nervous system in a much greater percentage of otherwise asymptomatic cases. In some of these diseases, e.g., herpes simplex, there is evidence of direct invasion of the central nervous system when the syndrome of acute encephalitis occurs. In other viral infections, e.g., mumps and measles, it is often unclear when central nervous system symptoms develop, whether one is dealing with an actual

viral invasion of the central nervous system producing an acute encephalitis (direct invasion of neurons), or whether one is observing an immunological reaction to infection elsewhere producing an acute allergic post-infectious encephalomyelitis, (white matter predominantly involved with perivenous demyelination).

Types Of Non-Neurotropic Viral Infections:

A. **The herpes virus family:** The members of this family of virus are widespread and may infect all individuals at some point during the life cycle. When the nervous system is involved, the effects may be devastating. The effects of infection on the fetus, or infant may differ from the effects in the adult. A characteristic of all herpes virus infections is that viral shedding may continue for weeks or months after the primary infection, thus, the clinical course may be acute, subacute or chronic with possible periodic reactivation.

1. The *Varicella - Zoster Virus* has already been discussed above. In the child with chicken pox, cerebellar ataxia or a post infectious encephalomyelitis may occur.

2. The *Herpes simplex virus (HSV)* has two types - *Type 1* associated with the common cold sore of the lip or oral cavity, often activated by fever and *Type 2* genital herpes with labial vaginal and penile infection. In both instances, the virus remains in a latent form in neural ganglia. (Baringer and Swoveland, 1973.), particularly the trigeminal ganglion in the case of Type I HSV and the sacral ganglia in the case of Type 2 HSV.

Type 1 HSV is the most common cause of non-epidemic; sporadic acute encephalitis in the United States. The early signs of headache and fever are followed by the development of signs that suggest involvement of limbic structures one or both temporal lobes, and at times orbital frontal (Fig.30-1). The virus apparently gains access to the central nervous system by infecting structures that are related to the olfactory system, perhaps by axonal transport along the olfactory bulb and its anatomical connections.

In some cases spread may be hematogenous (see review of Picard et al ,1993). Personality and behavioral changes may be present for days or a week; followed by seizures , hemiparesis and aphasia. Rapid or subacute progression to a stage of increasing coma then occurs. In a small number of cases, the patient may present with an overwhelming rapidly fatal state characterized by repeated generalized convulsions; myoclonic jerks of the extremities, decerebrate rigidity , coma and periodic complexes in the EEG. In contrast in a small number of cases, the clinical picture is that of a progressive subacute dementia and confusional state. The CSF demonstrates increased pressure, and a variable number of mononuclear cells plus or minus a variable small number of red blood cells. The electroencephalogram may provide evidence of focal or bilateral temporal lobe abnormalities, including slow waves. At variable points in the disease course, the radioactive brain scan, contrast enhanced CT scan or MRI will demonstrate focal or bilateral temporal (and frontal) abnormalities : enhancing necrotic lesions with considerable edema. Sequential serological studies of blood and CSF may be useful in the diagnosis. The treatment of choice is intravenous acyclovir which can be administered without serious side effects. The response to treatment is directly related to how long the symptoms have been present and to the level of consciousness. Therefore, if the diagnosis is strongly suspected on clinical grounds - treatment is begun as soon as possible, even though the ancillary laboratory studies are not yet confirmatory. In most instances, a brain biopsy is not obtained unless the patient fails to respond to therapy. Even with acyclovir therapy, 53% of patients will die or will be severely impaired. (See discussions of Hanley, 1990; Whitley, 1992).

Type 2 HSV in adults is associated with an aseptic meningitis or with severe radicular symptoms involving the sacral segments. The latter may include urinary retention (Caplan et al, 1977).

Type 2 HSV infection in the infant or fetus results in severe disseminated disease with multi-system involvement of brain and viscera.

3. *Cytomegalovirus (CMV)* another member of the herpes virus family is not usually associated with specific signs of clinical infection in otherwise healthy adults. Occasionally, such patients will have a mild infectious mononucleosis - type syndrome which is heterophile negative (see below). However, in adults who are immunosuppressed, a subacute or chronic encephalitis may occur. Infection of the fetus in utero is a more frequent problem. An estimated 33,000 infants are born with congenital CMV infection - and of these 10% are symptomatic at birth with hepatomegaly, splenomegaly, and microcephaly. Still birth and prematurity are early complications. Mental retardation, seizures, learning disabilities are late complications.

4. *Epstein Barr (EB) virus* is the cause of infectious mononucleosis (glandular fever: a syndrome manifested by lymphadenopathy, fatigue, pharyngitis, and fever and occasionally hepatomegaly and splenomegaly). The neurological manifestations are estimated to occur in 2% of cases. Aseptic

meningitis may be the most frequent but rarely encephalitis and cerebellar involvement may occur. Some of the reported neurological complications including Guillain Barre syndrome, (acute post infectious polyneuritis), facial paralysis and transverse myelitis may reflect immune complications rather than direct viral invasion of the nervous system. The laboratory tests providing confirmation of the diagnosis include the differential blood count demonstrating an increased percentage of lymphocytes with the appearance of atypical lymphocytes. Serological tests include the heterophile antibody and rapid Monospot test. If aseptic meningitis or encephalitis is present, CSF examination will reveal the usual CSF formula of a mild lymphocytic pleocytosis and a normal CSF sugar. The prognosis for recovery is usually excellent.

B. Paramyxovirus groups

1. *Mumps*: This virus commonly involves the salivary glands (parotitis), gonads (orchitis) and pancreas (pancreatitis) in children and young adults. Headache and some neck stiffness are common 2-4 days after onset of symptoms and if a lumbar puncture is performed in such cases, some evidence of a low grade meningitis will be found. More overt involvement of the nervous system is rare and it is uncertain whether encephalitis or myelitis occurring 7-14 days after onset of symptoms represents actual viral involvement or a post infectious demyelinating syndrome.

In the fetus and neonate, mumps virus infection has been implicated as a possible cause of aqueductal stenosis producing hydrocephalus (see Johnson and Johnson 1969).

2. *Measles virus* infection may be associated with a variety of central nervous system syndromes including:

- a. an acute or subacute encephalitis
- b. a post infectious encephalomyelitis
- c. subacute sclerosing pan-encephalitis: (SSPE) a form of progressive chronic encephalitis manifested by dementia, ataxia, seizures and myoclonus. The disease usually develops - in a delayed manner after an early childhood measles infection and is discussed below.

C. Retrovirus - Human Immunodeficiency Virus (HIV-1):

This virus infects cells of the immune system (e.g., T helper lymphocytes) - producing an acquired-immune deficiency state (AIDS). Carriers who may be in an early or asymptomatic stage of the disease outnumber actual cases of AIDS or AIDS-related complex (ARC). In the United States during the 1980's specific groups were at high risk: (a) homosexual or bisexual men (66%); (b) intravenous drug users (17%); (c) heterosexual - sexual partners of patients with AIDS (4%); (d) recipients of blood and blood products (3%); and (e) combined risk - homosexual or bisexual male - also drug user

(8%)⁶. By the year 2001, Sekowitz quoted figures of 36 million people world wide infected with HIV, with an additional 21.8 dead of AIDS. Approximately 70% of cases occur in sub-Saharan Africa where there are two types of epidemics : a horizontal transmission in adults spread primarily by heterosexual contact and to a lesser degree by shared needles and a vertical transmission ,infected mothers give birth to infants who have been infected in utero. Significant numbers of cases are also occurring in the Caribbean, southeast Asia, and South America.

The nervous system is involved in at least 60% of patients with clinical disease:

a. *Focal or generalized infection* due to the immunodeficiency state: thus, an increased incidence of focal granulomas of toxoplasmosis is found, as well as fungal and viral (CMV, HSV) meningitis and encephalitis. There is risk for all opportunistic infections: cryptococcal infections in 10%, toxoplasmosis in 5%.

b. *Direct invasion of the CNS* occurs in a large number of cases, 30%, producing a subacute progressive encephalitis referred to as AIDS dementia or HIV meningitis. The first signs may precede the systemic signs of the disease. In patients with acute HIV-1 infection , 24% have an aseptic meningitis (Kahn & Walker, 1998).

c. There is an increased incidence of *primary central nervous system lymphomas* (2%).

d. *Myelopathy and peripheral neuropathies* of variable causes also occur (30%).

Once, before the development of penicillin there was an old adage, that if the physician understood all of the manifestations of syphilis, he would understand much of medicine and neurology. Now for the modern era, much the same may be said of AIDS. The basic disorder of AIDS cannot be cured at this time. However most patients treated early can achieve a prolonged remission of disease with combination therapy with two nucleoside reverse transcriptase inhibitors plus a protease inhibitor. HIV-1 RNA falls to non detectable levels and there is a significant rise in the previously low levels of CD 4+ T helper cells. Specific focal and generalized infections can be treated. CNS lymphoma is sensitive to radiotherapy. Untreated cases including most patients in the non-developed world are eventually fatal. Overviews are provided in the reviews of McArthur, 1992, Kahn and Walker, 1998.

CHRONIC ENCEPHALITIS:

Spirochetal: dementia paralytica, general paresis: As indicated in our earlier discussion of syphilis, evidence of involvement of the parenchyma of the central nervous system may emerge as a tertiary

⁶ These percentages vary markedly in different geographic areas and in different population groups. Heterosexual cases are increasing significantly among drug users or their contacts and in Africa, South America and Southeast Asia. New cases among homosexual males are decreasing.

manifestation of the infection, many years (10 to 25) after the primary infection. Of the parenchymal varieties of infection, *tabes dorsalis* has been discussed previously. The problem of general paresis is pertinent for the present discussion. From a pathological standpoint, several features are noted: 1. A chronic mononuclear meningoencephalitis with greatest involvement of the frontal and anterior temporal cortex. 2. A granular ependymitis. 3. Diffuse loss of neurons most prominent in the frontal and anterior temporal areas, resulting in a gross cortical atrophy. 4. Microglial proliferation in the form of rod cells. 5. With special stains, the presence of spirochetes within the cortex. 6. Characteristic deposition of iron pigment in the involved areas.

The *clinical manifestations* are those of a progressive alteration in personality and a progressive dementia (reflecting the major involvement of the frontal or temporal areas) with progression to a fully psychotic and a terminal bedridden state. Refer to the case history provided in the chapter on dementia.

Subacute or chronic viral infections

1. *Herpes Simplex and a Syndrome of Subacute Dementia* has been considered above.
2. *Measles Virus and Syndromes of Subacute Inclusion Body Encephalitis (Subacute Sclerosing Panencephalitis)*. This is a progressive (months to years) disease of children and adolescents characterized by a progressive impairment of memory (dementia), generalized seizures, myoclonic jerks and ataxia with eventual development of a bedridden, decorticate state. Evidence suggests that the disease represents a reactivation of a defective measles virus within the central nervous system in patients who have had uncomplicated measles infections several months or years previously (Anderson et al 1987). The pathological findings are those of a chronic encephalitis with mononuclear infiltration of the cortex and white matter, inclusion bodies within the neurons, and degeneration of neurons. White matter is also involved; spotty demyelination occurs. Note that a post infectious encephalomyelitis complicates acute measles most likely as an immune basis, Johnson et al 1984.
3. *Polyoma-Papova Virus and Progressive Multifocal Leukoencephalopathy (PML)*: This progressive disorder was first recognized as a syndrome occasionally occurring in patients with chronic disease of the reticuloendothelial system, e.g., lymphomas, Hodgkin's disease or leukemia or sarcoidosis, in which impaired cell mediated immunologic responsivity had occurred. Increasing numbers of cases have now been reported reflecting a complication of the use of immunosuppressive drugs and in 3.8% of patients with AIDS. Multiple areas of demyelination occur in the central nervous system over the course of several months. The clinical picture consists of multifocal signs such as hemiplegia, cranial nerve palsies and dementia (Holman et al, 1991).

Richardson (1988), has reviewed the discovery of the viral etiology of PML. The possibility of a viral etiology had been suggested by the presence of a perivascular inflammatory cell

infiltration and by the presence of virus-like particles in the nuclei of oligodendrocytes on electron microscopy. These virus particles were similar to one of the Papova viruses, a DNA virus family, that otherwise resides outside the CNS and has wart producing or oncogenic properties. (Zu Rhein & Chou ,1965). Subsequently, Padgett et al, cultivated the more specific JC virus from the brain of a patient with PML . The subsequent studies of Houff et al, 1988, have demonstrated that in PML, the JC virus DNA and capsid antigen are present in B lymphocytes in bone marrow and spleen and subsequently in the perivascular mononuclear cells within the brain suggesting a hematogenous route of infection to the brain. The subsequent selective involvement of oligodendrocytes may occur based on possible selective transcription factors within the nucleus of the oligodendrocytes necessary for virus expression and replication. The consequences of involvement of oligodendrocytes is the subsequent myelin damage.

Prion Disorders and Degenerative Diseases:

The research of Gajdusek and his associates (Gibbs & Gajdusek, 1969) raised the possibility of a chronic slow viral infection as an explanation for several chronic and progressive diseases of the nervous system previously classified as degenerative in nature. These disorders are now associated with small infectious protein particles termed prions all of which produce a spongiform encephalopathy. Examples are Kuru, a progressive cerebellar degeneration found in the Fore tribal group in New Guinea, (where the brains of the dead were ingested in a ritual predominantly by women and children), Creutzfeldt Jakob Disease and several related familial disorder . Creutzfeldt-Jakob disease is a subacute progressive syndrome characterized by dementia, generalized convulsions, myoclonic jerks, ataxia, extrapyramidal findings, and fasciculations suggesting a diffuse central nervous system involvement The latter disorder is illustrated in chapter 30. (Fig.30-8 ,30-9). Both of these diseases have been transmitted from human patients to chimpanzees with an incubation period of 1 to 2 years after inoculation of brain suspensions from the affected patients. The pathological picture is characterized by a spongiform encephalopathy (Fig 30-8). Recent reviews include Haywood (1997) Johnson & Gibbs (1998) and Prusiner (2001).

Chronic Diffuse Protozoal Infections of the Central Nervous System :

Although central nervous system symptoms may occur during the course of malaria, the diseases usually considered under this category are trypanosomiasis and toxoplasmosis. Others parasites

producing chronic granulomas are considered above. The parasitic infections of the nervous system are considered in greater detail in Bia (1993)

1. *Trypanosomiasis* has an African form transmitted by the tsetse fly (African Sleeping Sickness) and a South American form (Chagas' Disease) transmitted by a blood sucking insect. The African form presents the picture of a chronic meningoencephalitis with fever, lethargy, convulsions and coma. The South American form presents acute picture of a disseminated multifocal granulomatous process with multifocal neurological symptoms. The organisms are sensitive to pentavalent arsenical drugs.

2. Infections with *toxoplasmosis* occur predominantly in utero, producing disseminated but multifocal areas of chronic inflammation and granuloma formation within the cerebral hemispheres. Ependymal involvement is frequent; granulomas in this location may result in blockage of the ventricular system with hydrocephalus. The areas of granuloma formation are often calcified and may be visualized on X-rays of the skull. In addition, involvement of the retina is frequent producing a characteristic chorioretinitis. Involvement of liver and spleen is frequent.

Microscopic sections demonstrate the characteristic organisms within the epithelioid cells of the granulomas and often, as well, within neurons and blood vessels. The congenital form presents the clinical picture of an infant who fails to thrive and manifests generalized convulsions and decorticate and decerebrate states, with abnormalities of eye, retina, liver and spleen. Less frequently, an "acquired" form of toxoplasmosis is seen in children or adults. With the emergence of AIDS, more cases are seen reflecting an opportunistic infection. The adult form may present a picture of an encephalopathy, of a meningoencephalitis or of focal or multifocal granulomas (see below). The diagnosis may be established by demonstrating a rising antibody titer. The organism has some sensitivity to sulfa drugs and pyrimethamine (Refer to Porter and Sadde, 1992)

3. *Other Parasitic Infections of CNS.* These may produce an acute or chronic picture. Lesions may be diffuse or focal. Focal processes are considered below. Amebic infection of the CNS may present meningoencephalitis or acute or subacute onset. Trichinosis may present an acute meningoencephalitis as well as the more common myositis.

Intrauterine Infections Producing Malformations.

Intrauterine infections have been implicated in a small percentage of congenital disease of the nervous system. Toxoplasmosis has been discussed (Fowler et al 1992). Several viral agents should also be considered.

1) *Rubella (German Measles)* virus infection during the first trimester of pregnancy may result in defects in the eye, deafness and severe malformations of the heart and in some cases, malformations of the cerebral hemisphere, such as microcephaly.

2)Cytomegalic Inclusion Body Disease (salivary gland virus), occurring during intrauterine development, has resulted in hydrocephalus and microcephaly with severe retardation and seizures. The encephalitis and ependymitis produce a periventricular calcification which may be demonstrated on X-rays of the skull. Liver, spleen, and hematologic involvement and still births, premature births, or death shortly after birth are all frequent.

Mumps virus infection in the fetus or neonate has been implicated by the studies of Johnson and Johnson 1968 as a possible cause of aqueduct stenosis producing hydrocephalus.

IV DIFFUSE DISORDERS OF THE NERVOUS SYSTEM:

A.INTRODUCTION

B. DEGENERATIONS

C. NUTRITIONAL DISORDERS

D. TOXIC DISEASES

E. COMPLICATIONS OF SYSTEMIC METABOLIC DISEASE

A. INTRODUCTION

In this section we will survey those disorders which affect the nervous system in a nonfocal manner. These are disorders of systems: some of which have already been encountered in the study of disorders affecting muscle and peripheral nerve (Chapter 8) or spinal cord(Chapter 9). Some involve several systems in a diffuse manner as in anoxia. Other disorders provide multifocal involvement- and have already been encountered in terms of multiple sclerosis at the level of spinal cord(Chapter 9) and brain stem(Chapter 13).This chapter can be no more than a very brief survey outline and should serve only to introduce the student to the range of disorders.

B. DEGENERATIVE DISORDERS

A variety of degenerative processes may involve the central or peripheral nervous system. In this section we will consider these problems in a general manner. Since many of these diseases have as their major manifestations a progressive impairment of memory (dementia) or a progressive impairment of motor function, they will be considered only briefly in the present section. A more detailed discussion with illustrative case histories will be found in the chapters dealing with memory and the motor system.

In considering this category of disease, several general rules should be listed:

1. *Systems are involved.* In general, the primary involvement is of neurons for example, the large motor neurons in amyotrophic lateral sclerosis. At times, the degenerative process is limited to the central nervous system; at times, to the peripheral nervous system. At times, as in certain spinocerebellar degenerations, both peripheral and central nervous system are involved.

Degenerative diseases have been classified on the basis of the system(s), of neurons, involved. To a certain extent, then, there is a continuum or spectrum of degenerative diseases.

2. *When fully developed, the system involvement is bilateral* and, in general, symmetrical.

3. *Onset is usually insidious*; the course is slowly progressive. In general these are chronic diseases.

4. *The basic molecular biology in most degenerative diseases is now under active investigation* and major advances have already been made. It should be evident to the student that this diagnostic category was formerly a catch-all basket in which progressive diseases of unknown etiology had been included. A number of diseases previously included in this degenerative category have been found to have a specific metabolic etiology. Thus cases of combined system disease (posterior lateral sclerosis) were once included in this category, until the actual cause was discovered: a nutritional deficiency of vitamin B 12, owing to a lack of the intrinsic factor required for absorption of this compound. Similarly, Wilson's disease (hepatolenticular degeneration), has now a clearly established etiology - the toxic effects resulting from unbound copper in the blood entering brain, liver and kidney. Several diseases resulting from exogenous toxins may also mimic degenerative disease of the nervous system. Thus, chronic exposure to manganese may produce a Parkinsonian syndrome because of damage to the basal ganglia. The ingestion of an illicit laboratory designed drug, MPTP has produced a cluster of Parkinsonian cases in young adults. Chronic exposure to mercury (as once was the case in the hatting industry) may produce a progressive cerebellar syndrome with a prominent component of upper extremity tremor. Chronic heavy alcohol intake (with a possible additional nutritional deficiency) may be associated with a severe cerebellar degeneration (anterior superior portions of the vermis) with a prominent gait ataxia that may be indistinguishable from a late onset of familial cerebellar degeneration. Other possible etiologic factors must be searched for in these degenerative diseases. Thus as we have indicated, prion disorder at times infectious, at times familial has been recently implicated in several rare chronic progressive diseases formerly classified as degenerative: kuru, and Creutzfeldt- Jakob- syndromes. Reactivation of measles virus has been implicated in subacute sclerosing panencephalitis(SSPE).

Thus the student, faced with a patient manifesting a progressive disease syndrome, should, before diagnosing the condition as degenerative disease, rule out the possible treatable causes of

that syndrome - nutritional, toxic, and metabolic. Eventually treatment of many “untreatable degenerative disorders” may become available due to the advances of molecular biology.

5. *In general, the pathological picture, at a histological level is characterized by a loss of neurons and of their axons in the particular system involved or in related systems.* Surviving neurons in the involved system may show various degenerative changes, including lipid inclusions. To a variable degree, some proliferation of glia and glial fibers may be present. Cellular response, however, is never prominent. Grossly, the loss of neurons and axons is often indicated by the loss of bulk of the involved areas - atrophy. In several of the pediatric disorders, maldevelopment of myelin occurs.

Clinical syndromes: Since several levels of the neural axis (and one or more systems) may be involved in these diseases, the best approach is to group these disorders according to the predominant clinical features.

The following classification of clinical syndromes follows, in general, that of Richardson, Torvik, and Adams (Harrison et al., 1966).

I. Syndromes in which dementia predominates. The major example is Alzheimer’s disease. In these conditions involvement of the cerebral cortex is predominant. Other neurological signs are absent until late in the course of the disease. (refer to Chapter 30).

II. Syndromes in which dementia combined with other neurological signs. In these conditions, involvement of neurons in the cerebral cortex is combined with involvement of neurons in the basal ganglia or brain stem or retina. This category may be subdivided.

a) In the adult the major example is Huntington’ disease in which dementia and psychosis are combined with a disorder of gait and movement (due to involvement of the cerebral cortex and striatum- refer to Chapter 19).

b) in the infant, child and adolescent several varieties have been identified, many with specific genetic metabolic defects

1) *The lipidoses (lysosomal storage disorders).* In lipidosis abnormal accumulations of lipid occur in neurons. The best known example is probably Tay-Sachs disease or infantile amaurotic familial idiocy, in which dementia is combined with blindness, seizures, and a spastic quadriparesis. An autosomal recessive determined deficiency of the enzyme hexosaminidase results in the accumulation of GM-2 gangliosides within the neuron. The disorder was once frequent among Jews of eastern European origin. Carrier screening among the at risk population has markedly reduced the occurrence of the disease. For discussion of other varieties refer to Chapter 29 progressive myoclonus epilepsy.

2) *The leukodystrophies*. In these conditions a diffuse breakdown of myelin into abnormal lipid products occurs, that is, products not normally found in the usual breakdown of myelin in trauma or infarcts.

3) *The aminoacidurias*: Disorders of amino acid metabolism: progressive impairment of psychomotor function occurs in the aminoacidurias.(e.g.,). In the most common of these disorders, phenylketonuria conversion of phenylalanine to tyrosine is defective. The high level of phenylalanine results in abnormal maturation of the brain and defective myelination. Testing for this disorder and related disorders may be carried out at birth. Restriction of phenylalanine in the diet may avoid the development of the neurological disorder.

4) *Disorders of glycogen storage*. Various genetic defects in enzymes associated with the metabolism of glycogen may result in effects on muscle, brain, liver and heart.

III. Syndromes characterized by a progressive development of disturbances of posture and of movement due to diseases of the basal ganglia: The major examples are Parkinson's disease and the Parkinson plus syndromes (refer to chapter 19)

IV. Syndromes characterized by a progressive ataxia (unsteadiness of trunk, gait, or movement):the spinocerebellar degenerations.(Refer to chapter 20 and to chapter 9). In the child most are recessive ; Friedreich's ataxia is the major disorder. In the adult the various entities are grouped as the autosomal dominant cerebellar atrophies now termed spinocerebellar ataxias (SCA) and classified based on the more specific genetic defect.

V. Syndromes characterized by slowly developing weakness and spasticity. (refer to chapter 9). In the child and adolescent, hereditary spastic paraparesis is the major example. In adults amyotrophic lateral sclerosis with predominant lateral column involvement is the major example.

VI. Syndromes characterized by slowly developing muscular weakness and muscle atrophy due to motor neuron involvement, but without sensory changes (Refer to chapter 9). In children, the various types of progressive muscular atrophy such as Werdnig-Hoffmann disease must be considered. In the adult the various forms of motor system disease : (amyotrophic lateral sclerosis and its variants (progressive muscular atrophy, progressive bulbar palsy) must be considered.

VII. Syndromes characterized by progressive muscular weakness and muscle atrophy due to disease of peripheral nerve, but with less marked sensory involvement. The major example is peroneal muscular atrophy (Charcot-Marie-Tooth disease refer to Chapter 8.).

VIII. Progressive sensory peripheral neuropathy. These are relatively uncommon. The major example is the hereditary sensory neuropathy described by Denny-Brown with pathology in the posterior root ganglion.

IX. Progressive muscle weakness and atrophy due to muscle disease. The muscular dystrophies are the major example (see Chapter 6).

X. Progressive loss of vision. The major examples are: hereditary optic atrophy of Leber which results from degeneration of the retinal ganglion cells; and pigmentary degeneration of the retina (retinitis pigmentosa). In retinitis pigmentosa the rods and cones degenerate with displacement of cells from the pigment epithelium to the more superficial layers of the retina.

C. NUTRITIONAL, TOXIC, AND METABOLIC DISEASES

These diseases involve the metabolic activities of the nervous system. Nutritional deficiencies may remove certain vitamins required as coenzymes in vital metabolic energy transformations. Particular toxins may have their effects by interfering with specific enzymatic processes. We can consider most of these problems only briefly. The student should refer to the standard textbooks of clinical medicine and clinical biochemistry for a more thorough presentation.

Several general principles apply to these categories of disease:

1. The central and peripheral nervous systems have only a limited number of pathological responses. Different disease states may produce a similar clinical and pathological picture.
2. For the same reason these diseases may mimic degenerative or familial diseases of the nervous system.
3. The metabolic disturbance is usually not limited to the nervous system but involves many systems of the body. In some instances the nervous system appears to be predominantly involved.
4. Not all levels of the neural axis are equally affected. In specific metabolic disturbances a selective vulnerability of particular segments is often evident.
5. These diseases may alter physiological function and produce pathological changes at one or several levels of the neural axis: peripheral nerve, spinal cord, diencephalon, or cerebrum.
6. Specific treatment will arrest the progress of the disease and disordered function will often be corrected. Structural changes and their associated clinical changes however, will, usually be irreversible in the central nervous system).
7. At times, in nutritional problems, a specific deficiency has not been established but a general relationship to nutritional deficiency has emerged.
8. The developing nervous system (pre and postnatal) often has a marked vulnerability in these disorders with effects that differ from those of the adult nervous system. The specific effects are in part determined by the stage of CNS development involved. Consider the problem of fetal alcohol syndrome, the use of various drugs such as cocaine during pregnancy and of malnutrition during the years of development. Lead and organomercury exposure of the pregnant female may have

devastating effects on the fetus (See Miller 1991, Mayo et al 1992, Zuckerman et al 1989, Volpe 1992 Chiriboga, 1993 and Harvey & Kosofsky, 1998).

C.NUTRITIONAL DEFICIENCY DISEASE SYNDROMES

The following classification has been derived from a similar classification by Victor (1965). The classification is based on the anatomical levels or the systems predominantly involved. Table 27-8: Nutritional and Related Disorders of the Nervous System*

STRUCTURES INVOLVED	VITAMIN(S) DEFICIENT	MANIFESTATIONS
Cerebral Cortex	-Niacin -Pyridoxine -B12	-Pellagra: dementia, dermatitis, diarrhea -Seizures (possible hippocampal origin) -Dementia
Corpus callosum	Specific unknown, possibly toxic, described initially with excess of Italian red wine	Marchiafava –Bignami disease: dementia and apraxia
Diencephalon and brainstem and cerebellum-Periventricular	-Thiamine	Wernicke-Korsakoff syndrome (Chap 30)
Pons	Specific unclear but does follow too rapid correction of hyponatremia	Central pontine myelinolysis Mute, spastic (Chapter 13)
Cerebellum	Thiamine or multiple B	Alcoholic cerebellar degeneration (Chap.20)
Spinal cord	B12	Combined system disease (Chap.9)
Peripheral nerves	Thiamine, or pyridoxine or Or B12 or multiple B	Nutritional mixed sensory neuropathy or with thiamine beri-beri.
Optic nerves	Thiamine, B12, riboflavin	Optic neuropathy (retrobulbar neuropathy, usually bilateral)

- Muscle may also be involved in an alcoholic myopathy-specific unknown but multiple B suspected.
- In infants and children deficiencies of proteins and fat may retard development of nervous system.

Syndromes with cerebral manifestations

1) *Pellagra*: Pellagra results from a deficiency of nicotinic acid. Daily requirements are 10 to 30 mgm. per day but tryptophan in the diet may serve as a precursor of nicotinic acid. Cerebral

nicotinic acid derivatives are found in the form of nicotinamide adenine dinucleotides (NAD, NADP), which are of crucial importance in the energy yielding oxidative phosphorylations of the tricarboxylic acid cycle. The clinical syndrome may be considered as a triad consisting of mental changes, dermatitis, and diarrhea.

The earliest symptoms are usually related to the disturbance in cerebral function: depression, irrational fears, agitation, hallucinations, disorientation, and delirium.(Victor,1993) The characteristic histological change is that of central chromatolysis in large pyramidal cells of the cerebral cortex, particularly the motor cortex. Motor neurons in the brain stem and spinal cord horn will also demonstrate these same changes.

The neurological, dermatological, and gastrointestinal effects of the deficiency are rapidly reversed by the administration of nicotinic acid or nicotinamide (Sedaru et al 1988).

2) *Pyridoxine (Vitamin B6) Deficiency*: Pyridoxine deficiency may involve the nervous system at several levels. In the adult the deficiency occurs predominantly in patients receiving the antituberculous agent, isoniazid (INH, isonicotinic hydrazide), an antagonist of pyridoxine or in alcoholics with severe nutritional deficiency. The result is a peripheral neuropathy. Occasionally convulsions occur⁷.

In infants, however, the effects relate predominantly to alterations in the excitability of the hippocampus and neocortex, with the production of convulsions. These alterations in threshold for convulsions is not unexpected in view of the known metabolic activities of pyridoxal phosphate as a coenzyme. Thus the decarboxylation of glutamic acid to gamma aminobutyric acid (GABA) the major CNS inhibitory transmitter requires the presence of the coenzyme, pyridoxal phosphate. Pyridoxal phosphate also is the coenzyme required for the decarboxylation that produces serotonin from 5-hydroxytryptophane. Pyridoxal phosphate also functions in the vital transamination reaction which yields aspartate and alpha ketoglutarate from glutamic acid and oxaloacetate.

Pyridoxine deficiency is not common as a cause of convulsions in infants. However, a group of otherwise normal infants who were fed a manufactured baby food deficient in pyridoxine did develop severe convulsions and myoclonic seizures with rapid improvement on administration of this vitamin. In general, a normal infant or child has sufficient reserves of pyridoxine to continue on a pyridoxine-deficient diet for 8 weeks before the development of convulsions. However, a small group of newborn infants have been found to have a need for pyridoxine far beyond the normal daily requirements (15 mg, compared to normal requirements of 1.5 mg). These infants

⁷ It is therefore standard therapy to routinely administer pyridoxine whenever INH is utilized.

(referred to as pyridoxine-dependent) develop intractable seizures: generalized convulsions and myoclonic jerks which are rapidly controlled by administration of the agent. For additional discussion refer to van Gelder et al 1990.

3) *Progressive dementia of vitamin B12 deficiency*. Vitamin B12 (Cobalamin) deficiency in almost all cases reflects a failure to absorb this vitamin because of a deficiency of the intrinsic factor secreted by the gastric mucosa. A similar failure may occur as a result of gastrectomy. In some cases, the deficiency is a result of a malabsorption syndrome.

Vitamin B12 is utilized as a coenzyme in the formation of methionine and of the nucleotide, thymidine. The resultant disordered synthesis of deoxyribonucleic acid (DNA) leads to a failure of normal maturation of cells. The specific enzymatic role of Vitamin B12 in the nervous system remains unclear, however see discussion in chapter 9.

The neurological symptoms of Vitamin B12 deficiency relate primarily to the involvement of the posterior and lateral columns of the spinal cord and of peripheral nerve. The heavily myelinated fibers are initially and predominantly involved. These symptoms occur in 30 to 70 per cent of patients with pernicious anemia. In addition, however, a small percentage of patients also demonstrate changes in cerebral function unrelated to the degree of anemia but related to changes in cerebral white matter.

4) *Primary degeneration of the corpus callosum*: Marchiafava-Bignami Disease. This is a rare disease involving demyelination and necrosis of axons in the central portions of corpus callosum and the anterior commissure. Most of these cases have occurred in older Italian males who have consumed large amounts of crude Italian red wine.

Syndromes involving the diencephalon and brain stem

1) *Wernicke's encephalopathy*: This disorder which is discussed in Chapter 30, consists of a triad: mental disturbance (confusion and drowsiness), paralysis of eye movements, and ataxia of gait. The basic cause of the syndrome is a deficiency of thiamine. Since a deficiency of thiamine and of the other B complex vitamins also results in a peripheral neuropathy, symptoms relevant to degeneration of peripheral nerves will often be present as an associated finding.

Thiamine pyrophosphate functions as a coenzyme (cocarboxylase) in the decarboxylation of pyruvic acid. This step is the initial reaction in the energy producing tricarboxylic acid cycle. Thiamine also participates in the oxidative decarboxylation of alpha ketoglutaric acid at a later point in this cycle. In addition, thiamine pyrophosphate functions in the transketolase reaction, which is involved in the pentose phosphate pathway (hexose monophosphate shunt) for the breakdown of glucose, particularly for the conversion of ribose-5 phosphate to sedoheptulose-7 phosphate. Refer also to Brody and Wilkins 1968, Lindbo and Laberg 1989 and Victor et al 1989.

2) *Korsakoff's syndrome*: Patients with Wernicke's syndrome may continue to have severe deficits in the ability to record new memories remaining in a confusional state. These patients as discussed in chapter 30 have residual lesions in the medial thalamus.

3) *Central Pontine Myelinolysis*: This is a rare disease in which a diagnosis was usually established only at the time of autopsy. The clinical diagnosis now can be confirmed in life by MRI Scan (chapter 13) The basic pathology involves an area of demyelination with a relative preservation of axis cylinders and neurons in the central area of basilar and adjacent tegmental portions of pons. Most cases have occurred in chronic alcoholics; in a few cases, severe nutritional deprivation or malabsorption was present without the alcoholism. In some cases severe hyponatremia was present and this may have been too rapidly corrected. The etiology then is uncertain.

Nutritional deficiency diseases affecting the cerebellum.

1. "*Alcoholic Cerebellar Degeneration*". This problem has already been mentioned in relation to Wernicke's encephalopathy in thiamine deficiency. These are patients who have a persistent cerebellar ataxia due to degeneration of the anterior superior vermis. Not all patients have a preceding history of a Wernicke's encephalopathy The diagnosis now can be confirmed during life with MRI and CT scans. Refer to Chapter 20, Victor et al 1989 and Phillips et al 1987.

Nutritional deficiency diseases affecting the spinal cord.

1) *Subacute Combined System Disease: Vitamin B12 Deficiency*. This is the most common of the nutritional myelopathies. Refer to discussion above and Chapter 9.

2) *Folate Deficiency*: Rare cases of folate deficiency in the adult are accompanied by a myelopathy and peripheral neuropathy similar to that which accompanies B12 deficiency (Nincew et al 1972, Pincus et al 1972). A peripheral neuropathy alone is more common. In the fetus; folic acid may also have a significant role in decreasing neural tube defects when administered during the first trimester -Rosenberg 1992, and Cziel and Duda 1992. See also embryology chapter regarding neural tubes defects.

Nutritional deficiency diseases affecting the peripheral nerves

1) *Thiamine or multiple B vitamin deficiencies*. A peripheral neuropathy of variable degree is commonly encountered in patients on nutritionally inadequate diets, e.g., chronic alcoholics. The neuropathy is in general a distal symmetrical polyneuropathy of mixed sensory motor type. Often the neuropathy is mild, predominantly sensory, involving a loss of vibration sense at the toes, a minor decrease in pain sensation and an absence of Achilles and quadriceps deep tendon reflexes. The feet are often described as burning and painful to the touch. A distal weakness is usually present in the lower extremities with the development of drop foot. At times the full-blown peripheral neuropathy of "neuritic beri-beri" may be present. Although thiamine deficiency will

produce a distal peripheral neuropathy, many patients, such as chronic alcoholics, have been on diets which are deficient in many of the B complex vitamins, e.g., niacin, pyridoxine, pantothenic acid, folic acid and cobalamin (B12) each of which by itself may under experimental conditions produce a peripheral neuropathy. Diets high in carbohydrates may increase the requirements for thiamine and may precipitate symptoms.

The treatment consists of the oral or parenteral administration of the multiple B vitamins to include a thiamine dosage of at least 10 mg. per day. In very severe cases where Wernicke's encephalopathy, or the cardiac involvement of beri-beri is also present, the parenteral administration of 100 mg. of thiamine three times a day has been recommended. The usual human requirement of thiamine is 0.4 mg. per 1000 calories.

2) *Pyridoxine deficiency*: as discussed above a peripheral neuropathy may occur.

For additional discussion of the differential diagnosis of Peripheral Neuropathies refer to chapter 8.

Nutritional deficiency diseases affecting the optic nerve

1) *Nutritional or Tobacco Amblyopia Syndrome of Bilateral Retrobulbar Neuropathy*. In these patients there is a bilateral degeneration of the myelinated fibers of the optic nerve involving primarily the fibers coursing from the macula to the optic disk (the papillomacular bundle). Since the macula is concerned with high resolution central vision, there is a decrease in visual acuity and the presence of central or cecocentral scotoma on examination. The specific nutritional deficiency is unknown. thiamine, riboflavin, or vitamin B12 may be involved. Each of these when deficient in experimental animals such as the monkey may produce an optic neuropathy.

2) *Strachan's Syndrome*. This syndrome is composed of a sensory peripheral neuropathy (apparently due to the involvement of the dorsal root ganglion), retrobulbar neuritis (due to involvement of the papillomacular bundle), and deafness and vertigo (due to the involvement of cranial nerve VIII). The specific deficiency is unknown.

Nutritional deficiency diseases affecting muscle

Alcoholic myopathy :This relatively less common syndrome has been reported in alcoholics.

D) TOXIC DISEASES

METALLIC POISONS

Table 27-9: Heavy Metal Effects on the Nervous System

METAL	ACUTE AND HIGH LEVEL	CHRONIC LOW LEVEL
Lead	Encephalopathy: acute cerebral edema	In adults :motor peripheral neuropathy In children long term retardation of cognitive function /intelligence quotient
Inorganic mercury	Acute gastrointestinal, renal and hematologic effects	Cerebellar degeneration and the “mad hatter syndrome” : dementia and psychosis
Organic mercury	Blindness, cerebral cerebellar, pyramidal, and anterior horn cell degeneration primarily affecting fetus infants and children (Minimata Bay in Japan etc)	
Arsenic	Acute hemorrhagic encephalopathy	Peripheral neuropathy :sensory/motor
Copper		Hepatolenticular degeneration: Wilson’s Disease: Genetic defect-(Chap.19)
Manganese		Parkinson’s disease

1) **Lead:** Lead poisoning may result in the adult from industrial exposure, from accidental exposure to the fumes of burning batteries containing lead, or from the ingestion of whiskey which has been illicitly distilled in stills containing lead condensers and connecting pipes. In the child, lead poisoning usually results from the ingestion of paints containing lead. Layers of old paint containing lead are often found on the walls of older houses and apartments. The lead content of

house paint was reduced in the early 1950's and eliminated in 1977. The children of economically disadvantaged groups are more likely to be unattended and living in much older buildings and thus more subject to pica (the ingestion of inorganic materials). Deleaders of old houses may also be affected (Goldman 1987).

The specific action of lead on the brain is not clear. Apparently interference with various intracellular enzymes occurs, with damage to capillary endothelium and neurons. In the child, the result is an acute encephalopathy with massive cerebral edema, coma, and convulsions. Associated symptoms of constipation, abdominal pains, and anemia reflect the effects of lead on the gastrointestinal and hematopoietic systems. The morbidity and mortality from lead encephalopathy are high despite acute treatment designed to reduce brain edema (steroids, intravenous urea, and surgical decompression) and despite later treatment with chelating agents designed to mobilize lead from soft tissues for excretion (calcium disodium versenate and the oral agent dimercaptosuccinic acid). Most of those surviving the acute encephalopathy will manifest a significant degree of mental retardation. Even low level exposure to lead in early childhood (levels of 0.7 to 1.2 $\mu\text{mol/L}$) has been associated with delay in neuropsychological development. (See Baghurst et al ,1992,).The Public Health Service has estimated that 3-4 million children in the United States may have blood levels high enough to cause neurobehavioral problems. A program was instituted in the early 1990's to screen routinely for lead poisoning in all communities and to identify and treat initially those with levels of 1.21 $\mu\text{mol/L}$, and subsequently those with levels of 0.48 to 0.72 $\mu\text{mol/L}$. At the same time environmental resources of lead were to be eliminated (Mason,1991).The study of Rogan et al,2001 ,indicates that treatment of moderate levels will reduce the level of lead in the blood but will not reverse the cognitive impairment. Rosen & Mushak (2001) therefore conclude that the best treatment is prevention

In the adult, chronic lead poisoning is much more likely to result in a peripheral neuropathy than in central nervous system involvement. The peripheral neuropathy is predominantly motor, often involving the extensors of the hand, producing a characteristic wristdrop .Chelation therapy is employed .

2) **Arsenic**: Arsenicals are employed (as arsenates) in insecticides and were formerly used in the organic form in the treatment of syphilis. Arsenic binds to sulfhydryl group in proteins and thus interferes with a number of enzyme systems. Either the central or peripheral nervous system may be involved. An acute hemorrhagic encephalopathy manifested by headache, confusion, convulsions, drowsiness, and coma may occur in cases of severe acute poisoning. More chronic cases or less severe acute exposures are more likely to result in a distal symmetrical polyneuropathy. This is a mixed sensory-motor neuropathy with distal paresthesias and

dysesthesias as prominent symptoms. Associated symptoms reflect involvement of skin, mucosa, and the gastrointestinal tract. Diagnosis is based on determination of arsenic levels in the nails, hair, and urine. Treatment employs the agent BAL (British anti-lewisite; 2, 3 dimercapto-1-propanol) which combines with metallic ions such as arsenic and mercury. The BAL has such a strong affinity for these metallic ions, that it is able to remove these metallic ions from their binding to tissue sulfhydryl groups.

3) **Mercury**: Acute poisoning with mercury usually occurs in relation to the ingestion of soluble salt such as mercuric chloride. The symptoms reflect the predominant involvement of the gastrointestinal tract, the mucus membranes, and the renal tubules.

Chronic mercury poisoning from metallic mercury vapor results in neurological symptoms. Exposure to mercury in industrial processes was common in the jewelry and hatting industries prior to the introduction of alternate manufacturing processes during the 1930's. The expression "mad as a hatter" suggests the changes in personality and mood which were often noted among hatters, presumably due to the cerebral effects of the agent. Much more prominent and equally frequent as a symptom was the occurrence of the "hatter shakes" - a mixed type of tremor, present in the outstretched hands and present on movement and intention. The tremor may be correlated with the neuronal loss in the cerebellar cortex particularly loss of the granule cells (See Chapter 20). In some cases alterations in basal ganglia and anterior horn cells have also been reported.

Organic mercury: Methyl mercury poisoning results in chronic blindness, cerebral, cerebellar and pyramidal tract and anterior horn cell symptoms. Specific epidemics of methyl mercury poisoning have occurred around the harbors of Minimata and Nigata in Japan. In the Middle East epidemics have followed ingestion of contaminated grain.

4) **Copper**: Exogenous copper poisoning is uncommon. Endogenous copper poisoning does occur in Wilson's disease (hepatolenticular degeneration) and is discussed in relation to diseases of the basal ganglia (Chapter 19).

5) **Manganese**: A Parkinsonian syndrome has been noted in manganese miners. These patients demonstrate a loss of neurons in the substantia nigra. (Additional discussion of Parkinson's disease will be found in Chapter 19).

TOXIC DISORDERS :PHARMACOLOGICAL AGENTS

A variety of pharmacological agents have effects on the central nervous system. A detailed account of these agents is beyond the scope of this textbook; the reader is referred to the standard textbooks of pharmacology.

1) **Alcohol**. Several neurological syndromes complicate the use of alcohol. (Refer to Charness et al 1989, Porter et al 1990)

a) *Acute intoxication* in mild cases produces frontal-lobe and cerebellar dysfunction. The latter is manifested by the characteristic ataxia of gait, trunk, and limbs: movements lack coordination and speech is slurred. In severe intoxication, coma will occur (refer to Chapter 29 for discussion of coma).

b) *Various syndromes relevant to nutritional deficiency* have already been discussed.

c) *Chronic alcoholism* represent a complex physiological, psychological, and socioeconomic problem. A detailed discussion of alcohol addiction is beyond the scope of this survey.

d) *Alcohol withdrawal* after chronic ingestion produces a syndrome characterized by generalized convulsive seizures and delirium tremens (refer to Chapter 29 for discussion).

2) **Sedatives (eg short acting barbiturates) and the benzodiazepine (chlordiazepoxide , diazepam lorazepam) and Meprobamate.**(refer to Greenberg,1993) All of these agents may produce chronic toxicity manifested by symptoms of cerebellar system involvement: ataxia of gait, nystagmus, slurring of speech, and tremor. At times a drowsy confusional state may be present. Severe acute overdosage, as in a suicide attempt, will result in coma (see discussion, chapter 29). Sudden withdrawal after chronic use may produce a typical withdrawal state, characterized by convulsions and delirium tremens. The effects of long term use of phenobarbital in children on neuropsychological performances is discussed by Farwell et al 1990.

3) **Phenytoin (Diphenylhydantoin ,Dilantin).** The toxicity produced by this anticonvulsant reflects involvement of the cerebellar system with ataxia of gait, nystagmus, slurring of speech, and tremors. The symptoms usually disappear on reduction of dosage. In severe and chronic overdosage, usually in patients with poorly controlled seizures, significant cell loss in the cerebellum may actually occur. Whether this is due to the seizures or to the drug remains unclear.

In some patients chronic therapy with this agent may result in a mild peripheral neuropathy manifested by loss of deep tendon reflexes and a decrease in vibratory sensation in the lower extremities. Folic acid levels maybe depressed. Other anticonvulsants may produce a similar effect.

4) **Bromides.** Chronic use of bromides (which were formerly widely employed as sedatives) may frequently result in a confusional stage characterized by disorientation, hallucination, agitation, ataxia, and tremor. This state has in the past often been mistaken for a psychosis.

5) **Pheno thiazides and Reserpine:** The toxic effects of these tranquilizers relate to dopamine antagonism with effects on the basal ganglia system. Depending on the age of the patient, a Parkinsonian syndrome or a dystonic syndrome may develop. These problems are discussed in Chapter 19.

6) **Morphine and Heroin.** Acute severe intake of these narcotic agents may produce drowsiness, coma, and respiratory arrest. Characteristically the pupils are pinpoint prior to any onset of coma. During deep coma, the pupils may be dilated.

A number of neurological complications may result from the intravenous administration of impure mixtures of heroin by narcotic addicts (Refer to Richter ,1975). These complications, which may consist of a hemiplegia or a myelitis, may represent an allergic vascular response to some of the impurities contained in these mixtures. Local infections may involve peripheral nerves or muscle. Bacterial endocarditis with all of the neurological complications of this disease is seen frequently in intravenous drug users (See Chapter 26). Intravenous narcotic drug addiction also constitutes one of the major risk factors for acquired immunodeficiency disease (AIDS) due to sharing of needles. (See the infectious disease section of this chapter for a discussion of the many neurological complications of AIDS)

Withdrawal from morphine or heroin after chronic administration in the addicted state produces a state characterized by tremors, agitation, cramps, diarrhea, vomiting, and anorexia. The significant effects of maternal use on fetal development are discussed in Miller ,1991.

7) **Hallucinogens:** The effects of LSD, mescaline, and related hallucinogens on sensory and other central systems are reviewed by Smythies (1962). Acute psychosis may result.(See Brust,1993 for additional discussion of these agents and of phencyclidine).

8) **Amphetamines:** These stimulant agents are often used as street drugs. Complications of acute use may include psychosis, cardiac arrhythmia, hypertensive crisis with hemorrhage or thrombotic strokes. During an epidemic of methamphetamine use in Japan during the period 1945-1955, there were 200,000 patients with a psychosis similar to acute or chronic schizophrenia induced by this agent (Yui et al ,2000) .See also Sanchez-Ramos (1993).

9) **Cocaine:** This agent which is now a major illegal addictive drug, was once employed extensively as a local anesthetic. The CNS stimulant effects following intravenous administration or nasal snorting was also early observed by Freud ,other prominent medical leaders and figures prominent in literature(See Conan Doyle's- *Adventures of Sherlock Holmes*). Unfortunately, significant effects also occur on heart and blood vessels with the occurrences of ventricular arrhythmias, myocardial infarctions, cardiac arrest, acute elevation of blood pressure and cerebral hemorrhages and infarction. Tonic-clonic convulsions are also frequent(Refer to Lange et al 1989,Isner and Chokshi 1989). The effect of prenatal exposure are discussed by Volpe (1992) and in Harvey & Kosofsky (1998) and Ali (2000).

TOXIC DISORDERS :OTHER AGENTS

Carbon Monoxide. Accidents or suicide attempts with acute carbon monoxide poisoning result in significant neurological deficits. The patient is usually found to be in deep coma. These deficits reflect the interference of the carbon monoxide with proper oxygenation of the cerebral cortex and basal ganglia among other central nervous system structures. Carbon monoxide forms a stable compound with hemoglobin, thus reducing the oxygen-carrying capacity of hemoglobin. At pathologic examination, loss of neurons in the cerebral cortex may be noted, often in a laminar pattern. Significant destruction of basal ganglia may also be present, with particular involvement of the globus pallidus.

Chronic exposure of garage workers or traffic policemen to relatively smaller doses of carbon monoxide may produce headache and confusion.

E .COMPLICATIONS OF SYSTEMIC METABOLIC DISEASE

A variety of metabolic diseases may affect the central and peripheral nervous system. We may summarize the several syndromes. A fuller discussion is provided in Adams et al (1997).

1) **Acute or subacute impairment of consciousness (confusion, stupor, and coma).** The more frequent metabolic diseases in this category are: hypoxia, hypercapnia, hypoglycemia, acidosis (as in diabetes), uremia, hepatic failure, and Addison's disease. The differential diagnosis of coma and stupor is discussed in chapter 29.

2). **Chronic dementia or mental retardation plus or minus extrapyramidal or cerebellar motor deficits or seizures or myoclonus.** These disorders are discussed in relationship to the differential diagnosis of dementia in Chapter 30, in relationship to the basal ganglia in Chapter 19 and as regards myoclonus in Chapter 29. The following disorders fall into this category; hepatolenticular degeneration, chronic encephalopathy of hepatic failure, acute intermittent porphyria, chronic hypercapnia (confusion, tremor, and myoclonus), hypoparathyroidism (tetany, convulsions, and cerebral calcification), hypothyroidism, chronic uremia (confusion, obtundation, plus or minus myoclonus). In addition, several disorders seen primarily in childhood present as progressive retardation of intelligence: the aminoaciduria and the lipid storage diseases.

For additional discussion of the neurological complications of renal disease see Trompeter et al (1986).

3) **Neurological complications of diabetes mellitus.** Diabetes mellitus is widespread and the neurological complications are frequent. *The most frequently encountered complication is a distal symmetrical peripheral neuropathy* (see Chapter 8). In addition a *painful mononeuropathy or*

plexopathy or radiculopathy, usually proximal motor may occur, involving most frequently the sciatic or femoral nerve (See chapter 8). This mononeuropathy is due to vascular occlusion of the blood supply of the nerve. *Cranial neuropathies involving the sixth and seventh nerves* are also more frequent in diabetics. *Autonomic neuropathy* also occurs in severe diabetics producing a severe syndrome of diarrhea, bladder symptoms, and impotence. *Degeneration of cervical and lumbar intervertebral disks* appears to occur more frequently in diabetics than in the general population, producing significant root and spinal cord compressions due to cervical spondylosis.

4) Neurological complications of thyroid disease:

Primary manifestations of hyperthyroidism (Graves Disease) include psychomotor hyperactivity and accentuation of physiological tremor. In addition, *ophthalmoplegia* may be noted in relation to the exophthalmos which characterizes the disease⁸. *Thyrotoxic myopathies* have been reported. *Myasthenia gravis* may also be exacerbated. *Periodic paralysis* may also occur in relation to hyperthyroidism.

Hypothyroidism (myxedema) also is associated with a number of neurological symptoms. *Myxedema* may present as a chronic dementia or depression. Hoarseness is frequently noted. *Carpal tunnel syndrome and thoracic outlet syndrome* may occur (See Chapter 8). The patient also complains of a general sense of muscle weakness, of muscle pains and of paresthesias. The deep tendon reflexes are often delayed in their relaxation phase (referred to as pseudomyotonic). There is often an accentuation of myasthenia gravis. Ataxia has on occasion been noted. In severe cases, coma may result. (For additional discussion of thyroid disease see Halpern 1991 and Ingbar & Braverman 1986.

5) Pituitary adenomas

This group of extrinsic brain tumors, arising in the anterior lobe of the pituitary gland within the sella turcica is second to meningiomas in frequency. Moreover, small pituitary adenomas are an incidental finding in 25% of all pituitary glands studied routinely at autopsy. These tumors are of interest both to the endocrinologist and the neurologist. In many instances, the endocrine manifestations are primary and the neurological manifestations are absent. The endocrine manifestations include those symptoms related to overproduction of pituitary hormones by the adenoma and those symptoms related to the destructive effects of an enlarging tumor mass resulting in a deficiency of deficiency of pituitary hormones (microadenoma versus macroadenoma). Note that with an enlarging tumor,

⁸ The relation of exophthalmos to the hyperthyroid state is not precise since the development of prominence of the eyes and the lid lag may precede the hyperthyroid state or follow treatment of the disease. There may be a relation to thyroid stimulating hormone or to autoimmune factors.

infarction or hemorrhage within the tumor and pituitary may occur resulting in the syndrome of pituitary apoplexy and an acute increase of both endocrine and neurologic symptoms. An overview of the syndrome of hypopituitarism is provided by Vance (1994)

When neurological manifestations occur, it is because the tumor has extended out of the pituitary fossa to compress the structures at the base of the diencephalon - classically the chiasm, (suprasellar or extrasellar extension Fig. 23-9, 23-10, 23-11).

It was customary to divide these histologically benign tumors into three varieties based on the dominant cell type: (1) chromophobe adenoma (the most common), (2) acidophilic adenoma, and (3) basophilic adenomas. With the development of immunocytochemical techniques for the analysis of hormones, it is now possible to classify these tumors based on the anterior pituitary hormones secreted: (a) prolactin (70%), (b) growth hormone (15%), (c) adrenocorticotropin hormone (ACTH), (d) thyroid stimulating hormone (TSH) or luteinizing hormone (LH) or follicle stimulating hormone (FSH) (all rare), (e) no active endocrine agent (15-20%) (See Asa and Kovats 1983, Post et al 1980 and Cooper and Martin 1992).

Tumors of the anterior lobe are also classified into macro- adenomas (>10 mm in diameter) and microadenomas (<10 mm). Macroadenomas may be limited to the sella or may have extrasellar extent. Microadenomas are always intrasellar. Suprasellar extension often involves the optic chiasm producing a bitemporal hemianopia. The development of CT and MRI has provided noninvasive means of evaluating the anatomical relationships of these tumors to the surrounding structures, replacing the use of the pneumoencephalogram (Fig. 2-13). The MRI is now the study of choice (Fig. 23-11).

Before the development of these techniques, rare asymptomatic patients were found to have an enlarged sella turcica (pituitary fossa) on routine skull X-rays. Such asymptomatic patients with a pituitary mass are now found more frequently on CT and MRI scans performed for other purposes.

Prolactin Secreting Tumors: These are the most common variety of hormone secreting pituitary tumor. Many were previously classified as chromophobes or undiagnosed. In females, there is almost always an association with the syndrome of amenorrhea and galactorrhea. Because many females are evaluated for these early symptoms, diagnosis may be made at an early stage of microadenoma. There are, however, many other causes of amenorrhea and galactorrhea, some of which also produce elevation of prolactin levels. The administration of neuroleptic medications, which are dopamine antagonists, will block the normal inhibition of prolactin secretion by dopamine resulting in an elevated prolactin level and the accompanying symptoms. Dopamine is produced by the hypothalamic neurons whose terminals are closely related to the pituitary portal capillaries. Dopamine is the principal physiological inhibitor of prolactin release. In males, on the other hand, diagnosis often occurs at a later stage (macroadenomas)

when symptoms of visual field defects, diabetes insipidus and gynecomastia will clarify earlier symptoms of impotence, or decreased libido. The males will usually have, on plain skull X-rays, enlarged abnormal sellas, the female's normal sellas. Bromocriptine; a dopamine agonist, or similar agents will usually reduce tumor mass with a return of prolactin to normal levels and is the treatment of choice for patients with microadenomas (Webster et al, 1994, Serri, 1994). For rapidly progressive macroadenomas, particularly where visual loss is occurring or where bromocriptine can not be tolerated, trans-sphenoidal surgery is usually effective in removing the tumor, while preserving the function of both anterior and posterior lobes of the pituitary (Molitch et al 1980, Klibanski and Zervas 1991).

Growth hormone secreting (somatotroph) adenomas: (these tumors were formerly described as acidophilic or eosinophilic adenomas, however, some of these tumors were chromophobic). This adenoma presents predominantly the endocrine manifestations of increased secretion of growth hormone. The specific manifestations of this hyperactivity depend on the age of the patient. When the hyperfunction begins in childhood before closure of the epiphyseal lines, gigantism occurs owing to a generalized increase in size of the bones, particularly the long bones of the extremities. When the hyperactivity begins in the adult, after closure of the epiphyses of the long bones, the characteristic result is a progressive enlargement of hands, feet, skull, and mandible (acromegaly). Non skeletal tissues are affected as well with enlargement of the tongue, lips and nose.

As the tumor enlarges, the remainder of the pituitary gland maybe compressed and destroyed. The additional endocrine manifestations then are those of anterior pituitary hypofunction. Only late in the course, does this tumor extend outside of the sella and compress the optic chiasm. Most cases are now detected earlier in their course with the use of MRI (see hypothalamic chapter for an illustrative case).

Treatment usually involves transphenoidal surgery to avoid the long term systemic effects on multiple organ systems (with associated increased mortality). Treatment with bromocriptine a DOPA agonist may reduce tumor mass and function. More recently, there has been some success with the use of a somatostatin analogue. Somatostatin is a neuro-peptid found in hypothalamus and other brain sites which blocks the release of growth hormone induced by exercise and hypoglycemia, as well as determining basal levels of growth hormone. For additional discussion refer to Melmed 1990, Klibanski and Zervas 1991.

Corticotrophin secreting adenomas: (These tumors were formerly described as basophilic)

This variety, from the clinical standpoint, is the least common. These lesions do not grow to sufficient size to produce enlargement of the sella turcica and do not have any extrasellar extension. In 1932, Cushing described a syndrome of adrenal hyperfunction which he related to the presence of a basophilic adenoma of the pituitary (pituitary basophilism). The syndrome has since carried his name. It soon became evident, however, that many cases of Cushing's syndrome did not have a gross tumor of the

pituitary but were apparently due to primary overactivity of the adrenal cortex owing to hyperplasia (or less often to a tumor: adenoma or adenocarcinoma). In some instances, there was an association with malignant tumors involving the lung and, rarely, other organs. Subsequently, however with the development of modern imaging, most (80%) patients with adrenal hyperplasia have been found to have a microadenoma of the pituitary. These are referred to as Cushing's disease. The clinical and laboratory findings of Cushing's syndrome may be reproduced by administering ACTH (corticotropin) or cortisone.

The typical patient is a female, 25 to 50 years of age, with hypertension, obesity, elevated blood sugar, amenorrhea, and infertility. However the problem may also occur in children and adolescents where a growth retardation usually occurs(Magiakou et al ,1994). There is a characteristic plethoric facies and a "buffalo hump" dorsal kyphosis. The obesity is in contrast to the extremity weakness and actual muscle atrophy experienced by the patient. Hypertension occurs frequently. Dermatological manifestations include increased growth of hair on the face and extremities (hypertrichosis), and purple abdominal striae. Psychiatric disturbances are common with alterations in personality. Laboratory studies of urine and blood indicate increased output of steroids derived from the adrenal cortex and elevated levels of ACTH. Therapy relates to trans-sphenoidal surgical resection of the microadenoma. Where the adrenal problem is truly primary, surgery directed to the adrenal. For additional discussion refer to Frindling 1989, Turrell 1978, Klibanski and Zervas 1991.

Non-functional adenomas(residual of former chromophobe adenoma group).

These adenomas were formerly considered to be the most frequent tumor within the pituitary and the major type of macroadenoma. Most of these tumors are now found to be functional. Many are identified as secreting prolactin; some as secreting growth hormone. Approximately 15-20% of all tumors still remain within the non-functional group.

Progressive Course of Macroadenomas of the Pituitary: With progressive enlargement of the tumor, ballooning of the sella turcica may be visualized on plain X-ray of the skull (Fig. 2-13). As the tumor enlarges, it exerts pressure on the anterior pituitary, destroying the normal secreting tissue with resultant secondary hypofunction of the target organs - thyroid, adrenals, ovaries, or testes. Supra- or extrasellar extension is common with resultant compression damage to:

- a. *the optic chiasm* (or the adjacent optic nerves and tracts depending on the variable anatomical relationship of the chiasm to the sella and the direction of spread). The classic defect is a bitemporal impairment of the visual field from pressure on the chiasm - the syndrome of the optic chiasm (Fig. 23-10 and case 23-2).

- b. *the hypothalamus and the supraoptic-hypophyseal tract.* Many of the endocrine and metabolic alterations usually attributed to pituitary damage may reflect combined destruction of the pituitary and hypothalamus. Destruction of the supraoptic-hypophyseal pathways will result in diabetes insipidus.
- c. *the third ventricle* with resultant block of the ventricular system.
- d. *the third and sixth cranial nerves passing in the wall of the cavernous sinus* with resultant diplopia.
- e. *the temporal lobe as a result of lateral extension* with resultant temporal lobe seizures.

The actual extension of the tumor outside of sella is often preceded by severe headache, attributed to the pressure of the tumor upward against the diaphragm of the sella. It must be noted that the critical compromise of the optic chiasm with impairment of vision, , may occur in a sudden manner because of hemorrhage into and necrosis of the adenoma (a form of so-called pituitary apoplexy). The hemorrhage and necrosis result in a sudden increase in the mass of the tumor and a sudden increase in the degree of compression of the optic chiasm (See Riskind et al 1986 for an example).

The chiasmatic syndrome (bitemporal hemianopsia) is not always due to a pituitary adenoma. Other tumors in this area may invade and compress both the pituitary and the optic chiasm. The more common examples are aneurysms of the internal carotid artery, craniopharyngiomas, tuberculum sellae meningiomas, and optic chiasm gliomas. Thorough diagnostic evaluation, then, must be undertaken prior to surgery. The dangers of biopsy of an aneurysm in the belief that one is dealing with a solid chromophobe adenoma are obvious.

6) Neurological complications of other autoimmune disorders:periarthritis and lupus erythematosus. Neurological complications are frequent and include peripheral neuropathies of multifocal type(periarthritis) and acute demyelinating type(lupus), myelopathy, brain stem and cerebral infarctions, other neuropsychiatric cerebral disorders(ILupus). (Refer to appropriate Chapters for specific symptoms). (See also Bluestein ,1987, Lim et al ,1988,McCune et al ,1988, Sigal,1987.)

7) Remote (nonmetastatic) neurological complications of carcinoma. In these instances, either the central or peripheral systems may be involved. Presumably the lesions represent a toxic or immunological complication of the malignancy. In several instances specific immunological mechanism have been identified and specific antibody tests have been developed. Refer to Chapter 20 on the cerebellum.

The most frequent neurological manifestation is a combination of peripheral neuropathy and myopathy. The most frequent site of the primary lesion is the lung. A pseudomyasthenic syndrome has also been noted primarily with bronchiogenic carcinoma of the lung (See Chapter 6). *Limbic "encephalitis", encephalopathies, myelopathies, and cerebellar degenerations have also been reported.* The primary malignancy again has been usually in the lung, although on occasion ovary and breast have been the primary sites. Cerebellar degeneration has been reported prominently in ovarian malignancy and small cell cancer of the lung. (Specific immunological tests are available for diagnosis of cases with cerebellar degeneration). Another variety of encephalopathy, multifocal leukoencephalopathy, complicates malignant diseases which involve the lymphatic and reticuloendothelial system (lymphomas, lymphocytic leukemia, reticuloendotheliosis and sarcoid) and has been discussed earlier in the infectious section of this chapter. (Refer to Clouston et al, 1992, Dalmau et al, 1991 Posner & Furneau, 1991).

IV DEMYELINATING DISEASE

We have already discussed demyelinating disease in relationship to the spinal cord and brain stem. As we have indicated, there are essentially two types of diseases that affect myelin.

Type I: Destruction of normal myelin: the demyelinating disorders A primary destruction of normally formed myelin occurs with the production of the usual breakdown products of myelin. In this category are included: (1) the most frequent variety, multiple sclerosis; (2) acute disseminated encephalomyelitis (often a postinfectious type illness); (3) diffuse cerebral sclerosis, Schilder's disease (a diffuse demyelinating disease involving primarily the cerebral hemispheres and affecting children as a degenerative disease).

Type II: Mal development of myelin and the destruction of defectively formed myelin: the leukodystrophies.

Type I: Diseases involving destruction of normal myelin

Multiple Sclerosis. As we have indicated previously in chapters 9 and 13, there are in the early stages of multiple sclerosis several predominant clinical syndromes: the spinal cord form, the brain stem-cerebellar form, the cerebral form, and the optic nerve form. In most patients seen late in their disease course, a mixture of these various clinical syndromes is present. In general, a predominant cerebral form is less common than the other varieties. It should be noted, however, that the cerebral form tends to have a poor prognosis: significant progression tends to occur and remissions are less likely. The development of a significant and progressive dementia is not unusual. A typical example of a progressive cerebral form of multiple sclerosis is demonstrated in

Figure 27-28. The MRI scan of another progressive case is presented in Figure 27-29. Patients with severe cerebellar involvement also tend to pursue a progressive course (See Weinsbanker et al. 1989, 1991) The relationship between the relapsing /remitting form and the progressive form is discussed by Confavreux, et al (2000) and McDonald, (2000).

As discussed previously, (Chapters 9,13) not all cases are progressive. A significant proportion of cases (30-35%) with non cerebral and non cerebellar involvement follow a relatively benign course (Phadke, 1990). Treatment has been discussed in the earlier chapters in terms of immunomodulation with beta interferons, for patients with relapsing/remitting or secondarily progressive disorders. Acute exacerbations are treated with high dosage intravenous methylprednisolone.

There is no clear cut treatment for primary progressive cases, although immune modulation with high dosage methyl prednisolone and immune suppression with various agents has been attempted. (Refer to Beck et al 1992, Newcombe et al 1991, Winshenker et al 1991).

Recent overviews are provided by Waxman, (1998) and Noseworthy et al (2000).

Leukodystrophies. In the Type II group of diseases, there is a diffuse loss of myelin. The loss, however, involves the destruction of defectively formed myelin. The leukodystrophies are a rare group of diseases which occur primarily in infancy and childhood (Menkes 1990). Several varieties have been described:

Metachromatic leukoencephalopathy in which breakdown of myelin and engorgement of nerve cells with a metachromatic lipid occurs. The metachromatic lipid is chiefly composed of cerebroside sulfatides. The basic biochemical abnormality is an absence of the normal hydrolase activity of the enzyme cerebroside sulfatase. Peripheral nerve and central nervous system are involved.

Krabbe's disease, a form of leukodystrophy in which there are large multinucleated giant cells containing lipid-breakdown products (so-called globoid cells containing cerebroside). The enzyme which is deficient is galactoside cerebrosidase.

Adrenoleukodystrophy: This is an X-linked recessive disorder. A defect in the fatty acid oxidation system results in a failure to breakdown very long chains of fatty acids. Progressive neurological deterioration begins in childhood followed by evidence of adrenal insufficiency.

Pelizaeus-Merzbacher syndrome, a familial disease, in which there is a long chronic course with the white matter lesions distributed in a patchy manner but significantly affecting the cerebellum and brain stem out of proportion to other structures.

CHAPTER 29 EPILEPSY SLEEP AND COMA

Tables CHAPTER 29 EPILEPSY, SLEEP, COMA

Table 29-2: Incidence of Seizures of focal origin

PATHOLOGICAL PROCESS	INCIDENCE OF SEIZURES
1. Cerebral cortical infarction	25%. However infarcts limited to the internal capsule, basal ganglia brain stem and subcortical white matter do not produce seizures.
2. Trauma -penetrating head injuries -blunt (nonpenetrating) head injuries	In all types of head injury the risk of post-traumatic epilepsy is increased by the presence of :depression of skull fractures, dural penetration, or cortical laceration, or contusion or cerebral hemorrhage, or retained foreign body or prolonged unconsciousness or severe amnesia In all -40-50% -5%
3. Brain abscess	Overall 50%, with 25% of patients affected at onset.
4. Cerebral brain tumors*: Extracerebral (meningiomas): Intracerebral (gliomas):	(a) 50-60%. The actual incidence will depend on the location of the tumor, with a high incidence when tumor is close to the motor cortex. (b) 51%. Depends on the location, and grade of the tumor – high incidence when occurring close to the motor cortex or when a low grade astrocytoma or oligodendroglioma is present. Lower incidence in glioblastoma since course is shorter.
5. Porencephalic Cyst:	44%
6. Malformations (a) Focal cortical dysplasias, characterized by abnormal giant neurons and astrocytes and related to an early developmental event. This abnormality may merge with the syndrome of tuberous sclerosis	Note that not all of these focal or multifocal malformations (for example cortical microdysgenesis) will be detected by MRI studies. At the present time therefore the true incidence of seizures secondary to these malformations is unclear. Aberrant neural circuits have been postulated (Duchowny et al ,2000)

(b)Heterotopia ,and polymicrogyria related to events during neuroblast migration at 10-24 weeks prenatal gestation.	
7.Genetic defect	A specific mutation for a rare autosomal dominant nocturnal frontal epilepsy (see below).Other disorders such as benign Rolandic–Sylvian (mid temporal) epilepsy may occur on a familial basis

- Note in contrast that in the studies of Penfield and Jasper (1954) the incidence of seizures in infratentorial and thalamic tumors was insignificant.

Pathophysiology of Absence Seizures:

Despite much research over the last 55 years devoted to studies and hypothesis regarding the sudden appearance of the bilateral symmetrical and synchronous 3Hz spike wave discharge and the associated absence seizure considerable controversy remains. Several questions have been considered. (1) Where is the pathology located (cerebral cortex ,thalamus, thalamo -cortical interaction or reticulo cortical interaction or ,brain stem or all of the above)? (2)Why are the bilateral discharges relatively synchronous (thalamic or brain stem pacemaker or commissural systems)? (3)How does the discharge relate to the behavioral phenomena?

During the era of 1940s-1950s,two competing hypotheses emerged:1) the centrencephalic hypothesis of Penfield and Jasper (1947) which postulated a broadly defined pacemaker system involving thalamus,(and brain stem) driving a dependent cerebral cortex and 2)the diffuse cortical hypothesis advanced by Gibbs&Gibbs (1949).

Early Studies of Thalamic Stimulation and Recording: The centrencephalic hypothesis was an out growth of the earlier hypothesis of Jasper and Kershman (1941) regarding the role of a central subcortical (diencephalic or brainstem) pacemaker to explain the generalized synchronous discharges, and of the work of Dempsey and Morrison on the recruiting response.

The studies of Jasper and Droogleever-Fortuyn in 1947demonstrated that a stimulus-related 3 Hz. spike-and-wave pattern could, at times, be produced in the cat on stimulation of the mid-line or intralaminar nuclei of the thalamus (Fig.29-9The recruiting response and the more complex nature of the thalamocortical interaction has been discussed above . Hunter and Jasper subsequently demonstrated that arrest of movement may also occur from stimulation within the intralaminar system of the thalamus .However a similar response may also occur on stimulation of a number of cortical, subcortical, and brain stem sites. Williams (1953) reported origin of the

spike wave discharge in depth electrode recordings from thalamus in several patients with petit mal epilepsy. Most subsequent reports were unable to confirm this finding. The actual sites of recording in almost all of these studies were often unclear. Williams in a later paper concluded that a normal thalamus was required for the occurrence of the spike wave discharge.

The centrencephalic hypothesis was utilized to explain both primary and secondary bilateral synchrony and secondary generalization from a focus. The role of the corpus callosum was considered minimal.

Early Studies of the Role of Cerebral Cortex:

The cortical hypothesis was based on the observation that direct focal application of weak solutions of various convulsant agents such as pentylenetetrazol directly to a large area of cerebral cortex in the cat produced focal repetitive spike wave discharges which persisted despite severe bilateral damage to the thalamus (Gibbs and Gibbs, 1952). Subsequently, Ingvar (1955) demonstrated that spontaneous unilateral bursts of 2.5-3.0 spike-slow wave complexes lasting 3-4 seconds could be recorded from acutely isolated cerebral cortex in the cat. Such discharges could be enhanced by local application of convulsant agents. Similar repetitive spike wave discharges were obtained by Echlin et al (1959) by application of convulsant agents to chronic completely or partially isolated cerebral cortex in monkey and humans.

Bilateral Symmetrical Cerebral Cortical Foci Model:

Swank in 1949 demonstrated that the bilateral isolated frontal lobes of the dog, inter connected by the corpus callosum could generate synchronous spikes and slow waves after intravenous administration of the convulsant agent picrotoxin during sodium amytal narcosis.

In a series of experiments in the cat, Marcus and Watson in 1966 demonstrated that bilateral application of various convulsant agents to large symmetrical areas of cerebral cortex produced bilateral foci which rapidly interacted to produce bilateral synchronous and symmetrical patterns of discharge including 2-4 Hz spike or polyspike slow wave discharges. Behavioral correlation studies demonstrated phenomena appropriate for primary (idiopathic) generalized epilepsy including myoclonus of face and limbs, interruption of ongoing activities and generalized tonic-clonic seizures. As we will discuss below bilateral synchrony was mediated by the corpus callosum and did not require the mediation of subcortical structures such as the thalamus.

More definitive studies were then performed using the same experimental approach in the monkey (1968). Regional differences in capacity for bilateral synchronous discharge were apparent based on density of commissural fibers and threshold for discharge. Bilateral symmetrical foci of discharge in the parasagittal premotor areas of the monkey (areas 8-anterior

6) rapidly interacted to produce particularly well-developed bilateral synchronous and symmetrical bursts of repetitive 2.5-4.0 Hz spike slow wave complexes (Fig.29-10). The degree of synchrony for the discharge between the two hemispheres 0-15 msec was similar to the human patient. As in the human patient, the bursts of spike wave activity were triggered by hyperventilation and to a variable extent by drowsiness. In contrast bilateral synchrony in occipital and temporal areas was poorly developed.

The subsequent behavioral correlation experiments (1968) provided valuable information about the range of clinical phenomena associated with bilateral synchronous discharges.

1. Bilateral superior anterior premotor foci produced bilateral bursts of 3 Hz spike/slow wave discharges correlated with apparent absence seizures- short staring spells during which there was a variable interruption of ongoing motor activities and an alteration in capacity for response to visual and tactile stimuli (Fig.29-11).

Eyelid opening and variable myoclonus of head eyelids and eyes occurred. Responsiveness returned promptly at the end of the discharge.

2. Bilateral superior posterior premotor foci produced a bilateral discharge with greater polyspike components .The correlated absence seizure had greater myoclonic components involving face and forelimbs.

3. Bilateral precentral foci produced repetitive bilateral spike discharges associated with bilateral myoclonic jerks ,involving the legs for foci in the upper precentral area ;and the arms for foci in the middle precentral area. Eventually prolonged repetitive myoclonus and ,generalized convulsive seizures occurred. Generalized convulsive seizures also occurred in some animals with bilateral foci in anterior and posterior premotor locations.

4. Bilateral anterior prefrontal foci produced bilateral nonpropagated repetitive fast spikes and irregular slow wave discharges of 6-12 seconds duration but with no myoclonus and without an absence seizure.

The effects of bilateral foci within the anterior premotor area are predictable in view of the following facts:

- 1) the bilateral epileptogenic foci were produced in or close to the frontal eye fields.
- 2) There is a polysensory projection to this area of frontal cortex about the arcuate sulcus in the monkey
- 3) The widespread projections from area 6 to multiple sites within the ipsilateral and contralateral hemisphere have already been discussed above. A bilateral discharge in premotor area 6-8 would then alter the capacity of neurons in widespread cortical areas to carry out their normal activities in terms of perception and response. Certainly these cortical areas also project to various

subcortical areas which mediate behavior, for example area 8 has been characterized as a motor suppressor area with connections to the brain stem reticular formation.

In terms of the mechanisms underlying bilateral synchrony, in both the cat and the monkey, section of the major commissures essentially eliminated the synchrony of bilateral discharge in this model.

In contrast, when bilateral foci were produced in the bilateral cortical callosal preparation (Fig. 29-12) in which large blocks of cerebral cortex were isolated in each hemisphere from subcortical structures but remained connected via the corpus callosum, well-developed, bilateral synchronous bursts of 2-3 Hz spike or polyspike slow wave complexes or repetitive fast spike discharges occurred. The degree of interhemisphere synchrony was similar to that obtained in the intact animal. Similar results were obtained in cats with total ablations of thalamus, hypothalamus and rostral mesencephalon. The conclusions of the earlier studies of Marcus and Watson, employing acute and subacute epileptogenic foci have been confirmed in subsequent studies by Mutani and his associates (1969-1972) employing chronic cobalt/alumina foci in the cat. The interaction occurred with both symmetrical and asymmetrical foci (although the degree of interhemispheric synchrony was not as precise with asymmetrical foci (50-80 msec) versus the 0-15 msec of symmetrical foci).

Recent studies by Steriade and his associates (1998) have confirmed that the cerebral cortex provides the minimum substrate for the development of repetitive 2-4 Hz spike wave or polyspike slow wave complexes and the fast spike (10-15) Hz discharge in the cat after cortical isolation or thalamic ablation. The discharges were produced by topical or systemic administration of bicuculline, a GABA antagonist. The spike components of the complex were related to trains of depolarization in regular spiking neurons, with hyperpolarization occurring in these neurons during the slow wave of the complex. Fast rhythmic bursting cortical neurons fired many more action potentials during the spike-wave/polyspike-wave complexes. During the fast spike discharge, regular spiking neurons were tonically depolarized and discharged only single action potentials. Fast spiking neurons, in contrast discharged rhythmic spike bursts. Both types of activity, developed from the slow 0.5-0.9 Hz delta cortically generated oscillation as opposed to the spindle. Steriade et al consider the combination of the 2-4 Hz spike/polyspike complexes and the 10-15 Hz fast spike discharges to be analogous to the patterns found in the Lennox-Gastaut syndrome. These findings also mimic the patterns found in the bilateral cortical callosal cat preparation (Fig 29-12).

All of these observations do not rule out the role of the thalamus, basal ganglia, brain stem, or Substantia Nigra in modifying the occurrence of seizure discharges in the intact animal since in the intact animal there are clearly reciprocal relationships between these structures and cerebral cortex.

Julien et al (1975) demonstrated the selective effects of pharmacological agents in this model. Those agents effective against absence seizure in the human patient (ethosuximide and trimethadione) were also effective in the cat preparation with bilateral symmetrical cortical foci whereas, phenytoin exacerbated seizure discharges.

Feline General Penicillin Epilepsy Model (FGPE):

In 1968, Prince and Farrell first reported that intramuscular administration of large doses of penicillin in the cat could induce generalized bursts of 3.5-6 Hz spike slow wave discharges. Subsequently extensive investigation of this model of Feline Generalized Penicillin Epilepsy (Fig.29-13) has been pursued by Gloor and his associates. We may summarize the major conclusions.

1. The model is readily produced in the cat but to this point not in the monkey or rat. In the rat multifocal discharges occur. In man penicillin encephalopathy is associated with multifocal myoclonus and generalized convulsive seizures.
2. The discharges of spike and wave occur at 3.5-6 Hz not at the more usual frequency of 2 1/2-3.5 Hz for the monkey model and the human patient, but this is probably a function of phylogenetic differences.
3. There is a clear-cut behavioral correlation with the occurrence of myoclonus of face and extremities plus impairment of responsivity during the bursts.
4. Drowsiness clearly triggers the discharges. There is a close relationship of the discharges to the thalamocortical mechanism for the generation of sleep spindles, with an evolution of the normal drowsy related sleep spindles and or the thalamic (nonspecific system) recruiting response induced in the cerebral cortex into the spike-slow wave discharges. The intracortical mechanisms for this response have been discussed above. In contrast, arousal or stimulation of the brain stem reticular activating system eliminates the discharges.
5. This evolution to spike wave pattern occurs first in the cerebral cortex, later in the specific thalamic nuclei and late in the nonspecific thalamic nuclei. The thalamic nuclei are recruited into a cortical – thalamic-cortical oscillation.
6. The transformation of spindle to spike slow waves, results from penicillin-induced, increased excitability of cortical neurons. It has been clear since the initial studies of Gloor and of Fisher & Prince (19772) that the main action of penicillin is at the cortical and not at the thalamic level.

The spike of the spike-wave complex represents exaggerated spindle waves of summated EPSP's generated at the superficial axodendritic synapses; the slow wave, components the summation of IPSP's generated at a deeper cortical layer.

7.The synchrony of bilateral discharge is dependent on the corpus callosum .

8.In the cortical callosal preparation, the usual 3.5-6 Hz spike wave bursts fail to occur but penicillin does induce bilateral bursts of 1-2.5Hz spike-slow wave complexes. This is not surprising in view of the relationship to the thalamocortical spindle mechanism. A functional cortex and thalamus both appear to be required for the 3.5-6 Hz spike wave discharge in this model.

9.The prolonged hyperpolarization at the level of the pyramidal cell which corresponds to the surface slow wave is mediated by the action of GABA. In this model, the transition from the spike wave discharge of the absence seizure to the fast spike/tonic phase of the generalized tonic clonic seizure is correlated with a breakdown of the GABA related hyperpolarization.

10.The pattern of response to anticonvulsants is similar to that found in human absence seizures.

The Genetic Absence Epilepsy Rat From Strasbourg (GAERS):

A more recent model in the rat of the spike wave discharge has been developed by the Strasbourg group (1985). Their conclusions may be summarized as follows:

1.Generalized bilateral bursts of 7-11 Hz spike slow wave complexes occur in 30% of colonies of Wistar rats, usually during quiet wakefulness. The discharge begins at 4-5 weeks and persists throughout adult life.

2.Behavior during the burst is altered, animals are immobilized and have facial myoclonus.

3.By selective breeding a pure strain of GAERS may be achieved in which 100% of animals will have seizures with autosomal dominant transmission.

4.Discharges are predominant in frontoparietal cortex and posterolateral thalamus but medial thalamus and limbic structures are not involved.

5.Unilateral cortical depression eliminates both the cortical and thalamic discharge of the ipsilateral hemisphere.

6.Lateral thalamic lesions eliminate the cortical discharge of the ipsilateral hemisphere. Thus a thalamocortical interaction is required for the discharge to occur.

7.Section of the corpus callosum disrupts synchrony of bilateral discharge; independent spike wave discharges occur in each hemisphere.

8.The discharges are suppressed by those anticonvulsant agents effective against human absence epilepsy: ethosuximide and trimethadione. These agents have been postulated to have anti seizure

effects due to their capacity to decrease low threshold calcium currents. Such currents have a significant role at the level of the thalamic reticular nucleus. However low threshold calcium channels have also been found in cortical pyramidal and nonpyramidal neurons.

9.Administration of GABA/A agonists increases spike-wave discharges but GABA/A antagonists had no effect. In contrast while GABA/B agonists also increased discharges, GABA/B antagonists decreased the discharges.

Genetic Models in the Mouse:

At present 6 inbred mouse strains have been reported with spike wave discharges and absence seizures (Table 29-6). Five of these strains have 6-7hz spike-wave discharges; one strain has 3hz discharges. While these strains differ as regards the chromosome involved, genetic heterogeneity is present with at least 6 different gene mutations already identified. All have other neurological defects with ataxia, a frequent theme suggesting cerebellar degeneration is present in addition to the seizure disorder. The importance of these strains relates to the monogenic inheritance of presumed ion channel mutations.

The differences in frequency of the spike –wave discharges in these various species may reflect species differences in thalamocortical and callosal projections within the cerebral cortex and of the types of cerebral cortex as discussed above. In the monkey model with bilateral premotor foci, the essential discharge is at 2-1/2 - 3 Hz. In the monkey model utilizing gamma hydroxy butyrate (a GABA antagonist) not discussed here, the spike wave discharge also occurs at 3 Hz. In the cat, the discharge of acute bilateral symmetrical foci was variable, including 2-1/2 - 3 Hz. In the chronic studies of Mutani and Fariello (1969) of bilateral symmetrical foci, the bursts consisted of 5 Hz spike slow wave complexes similar to the feline penicillin model. The rat model has a 7 - 11 Hz discharge and the various genetic mice models primarily 6-7 Hz.

The other possible explanation is that these are models of different disease, with different mechanisms but with similar phenotypic expression in terms of behavior and EEG pattern .Thus the absence seizure may represent a spectrum of diseases as discussed by Bercovic et al (1987).

As regards the question of why awareness and responsivity are altered during the absence seizure ,several explanations are possible :

- 1)there is widespread involvement of cerebral cortex-particularly of the multimodality sensory projection areas and of other frontal and temporal association areas involved in working memory etc.,so that these areas can not participate in their normal activities
- 2.there is impairment in the capacity of the thalamus to transmit information.

3.both of these explanations are operational in the intact animal, since discharge of cerebral cortex secondarily spreading to thalamus via the cortico –thalamic system will also alter the capacity of the thalamus to transmit information.

TABLE 29-6 Single locus mouse models of spike wave seizure discharges

MOUSE NAME	EEG DISCHARGE	CLINICAL/PATHOLOGY (PHENOTYPE)(+absence)	GENE/PROTEIN
Tottering	6-7Hz spike- wave	Ataxia,cerebellar degeneration Focal motor seizures	Calcium channel a1A subunit
Lethargic	5-6Hz spike-wave	Ataxia Focal motor seizures	Calcium channel B4 subunit
Slow wave epilepsy	3 Hz spike-wave	Ataxia, cerebellar degeneration ,GTCS	Na ⁺ /hydrogen exchanger NHE1
Stargazer	6-7Hz spike-wave	Ataxia	Unpublished____
Mocha	6-7Hz spike-wave	Pigment dilution, increased bleeding. GTCS	Unpublished
Ducky	6-7Hz spike-wave	Ataxia, hind brain and spinal cord dysgenesis	Unpublished

Models of Myoclonus and of JME and Pathophysiology:

In each of the models discussed above in relation to absence seizures, myoclonus also occurs . In the bilateral foci model in the monkey discharging foci in the posterior premotor areas resulted in bilateral polyspike slow wave discharges with clinical absence seizures containing greater myoclonic phenomena involving face and forelimbs. With bilateral foci in the precentral area bilateral ,spikes associated with myoclonic jerks of the extremities occurred (legs if upper precentral, arms if middle precentral). In these examples the pathology is clearly cortical and he

underlying basis of the bilateral synchrony of discharge as already discussed involves the corpus callosum.

The penicillin model involves a generalized discharge of 3.5-6 Hz which although described as spike wave, at times as illustrated, resembles polyspike slow wave complexes. The described clinical phenomena clearly consists of absence with myoclonus of face and limbs. In both models, a transition from nonconvulsive absence seizures with myoclonus to generalized convulsive seizures may occur.

As regards the behavioral components of myoclonus, as we will discuss in greater detail below, the early studies of Muskens (1928) in the pre-EEG era, clearly indicated the essential role of brain stem structures since myoclonus could occur after decortication.

As discussed above, a significant proportion of the patients with JME will have the electrical discharges and accompanying myoclonus induced by the use of repetitive stroboscopic photic stimulation, with similar findings in the non seizure relatives.

In 1966, Killiam et al reported the discovery of a widely distributed model of photosensitivity in the baboon *Papio papio* - originating from Senegal. In many animals, as in human patients eyelid closure alone may be sufficient to induce discharges. Subsequent studies of this model of generalized epilepsy by Naquet and his associates (1972) demonstrated that the bilateral discharges of poly spikes and slow waves originate at a cortical level: "Frontal Rolandic Cortex" (Areas 4 and 6) and are accompanied by bilateral myoclonus of eyelids, face and limbs. At times, there is progression to generalized tonic clonic seizures. Other cortical and subcortical areas are secondarily involved by the discharge. The synchrony of bilateral discharge is dependent on the corpus callosum. Visual evoked responses in occipital cortex are normal, late (40 msec) components of the visual evoked response, in Areas 6 and 4, are markedly abnormal. For the response to occur, cortico-cortico pathways from Areas 18, 19 of the occipital region to these frontal areas must be intact.

Analysis at a more molecular level suggests that the discharges begin in the dendrites of superficial cortex. Possible abnormalities in calcium ion regulatory mechanisms have been described. Local chronic infusion of GABA into the motor cortex or into Areas 18-19 occipital cortex, eliminates both the frontal Rolandic discharges and the myoclonus. Administration of drugs that impair GABAergic transmission or production may increase photosensitivity in predisposed animals or produce occipital discharge in non-photosensitive baboons (e.g., isoniazid, thiosemicarbazide, allyl glycine). Studies of amino acids in cerebrospinal fluid of the photosensitive baboon demonstrated a decrease in inhibitory transmitters such as GABA and taurine and an increase in excitatory amino acids such as aspartate.

In terms of other models of primary generalized epilepsy, already discussed in relationship to the petit mal absence seizure and myoclonus, the feline generalized penicillin epilepsy model is photosensitive. Bilateral bursts of spike wave discharge are triggered in 51-55% of animals tested, 60-90 minutes after IM penicillin. The dopamine agonist apomorphine administered on a systemic basis, reduces photosensitivity. This agent was even more effective in blocking photosensitivity in photosensitive patients (12/14 total block) but had no effect on spontaneous bursts of spikes and waves, in these patients with primary generalized epilepsy. Total block or reduction was also obtained in 6 patients in whom photosensitivity was one component of a progressive myoclonic disorder of the types discussed above. On the other hand, diffuse cortical application of 6-hydroxy- dopamine bromide (6 OHDA) which depletes dopamine in nerve terminals, significantly increases photosensitivity in the cat. As discussed by Quesney and Reader (1990), intermittent photic stimulation reduces the release of endogenous dopamine in both visual and somatosensory areas of cat cerebral cortex. Dopamine mediates cortical inhibition and if the cortex were already in an abnormal or borderline state of hyperexcitability, photic stimulation might well trigger paroxysmal discharges.

The other model of petit mal absence epilepsy and of petit mal absence with myoclonus discussed above, bilateral foci in premotor areas of the monkey (anterior or posterior) does not trigger discharges effectively with photic stimulation but is very sensitive to hyperventilation. **It is likely then as will be evident from the studies of pentylenetetrazol, that the photosensitive baboon has a more widely distributed alteration in excitability affecting neocortex and possibly other structures.** Some of these baboons also have myoclonus without neocortical discharges and without the photic stimulus presumably originating at a subcortical site(s). In general however, in the photosensitive baboon, the discharge begins in motor cortex-since this is the neocortical area of lowest threshold (see **chapter 17**). The feline penicillin model also involves a diffuse cortical hyper excitability. The photo pentylenetetrazol model in the cat, combines a subthreshold dose of pentylenetetrazol with photic stimulation and also involves a diffuse increase in cortical excitability. There are however significant species differences among primates as regards the distribution of the trait of photosensitivity. Even among the baboons found in Senegal, the frequency of the trait varies based on geography raising the question of possible genetic inbreeding factors.

From a genetic standpoint, Dooze et al (1973), have suggested that photosensitive primary generalized epilepsy may represent a separate disease from the primary generalized childhood

absence epilepsy .The majority of patients with childhood absence epilepsy are not photosensitive, but are sensitive to the effects of hyperventilation.

Pathophysiology of generalized tonic-clonic seizures

The anatomical substrate of the generalized convulsive seizure may be briefly considered. As in the absence seizure, two aspects of the question must be considered: the cortical electrical discharge and the behavioral phenomena.

Studies of the cortical electrical activity.

The studies regarding the origin of the associated electrical discharges are relatively clear .Threshold and subthreshold dosage of pentylenetetrazol have been employed to induce the generalized seizure activity. The initial studies by Starzl et al (1953)in the cat indicated that the electrical seizure started in the cerebral cortex and then radiated to deep structures involved particularly the specific thalamic sensory relay nuclei. The nuclei of the diffuse thalamic system were implicated at a much later point. The spike wave activity seen in the clonic phase was never seen in the thalamic nuclei. Complete destruction of the thalamus and midbrain sparing the auditory pathway allowed triggering of cortical discharge by auditory or medial geniculate stimulation. When cortex was completely isolated ,the dose required to produce the electrical seizure (15 mg/kg) and the pattern of discharge was similar to the intact cat. Seizure activity could be produced in the thalamus deprived of all cortical connections and demonstrating its normal activity ,only at a much higher dose (90-120mg/kg).

Pentylenetetrazol Studies In The Monkey

Subsequent studies in the monkey and cat by Marcus et al (1969,1985) have confirmed these conclusions and emphasized the role of cortical and callosal factors in this model.

Repeated Subthreshold dosage intact monkey: Bilateral discharges occur in the precentral recording areas ,regions of low threshold to electrical stimulation.

Threshold dosage intact monkey (15-20mg/kg): (fig 17-25) There is significant regional variation in sites of onset and in the synchrony of bilateral discharge. In the early stage of discharge, bilaterally synchronous discharges of spikes, poly spikes/slow waves occur in the precentral/premotor recording areas .The subsequent bilateral fast spike discharges and then the spike slow wave stage begin as well in these same areas of low threshold and dense interhemispheric callosal connection. Actual degree of bilateral synchrony for poly spike discharges was similar to that resulting from bilateral symmetrical cortical foci. In contrast, middle/superior temporal and occipital recording areas of higher threshold and sparser callosal connection demonstrate a later multifocal discharge. Subsequently, a generalized spike slow wave

discharge occurs in all recording areas initially rapid then slowing to be followed by a period of electrical silence.

Complete section of major commissures in the acute cat and monkey and the subacute monkey: Bilateral synchrony in all stages of discharge was abolished (fig 17-26)

Partial section of commissures subacute monkey-with preservation of posterior 40% of corpus callosum: A greater degree of bilateral synchrony was preserved in temporal occipital areas and in superior frontal areas at onset and at cessation in temporal –occipital. Precise synchrony was thereafter disrupted .

Bilateral cortical Callosal isolate (Cat): The general pattern of bilateral discharge including the bilateral synchrony were similar to the intact cat (Fig 17-27)

Studies of the Behavioral Aspects of the Generalized Tonic/Clonic Seizure.

Conflicting conclusions have resulted in part related to differences in species, methods and age of animals.

The earlier work of Muskens employing the dog clearly indicated the capacity of the midbrain preparation and the decerebrate preparation to develop both myoclonus and generalized convulsive seizures . Lombroso and Merlis reported depression of reflex myoclonus induced with subconvulsive dosage of pentylenetetrazol in the monkey following ablation of motor cortex. Rodin et al (1971) reported a dissociation between the EEG and behavioral aspects of the megimide induced seizure in cat and man. The onset of the myoclonic jerks and the tonic phase of a generalized convulsive seizure induced in the cat by the convulsant agents, megimide, or pentylenetetrazol, coincided with bursts of high voltage, high frequency discharge in the brain stem reticular formation at mesencephalic and pontine levels. The studies of Velasco & Velasco (1990) in the cat- confirmed onset of discharges in the mesencephalic reticular formation, and then pontine reticular formation, midline thalamic nuclei and the orbital frontal cortex - (all prior to onset of cortical electrical seizure activity and reflecting the ascending and descending pathways from the mesencephalic reticular formation). In related experiments, in the cat, lesions at the level of mesencephalic reticular formation and lesions between midline thalamus and orbital frontal cortex prevented EEG seizures induced by threshold doses of pentylenetetrazol, and suggested an ascending facilitatory influence. These findings however are at variance with the conclusions presented above regarding the basic substrate for the EEG discharge. Other studies suggest a descending inhibitory effect mediated by orbital frontal cortex on this system. Their conclusion was that the mesencephalic reticular formation is crucial for the development of the tonic phase whereas the clonic phase depends on forebrain structures.

Magistris et al (1988) found that threshold for EEG discharge following pentylenetetrazol in intact, pre collicular or spinal transected cats was similar (26mg/kg.) At this dose level only in the intact cat did generalized convulsions occur. In cats with pre collicular transection seizure threshold for induction of convulsions required a much higher dose (63mg/kg) and the seizures consisted of generalized tonic contractions. In cats with high spinal cord transections, convulsions required an even high dose (167mg/kg) and the convulsions consisted primarily of bilateral asynchronous jerks although tonic contractions were also observed.

In the rat, facial and forelimb myoclonus is associated with limbic structures [131].

CONCLUSIONS REGARDING THE BILATERAL SYNCHRONOUS DISCHARGES OF IDIOPATHIC EPILEPSY:

- 1. All of the models leaving aside the mouse models suggest that the basic pathology involves an increased hyper excitability of neurons at the cortical level. This is consistent with the now available neuropathological data and MRI data in the human. The PET scan data is unclear.**
- 2. The bilateral synchrony in the various models in the monkey, baboon, cat and rat is dependent on the corpus callosum and the related major commissures. There is no direct anatomical substrate in the thalamus of the human providing the basis for the bilateral synchrony found in idiopathic epilepsy.**
- 3. There may be multiple possible mechanisms providing the substrate for the oscillations of excitation and inhibition responsible for the spike-slow wave discharge. The minimal substrate is built into the design of cerebral cortex and of the cortical –callosal circuits. There is little doubt that discharges having begun in cerebral cortex do subsequently spread to the thalamus, basal ganglia, the brain stem and spinal cord and these structures do reverberate back to cerebral cortex. However to what extent, the cortico-thalamo-cortical oscillation is necessary to produce and sustain the spike –wave complex in the human is uncertain. The idiopathic epilepsies and the spike wave discharge may represent a biological spectrum, rather than a unitary disease.**
- 4. Behavior is a more complex matter. There is a representation and re representation of patterns of behavior at various levels of the neural axis.**

GUIDELINES FOR MANAGEMENT OF SEIZURE DISORDERS:

Evaluation: Over 75% of diagnosis in neurology is dependent on the history, this is even

more important with regard to seizure disorders. However in this case, information must be obtained from witnesses regarding events for which the patient may have little recollection. Information from the patient and witnesses regarding focal manifestations, aura etc are vital. The neurological examination is critical in terms of the presence or absence of signs suggesting focal cortical pathology. Laboratory studies should include a complete blood count, blood sugar, calcium, electrolytes and creatinine/BUN. The electroencephalogram performed during awake and sleep states may provide information regarding focal or generalized electrical seizure discharges or slow wave activity. The yield of the EEG may be increased by such activation procedures such as sleep deprivation, hyperventilation and photic stimulation. All patients should have an imaging study. Based on the information considered above, this should be whenever possible an MRI. When this is not possible, then a CT scan with and without contrast should be obtained. With a single nonfocal seizure as discussed below, a CT scan probably would suffice until the costs of MRI studies is reduced, etc.

Management of a single generalized tonic clonic seizure The diagnosis of epilepsy implies recurrent seizures. Many patients experience only a single generalized convulsive seizure. Serious questions have been raised as to whether such patients require any therapy with anticonvulsants. At the time of the initial seizure, one does not know whether additional seizures will occur. The risk of recurrent convulsions has been discussed by Hauser, 1985. Essentially, the following guidelines are suggested, based on the data of these studies. The risk for recurrence is relatively low if the following conditions are met: (a) The single seizure had no possible partial onset or components, based on reliable descriptions (b) The seizure occurred under conditions where - sleep deprivation, stress and/or some degree of alcohol/drug withdrawal \pm fever were present. (c) With detailed history from relatives and witnesses, there were no possible prior minor seizures such as absence, myoclonus or simple partial or complex partial seizures (d) The birth history and growth and development have been normal (e) No family history of a seizure disorder is present (f) The neurological examination is normal (g) No mental retardation is present (h) The complete EEG, particularly with sleep deprivation, photic stimulation and hyperventilation, is normal. (i) the imaging studies are normal.

If these conditions are met, then the likelihood of recurrence is relatively low⁹ and the use of anticonvulsants may be deferred until a recurrence intervenes.

⁹ The study of Annegers, et al (1986), included most of these requirements and suggested recurrence rates of 16% at one year, 22% at 3 years and 26% at 5 years. Moreover prescribed medications (? levels) did not alter the results.

Management of seizures secondary to specific underlying metabolic or structural pathology: Obviously, patients in whom seizures are secondary to a discrete metabolic disturbance require correction of the underlying biochemical or endocrine abnormality. Patients in whom seizures are secondary to a progressive space-occupying lesion will require additional evaluation and surgical therapy when indicated, in addition to anticonvulsant therapy.

Management of patients with recurrent seizures (epilepsy): The epileptic was formerly considered an incurable, in a sense, marked by the Gods or possessed by demons.¹⁰ Occasionally in history or in certain cultures, such a sacred stigma might convey some benefits. In general, however, the epileptic has been considered a social outcast subjected to various legal restrictions as regards employment, operation of a motor vehicle, marriage, procreation and immigration. These restrictions were usually imposed irrespective of the cause of the seizure disorder. With the introduction of successful methods of therapy, many of these restrictive regulations have now been removed. Anticonvulsants provide the mainstay of therapy. **Table 29-8 in the text** outlines the pharmacologic properties of the major anticonvulsants. **Table 29-9 in the text** lists the putative molecular basis of anticonvulsant action.

In general anticonvulsants which are effective against partial and secondarily generalized seizures are effective in the experimental maximal electroshock test, a model of seizure spread and produce Na⁺ channel blockade. In general those drugs that are effective against spike wave epilepsies, particularly absences are effective against experimental pentylentetrazol induced seizures, elevate threshold and produce T Ca⁺⁺ channel blockade. However benzodiazepines and barbiturates are also effective against this type of experimental seizure.

Table 29-10 in the text relates drug choice to seizure type. *Partial and secondarily generalized seizures* are usually responsive to phenytoin, carbamazepine, valproic acid or phenobarbital. Newer add on agents include lamotrigine, topiramate, tiagabine, gabapentin, felbamate, zonisamide and vigabatrin. *Absence seizures* are responsive to ethosuximide and valproic acid. *Myoclonic seizures (juvenile myoclonic epilepsy)* respond to valproic acid. *Primary generalized tonic clonic seizures* respond to valproic acid, phenytoin or to carbamazepine. *Infantile spasms* respond to ACTH or to benzodiazepines. Lennox-Gastaut syndrome may respond to lamotrigine.

¹⁰ For a historical review see Temkin, 1947.

Many seizure patients, however, remain subjected to a form of discrimination in employment which is usually not imposed on workers with other types of disability or handicaps.

Status epilepticus (generalized or partial) responds to intravenous benzodiazepines.

Status Epilepticus: (Refer to table 29-11 for epidemiology of status.) This is a serious condition requiring acute treatment. One may encounter continuing generalized tonic clonic, (primary or secondarily generalized partial)complex partial, or absence seizures. The latter two types may be manifested as prolonged confusional states. The condition, however, is usually defined, with regard to generalized convulsive seizures, as a state in which seizures continue beyond the usual duration of a single seizure or in which seizures recur so frequently that consciousness is not regained between seizures. Note that the usual duration of the tonic-clonic phase of a generalized convulsion is one minute or less. Although the old definition defined the duration prior to assignment of the term epileptic status as 30 minutes, most experts would now shorten this duration to 5-10 minutes ,therefore allowing earlier treatment . If allowed to continue, generalized tonic clonic (grand mal) status is a threat to life with cerebral anoxia, cerebral edema, aspiration pneumonitis, hyperthermia, hypotension and cardiac arrest as possible complications. Prolonged grand mal status may be followed by prolonged confusion and a residual impairment of recent memory due to damage to hippocampal areas (see Chapter 30). Temporal lobe seizures may be sequelae of such a prolonged state. Therefore the earlier the recognition and treatment, the better the results.

The etiology of status epilepticus can be divided into three major groups:

I. Status in patients with prior seizures

II. Status as the initial acute presentation of a focal or generalized CNS process.

III. Status as the acute manifestation of overwhelming systemic disease.

I. Prior Seizures: The most common causes of status are (a) acute withdrawal or omission of medication (b) new metabolic factors and fever.

II. Initial manifestation of CNS process: (a) Focal - Tumors, abscess or subdural empyema. (particularly in the frontal area) or embolic infarcts or hemorrhagic infarcts ,(b) Diffuse Disease - Encephalitis or meningitis (particularly in children).

III. Systemic diseases:(a) metabolic disturbances in infancy, (b) hypertensive encephalopathy or uremia, (c)respiratory failures particularly in infants, (d)toxic complications (aminophylline and high dosage intravenous penicillin,the latter in the presence of renal failure and prior CNS insult)

Treatment of status epilepticus has 4 essential components:

(1) *Assure stability of vital functions* : (a) Airway (b) Breathing (c) Circulation : maintain blood pressure in normal range (d) maintain temperature in normal range

(2) *Stop the seizures:* intravenous benzodiazepines: lorazepam, (0.1mg/kg at rate of 1-2

mg/min to maximum dose of 8 mg) or diazepam (5-20 mgs at rate of 1-2 mg/min), or midazolam.

(3) *Prevent additional seizures*: load with intravenous fosphenytoin (18-20 mg/Kg at rate of 50 mg/min).

(4) *Determine the cause*: this will require EEG and CT scan or and /or MRI blood levels, etc as well as neurological examination and observation of the seizures. Must still make distinction - focal versus generalized. If status does not end rapidly at the Emergency Room level continued intensive care unit monitoring, including continuous EEG will be required. General anesthesia including intravenous pentobarbital may be required.

Non-convulsive status: For acute onset of confusional states, consider the diagnosis of complex partial and absence status: The diagnosis will depend on both immediate neurological examination and immediate EEG as well as trials of intravenous therapy.

This is a skeleton outline of management of status for greater details see Delgado-Escueta, 1982 and Pellock&Delorenzo, 1997.

EXPECTED RESULTS OF EPILEPSY TREATMENT

When all cases of recurrent seizures are considered, complete control can be obtained in 50 to 60 percent. An additional 25 percent will have a reduction in seizure frequency. Approximately 15 percent will remain as a refractory group in whom seizure control will not be obtained with standard medications (The majority of this refractory group will have either complex partial seizures or Lennox Gastaut Syndrome).

Whether control is attained depends on whether generalized or complex partial seizures are considered. In generalized epilepsy, complete control should be achieved in 63% with significant reduction in 25%¹¹. In complex partial epilepsy, the results are less encouraging with complete control in 20-35%.

When cases are controlled on medication, treatment should be continued for at least a seizure-free period of 3-5 years. The EEG should no longer demonstrate any discharges before any consideration is given to a gradual discontinuation or reduction of medication. If patients are seizure-free 2 years and medication is withdrawn - 36% will recur over the next 4 years (most in the first 2 years). If seizure-free 5 years, the relapse rate is 30% over next 10 years - with largest number in first year.

How long to treat when the patient is seizure-free then remains unclear. The decision

¹¹ Complete control is obtained in most patients with classical absence seizures.

to discontinue medication must be individually tailored to the specific patient and will include considerations such as:

1. The type of seizure: whether partial or primary, generalized: patients with partial seizures are much more likely to recur compared to primary generalized¹².
2. Whether focal neurological findings are present: Patients with focal neurological findings are more likely to recur.
3. How long seizures were present before control attained. Those with a long time to seizure control are more likely to recur.
4. Whether seizure discharges are still present in the electroencephalogram: Some but not all, suggest recurrence is more likely if seizure discharges persist.
5. Concerns of the adult patient, as to whether a seizure recurrence will impact on continued ability to operate a motor vehicle and on employment.
6. Concerns regarding side effects of anticonvulsants particularly, teratogenic effects in the offspring of the pregnant seizure female. In general, the non-seizure population has a 2.5% risk of malformation, seizure patients not on anticonvulsants - a 3.5% risk. Seizure patients on anticonvulsants - 5.5% risk.

Teratogenic effects occur primarily in the first trimester and consist of cleft lip, neural tube closure defects and congenital heart disease. *The risk of malformation is increased if any of the following factors is present. a. poor seizure control b. polypharmacy c. high blood levels d. use of trimethadione.* Risk of neural tube defects can be significantly reduced by administration of folic acid.

Other side effects of anticonvulsants fall into general groups:

- a. Allergic - dermatological, hepatic, immune for which the drug must be discontinued
- b. Dose related (ataxia, drowsiness, dizziness, diplopia)- for which the dose must be lowered
- c. Chronic - hematological, lymphatic, lupus, etc.

For discussion of remissions and relapses see Callahan, et al, 1982; Juul-Jensen, 1983; Shinnar, et al 1985; Pedley, 1988; Thurston et al, 1982. For discussion of anticonvulsants and teratogenesis see Janz, D., et al, 1982, Delgado-Escueta, 1992. For discussion of side effects of anticonvulsants see Schmidt, 1986.

¹² An exception to the primary generalized rule relates to juvenile myoclonic epilepsy: Response to valproic acid is excellent with prolonged remission but discontinuation of medication will result in seizure recurrence.

In the refractory patient, if a persistent focal origin of the seizure is evident from a clinical or electroencephalographic standpoint, consideration may be given to the surgical removal of the focal cortical area of pathology (atrophic scar, cyst, low grade glioma, vascular malformation). The most frequent refractory patient is the patient with complex partial seizures. In most instances, the underlying pathology involves hippocampal sclerosis. In such cases, temporal lobectomy may be the appropriate and most effective procedure (Wiebe et al, 2001). Other cases, refractory to treatment, include the symptomatic myoclonic and akinetic or tonic seizure types. That is, the progressive myoclonic epilepsies, infantile spasm and Lennox Gastaut syndrome. In these and other cases, a vagal nerve stimulator may reduce seizure frequency.

There are, however, various cases which represent apparent failures of treatment in a situation where control should be obtained or where seizure control once established, has been lost. The following reasons then should be considered in their approximate order of frequency:

- (1) Patient compliance. A withdrawal effect can occur if the omission has been abrupt. Check blood levels
- (2) The Patient is taking his medication but is not receiving a sufficient amount to establish an adequate anticonvulsant blood level. Check blood levels and if necessary with phenytoin the free unbound fraction (usual therapeutic range is 1- 2 ug/ml). Alternatively push dosage of medication until therapeutic effect is attained or dose related toxicity occurs.
- (3) The patient is receiving the wrong medication for the particular type of seizure. Phenytoin (Dilantin) and Carbamazepine (Tegretol) have no effect on absence seizures. Ethosuximide (Zarontin) has no effect on focal or temporal lobe seizures. Juvenile myoclonic epilepsy is very responsive to valproic acid but is often poorly responsive to other medications
- (4) Sleep deprivation has been present significantly increasing clinical and electrical seizure discharges.
- (5) The patient has been ingesting alcohol with a subsequent alcohol withdrawal effect.
- (6) Significant underlying emotional disorder or stress are present.
- (7) An underlying metabolic disorder or infection with fever is present.
- (8) An underlying progressive neurological disorder is present.
- (9) In the course of seizures, head trauma has occurred with additional areas of discharge: orbital frontal and anterior temporal.
- (10) Status epilepticus has intervened with the development hippocampal sclerosis. As a result, the patient who initially had primary generalized epilepsy of tonic clonic (grand mal type) now also has developed complex partial seizures.
- (11) Secondary epileptogenesis has occurred with development of multiple foci

(Mirror focus and kindling, see discussion above).