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Editorial

This issue of the International Journal of Neurology is devoted to pathology of the peripheral Nerve.

This Editorial will deal with its fundamental principles in a concise form.

The peripheral nerve is constituted by bundles of nerve fibers that are neuronal prolongations enveloped in the sheath of Schwann.

In the case of motor fibers, their neuronal body is situated on the anterior corn of the gray matter of the spinal cord.

Concerning sensitive fibers they are linked to the cells seated in the rachidean ganglia, the vegetative fibers have their cellular body located in a ganglion of the sympathetic chain.

The nerve fibers are covered by a conjunctive envelope.

The neuronal elongations that constitute the nerve fibers are covered in all their trajectory by the Schwann cells.

The Schwann's cells have two different ways in enveloping the nerve fibers, they may take several fibers at the same time, or be limited to just one of them.

In the first case they are regarded as "amyelinic" fibers and in the second, when just one fiber is covered by the Schwann cells, when it is considered a segment of the myelinic sheath, it's called "myelinic" fiber.

The amyelinic fibers have a slow velocity of conduction, the myelinic ones propagate the nerve influx with great velocity, the myelinic sheet is an important factor in the acceleration of the conduction of the nerve fibers and this velocity is increased when it has a greater diameter.

Through the axon is conducted a molecular flux originated fundamentally in the neuronal body, that sustains the myelin sheath that is produced by the glial cells.

The axon may have a considerable length, in the man it may surpass a meter.

The sheath with molecules in it located, have their biosynthesis almost exclusively in the cellular body, and in order to maintain their functions they are constantly renovated.

They neuronal body, the dendrites and the axon, the axonal membrane, the neurotransmitters and the trophic interactions between the pre and postsynaptic elements demande a constant biochemical activity, whose center of synthesis is fundamentally sited in the neuronal body.

In the axon is produced a two way molecular traffic, one called orthograde oriented from the neuronal body toward the distal end of the axon. Inversely, the macromolecules addressing to the neuronal body constitute the retrograde axonal transportation.

It is important to remark that the Schwann myelinic cells receive a trophic contribution from the axon and in this way the integrity of the myelinic sheets is preserved. The Schwann cells promote the elaboration of the myelin sheaths, securing the integrations of their specific proteins and their phospholipids. It must be emphasized that myelinic sheaths are affected when the axonal conduction is suffering.

Pernicious factors, toxic, metabolic, mechanics, may deteriorate the molecular interchanges that are sustained between the axonal unity and the annexed cellular elements, with which essential interchanges are performed.

This determines a functional damage of the nerve fibers and are at the basis of their neuropathic disturbances.

Concerning the orthograde axonal transportation, which we have already mentioned, we wish to remark that there exists two different types, the rapid axonal flux, and the slow axonal flux.

The rapid axonal flux has a velocity of 300 milimeters per day, transporting the constituents of the axonal membrane in addition to those belonging to the presynaptic membranous system, in this way the enzymes like acetylcholinesterase, phospholipides, glucoproteins, and other elements are renewed. The intra-axonal pathway taken in general by the membrane constituents is the reticulum endoplasmique. In this axonal transport it is possible that the actine may be at the base of its mechanism, that may occur by the actine-myosin combination, similar to those of the muscles or by the possibility of the reversible polymerization.

Regarding the slow axonal flux, its mechanism of propulsion, has not been up to now well defined.

By this slow axonal flux the majority of the axonal proteins are mobilized to velocities between 1 and 10 mm per day. By its means are transported the tubulin of the microtubules.

The elements of neural filaments the actine, and the analogues of the myosine, are all elements formed from the cytoskeleton axonal. Also the axon is provided of enzymes solubles of the axoplasma, notably, the choline-acetyltransferase.

By both axonal fluxes, the rapid or the slow, the enzymes that control the biosynthesis of the neurotransmitters in the neuronal terminals are mobilized above all for the cholinergiques, monoaminergiques, gabaminergiques, neurons.

We will refer now to the retrograde axonal transport which determines that numerous membranous macromolecules are conducted from the nervous terminale to the body of the cellular neuron, to contribute there to the integration of new macromolecules organized to be mobilized in an orthograde direction.

The retrograde movement is performed by means of mechanisms involved in the orthograde movement.

Some of the molecules mobilized from the nervous terminals to the cellular body has an informative function and in reaching the cellular body modify the production of certain molecules.

It is understood that these molecular mobilization in both orthograde and retrograde sense, give place to the neuronal bodies, and its elongations are adapted to its functional requirement in an accurate way.

We will refer now to the degeneration and regeneration of the nerve fibers in the course of the peripheric neuropathies, emphasizing in the marked interdependency of the axon and the Schwann cells.

When a primitive attack of the neuron happens that generates a localized blockade of axon, a wallerian degeneration is produced that is installed on the distal sector of the fiber that has been separated from the cellular body.

The axon degenerates and the Schwann sheath loses its characteristic details, the myelin is absorbed by the macrophages. After severing the nerve the functions of conduction of the distal end of the fiber disappear in a few days. The regeneration takes place from the central extreme of the damaged axon or from the collateral of neighboring axons. In these have mediate the persistence of the endoneural sheaths. The remyelination is performed by means of the persistent Schwann's cells. With the regenerative process the velocity of conduction is regained and progressively reaches its initial value.

A retrograde distal degeneration may occur caused by perturbations of the neurons' cellular life, and disturbs from the very beginning in the more distal fiber regions.

In these conditions, the demyelination and the degenerative process of the axon are developed from the end of the nerve fiber toward the neuronal body. The regenerative process determines a collateral proliferation of the nerve fibers that were not damaged.

The velocity of the nerve conduction may remain unaffected as a consequence that in the nerve there exists healthy fibers as well as degenerated ones.

The nerve potential has its amplitude diminished because of its fiber degradation.

When the Schwann cells are originally damaged the segmentary periaxial neuritis is generated, and it is accompanied by the disappearance of the myelin sheet, in different segments between two narrowing of Ranvier. The continuity of the axon is preserved, sometimes morphologic degeneration are present as a consequence of the demyelination. The amyelinic fibers are the ones that suffer more when the Schwann cells are originally disturbed.

In this type of neuropathy a slowing of the velocity of the nerve conduction is present, and a diminution of the amplitude of the nerve potential is also observed.

The perspective of regeneration of the lesion of the myelin sheath relative to those of the axon, it may be assured that in the first one the lapse of time necessary for its recovery is shorter than in the second ones.

It is necessary to remark that it is not possible to establish in the clinical practice a clear division between the different kinds of deterioration of the nerve fibers, because between the neurons and the myelin sheets exist in its structures and functions a close relationship, because of that when a lesion is originated in one of its parts, for the above mentioned anatomical condition affects the others.

This means that from the clinical point of view it is not possible to establish a physiological clasification of the peripheral neuropathies. It is preferable to establish as a basis to clasify the different groups of peripheric neuropathies in the topography and the etiologial factors.

We will refer now to the different anatomo clinical types of the peripheric neuropathies.

The mononeuritis constitutes the isolated suffering of a nerve or one root and its cause is generally traumatic or at least mechanical.

If simultaneous damages exist in several nerve trunks a multineuritis takes place. Each nerve is affected isolated, and the functional disturbances are afterwards shown in an asymetrical way. There is not a general causal reason and they are not originated by unique mechanism. The focal ischemia may be present with a certain frequency as an ethiological factor.

The polineuritis is characterized by a peripheral nervous compromise in a symetric form, and with a distal predominium, without noticing a systematization of the roots or trunk.

The different types of fibers that integrate the sensitive, vegetative and motor nerves are affected. The cause of the process may be of a degenerative, toxic or carencial order, and be involved in anunequal involvement of the different fibers.

In the polyradiculoneuritis the proximal and distal parts of the limbs, are affected and it may be observed that the compromise are proyected towards the trunk muscles and to the cranial nerves.

Generally an inflammatory neuropathy produces a demyelination of the peripheric nervous fibers in all its trayectory predominating in its proximal part.

The functional disturbances have a relatively rapid improvement because

the neuropathy is originated by a demyelination.

Sometimes the clinical picture is a consequence of a neoplastic demyelination that damages in an extensive manner the roots.

POLYNEURITIS

This process has extensively damaged the peripheral nerves and thus generates a loss of strength; the sensibility and reflexes are also diminished.

Concerning their etiology this may be due to toxic or metabolic factors.

In general terms it may be affirmed that many times the exact cause that starts the degenerative process in the peripheral nerves is unknown.

It is possible that a deficit in the vascularization of the nerves be the cause of the degenerative process in the periarthritis nodosa, lupus erythematosus and in the mononeuritis of diabetes mellitus.

This factor has not a major importance in the genesis of the polyneuritis in which toxics or metabolics perturbances are involved. It is possible that in these cases biochemical disturbances particularly enzymatic are involved, that damage the nutrition of the nerves.

When isoniazid and hydralazine is administered and a polyneuritis is generated, these happen when the metabolism of the pyridoxine is disturbed.

Many of the heavy metal chemical compounds used in industry and in medical therapy, toxins of bacterial origins and other compounds, are the responsible factors of the genesis of the polyneuritis.

We will refer now to the metabolic perturbances related to the polyneuritis. They are: general dietary deficiency, lack of vitamins, illnesses with cachexia, endocrinal perturbances, amyloidosis, sarcoidosis, infectious diseases and uremia.

PATHOLOGY

Generally a non inflammatory degeneration of the peripheral nerves is present. It is observed at the beginning of the process swelling and fragmentation of the myelin. With the evolution a damage of the axis cylinders appears.

Retrograde alteration that leads to a suffering of the neurons ventral horns. In chronic cases a degeneration of the fibers of the posterior funiculi.

In some cases no damage of the myelin sheet or axis cylinder is observed. The conduction by the axis cylinder is apparently interrupted by a swelling of the axis cylinder or of the myelin sheet.

It is possible that in these cases a real improvement may be achieved in a short lapse of time. On the contrary the improvement in the clinical picture when this is configured from the anatomical point of view for a true destruction of the myelin sheets and axis cylinders, is slow.

It is necessary to remark that the possibility of recovery is in direct relationship with the entity of the damage suffered by the axon.

In the multiple peripheral neuritis the process followed for the regeneration of the nerves is similar to that originated by the damage inflicted in an individual nerve by a trauma.

CLINICAL ASPECTS

The polyneuritis may appear at any age; but is more frequent in young people or middle-aged adults. It is also more frequent in men than in women.

The clinical picture has a different lapse of time for its installation, in the case of infections the polyneuritis appears from 24 to 72 hours; the alcoholic

polyneuritis by vitaminic deficiency is also rapidly installed; and other cases that are more frequent the clinical picture its developing is slower and its installation may evolve in several weeks.

The symptomatology is as follows, paresthesia, pains, loss of sensibility muscular weakness.

The nerve's suffering is that which causes the polyneuritis clinical picture, which means that the different etiologies may give place to similar symptomatology; but it may be variation in the distribution of the paralysis, and in the perturbation of the sensibility, linked to the underlying causes.

Related to the importance of the nervous damage a division of the polyneuritis cases may be done: 1) clinical picture of pain and paresthesias with slight or no motor compromise, 2) somewhat more severe. Pain and paresthesias, moderate weakness in the four limbs, hypoesthesia distal in the limbs and tendinous reflexes diminished, 3) cases with symptomatic severity, total paralysis of the limbs, weakness in the trunk muscles, it may be also accompanied by weakness in the face pharyngopalatine muscles, anesthesia in the distal part of the limbs and cutaneous and tendinous a reflexia.

The muscle weakness is generally more pronounced in the distal part of the limbs. Only on rare occasions are the proximal muscles more affected.

If the cases are of a moderate severity, the fingers are paralyzed with weakness in the wrist and ankle, which determines the hand and foot fall. There are very severe cases in which the paralysis of the four limbs is complete and also are affected muscles of the trunk, sometimes with sphincterian perturbations and the muscles of the cranial nerves are also affected.

Concerning the sensibility, when we are dealing with an alcoholic polyneuritis, this is extensively affected, and all the sensibility is compromised, in a stocking like fashion.

Pain is originated by pressing the nerves, and the muscles are tender to pressure.

The cutaneous and tendinous reflexes are abolished.

The skin is smooth and shiny. Vasomotor and trophic perturbations may be observed.

In any of the polyneuritis forms, but more frequently in the alcoholic, psychic perturbances may be observed. Confusion, disorientation, amnesia, and confabulation, the so called "Korsakoff psychosis".

The cerebro spinal fluid may be altered in the polyneuritis in any kind of etiology. Frequently an increase of the proteins is observed, and also of the fluid pressure. On very few occasions a slight pleocytosis is added. The proteins with scarce frequency may reach elevated figures.

Blood and urine examinations may show the excretion of porphyrins in the neuritis of acute porphyria, in the cases of intoxication by lead or arsenic with polyneuritis an excessive quantity of these metals may be found in the blood and urine.

In cases of diabetic polyneuritis an elevated blood sugar is found.

The polyneuritis generally have, a good evolution with a total or partial recovery. Death is not frequent, except in the infectious or porphyric forms. This may also happen if this illness is complicated by bronchopneumonia, cerebral disturbances, such as Korsakoff psychosis or polyencephalitis hemorrhagica superior if severe vitamin deficiency exists.

Its evolution is related to the intensity of the nerve's damage; if there is destruction of the myelin sheet and axis cylinders, the recovery will be very slow.

In this last condition muscular wasting is severe and a complete recovery is not achieved.

Concerning the treatment it is necessary to eliminate the noxious condition that determined the polyneuritis and to treat the metabolic alteration that may be the determinant factors of the polyneuritis; at the same time, treat the neuromuscular ailment. The patient must be kept in bed with the limbs protected from bed covers by means of a cradle.

The diet must be integrated with vitamins which are indispensable if the clinical picture shows a scarcity of vitamins.

It is necessary to consider if the polyneuritis shows paralysis of the diaphragm and intercostal muscles, artificial respiration may be indicated. It is necessary to be careful in avoiding the production of pressure sores.

THE RAPUTIC INDICATIONS

Physiotherapy, mobilization, exercises, massages. Do not allow the patient to leave the bed, and do not let him walk, until it is sure that he is able to endure the effort.

Alcohol and Polyneuritis. *The factors implicated in this kind of polyneuritis are discussed. It is generated in persons who during many years drank a great deal of alcoholic drinks. This patient generally has a daily defficient diet. It is possible that the neurological ailment may be due to the alcoholic intoxication to which nutritional defficiency is added. This causes this ailment to be called alcohol-vitamin defficiency.*

It is necessary to remark that this polyneuritis is more frequent than all other kind of polyneuritis considered altogether.

It is more frequent between the fourth and seventh decade of life; but it is possible that it may occur before and after this lapse of time. It also happens that it is five or six times more frequent in men than women.

It is also necessary to remark that the alcoholic polyneuritis symptomatology appears very slowly during several weeks or months.

It is very rare that this kind of illness develop its clinical course in several days.

The simptomatology that first appears are pain in the leg and paresthesia in hands and feet. Followed by a muscular weakness in the legs with locomotor ataxia and dropping of the foot. A progressive paralysis of the legs is observed, and the motor declination is spread to the muscles of the trunk and superior limbs.

The muscular weakness is superior in the distal sector of each limb and the extensors are more involved than the flexors. The sensibility seems to be more compromised in the distal sector.

The muscle compression promotes a painful reaction, and nerves are also sensitive to the pressure.

The deep reflexes in the inferior limbs are abolished, and also in the superior limbs if the case is severe. The abdominal cutaneous reflexes are diminished or abolished, and there is no plantar cutaneous response. Concerning laboratory findings it may be said that a secondary type of anemia and a moderate leukocytosis may be observed. In about the third part of the cases a decrease or absence of hydrochloric acid in the gastric juice is detected.

It is possible to observe alcohol in the blood and the cerebro spinal fluid, if these studies are carried out immediately after examining the patient for the first time. In the cerebro spinal fluid a high pressure may be found, and in some

occasions a slight pleocytosis and an augmentation of the proteins may be observed, also mid-zone colloidal gold curve may be present.

This process has a prolonged evolution; it sometimes occurs that even when the treatment is initiated the clinical picture gets worse.

If mental symptoms, involvement of the hypothalamus and midbrain for hemorrhagic polyencephalitis exists, the possibility of a fatal evolution increases.

The intensity of the clinical picture is of a variable degree, if the process is severe several months may elapse before the patient may leave the bed, and sometimes it may take even two years before he may return to his daily duties.

In 1887, Korsakoff described a psychical picture associated with the polyneuritis, characterized by confusion, disorientation, loss of memory and a tendency to confabulate. This syndrome of Korsakoff is more frequently associated to alcoholic polyneuritis; but sometimes it is present in the polyneuritis of pregnancy and in other etiologies. The alcoholic may present the syndrome of Korsakoff even if a polyneuritis is not present, and also appears in patients suffering from meningitis, cranio-encephalic trauma, subarachnoid hemorrhage or brain tumors.

It is observed with twice as much frequency in men than women. In these patients symptoms and signs of hepatic disturbances may be observed, and also convulsive crisis.

The patients with a Korsakoff's syndrome frequently have anemia, also a leukocytosis.

In the cerebro spinal fluid the same changes as in the polyneuritis may be found, even if the increasing of protein is more frequent and may reach higher levels.

In untreated cases the mortality is of 50 %. The recovery is slow and may be incomplete in surviving patients. The mental defects may conduce to the incapacity of the patient.

Wernicke in 1881 made the description of a clinical picture with an oculomotor paralysis of a sudden installation, locomotor ataxia and impairment of consciousness.

Generally this syndrome is associated with chronic alcoholism, but it has been also observed in pernicious vomiting of pregnancy cases, and in states of undernutrition or avitaminosis. In the case of alcohol its cause is in the associated nutritional deficiency. The lesions found at the necropsies are located in the hypothalamus, in the peri-aqueductal gray and in the neighborhood of the third ventricle. Necrosis of neurons and vascular alterations are also observed.

The evolution of the Wernicke's syndrome cases are variable, if the lesions are of a moderate entity, the recovery is achieved. A mortality of 14 % has been observed. It generally attacks the men between young and middle ages.

Sometimes is associated with a Korsakoff's type of psychosis and of polyneuritis. Several types of oculomotor palsies, nystagmus, ataxia, tremor and changes in the states of consciousness, from coma to a mild confusion may be found. Sometimes, convulsive seizures, optic neuritis, anemia, and liver diseases may be present.

Of the clinical manifestations enumerated the ataxia, and ocular symptoms improve with treatment in days or a few weeks. The polyneuritis and the mental symptoms last for months.

The basic treatment is a high calory diet and concentrated vitamins parenterally and by mouth.

Nutritional deficiency

We will mention now other neuropathies due to nutritional deficiency.

The beri-beri is the clinical manifestation of a severe lack of vitamin B₁.

Whether or not signs of cardiovascular deficit exist, the neurological manifestations habitually show the form of a polyneuritis syndrome similar to that observed in an alcoholic intoxication.

A polyneuritis due to deficiency of vitamin B₁, may also be observed in people subjected to a prolonged restrictive diet, who suffer digestive ailments that provoke an abnormal absorption and an undernutrition.

It is also seen in cases of increased metabolic needs, (gravidic polyneuritis)

The pelagra appear as a consequence of a deficiency of several factors pertaining to the complex of Vitamin B, and mainly the vitamin PP.

The polyneuritic syndrome appears mainly as a sensitive disturbance, psychic perturbances (confusion, mental deterioration) cutaneous ailments, (erythema). burlous eruption) are frequent. It is necessary also to consider a possible participation of the spinal cord and the brain stem (hypertonia, pyramidal syndrome, nystagmus).

Toxic and medicaments

We will consider now the polyneuritis generated by toxics and medicaments. The toxic substances generally act upon the cellular metabolism of the neuron, more rarely its action is electively executed on the Schwann's cells.

Its clinical aspect depends on the nature of the intoxication and the affinity of the toxic for such type of fibers; but it also depends on the modality of the intoxication. (acute, subacute, and chronic) and the action of the toxic upon the organisms' tissues, aside of that of peripheral nervous system. We will choose now some samples considering its frequency and the general experience extracted from each one of them.

We will not deal with a limited list. In studying any polyneuritis, the quest for a toxic cause either professional or medicamentous, must be methodically handled.

The arsenical medicaments capable of originating a neuropathy are almost disused now, and the arsenical intoxications observed at present are accidental or criminal.

The neuropathy is a sensitive motor polyneuritis very similar to the alcoholic polyneuritis; but it calls our attention because of the unusual importance of its pains. This kind of polyneuritis may follow digestive troubles (nausea and vomits) isolated or repeated when it is generated by an acute intoxication. Its onset has an insidious character, when the intoxication is prolonged, due to doses relatively feeble.

An hyperkeratosis palmo plantar, anestrated aspect of the fingernail, facilitates the diagnosis that will be reaffirmed by the dosage of the arsenic in the urine (demonstrating an actual intoxication) and for the dosage in the hair and the finger nails, allowing in a certain measure to detect the date of the intoxication. The medical treatment is the B.A.L.

British anti, lewicite, which must be administered in doses of three mg per kilo of body weight every four to six hours, during two or three days, and after twice a day during ten days. The intoxication by Thallium is generally due to the accidental ingestion of this metal in rats poisons. Or by the use of depilatory creams that contains thallium acetate, or by the employment of salves for treating the ring worm.

The neuropathy generated by the intoxication by tallium is similar to the pcyneuritis arsenical. Gastrointestinal symptoms are present which are followed after two to five days by numbness and weakness of the limbs, convulsions, delirium, craneal nerves palsy, and blindness.

This clinical picture corresponds to the ingestion of great quantities of thallium.

If the intoxication occurs in a chronic form, the clinical picture is constituted by a polyneuritis similar to the arsenical, with intense pains, associated frequently with an optic neuritis and alopecia. The optic discs get to be atrophied, there is a blurred vision and there is a narrowing of the peripheral fields and loss of central vision.

In the chronic form of the intoxication the pronostic for life is good. The polyneuritis may arrive at a complete recovery. The treatment consists in avoiding the use of the toxic substance and the employment of B.A.L.

An Intoxication by Triorthocresyl Phosphate, engenders polyneuritis.

The toxic may come by ginger extract contaminated with triorthocresyl phosphate also in a sporadic way, the intoxication by the drug may be originated by the use of apiol as an abortifacient. It may be also the case that the toxic, contaminates the cooking oil.

Like in other intoxications the polyneuritis appears after digestive perturbances. The symptoms of the beginnings are pain and paresthesia and weakness of the legs. In some cases the weakness has an evolution to a complete paralysis of the lower extremities and weakness in the upper extremities.

It is observed in the distal part of the limbs a defect in the cutaneous sensibility; the vibratory sense may be also disturbed. A diminution or abolition of the deep reflexes may be also observed.

The regressive process is slow frequently, a complete recovery is not achieved and in the evolution there may appear signs of spinal cord damage.

The intoxication by lead generates a polyneuritis with deficitary predominance in the motor function. It is affected above all the extensor muscles of the muscles of the fingers and wrist.

Frequently the intoxication is occupational in workers dedicated to the lead, painters, typographers, pottery glaziers, accumulator makers. In these cases the lead is principally absorbed by the lung and skin.

There is also the accidental intoxication, as a consequence of the ingestion of lead by mouth by means of food and drinks contaminated by lead. The children may be intoxicated by the ingestion of lead paint.

In the polyneuritis by lead the motor defect is habitually bilateral but an upper limb may be more affected than the other. Generally disturbances of the sensibility are not observed. It is difficult that the muscle of the lower limbs become compromised; in some cases the vocal cords are involved.

In the child it may be observed an encephalopathy that originates convulsions, disturbances on the watchfulness, in some cases hemiplegia, also papilledema.

The cerebro spinal fluid shows an elevated pressure, the protein content may be increased, sometimes an hypercytosis is observed.

Particularly in the boys another sign of lead poisoning is observed. Anemia with basophilic stippling of the red cells, lead colic, hypertension, deposition of lead pigments at the gingival margins.

The lead may be dosed in the urine and the excrements, and the spinal cord fluid.

Concerning its evolution, fatalities are very rare; cases who have suffered an encephalopathy due to an intoxication has been observed in children.

The polyneuritis in its evolution reaches the highest levels in its symptoma-

tology, after several days or weeks. Generally it has a good evolution toward a complete or nearly complete recovery. The treatment imposes the removal to the exposure to lead, and to apply the techniques used to treat the polyneuritis.

In a few cases it has been observed the onset of symptoms and signs akin to those of amyotrophic latero sclerosis.

An important therapeutic measure is to precipitate the lead that exists in the bones and blood and this may be achieved giving milk basic disodium phosphate, calcium salts, and biosterol to the patient.

The lead of the body may be eliminated, employing iodides, acid salts and citrates. Good therapeutic results may be obtained by the use of EDTA (ethylenediaminetetraacetic acid).

Certain professional activities that use toxic materials may generate intoxication that produces polyneuritis, we will mention the carbon sulphur, acrylamid, insecticide.

The polyneuritis may also have a medicamentous cause. We will mention in the first place the isoniazid. Its toxic effect is increased by the alcoholic habit of the patient. There also exists a genetic predisposition. The neurological picture shows a painful polyneuritis of the four limbs with a moderate motor deficit. It is considered that the process is produced by a deficit of B6 vitamin (pyridoxine)

This vitamin has a very satisfactory action in the treatment of this polyneuritis.

Nitrofurantoin, a urinary antibacterial agent is another medicamentous factor of polyneuritis, with sensitive motor symptomatology. This clinical picture is highly facilitated for its development, when renal insufficiency exists.

Another toxic factor that produces polyneuritis is the disulfiran, an antioxidant which interferes with the normal metabolic degradation of alcohol in the body. It is frequently used in the alcoholic treatment.

Vincristine sulfate has an antineoplastic activity, is used in cases of breast cancer, leukemia, lymphoma, sarcoma Wilm's tumor. It is a medicine that may have a toxic action over the nervous system.

It generates paralytic and amyotrophic neuropathies with a symmetrical distribution on the limbs. At the onset the clinical picture shows pains and paresthesia and abolition of reflexes in the lower limbs.

Very frequently neurovegetative manifestations are present, characterized by abdominal pains and disturbance in the intestinal transit.

The peripheral nervous pathways are impaired in the axonal sector.

The toxic action of this medicine reaches also the central nervous system, originating convulsive seizures and damage on the spinal cord.

The metronidazole, an orally effective trichomonicide used in the treatment of infections caused by *Trichomonas vaginalis*, in some cases may produce a polyneuropathy in which the sensitive disturbances predominates.

Toxic infectious polyneuritis

We will study now the toxic infectious polyneuritis. We will mention in the first place the diphtheritic neuropathie.

This kind of neuropathies are originated by the diphtheritic toxin that damages the Schwann's cells directly, giving place to the periaxial segmentary neuritis.

The damage of the peripheric pathways is present between the third and fifth week. Before the motor perturbances are evident the paralysis of the muscle appears after a palatal paralysis and of the accommodation. The lower limbs show clear evidence of deficitary elements, and it is in them where the symptoms are more pronounced. The sensibility disturbances, are marked particularly on

the deep sensibility, and the motor deficit is in general moderated, the reflexes are abolished.

Ophthalmoplegia, transient dizziness, numbness and loss of taste on the tongue and paralysis of the vagus and phrenic nerves are sometimes present in the clinical picture.

The evidence of a paralysis of accommodation or palatal weakness as an initial symptom of a polyneuritis of a progressive and slow evolution suggests the possible diphtheric etiology of the process.

It may be associated with a moderated hyperalbuminorrachia.

The evolution is slowly regressive. Aside of prevention there is not another specific therapy.

In the past the diphtheric polyneuritis was considered as a common complication of infections with *Corynebacterium diphtheriae*, actually it is less frequent due to the passive immunization of the population and to the precautions use of serum when the infection appears.

The frequency of the incidence of the nervous lesion is related to the severity of the infection, and in the delay in the administration of antitoxin for the original infection.

Botulism is another cause of polyneuritis, originated by the ingestion of food in which the proliferation of the bacillus of botulism has originated the accumulation of a toxin.

Six immunological types of the clostridium *Botulium* has been identified.

In the human being botulism frequently is produced by the ingestion of toxin originated by the types A, B, and E. The botulism of the A and B types are due to the ingestion of vegetables or meat badly processed. The type E is associated to sea food.

Neuropathies originated by botulism are due to a blockade of the emission of acetylcholine at the nerve's ending levels. It acts on the cholinergic system in the junction of the striated muscle and nerve, and also at the autonomic system level.

The neurological ailments appear a few hours or days after the ingestion of the toxin, preceded or not by digestive troubles. Oculomotor disturbances appear, that predominate in the intrinsic motricity, with fixed and non reactive mydriasis, deglutition and phonation, troubles may be added with deficit in the neck and the proximal limb muscles. Intense dryness of the mouth has been observed a paresis of the bowels and bladder may be also present.

The process's treatment deserves the antitoxin injection. Considering that this ailment has a neuromuscular blockade, guanidine may be prescribed because it elicits the outflow of acetylcholine from the nervous endings. In some cases in which the respiratory muscles are involved, there may be the need to practice a tracheotomy.

In this kind of ailment there generally are several members of the same family suffering from it. This fact must be taken into account if the diagnosis of the illness is posed. The contaminated food must be also studied in order to establish its nature.

The diagnosis of the illness may be posed with acute anterior poliomyelitis which may be discarded if the lumbar puncture gives a normal cerebro-spinal fluid. When the intoxication is slight generally a complete recovery is achieved. When the intoxication is of great intensity death is the final result as a consequence of pulmonary involvements, circulatory failure, or respiratory paralysis.

Metabolic disturbances

We will refer now to the neuropathies provoked by generalized metabolic

disturbances.

We will consider in the first place the diabetic neuropathy.

The lesion of the peripheral nerves in the diabetes are the consequence of a degenerative process. In some cases it is limited to an abolition of the reflexes and isolated perturbances of the vibratory sensibility.

In some cases there is a latent neuropathy that may be evident by the slowness of the conduction velocity; this is a fact that may be observed very frequently.

There does not exist a relationship between the severity of the neurological troubles and the importance of the metabolic disturbances. It may happen that the discovery of a neuropathy allows to recognize an undetected diabetes. It may be observed that the diabetic neuropathy is less frequent in the diabetic below 30 years than in those that are over fifty.

It may be established that 4 per cent of the diabetics show a neuropathy.

Men and women are affected in the same proportion. It may be also seen in children.

Generally the clinical picture shows a motor weakness, paresthesias, and reflex loss. A severe disease of polyneuritis is seldom observed.

It has been attempted to explain the neuropathy as related with the arterio-sclerotic disturbances in the nerve, vitamin deficiency or an interference with carbohydrates metabolism.

Up to now, it has not been possible to obtain proofs that give credit to this possibility.

Degenerative changes in the peripheral nerves, nerve roots, and posterior column of the spinal cord, have been observed retrograde or degenerative changes may be present in the ventral horn cells.

There is a lesion on the Schwann's cells, that it is clinically evident by the slowing of the conduction velocity. There are also lesions of segmentary demyelination with the integrity of the axon. In some cases lesions on the axons may also appear.

Generally in the clinical picture predominate the sensitive symptoms, paresthesias and intense pain in the lower limbs.

Afterwards a decreasing of the leg strength occurs, without generally reaching the state of paralysis.

There is weakness in the deep reflexes, it has been also observed cutaneous hypoesthesia, and a deficit of the vibratory and positional sensibility.

The facial diplegia and oculomotor palsies are less frequent.

A modification in the size, format and reaction of the pupils may be observed. Sometimes sphincter disturbances are observed.

In the diabetic may appear uni or bilateral paralysis of the third, fourth or sixth cranial nerves, even without other signs of polyneuritis. These kinds of manifestations are due to small lesions in the brain stem.

The diabetic polyneuritis may have complication such as orthostatic hypotension and tachycardia, peripheral vascular diseases, and retinitis. Arthropathies, mal perforant, that has the characteristic of the neurotrophic ulcerations have also been observed.

The vegetative neuropathy is very frequent and may show an orthostatic hypotension, perspiration disturbances, impotence, vesical and intestinal troubles.

When in a diabetic an acute and extensive polyradiculoneuritis is present accompanied by cranial nerve lesions, and a dissociated hyperalbuminorachia,

there is the possibility that we are dealing with a true diabetic polyradiculoneuritis of a syndrome of Guillain Barré. In these cases the disturbances are less regressive and frequently there are persistent deficitary signs present.

In the diabetic there may exist a hyperalbuminorachia with no signs of neuropathy.

A peripheric facial paralysis frequently relapsed or alternating may be due to the existence of a causal diabetes.

In order to establish an adequate treatment the principle measure is to correct the metabolic disturbances. To accomplish this it is necessary to administrate fractional injection of insulin before the meals at the same time to prescribe ample vitamin therapy.

Kinestherapy, with mobilization and exercise performed in a sustained way with the purpose of promoting the rapid development of the amyotrophy. It is important to remark that these are more reversible than the sensitive neuropathies that frequently are persistent.

Hypoglycemic Neuropathy

Important amyotrophies of the limbs have been clinically observed. It may be detected when an insulin secreting tumor exists.

Neuropathies of Pregnancy - Gestional Neuropathy

It must be emphasized that it is not frequent that a pregnancy become complicated with polyneuritis. The symptomatology linked to the neuritis will develop slowly during the middle months of the pregnancy or later, also it may be initiated after the delivery.

The clinical picture of this process may be preceded by signs and symptoms of toxemia of pregnancy, especially pernicious vomiting; this neuritis is attributed to a dietary deficiency.

It has been observed that the gestional polyneuritis occurs more frequently in the first or second pregnancy. In this neuropathy the presence of mental symptoms and Korsakoff's syndrome is frequently observed and generally the symptoms and the evolution, are similar to those that are seen in the alcoholic form of polyneuritis. Very often tachycardia and a hypochromic or macrocytic anemia.

Concerning the pronostic it may be said that kind of polyneuritis has a great rate of deaths. In the surviving patient the recovery is very slow and residual defects may be present.

The treatment is similar to those prescribed for the other kinds of polyneuritis.

Neuropathy of the Renal Insufficiency

In renal insufficiency cases, performing the study of the velocity of nerve conduction, a latent neuropathy is frequently observed. The neuropathy may produce paresthesias, pains, burning sensations, to the low limbs level, or one truly polyneuritis sensitivo motriz with distal predominance.

Concerning the lesions of the axonal neuropathies and of the segmentary demyelination they are discussed. The nervous lesion may improve with the treatment of the metabolic disturbance by means of the dialysis.

One important resource for the improvement of the neuropathy is the renal transplant.

Nervous complications of porphyrin metabolism. *It is necessary to establish that the disturbances in the porphyrin metabolism with an augmented elimina-*

tion in the urine and feces are divided in to two groups: the symptomatic and the hereditary.

Regarding the symptomatic group, the ingestion of poisons such as lead and other pathological states originate excretion of porphyrin.

Hereditary porphirias may be present in several forms.

The acute intermittent porphyria is a genetic ailment as a Mendelian dominant characterized by a perturbation of the metabolism of the porphyrins that produce an excessive urinary elimination of uroporphobilinogen and of its precursor delta-aminolevulinic acid.

Symptoms and signs isolated or combined, gastrointestinal, psychiatric and neurological, are originated.

The neurological disturbances have an acute onset, on some occasions they may be promoted by the use of some drugs especially barbituric.

The paralysis are more or less extensive and assymmetric, the reflexes are abolished. The sensitivity is not very much involved, some paresthesias may be present; sensitive objective signs are not important.

The weakness is more severe in the distal sector of the limbs. The cranial nerves are also involved, dysarthria, dysphagia, and facial dyplegia, transient amblyopia may occur, probably due to spasms of retina vessels.

Frequently the patients are affected by mental confusion, or show a delirant condition, or any form of psychosis. Convulsions have been also observed. Besides the nervous system affected, pigmentation of the skin, tachicardia, abdominal pains are observed, that appear in a paroxistic way, very frequently associated with dilatation of the stomach.

The neuritic symptoms generally are completely established during the course of a week. About the mortality in this kind of patients there exists in the medical literature certain variations that oscilate between 40 and 50 %. Death may be more imminent when the bulbar musculature is involved.

When the patient survives, his total recuperation takes several months. Recurrence of his neuritis may also occur.

The diagnosis is related to the concomitance of acute abdominal pains that precede or accompany the neurological manifestations, and the excretion of burgundy-red urine. The urine turns black when exposed to the light.

The differential diagnosis between hematoporphyrinurie polyneuritis and infectious polyneuritis, may be established demonstrating the presence of porphyrin precursors in the urine.

To reach exactness in this analysis, it is necessary to perform several of them, because the first are not very demonstrative.

The analysis of the blood generally has normal results. Concerning the cerebrospinal fluid, this is generally normal, sometimes and in a small percentage of cases there may be a slight augmentation of the proteins.

As we have already demonstrated the real diagnosis is done by the urine analysis, for the elimination of noticeable quantities of porphyrin precursors, uroporphobilinogen and delta-aminolevulinic acid.

In fresh liver tissue one can observe an increasing of the activity of the delta-aminolevulinic acid synthetase.

Concerning the treatment actually the resources to correct the metabolic disturbance is unknown. When the aim to prevent the outburst of the clinical manifestation, it is necessary to avoid the use of barbiturics in these patients. The acute crisis deserves a symptomatic treatment.

The adequate respiratory care in the paralysis patients has reduced the death rates. Chlorpromazine may be used to treat abdominal pains and mental disturbances.

A diet rich in carbohydrates or ovulation suppression therapy, may prevent recurrence.

Amyloid Neuropathy

Amyloid neuropathy is present in the process of primitive amyloidosis in about 15 % of the cases, this neuropathy is frequently in the first place in the clinical picture. It is a polyneuritis in which the sensitive disturbance prevails, and it is also involved in a remarkable way the autonomic nervous system. The heart, the tongue, kidneys, gastrointestinal tract, skeletal muscles, are generally affected. The peripheral nerve, may be involved but the spinal cord and brain are generally not compromised.

The illness is of unknown etiology, it is evident by the deposition of amorphous hyaline-like material around black vessels and that is also localized in connective tissue.

A careful study of these patients, show a plasmocitary dyscrasia and monoclonal protein.

A polyneuritis symmetric and progressive may be the dominant finding, it is the familiar type of primary amyloidosis with the onset of symptoms in the second to fourth decades.

In this kind of patient it is frequent to find the carpal tunnel syndrome, also, pupillary irregularities and retinal perivascular exudatis may be present.

The neurological symptoms are less frequent in secondary amyloidosis linked to the process of chronic evolution, inflammatory or suppurative peripheral neuropathy may be the consequence of a direct infiltration complicating multiple myeloma.

When the amyloide neuropathy are hereditary it may be of several types.

The Portuguese type corresponds to a clinical picture with a sensitive predominance, with noticeable neurotrophic perturbances. In the Swiss type a syndrome of the median in the carpal tunnel.

The diagnosis is established by performing biopsies at the nerve level or of other tissues, such as rectum, small intestine, liver, kidney, giving evidence of the amyloid substance.

Dysglobulinemias

During the course of the dysglobulinemias; Waldenstrom's macroglobulinemia, Kahler's disease, cryoglobulinemia, may develop neuropathies. They may show as mononeuritis, multineuritis, polyneuritis, polyradiculoneuritis.

There are several mechanisms involved that produce the lesions, they may be inespecific degenerative lesions, infiltration of the nerves by an amyloid element, ischemia may be an active factor, if a glyoglobulinemia exists also in cases of important sanguineous hyperviscosity.

Cáncer

For many years references have been made about cases of polyneuritis that occurs in the terminal stage of cancer. But in the last years, it has been emphasized, the possibility of the symptoms of neuritis may be evident before the signs of primary lesions may be observed. Generally this occurs with carcinoma of the lung, but it may be associated with different malign processes such as multiple myeloma, lymphoma, Hodgkin's disease and leukemia.

It may be the case that the nerves or nerve roots were infiltrated with neo-

plastics cells. When this does not happen it is believed that a factor of a general character may mediate, such as a dietary deficiency, chronic malnutrition, metabolic or toxic factors which may damage the nerves and the roots.

The clinical picture may be similar to the other polyneuritis of different etiology. Generally a combination of muscular weakness, defects in the sensibility and lack of reflexes is observed. In a few cases there may be seen a predominant lack of sensitivity.

In the cerebro spinal fluid a slight augmentation of the proteins may be observed.

Mental disturbances, dementia, confusion, loss of memory may be present because this is a multifocal leucoencephalopathy, or so called central neuronitis.

Sometimes there is a remission of the symptoms; but usually these states are maintained, ending in death due to the malign process.

It may be also observed in patients with multiple carcinoma affecting several organs, a similar clinical picture to the amyotrophic lateral sclerosis that has a benign evolution if the tumor may be extirpated.

When the main factor is the neoplastic infiltration in the nervous tissue, it generally shows a plexic syndrome sensitive motor, in which it is relevant the pain intensity, frequently regional circulatory disturbances may be present, due to vascular compressions and vasomotor troubles.

In uterine cancer cases, infiltration in the pelvis may occur.

In breast cancer there are infiltrations in the brachial plexus, in this case the question may be posed if the neuritis is not due to radiotherapy.

The Pancoast-Tobias's syndrome is originated by the infiltration of the lower part of the brachial plexus by cancer of the vertex of the lung.

Radicular syndromes may be also present as a consequence of extensive epidural infiltrations, wheter they are due to metastasis of a visceral cancer or to the localization of a malignant hematologic affection, Hodgkin's disease, leukocis. In these cases may be associated spinal cord signs, with a syndrome of blockade, which makes this mechanism recognizable; Besides bone lesions, strong pains, assymetry in the radicular sufferings is addes.

With this malignant etiology, the poliradicular syndromes may be the consequence of a neoplastic metastatic meningitis, or of a leukoblastic meningitis. The clinical picture shows diffuse symptoms with paralysis of the cranial nerves, the paresthesias predominate surpassing the pain, with an extended areflexia.

In the cerebro spinal fluid hyperalbuminorachia is observed associated with a hypoglycorachia, besides with the citological examination of the elements that are not numerous the diagnosis may be achieved. As treatment an intrarachideal injection of medicine such as the metatiexate may be performed with positive results.

In a person of middle or old age a polyneuritis of unknown cause, may suggest the presence of a malignant process. Sometimes the diagnosis is confirmed in observing metastatic infiltrations in nervous biopsies.

Inflammatory neuropathies - Guillain - Barré Syndrome

We will refer now to neuropathies linked to infectious diseases. All the inflammatory neuropathies will be considered. The inflammatory polyradiculoneuritis (Guillain-Barré syndrome) will be studied.

The nervous leprosy; the collagenosis.

The inflammatory polyradiculoneuritis, integrates a syndrome of unknown etiology that damages peripheral and craneal nerves with acute onset. In making

the clinical history it may be observed that the majority of the cases exist before the installation of the neurological picture, an infectious state of the upper respiratory or gastrointestinal tract.

The studies of Guillain, Barré and other scientists concerning these kind of illnesses were done during the second and third decade of this century.

In these processes may be observed degenerative changes of the spinal and cranial nerves, with retrograde modification in the motor cells of the spinal cord and medulla. An association of lesions exists, of segmentary demyelination to an inflammatory process with no specific characteristics in which, oedema, interstitial and perivenous lymphocitary infiltration prevail.

The cause of the polyradiculoneuritis is still unknown. The clinical picture in the typical cases suggest the existence of some common etiological factors; but up to now it was not possible to detect it.

It is determined by alcohol, or metallic poisons, or dietary deficiency. It has been thought that it is possible that it is produced by a viral infection, because the neurological picture appears after a respiratory infection in its upper portion. It is significant that all the studies performed in order to isolate a virus from the blood, cerebrospinal fluid, brain, or spinal cord has not given any results. To this must be added that all the anatomopathological findings are not similar to any infectious disease of the nervous system.

It is possible that the nervous process is linked to an immunological mechanism. This is based on the type of lesions and the analogy of the process with the allergic and experimental polyradiculoneuritis.

The disturbance of the peripheral nerve fibers is diffuse. The predominance in the suffering of the roots is originated because they are very accessible to the circulating antibodies, and by their mechanical strangulation in the radicular sheaths.

The origin of this polyradiculoneuritis is unknown. The clinical picture in the typical cases justify the concept that some common etiological factors may exist; but up to now, it was not possible to detect it. It is not determined by alcohol or toxic metals, or dietary deficiency. It is thought that probably a viral infection participates, because generally the neurological picture is preceded by a respiratory infection of its upper part. It is necessary to emphasize that all the attempts to isolate a virus from the blood, cerebro spinal fluid, brain or spinal cord, did not give any results. It must be added that the pathological findings are not coincident with any known viral infection of the nervous system.

The syndrome of Guillain-Barré that is present as an acute polyradiculoneuritis, with albumino cytological dissociation in the cerebro spinal fluid, may be present at all ages.

It is significant to stress that in half of the cases it appears from eight to ten days after a vaccination or an injection for serum or an infectious disease particularly if this is an eruptive fever.

When the neurological manifestation appears to be primitive, if we search carefully frequently the biological evidence of a recent viral infection is found.

We will start with the description of the clinical picture of the Guillain-Barré syndrome, frequently a slight respiratory infection of the upper part, and in a few cases a gastroenteritis, preceded the neuritis onset.

The symptomatology of the infection lasts a few days, and recedes before the neurological symptoms appear.

The beginning is insidious, characterized by paresthesias, pains, and motor deficits in the limbs. The attack is diffuse, but more pronounced in the lower limbs.

This symptomatology progresses rapidly and from eight to ten days reaches its maximum development. Sometimes the muscular weakness is increased, during a period of two or three weeks.

The four limbs are affected by the motor deficit, in a variable degree, and it may reach a total paralysis.

The facial muscles are also involved. Facial deplegia in 85 % of the cases occur. Dysphagia or dysarthria are in 50 % present, troubles in the innervated muscles for the eleventh cranial nerves are observed in 20 % of the cases, the trigeminal paralysis is also frequent, the oculomotor paralysis and of the jaw muscles are rare.

Choked discs produced by an increasing of the intracranial pressure as a consequence of the respiratory troubles and because the mechanisms of absorption of the cerebro spinal fluid is perturbed as a consequence of the high protein content of the fluid may be observed.

As a consequence of the extension of the paralysis to the cranial nerves a close vigilance of the swallowing is justified. There are no sphinterian perturbances, sometimes a transitory urine retention may be detected.

Concerning the limbs a moderate amyotrophy is generally observed.

The deficit is symmetric and the proximal and distal muscles are compromised in the same degree; sometimes the proximal sector is more involved than the distal one. In this process the muscles of the neck and trunk are affected in quite a severe way.

In about the fourth of the cases, weakness of the breathing muscles may be observed, which makes necessary the use of a respirator.

We must consider that between the onset of the clinical picture and the evidence of a respiratory insufficiency there is a lapse of time oscillating between 2 to 21 days with an average of 12 days.

The paresia is accompanied by an hypotony, of a tendinous areflexia. The areflexia is in retard in relationship with the sensitive motor disturbances. The plantar and abdominal skin reflexes are usually absent. The attack of the sensitive fibers are manifested by the persistency of deep pains, also of distal paresthesias.

The sensitive disturbances are generally not considered an important element of the clinical picture, except in certain forms of ataxia in which the troubles of the sensibility of position are severe.

In a third of the cases there is a cutaneous hypoaesthesia in the distal parts of the limbs. In the same proportion a moderate diminution of vibratory sense is present. In some cases the cutaneous sensibility may be greatly affected. In the majority of the cases with a moderate intensity a muscle tenderness or sensation to the nerve to pressure is observed.

In the severe clinical picture, a slight feverish state, tachycardia, and a moderate hypertension may be present.

In some cases the symptoms and signs are limited to ataxia of gait, absence of tendon reflexes and ophthalmoplegia, with a benign evolution and a complete recovery between one and three months.

The electrical examinations in the inflammatory polyneuritis, show signs of a partial innervation, without fibrillation and a precocious and very marked slowing of the velocity of conductions.

The routine laboratory examination of blood and urine are habitually normal, in some few cases a slight anemia is detected. High corporeal temperature with leukocytosis in infectious complications may be observed. When the neuritis is associated with the infectious mono nucleosis the characteristic changes of this illness are appreciated.

The cerebrospinal fluid examination shows an increase of the proteins which may be moderated or reach high levels and that is not accompanied by hypercytosis (albumino-cytological dissociation) or of a blockade with the test of Stookey.

At the beginning of the illness, there is no augmentation of the proteins, and during the course of its evolution an increase of the proteins appears. The study of the proteic formula very frequently shows an increase of the rate of the gamma globulin.

It is important to remark that the changes appreciated in the cerebro spinal fluid reaches its peak after an evolutive course of several weeks.

Concerning its evolution it may be said that the clinical picture generally reaches the maximum of its manifestations within a week of the onset.

There are cases in which the illness continues worsening for three weeks or more. After one or two weeks of stabilization the clinical manifestation begins slowly to recede.

This course of recovery has an evolution of weeks or months. It may reach a total recuperation, sometimes minor sequels persist, such as areflexia, slight weakness of the facial muscles or weakness and atrophy of the muscles of the extremities.

Fatal cases may also occur, which is due to respiratory failure, or by intercurrent infection.

The respiratory accidents are the consequence of the paralysis of the respiratory muscles, and also from the aero-digestive carrefour.

This requires a careful attention and in the case that these complications are possible, it is necessary to send the patient to a specialized center where it is possible to practice a tracheotomy, and an artificial respiration, maintained until the process evolves to normality.

The return to normality of the cerebro spinal fluid may occur in retard in relation to the clinical recovery.

The diagnosis of the Guillain-Barre syndrome is achieved by recognizing the symptoms and signs and discarding illness with a similar clinical picture.

The neuritis of acute porphyria may be recognized by its prodromal abdominal pain, the existence of convulsions and mental symptoms and the presence of porphyria.

Diphtheric polyneuritis are characterized by a long period between the upper respiratory infection and the initiation of the symptoms of neuritis, besides the symptoms of the neuritis has a slow evolution and a paralysis of accommodation may be present.

When following vaccination an acute suffering of the peripheral nerves appears, the diagnosis is done by the clinical history.

In the cases of acute anterior poliomyelitis, the diagnosis is oriented by the asymetry of the paralysis, and the evidence in the cerebro spinal fluid of a pleocytosis, in the course of the first week of infection.

Concerning the treatment we must indicate that regarding the muscular weakness, the indications are similar to other forms of polyneuritis.

It is necessary to be prepared for the emergency of paralysis of the respiratory muscles. The corticosteroids may have action upon the subjective sensitive dis-

turbances, and if it is precociously instituted may have influence on the course of the illness.

When the paralysis is installed, the corticoids are effective upon them. With the aim to avoid the venous thrombosis, a precocious mobilization of the paralyzed limbs must be performed.

When the recovery is initiated, then, the motriz reeducation must be instituted.

We will refer now to cases of inflammatory polyradiculoneuritis that are not included in the syndrome of Guillain Barré, in some cases disturbances of extension, for example processes of limited extension such as the syndrome of the amyotrophic neuralgia of the scapular waist; on the contrary in others there is a greater involvement and participation of the central nervous system.

The albuminocitological dissociation in the cerebrospinal fluid may be lacking.

Polyradiculoneuritis may be produced by the insects' biting.

An erythema appears surrounding the place of the bite. Afterwards the neurological signs and symptoms appear, that are differentiated from the Guillain Barré syndrome by the intensity of the painful manifestations and for the asymmetric motor impairment in the cerebral blood flow and important hypercytosis occur.

There are relapsing and prolonged types of cases that may originate an acquired hypertrophy of the trunk nerves.

Nervous Leprosy

During the course of the leprosy, compromises of the peripheral nervous system are frequently generated. This seems to be due to the affinity of the Hansen's bacillus by the Schwann cells.

Three clinical forms are recognized to the leprosy: nodular cutaneous maculo-anesthetic and mixed. The lesions of the cutaneous nervous endings, are the cause of the anesthetic maculae which damage the nerves trunks producing an hipertrophic and difuse inflammatory lesion, or are studded with nodular swellings. An overgrowth of connective tissue accompanied with a degenerative process of the axon and myelin sheet is originated. The microbe besides of being localized in the peripheric nerve has been detected in the dorsal root ganglia, the spinal cord and brain, without provoking trascendental on these sectors of the nervous system. The peripheral neuritis originates in some cases degenerative changes in the posterior funiculi of the cord. The peripheral nerves compromise originate symptomatology of the trunk, a clinical picture of multiple neuritis, with some territories of election, ulnar, great auricular, anterior tibial, external popliteal nerves and fifth and seventh craneal nerves.

The motor defect shows amyotrophy and fasciculations.

Concerning the sensibility, the superficial is observed to be affected sometimes lost in the territory of the nerves involved, in a somewhat irregular fashion. The sensitive defect may have the distribution of a nerve or root; but it is more frequent that it take the form of a glove and stocking type.

The deep sensibility, the recognizing of vibration, position sense, pressure pain, are generally preserved or at least involved with less intensity than the superficial sensibility.

The tendinous reflexes are generally preserved, but during the illness evolution may be diminished or even abolished. The cutaneous abdominal and plantar reflexes are normal. Vasomotor, and sweating disturbances, trophic perturbations, mal perforant, arthropathies, resorption of the bones of the fingers, are frequent and sometimes predominant.

Concerning the laboratory findings it is possible to detect in the blood a positive wassermann, Cahn or similar tests. In the cerebro spinal fluid a slight augmentation of the proteins, may be found Hansen's bacillus may be localized in the cutaneous lesions.

The diagnosis may be posed by the neurological symptomatology with the hypertrophic interstitial neuritis the syringomyelia, the bone Recklinghause's disease. The problem is solved considering the existence of the possibility of contamination in an endemic zone.

It must be considered that the period of incubation may last several years. The existence of the bacillus on the lesion must be investigated. From the point of view of the pronostic, it may be affirmed that the neural form of the disease is less serious than the cutaneous form, and frequently it is not fatal. The evolution of neuritis is slow and it may be stopped.

The cutaneous form is severe and generally ends in death in a lapse of ten to twenty years. The specific treatment allows to arrest the evolution. There are drugs of the sulfone class, DAPSONE, P.Q.-sulfonyldianiline, that have a bacteriostatic effect. In certain cases it may be associated with an antinflammatory drug. There are occasions in which it is necessary to liberate the nerve fibers surgically from the tissular reactions that are compressing them.

Disease of Collagen Tissues

We will refer now to the nervous manifestations of the diseases of collagen tissue. In what concerns the periarteritis nodosa, during its evolutive course the aparition of paralisis of the peripheral nerves is frequent. They take the characteristic of multiple neuritis and are promoted by an ischemic mechanism. This paralisis are unequal and asymetric with different evolutive course in time. These are accompanied by pain generated by the exient muscular lesions Sympathetic nerves may be damaged.

The patient presents the general signs of the illness, fiber, becomes thin, eosinophilia, velocity of sedimentation augmented, renal or cardiovascular disturbances, elements that lead to the clinical diagnosis.

To confirm the findings it is necessary to perform a muscle biopsy that evidences the characteristic periarteriolar lesions. There exists a diffuse widespread panarteritis. An infiltration of the adventitia and vasavasorum with polymorphonuclear leucocytes, lymphocytes and eosinophiles.

If a corticotherapy is practised a favorable results is obtained, improving the neurological disturbances. The cause of the periarteritis nodosa, is unknown, for an anaphylactic type of hypersensitivity as the etiologic factor.

Less frequent than in the periarteritis nodosa is a participation of the peripheral nerve in the polymyositis, lupus erythematosus and the scleroderma.

Lupus erythematosus is a complex illness with widespread inflammatory change in the connective tissue of the skin and the different organs of the body. The symptoms habitually are evolved in the second or third decade of life.

The compromise of the nervous system appears with scarce frequency, then convulsions, mental deterioration, cranial nerve palsies, polyneuritis, hemiplegia or other focal localization may be observed. These clinical perturbances are due to thrombosis of small vessels or multiple petechial hemorrhage.

The cerebro spinal fluid is usually normal; but an augmentation in the protein content and an abnormal colloidal gold reaction may be detected when neurological lesions exist.

There is not an adequate therapy. It is possible to calm the severity of the symptom by using corticosteroids.

The scleroderma is a chronic process that originates a diffuse fibrosis and vascular anomalies in the skin, articular structures in viscera digestive tract, heart, kidneys and lung. It is generally observed in woman from thirty to fifty years.

The vessels are generally disturbed by the proliferation of the intima and the leukocytic wall infiltration.

The small damaged arteries perturb the circulation in the skin muscles and organs.

The sclerodermic skin is smooth shining with pigmentation and depigmentation zones. Sometimes it is possible to observe the underlying atrophied muscle.

In the visceral lesions dysphagia is a frequent symptom, intestinal obstruction and chronic constipation, dyspnea, alteration in terminal phase of the electrocardiogram, sometimes cardia insufficiency, Raynaud syndrome, are observed. A severe renal illness may be present due to hyperplasia of the intima of the renal arteries. This is the most frequent cause of death.

Medical treatment with ACTH and cortisone. Symptomatic treatment according to the visceral manifestations; physiotherapy in order to preserve the movements.

PERIPHERAL MANIFESTATIONS OF THE HEREDODEGENERATIVE DISEASES

It is necessary to mention the Charcot-Marie disease (motor neuropathy)

The Thevenard's disease (sensitive neuropathy), the Dejerine-Sottas's disease (hypertrophic familial neuritis) the Refsum's disease.

The Charcot-Marie - Tooth is characterized by the following symptoms, cub feet and muscular wasting that begins on the legs and that later damages the distal sector of the thigh and superior limbs. This is a very rare process, with familial character.

Peripheral neuritis changes are observed, and the spinal cord may be also involved. Sometimes fractures of hereditary cerebellar ataxia may be present, which indicate that the lesions may be diffuse.

Regarding anatomical lesions, loss of myelin may be detected, and degeneration of the nerve fibers in the distal sector lower limbs, afterward it is spread to the nerves of the forearms. Hypertrophied nerves may be present due to the proliferation of the Schwann's cells, with onion bulb formation. The degenerative changes in the muscles are the consequence of the nerves lesions. Some authors affirm that changes of primary miopathy may also be present. Alterations of different entities have been observed in the spinal cord. The degenerative lesions in the roots, anterior horn cells, and posterior columns are consequence of changes in the peripheral nerves.

The process is three to five times more frequent in the masculin sex than in the femenin one. The illness is generally transmitted as a dominant character, less frequent as a recessive character.

The symptoms begin to appear in the first or second decade of life; but sometimes they may also appear in the fifth or sixth decade of life, almost all the patients show pain, paresthesias, and muscular cramps, club feet is also frequent.

The muscular atrophy usually begins in the legs, sometimes this also happens in the hands; but it may also occur that they appear simultaneously in both sectors. In the legs the muscle atrophy show the characteristic stork-leg appearance. The hand may be clawed. Conductive velocity in the affected nerves is decreased.

The deep sensibility shows a greater deficit than in the superficial one.

The ankle jerk is abolished since the beginning of the process. Afterwards the knee jerks are also involved.

The arm reflexes and the abdominal skin reflexes are in general preserved. Plantar responses are absent.

Concerning laboratory data, a normal spinal fluid has been found, in some cases a slight augmentation of proteins has been observed. Patients suffering from extensive atrophy may have disturbances of creatinine and creatinine metabolism.

The evolution of the illness is very slow and may reach many decades. It may occur an apparent spontaneous arrest.

The diagnosis is made by means of familial history, the absence of nerve tenderness, the existence of club feet and the distribution of the atrophy in peroneal muscular atrophy.

The majority of the patients by using orthopedic resources, may correct the foot drop and be able to carry out an ambulatory activity.

Hypertrophic interstitial neuritis Dejerine - Sottas disease

In this illness an hypertrophy of the nerves trunks is associated with a sensitive motor neuropathy of slow evolution. This is a less form of chronic progressive polyneuritis. Several members of the same family are generally suffering from this illness; but there are some sporadic cases.

The genetic transmission in many cases is done in the autosomal dominant form, and it is possible that in the same family group this disease is associated with the Charcot-Marie-Tooth. A slight preponderance in the feminine case exists. It may have its onset in child hood; but sometimes is delayed to middle life.

The lesions are similar to those observed in the Charcot-Marie-Tooth, an important development of the conjunctive interstitial proliferation and of the sheet of Schwann. The myelin is destroyed and the axis cylinder suffers and may be destroyed. At the histological examination the onion skin appearance may be present, with certain magnitude and in a great number, due to repeated episodes damaging the nerve.

In the spinal cord sector degeneration of the posterior funiculi specially that of Goll is observed, degenerative process may be also observed, in the ventral horn cells.

The sensitive deficit in this illness is marked, than in the Charcot-Marie-Tooth, lightning pains, and ataxia perturbances. The nerves trunks are hypertrophied mainly at the cervical plexus, cubital, sciatic, external popliteus.

Weakness and atrophy of the distal part of the extremities appears.

Generally the lower limbs are first involved. Pupillary anomalies may appear generating an Argyll-Robertson signs.

Very rarely involvement of the cranial nerves may be seen, oculomotor, or facial palsy sometimes may be present. The reflexes are usually absent. The presence of an extensor plantar response has been observed, maybe originated by a slight compression of the cord by enlarged roots.

Marked relationship between Dejerine Sottas and Charcot-Marie-Tooth diseases seems to exist; it is possible that both have the same origin with a different degree of pathological process.

Signs alien to a polyneuritis sometimes appear, we will mention nystagmus,

dysarthria, scanning speech, intention tremor, indications that the polyneuritis has been integrated with other heredodegenerative diseases.

The illness has a low evolution and allows to maintain activities, with the evolution it may lead to a complete incapacity.

A specific treatment does not exist. It is necessary to institute physical therapy. Corrective braces must be employed aiming to avoid deformities and contractures.

Refsum's diseases - heredopathia atactica polyneuritis-formis

In this process there exists an association between a familial peripheral neuropathy and a genetically determined metabolic abnormality.

It is a an inherited disease due to an autosomal recessive trait.

The sensitive motor neuropathy concerning its evolution is characterized by advances and remissions.

The hypertrophic familial neuritis is associated to an atypical retinitis pigmentosa and constrictions of the visual fields; cerebellar ataxia, may be also observed mild in most cases; involvement of the eighth nerve with decreased hearing.

There are motor deficits in the four limbs in its distal sector with atrophy. Variable sensory loss in the four limbs regarding the deep and superficial sensitivity. Deep tendon reflexes diminished or absent.

Cardiac disturbances similar to those of Friedreich disease, an ichthyosis, skeletal malformations, pes cavus, a high arched palate.

The cerebro spinal fluid shows a dissociated hyperalbuminorrachia.

An abnormal urinary elimination of phytanic acid. This indicates an enzymatic disturbance, due to a phytanic - oxydase deficit.

This metabolic perturbation originates defects in the peripheral nerves involving also other organs. This fact gives to the Refsum's disease the value to establish a relationship between the lipidosis and the heredodegenerative disease.

Hereditary sensory neuropathy - Thevenard-Denny-Brown

This is a clinical picture that appears in childhood or early in adult life, in which the polyneuritis signs are predominantly marked in the sensitive sector.

The hereditary transmission is generally of a dominant character.

The recessive cases are more rare and are characterized for being of more severe evolution and for having its onset early in life; but if it is present in adult life this is usually due to another factor such as alcoholism and diabetes.

Degeneration of the posterior root ganglia, has been anatomically observed in the peripheral nerves, olivary nuclei, cerebellum and the optic nerve.

The process begins with a mal perforant plantar besides vasomotor disturbances and nervous arthropathy of the foot.

The patient suffers lightening pains, termic and painful hypoesthesia of distal topography, loss of tendon reflexes. Painful abdominal crisis has been present in some families that reminds the visceral tabetic crisis. Cochleovestibular disturbances has been observed. Sometimes it is associated to the clinical picture an amyotrophy which establishes a link of this illness and the Charcot-Marie-Tooth disease.

This illness is compatible with life even if it has a progressive evolution.

Prof. Dr. VICTOR SORIANO

Acute and Chronic Inflammatory Polyneuropathies - Clinical and Therapeutic Considerations

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INTRODUCTION

The Inflammatory Polyneuropathies (IPN) are an important group of acquired neuropathies characterized pathologically by infiltrates of mononuclear cells in the endoneurium, and segmental demyelination and remyelination. Their pathogenesis is thought to be autoimmune, perhaps from an alteration in the immune recognition of "self" proteins in peripheral nerve myelin, or from alterations in those proteins, for instance by a viral infection. In this paper, we review clinical, etiological and therapeutic features of IPN.

IPN associated with vasculitis, perineuritis, endoneurial infiltration in malignant lymphoproliferative disorders, and specific infectious agents are excluded from this review. We have also excluded the occasional case of IPN associated with a dysproteinemia, which appears to result from antibody activity of the abnormal monoclonal immunoglobulin (1-5).

In most cases of IPN the cause of the immune response is unknown and classification is based on clinical characteristics. Most cases have an acute or subacute onset and a monophasic course with early resolu-

tion (Acute Inflammatory Polyneuropathy [AIPN] or the Guillain-Barré Syndrome) (6). A smaller group have an insidious onset and chronic evolution (Chronic Inflammatory Polyneuropathy [CIPN]) (7). The spinal nerve roots are involved in both types, leading to the term polyradiculoneuropathy. The separation of AIPN from CIPN is somewhat arbitrary, and based on clinical grounds. Cases with a duration of worsening from onset to nadir of greater than 4 weeks are generally excluded from the diagnosis of AIPN (8,9). The term chronic Guillain-Barré Syndrome should be avoided.

CLINICAL CHARACTERISTICS OF THE INFLAMMATORY POLYNEUROPATHIES

Acute Inflammatory Polyneuropathy:

Patients with AIPN have an acute or subacute onset of motor weakness and areflexia that usually ascends rapidly from legs to arms or affects the four limbs simultaneously. The weakness is generally symmetrical and it reaches its peak of disability within one day to four weeks (8-10). Involvement of respiratory and bulbar nerves may necessitate tracheostomy and assisted ventilation in 10 to 20% of the patients (10-13). Bilateral facial weakness is seen in 40 to 50% of the patients and occasionally it may be the presenting sign (11-12). Extraocular muscle involvement occurs in less than 10% of the cases and is rarely severe (11-12). Sensory symptoms such as paresthesiae are common during the first days.

Neuritic pains may be present in up to a quarter of patients and may last for weeks, but sensory findings are characteristically minimal or absent (10-13). Transient autonomic dysfunctions of the cardiac rhythm, blood pressure and bladder are present in 10 to 20% of cases, and may occasionally be sufficiently severe to cause death (13-15). Other syndromes with similar subacute onset and monophasic course affecting preferentially the oculocranial nerves (Miller Fisher Syndrome) (16), the autonomic or the sensory system may have a similar autoimmune mechanism to that present in the Guillain-Barré Syndrome (GBS). The occasional presence of severe ataxia or Babinski responses do not exclude the GBS (9,17). An antecedent event such as gastrointestinal and respiratory "virus-like" illnesses, vaccinations, and mycoplasma infections, occurring 2 to 4 weeks prior to the onset of the neurological disorder, is found in more than half of the patients (11, 13, 18, 19). Most patients begin to recover 2 to 4 weeks after the weakness has reached its nadir, and in about 85% of the cases will recover in a few months (13). Minor neurological deficits may be present in about 40% of the patients for several years after the acute episode (12), but serious permanent disability occurs in less than 10% of the cases (13).

Longterm disability may be predicted by the severity of the weakness during the acute state (11-13) or by the time span between maximum weakness and onset of recovery (11, 12). Relapses, sometimes caused by viral infections or vaccinations, occur in 3% of the patients (12, 13). The mortality rate has dropped to below 6% with modern critical care. Death is usually due to cardiocirculatory disturbances or to pulmonary embolism in the older age group (11-13,15).

Elevated CSF protein with normal or slightly increased number of cells after the first week is characteristic of the syndrome, and is probably due to nerve root inflammation (6). Increased gammaglobulin and transient oligoclonal bands in the CSF may also be present (20). The nerve conduction studies are generally characteristic of a demyelinating neuropathy, though the di-

sease is very patchy in its distribution, and many peripheral nerve segments may be normal especially early in the disease. In affected segments, conduction velocities may be low, distal latencies prolonged and conduction blocking frequent. Abnormal late responses and somatosensory evoked potentials confirm the involvement of the proximal segments of the nerves. In severe cases, axonal degeneration may occur, producing abundant fibrillations and positive sharp waves on electromyography. This change indicates longer and probably incomplete recovery (21). Pathologically, inflammatory lesions are scattered throughout the peripheral nerve trunks and roots. Lymphocytes and macrophages can be observed close to demyelinated axons. Macrophages may be found under the basement membrane of normal-appearing Schwann cells stripping away layers of normal-appearing myelin. Demyelinated Schwann cells lose their granular endoplasmic reticulum and ribosomes and undergo mitosis. Healthy-looking Schwann cells remyelinate the demyelinated axons (22).

Chronic Inflammatory Polyneuropathy:

Patients with CIPN have a similar pathological picture, though in the sural nerve biopsy the presence of segmented demyelination may only be seen with teased nerve fiber preparations. "Onion bulbs", indicative of frequent demyelination and remyelination, are typical of long-duration cases. They may be associated with nerve hypertrophy in severe chronic cases (23). The electrophysiological findings in the CIPN are also similar to those in AIPN, with conduction velocities as low as 10 m/sec (24). Clinically however, CIPN are characterized by a sensori-motor polyneuropathy of insidious onset that may plateau after 6 to 12 months. Some CIPN patients have recently been reported to have a clinical picture of mononeuritis multiplex, and persistent multifocal conduction block on the electrophysiological studies (25). CIPN may progress steadily or stepwise or be relapsing and remitting (24,26). In this last form, relapses can last weeks or months and their appearance may be provoked by a viral infection or vaccination (26-27).

Remissions may be spontaneous or indu-

ced by therapy and last from months to years. Relapses frequently have a subacute onset and incomplete recovery, and may be precipitated by too rapid withdrawal of the maintenance corticosteroid therapy (28-29). Involvement of the cranial nerves, autonomic dysfunction and respiratory failure are much less common in CIPN than in the AIPN, although the long-term prognosis for disability is worse on the average (24,26). The presence of a single monoclonal band of protein in the CSF (30) and the preponderance of certain HLA haplotypes (31, 32) also differentiate CIPN from AIPN.

IMMUNOPATHOGENESIS OF THE INFLAMMATORY POLYNEUROPATHIES

The mechanism of the immune damage to the peripheral nerves in the IPN is still unclear. The relative role of cell-mediated immunity (CMI) and humoral-mediated immunity (HMI) is uncertain. CMI has long been considered responsible for AIPN, but recent findings indicate HMI may also play an active role. Clinical differences between AIPN and CIPN may be due to different neuritogenic antigens or to different host immune response to the antigen.

Humoral-Mediated Immunity:

Organ-specific IgG and IgM antibodies against peripheral nerve tissue have been found in 27-100% of AIPN sera (3,33). IgG, IgM and complement deposits have been described in sural nerve biopsies of AIPN patients (34,35) and AIPN sera have been reported to produce demyelination in cultures (36) and demyelination and nerve conduction slowing in experimental animals after intraneural injection (37-39). Other authors, however, have found no significant slowing of nerve conduction in such experiments (40,41). Antibodies against one component of the myelin proteins, the P2 protein, though present in animals with experimental allergic neuritis, have not been found in IPN patients (42,43).

Fewer studies of HMI in CIPN have been reported. Antimyelin antibodies have been described in 2 out of 9 CIPN patients

(3), but the intraneural injection of serum from CIPN patients produced no greater effect than control sera (39). Linear deposits of IgG and IgM in the absence of complement have been described in sural nerve biopsies of CIPN patients (30). As will be discussed below, the effect of plasma exchange therapy in CIPN patients suggests a pathogenetic role for HMI mechanisms.

Cellular-Mediated Immunity:

Based on the pathological features CMI has long been considered to be responsible for the demyelination in the IPN, though studies of CMI have been far from uniform. Peripheral blood lymphocyte transformation to P2 protein has been reported (44,45) but not confirmed (42,43). P2 protein does not seem to be the neuritogenic antigen in human IPN. Buffy coat cells from AIPN patients caused demyelination of rat peripheral nerve in tissue culture (46), but the demyelination could have been produced by antibody secreted by the lymphocytes present in the cultures (47). The decreased suppressor T-cell response in IPN patients (42) and the circulating cytotoxic antibodies against T-cells in the acute stages of AIPN (48) may be of major significance in the immunogenesis of these neuropathies.

Circulating Immune Complexes:

The existence of circulating immune complexes in AIPN patients is controversial (33) and their significance unclear. Damage to the blood-nerve barrier produced by deposition of immune complexes in the endoneurial capillaries might facilitate the passage of myelinotoxic agents into the endoneurial space. Immune complexes and their pathogenetic effects need further investigation.

Viruses:

Mareck's disease is a demyelinating neuropathy of chicken, which is caused by an avian herpes virus and is pathologically similar in its early stages to the human AIPN (49). This prompted the search for

viruses in peripheral nerve tissue from such patients, with inconsistent results (50). Elevated antibodies against cytomegalovirus (CMV) or Epstein-Barr virus (EBV) have been reported in 25 % of patients with AIPN during the acute stage, with decline during recovery (51). CMV and EBV are herpes viruses which frequently damage lymphoid cells. These viruses might provoke an acute autoimmune attack on peripheral myelin by mechanisms other than a direct invasion of the Schwann cell. Healthy immune cells might direct an attack against virus-infected lymphoid cells which may share an antigenic determinant with peripheral myelin. The frequent occurrence of AIPN in patients with Hodgkin's disease and malignant lymphomas, and the association of these disorders with herpesviruses is compatible with this possibility. Less probably, infected lymphoid cells might produce autoantibodies against a myelin antigen. The presence of IPN in plasma cell dyscrasias favors this conception. Finally, viruses may act directly on suppressor T-cells, disturbing the balance that normally prevents a symptomatic autoimmune reaction. Abnormalities in the suppressor T-cell response and the tendency of the herpesvirus to remain latent for long periods of time might explain CIPN or relapses in AIPN.

In summary, the evidence does not indicate preferential involvement of any one immune mechanism, and it is possible that their actions are combined. Though CMI has long been considered to have the prime role in the demyelination, it seems unlikely that T-cells mediate it directly. T-cell-mediated phagocytosis, whether the effector cell is a lymphocyte or a macrophage, is regarded as an event that requires the previous death or disintegration of the target cell (52), and phagocytosis of intact living cells or their parts is not a recognized method of T-cell-mediated phagocytosis. On the other hand, antibodies are generally believed to be able to destroy their target, either directly by lysis with or without complement, or indirectly by opsonization and macrophage attack (53,54). This could be the mechanism in human IPN. AIPN has been reported in one case of agammaglobu-

linemia (55), and in cases with drug- or disease-induced CMI suppression (56,57). It has been suggested that CMI suppression by an antecedent event like vaccination or by the presence of lymphocytotoxic antibodies may be necessary to initiate AIPN, and that restitution of CMI leads to clinical recovery (57).

MANAGEMENT OF ACUTE INFLAMMATORY POLYNEUROPATHY

General Care in AIPN:

Care must be focused on the prevention and treatment of respiratory failure, cardiovascular disturbances and pulmonary embolism, which are the major complications. In severely paralyzed patients, nursing care must be directed to the prevention of pressure palsies of peripheral nerves and decubitus ulcers. Early physiotherapy and major psychological support are of great importance.

Incipient respiratory failure can be recognized by daily determination of the vital capacity (VC) and mean inspiratory force. Alterations in the blood gases do not appear until respiratory failure is already established. Intubation should be done if the VC drops below 20 ml/kg or if poor deglutition threatens to provoke aspiration. As a quick bedside test, if a patient cannot count to 20 on one breath, incipient respiratory failure is present.

Tracheostomy should be done if respiratory failure lasts for more than 7 to 10 days because of the risks of prolonged oro-tracheal intubation. Active and passive respiratory physiotherapy should be instituted as soon as respiratory weakness is detected in order to prevent sputum retention and atelectasis.

Anticholinergics are usually adequate to control bradycardia. Tachycardia, if severe, requires beta adrenergic blockers. These last drugs should be avoided in the control of blood pressure elevations because of their potential for bradycardia, and thus hydralazine should be used. Temporary pacemakers may be required if cardiac arrhythmias cannot be controlled with drugs.

Phlebothrombosis is best prevented with

low-dose subcutaneous heparin, compressive stocking and passive movements of the limbs.

The hyponatremia that occasionally occurs is attributed to inappropriate ADH secretion produced by abnormal signals coming from the peripheral volume receptors (58), and is readily controlled with fluid restriction. Neuralgic pains may be resistant to conventional analgesics and may require quinine (59) or carbamazepine. Pressure palsies of the ulnar and peroneal nerves can be prevented with careful positioning and pads. Passive physiotherapy of the affected limbs should be instituted from the first day of the disease and combined with active exercises as soon as the recovery period starts. Finally, psychological support and reassurances of the usually good prognosis of the disease should be emphasized.

Immunesuppression in AIPN:

From 1952 (60) there were many reports of cases of AIPN that improved after therapy with corticosteroids, yet their efficacy remained in doubt since the normal spontaneous recovery of most patients was difficult to differentiate from a drug-induced recovery. In 1976, the first controlled trial was reported (61). Patients who required respiratory support were excluded. Seven patients were given daily IM injections of 100 units of ACTH for 10 days and compared with 8 non-treated control patients. There was no immediate improvement in treated patients but the duration of their disease was significantly shorter (4.4 ± 2.5 months vs. 9.0 ± 5.2 months). However, in 1978 different results were reported in a larger controlled trial (62). Twenty-one patients were treated orally with prednisolone, 60mg daily for one week, 40mg daily for four days, 30mg daily for 3 days and then maintained or tapered. Comparison was made with 19 non-treated patients. No differences were found in the rate of improvement between the two groups. Moreover, the subgroup of treated patients in which therapy was commenced within one week of the onset had a delay in the commencement of improvement, and 3 treated patients relapsed in the first year.

The conclusion to be drawn is that corticosteroids play no part in the treatment of AIPN.

There have been several reports of patients who benefitted from the use of cytotoxic agents (63-65). In the largest series (66), 15 patients improved after high-dose cyclophosphamide therapy. However the appearance of relapses in 4 cases and 4 deaths in the group cast significant doubts about the efficacy of this form of therapy.

Again, the spontaneous recovery in AIPN precludes conclusions on the results of this therapy without randomized controlled trials.

The reported presence of myelinotoxic antibodies in serum (36) and immunoglobulin deposits in nerves of AIPN patients (35) prompted Brett et al (67) to use plasma exchange therapy in this condition, with apparent benefit. After this report, the number of cases published boomed, and though most of them reported immediate benefit after the first or second exchange procedure (67-81), cases without benefit have also appeared (80-83). A multicenter randomized controlled trial of plasma exchange is at present in progress in the USA and Canada that will include a total of 240 patients. A progress note of the trial (84) indicates that review of the first 115 patients shows no significant evidence or benefit. The need for this controlled trial is highlighted by one of our patients incorporated into the multicenter trial, who improved dramatically and rapidly after entering the randomization but who was not receiving plasma exchange.

MANAGEMENT OF THE CHRONIC INFLAMMATORY POLYNEUROPATHIES

Corticosteroids:

Corticosteroids have been reported to be beneficial in many CIPN patients since the first description in 1958 (28). In the only controlled trial to date 14 patients treated with an alternate-day dose of 120mg of prednisone which was gradually tapered within 3 months, showed a small but significant improvement over 14 non-treated patients

(85). Both forms of CIPN (progressive and relapsing) responded similarly.

Despite these results, corticosteroids are far from being a satisfactory treatment of CIPN. There are patients who do not respond to corticosteroids or rare patients who may even be worsened by them, as was seen in the following case:

as was seen in the following case:

A 60 year old woman with some months of distal numbness and mild weakness was seen elsewhere and diagnosed as having a probable CIPN. She was treated with ACTH, 100IU daily tapered in one week, and had a profound exacerbation becoming quadriplegic for about six months. She made a gradual recovery and was seen again by the same neurologist who considered it likely that this relapse was a fortuitous episode, and again prescribed ACTH. Again she had a profound relapse and remained totally quadriplegic though without significant respiratory or bulbar involvement for the next two and a half years. Plasma exchange combined with cyclophosphamide produced a subacute and dramatic restitution of function (see below).

Other patients require high doses of corticosteroids for years and become corticosteroid-dependent (86). Complications of long term corticosteroid therapy are well known: vertebral collapse, cataracts, aseptic necrosis of the femoral head, exacerbations of latent diabetes mellitus, hypertension, gastrointestinal hemorrhages and added risk of infection. These must be considered when long term management is planned.

Prednisone and prednisolone have proved effective but their dosage and duration of treatment is not clearly established. Different regimens have been published (30,85) but treatment should be individualized. The general medical status, the evolution and severity of the disease in the past and during the treatment, and the possible complications of the therapy must be evaluated before starting corticosteroids.

Some general considerations of corticosteroid therapy are also important. Prednisone requires activation to prednisolone in the liver (87) and therefore the latter is indicated if liver dysfunction is suspected. Alternate-day regimens may never bring the

disease under control because the immunosuppression is cyclic, and therefore, incomplete (87). Daily or divided doses are indicated at the beginning of the treatment. Once control of the disease is achieved alternate-day therapy may be successful in maintaining suppression of the disease. Doses of prednisone higher than 80mg have prolonged biological effects which carry over to the next day and they should be considered like daily dose regimens when administered on alternate days (88).

Change from daily to alternate-day dose should be accomplished by slowly tapering the even-day dose, with or without previous increase of 50 to 100% of the odd-day dose. Doses of 60mg per day or higher must be maintained for at least three months from the beginning of the therapy before the therapy can be rejected as ineffective. Once the disease is in remission, tapering must be done very slowly. Frequently there is a critical level under which the disease relapses. When the critical level is known from previous experience with a particular patient, slightly higher doses should be maintained for months to years. Maintenance of small doses (10 to 20mg alternate days) seems to prolong the duration of the remission. After the dose has been reduced below a critical threshold a relapse may occur from a few days to 12 weeks.

Taking into account the above considerations, the regimen which in our experience has proved effective is:

1. 60 to 80mg of prednisone daily for up to 3 months, depending on response.
2. When adequate disease suppression has been achieved, taper odd-day dose by 20mg/week to 40mg, by 10mg/week to 20mg, and by 5mg/week thereafter.
3. Taper even-day dose by 5mg/week to 40mg, and by 2.5mg/week thereafter.

Antacids and supplemental potassium are usually added to the therapy.

Cytotoxic drugs:

Azathioprine and cyclophosphamide have been reported to be effective in CIPN in several uncontrolled studies (26,30,64,66, 89-92), although no benefit has been reported in other limited studies (65,89,93-95).

Cytotoxics have been effective in patients who could not be controlled with corticosteroid either because lack of effect or significant side effects. They have also been of benefit in patients with unstable and corticosteroid-dependent states, allowing the prednisone dose to be lowered.

Cytotoxics are traditionally regarded by the neurologists as second-choice drugs to treat dysimmune disorders. They prefer corticosteroids and perceive these drugs as a less aggressive therapy. However, CIPN patients frequently require high doses of prednisone maintained for years. Cytotoxics, at the doses used to control dysimmune disorders, have toxicity which is frequently less than that of the corticosteroids.

Cytotoxics should be used when high doses of corticosteroids are required to control the neuropathy, when long duration treatment is anticipated, when the condition is very unstable, or when other diseases preclude the use of high dose corticosteroids. There is no proof at the present time that one cytotoxic is more effective than another in controlling CIPN. Their different characteristics, toxicity, and the familiarity of the physician should all be considered when deciding which drug to use.

Azathioprine is the most commonly used cytotoxic. It exerts its effects on immunologically-active cells mediating both cellular and humoral responses (96). The oral dose required is up to 3mg/kg/day in divided doses. At this dose leukopenia may occur in 1 to 2 weeks. Clinical improvement can be seen in the next weeks but occasionally it may be delayed for up to 2 to 3 months. Bone marrow toxicity must be assessed with periodic (weekly to monthly) blood counts. The total number of lymphocytes should be reduced to 700-1000 per mm³. The total leukocyte counts should not be allowed to fall below 2500-3000 per mm³ [a total granulocyte count higher than 1500-2000 per mm³ seems adequate to prevent bacterial and opportunistic infections (97)], the platelet count should not fall below 120,000 per mm³ and the hemoglobin count should not fall below 11 gm%. Clinical improvement may be obtained with doses that do not produce significant leukopenia, and in those cases no further increase in dose is

indicated. Side effects are rarely significant. Gastrointestinal intolerance, fever and skin rashes are the most common and they respond well to the lowering or discontinuation of the drug. It is important periodically to look for biochemical evidence of liver damage. Cyclophosphamide can be used as an alternative to azathioprine. It inhibits cell replication and seems to act preferentially on B- rather than T-cells, possibly because of differences in their rates of proliferation (96). The average oral maintenance dose is 1 to 2 mg/kg/day in a single or divided dose. At this dose, leukopenia may occur in 1 to 2 weeks and clinical benefit may appear shortly thereafter. One side effect, hemorrhagic cystitis, can be prevented if urine output of 3 liters per day is maintained. Toxic effects upon sperm and ovocyte production and hair growth are frequently seen. Chlorambucil is another alkylating agent with similar bone marrow and immunosuppressive effects. The oral dose required is 0.1 mg/kg/day, in a single dose (98).

6-Mercaptopurine is a precursor of azathioprine that seems to be less effective in controlling CIPN (93,94). The use of methotrexate, a folic acid antagonist, has not been reported in CIPN.

Corticosteroids appear to occupy a unique role in relationship to immunosuppressive therapy. Many cytotoxics exhibit minimal therapeutic benefit when administered alone but are highly effective when small daily doses of prednisone are added to the treatment regimen (99). The effects of the corticosteroids are seen soon after their administration (100) and in patients whose condition is severe and immediate immunosuppression is desired, corticosteroids should be added at the beginning of treatment.

Reports of some benefit in CIPN patients with the use of different modifiers of the immune response have also been published. A interferon inducer and potent lymphocytopenic agent, polyinosinic-polycytidilic acid, was effective in 2 out of 4 patients (101), and a diet of poly-unsaturated fatty acids improved one CIPN patient (102).

Plasma Exchange:

Plasma exchange therapy has recently been introduced in the management of

CIPN patients. Its efficacy is controversial and its indications unclear. Plasma exchange has been reported to be effective in 10 patients, mildly beneficial in 6 and not effective in 4, and the response does not appear related to whether the course is progressive or relapsing (30,72,103-109). During the last three years, we have treated 8 CIPN patients with plasma exchange (4 with the progressive form, 3 with the relapsing and 1 with a chronic relapsing form with acute onset). All patients had at least one course of one plasma volume (3-4 liters) exchanges repeated 5 to 6 times in 2 weeks. Three patients improved while five did not benefit. Improvement, when present, was seen soon after the first exchanges and its maintenance required periodic exchanges. One patient who had a corticosteroid precipitated CIPN (see above) improved from a state of complete quadriplegia for two and a half years to walking with below knee braces and canes within 8 weeks of starting plasma exchange therapy and cyclophosphamide. One plasma volume exchanges every 10 to 14 days are required to maintain and continue the improvement. Effectiveness of the therapy is clearly demonstrated in this patient by the titrability of clinical deficit and exchange frequency.

Plasma exchange, like any other form of therapy, must be done correctly before it is regarded as ineffective. Exchanges of 40-55 ml/kg daily for at least four days are required to remove 95% of any intravascular factor per exchange and 90% of total body immunoglobulin all told (110). One plasma volume exchange, every other day, repeated 5 or 6 times achieves similar results, removing also any extravascular factor that may enter the intravascular space during the initial re-equilibration.

The removal of large quantities of plasma may not deplete circulating antibody so long as antigenic stimulation persists since a rebound increase in antibody production by the responsible immunocytes may follow the rapid decrement in serum antibody levels. Alkylating agents, used concomitantly with plasma exchange, will be most active against those productive cells and will produce a longer lasting immunosuppression.

In our series, the three patients who improved received daily 100-150 mg of cyclophosphamide during and immediately after the plasma exchange therapy. Only one of those who did not improve, with a progressive form of long duration, received cytotoxics. In the published cases, some improved without cytotoxics, some who did not improve were taking cytotoxics during the plasma exchange, and in some reports there are not details concerning cytotoxic drugs.

The need for combined drug and plasma exchange therapy is however, far from being clear. Decreased suppressor T-cell response (42) and lymphocytotoxic antibodies during the acute stage of AIPN (48) have been reported. Removal of autologous plasma may permit proliferation of cell-mediated effector cells and facilitate a clinical improvement which otherwise would be limited by combined therapy with cytotoxic drugs. To date, there are no studies of the suppressor T-cell response in convalescent AIPN patients or in CIPN, and it may be possible that an antibody-mediated decreased suppressor T-cell response is the cause of chronicity in some cases of AIPN or CIPN. Different factors such as viral infections (111), swine flu vaccine (112), and tetanus toxoid (27) which trigger AIPN or relapses in CIPN may have in common depression of the suppressor cell function. Thus, the combined use of cytotoxics and plasma exchange might be harmful.

The reasons for failure of the plasma exchange in some CIPN patients are unknown. Plasma exchange therapy will be less effective if the duration of the disease is long and there is major axonal loss. In our series, the three patients that improved had symptoms for less than three years. One patient without response who had had symptoms for only 20 months had clear evidence of axonal degeneration in the EMG and sural nerve biopsy. The remaining had the disease for five years or more.

The mechanism whereby improvement occurs after plasma exchange therapy is unknown. Plasma exchange may produce benefit by removal of antineural antibodies, circulating immune complexes, lympho-

cytotoxic antibodies to suppressor T-cells, the chemical mediators of inflammation, the complement system or the antigen itself.

The reasons for the rapidity of the clinical improvement are also unclear. Effective remyelination probably requires 5 or more days to take place. Thus, the clinical improvement seen in some of our patients less than 48 hours after commencement of plasma exchange therapy must be due to another reason. Endoneurial and intramyelinic edema and "watery" Schwann cells have been reported in CIPN (26), and may be responsible for a functional conduction block. The resolution of that edema by corticosteroid treatment or by the removal of

factors that might provoke it, could rapidly reverse the conduction block.

In summary, the efficacy of the plasma exchange in CIPN is as controversial as its efficacy in AIPN. Some patients seem to improve rapidly after the first exchanges while others do not benefit. Since plasma exchange is not free of risks, is time consuming and expensive, it should only be used in very specific situations. We tend to use plasma exchange therapy when corticosteroids and cytotoxics have failed, when serious side effects or complications have arisen after their use, or when the severity of the disease is such that the patient is bed-ridden or requires assisted ventilation.

S U M M A R Y

The Inflammatory Polyneuropathies (IPN) are an important group of acquired neuropathies characterized pathologically by the presence of inflammatory lesions scattered throughout the peripheral nervous system associated with segmental demyelination and remyelination, high protein content and normal cell count in the CSF, and low nerve conduction velocities. Clinically, patients may present with an acute or subacute onset of weakness and areflexia and recovery in weeks or months (Acute Inflammatory Polyneuropathy [AIPN] or the Guillain-Barré Syndrome), or with an insidious onset of a distal sensory-motor polyneuropathy with a progressive or relapsing-

remitting course (Chronic Inflammatory Polyneuropathies [CIPN]). Their pathogenesis is unclear though related to abnormal immune responses with the possible implication of both cell-mediated and humoral-mediated immunity. The efficacy of modifiers of the immune response in the management of the IPN is controversial. Corticosteroids and cytotoxics have not proven a benefit in the acute cases, but they seem effective in the chronic ones. Plasma exchange therapy has been reported effective in uncontrolled trials in AIPN and in some CIPN cases, but failures have also been reported.

R E S U M E N

Las polineuropatías inflamatorias (P.I.) constituyen un grupo importante de neuropatías adquiridas caracterizadas patológicamente por la presencia de infiltrados inflamatorios en el Sistema Nervioso Periférico, asociados a desmielinización segmentaria y remielinización axonal, incremento de proteínas en el l.c.r. con un número normal de células, y conducciones nerviosas lentas.

Clínicamente, pueden presentarse con un cuadro agudo o subagudo de debilidad muscular y ausencia de reflejos tendinosos, con una recuperación en semanas o meses (Polineuropatía Inflamatoria Aguda [P.I.A.] o Síndrome de Guillain-Barré), o bien con un cuadro insidioso de polineuropatía sen-

sorial y motora de curso progresivo o con recaídas y remisiones (Polineuropatías Inflamatorias Crónicas [P.I.C.]). Su patogénesis no está totalmente clarificada, pero parece estar relacionada con respuestas inmunológicas celulares y humorales anómalas. El tratamiento de las P.I. con modificadores de la respuesta inmunológica es controvertido. Los corticosteroides y las drogas citotóxicas no tienen un beneficio demostrado en los casos agudos; sin embargo, parecen ser efectivos en los crónicos. Casos de P.I.A. y P.I.C. que han mejorado tras plasmáferesis han sido publicados; sin embargo, casos sin mejoría han sido también descritos.

R É S U M É

Les polyneuropathies inflammatoires (P.I.) sont un groupe important de neuropathies acquises, caractérisées pathologiquement par la présence de lésions inflammatoires éparpillées d'un bout à l'autre du système nerveux périphérique, accompagnées de démyélinisation segmentaire et remyélinisation, un niveau élevé de protéines avec un nombre normal de cellules dans le l.c.r., et des vitesses de conduction diminuées dans les nerfs. Cliniquement, elles peuvent se présenter avec une attaque aiguë ou sous-aiguë de faiblesse et d'absence de réflexes et un rétablissement de quelques semaines ou mois (Polyneuropathie Inflammatoire Aiguë [P.I.A.] ou Syndrome de Guillain-Barré), ou avec un attaque insidieuse de polyneu-

ropathie distale sensorielle et motrice dont le cours peut être progressif ou avec rechutes et rémissions (Polyneuropathies Inflammatoires Chroniques [P.I.C.]). Leur pathogenèse n'est pas claire, mais semble correspondre à des réactions immunologiques cellulaires et humorales anormales. L'efficacité d'agents modifiant la réaction immunologique dans le traitement des P.I. est sujet à controverse. Les corticostéroïdes et cytotoxiques n'ont pas prouvé bénéfiques pour les cas aigus, mais semblent efficaces pour les cas chroniques. L'échange de plasma a été efficace dans certains cas de P.I.A. et P.I.C., mais son échec a aussi été rapporté.

ZUSAMMENFASSUNG

ohne Besserung auch beschrieben worden.

Die entzündlichen Polyneuropathien (P.I.) sind eine wichtige Gruppe von erworbenen Neuropathien, charakterisiert pathologisch durch die Anwesenheit von entzündlichen Infiltrationen im peripheren nervösen System, begleitet von segmentärer Desmyelisation und axonaler Remyelinisation, bestehend aus Proteinen im l.c.r. mit einer normalen Anzahl von Zellen und langsamen nervösen Konduktionen. Klinisch können sie sich präsentieren durch ein akutes oder subakutes Bild von Schwäche der Muskeln und Abwesenheit der Sehnenreflexe, mit einer Wiederherstellung in Wochen oder Monaten (Akute entzündliche Polyneuropathie (P.I.A.) oder Syndrom von Guillain-Barré), oder besser als ein insidues sensitives und fortschreitendes motoris-

ches Bild einer Polyneuropathie, oder mit Rückschlägen und Remissionen (chronische entzündliche Polyneuropathien (P.I.C.))

Ihre Pathogenese ist noch nicht ganz geklärt, aber scheint zusammen zu hängen mit zellulären immunologischen und anormalen humoralen Reaktionen. Die Behandlung der P.I. mit Modifikationen der immunologischen Reaktionen ist widersprechend. Die Corticosteroiden und die Cytotoxischen Drogen haben keinen günstigen Effekt in den akuten Fällen gezeigt; dahingegen scheinen sie effektiv zu sein bei den chronischen.

Fälle von P.I.A. und P.I.C., die nach Plasmaphorese sich gebessert haben, sind veröffentlicht worden, zweifellos sind Fälle

B I B L I O G R A P H Y

1. Kahn SN, Riches PG, and Kohn J. (1980): Paraproteinemia in neurological disease: incidence, associations and classification of monoclonal immunoglobins. *J. Clin Pathol* 33:617-621.
2. Latov N, Sherman WH, Nemni R, Galassi G, Shyong JS, Penn AS, Chess L, Olarte MR, Rowland LP, and Osserman EF. (1980): Plasma-cell dyscrasia and peripheral neuropathy with monoclonal antibody to peripheral nerve myelin. *N. Eng J. Med* 303:618-621.
3. Kahn SN, Smith IS, Eames RA, Thomas PK, and Lacey BW. (1980): IgM paraproteinemia and autoimmune peripheral neuropathy. *N. Eng J. Med* 304 (letter): 1430-1431.
4. Latov N, Gross RB, Kastelman J, Flanagan T, Lamme S, Alkaitis DA, Olarte MR, Sherman WH, Chess L, and Penn AS. (1981): Complement fixing antiperipheral nerve myelin antibodies in patients with inflammatory polyneuritis and with polyneuropathy and paraproteinemia. *Neurology* 31: 1530-1534.

5. *Besinger VA, Toyka KV, Anzil AP, Neumeier D, Rauscher R, and Heininger K.* (1981): Myeloma neuropathy: passive transfer from man to mouse. *Science* 213:1027-1030.
6. *Guillain G, Barré JA, and Strohl A.* (1916): Sur un syndrome de radiculo-névrile avec hyperalbuminose du liquide céphalo-rachidien sans réaction cellulaire. Remarques sur les caractères cliniques et graphiques des réflexes tendineux. *Bull Soc. Med Hop Paris.* 40:1462-1470.
7. *Hinman R, and Magee KP.* (1967): Guillain-Barré syndrome with slow progressive onset and persistent elevation of spinal fluid protein. *Ann Intern Med* 67:1007.
8. *Asbury AK, Arnason BG, Karp HR, and McFarlin DE.* (1978): Criteria for diagnosis of Guillain-Barré syndrome. *Ann Neurol* 3:565-566.
9. *Asbury AK.* (1981): Diagnostic considerations in Guillain-Barré syndrome. *Ann Neurol* 9 (Suppl): 1-5.
10. *Bradley WG.* (1981): The neuropathies. In: *Disorders of Voluntary Muscle*, Walton J. (Ed). Churchill Livingstone, Edinburgh. pp 753-784.
11. *Ravin H.* (1967): The Landry-Guillain-Barré syndrome. *Acta Neurol Scand (Suppl)*: 30:1-64.
12. *Mumenthaler M, Ludin HP, Rossi LN, and Loeffel NB.* (1978): The long-term issue of acute idiopathic polyneuritis (Landry-Guillain-Barré syndrome). In: *Peripheral Neuropathies*, Canal N and Pozza G. (Eds). Elsevier/North Holland Biomedical Press, pp. 391-400.
13. *Anderson T, and Siden A.* (1982): A clinical study of the Guillain-Barré syndrome. *Acta Neurol Scandinav* 66:316-327.
14. *Tuck RR, and McLeod JG.* (1978): Autonomic dysfunction in the Landry-Guillain-Barré syndrome. *Proc Aust Assoc Neuro* 15:197-203.
15. *Keenlyside RA, Schoenberger LB, Bregman DJ, and Sullivan-Bolyai* (1980): Fatal Guillain-Barré syndrome after the national influenza immunization program. *Neurology* 30:929-933.
16. *Fisher CM.* (1956): An unusual variant of acute idiopathic polyneuritis (syndrome of ophthalmoplegia, ataxia and areflexia). *N. Eng J. Med* 255:57-65.
17. *Swash M.* (1979): Clinical aspects of Guillain-Barré syndrome: a review. *J. R. Soc Med* 72:670-673.
18. *Schonberger LB, Hurwitz ES, Katona P, Holman RC, and Bregman DJ.* (1981): Guillain-Barré syndrome: Its epidemiology and association with influenza vaccination. *Ann Neurol* 9 (Suppl): 31-38.
19. *Hurwitz ES, Holman RC, Nelson DB, and Schonberger LB.* (1983): National surveillance for Guillain-Barré syndrome: January 1978-March 1979. *Neurology* 33:150-157.
20. *Link H.* (1978): Demonstration of oligoclonal IgG in Guillain-Barré syndrome. *Acta Neurol Scandinav* 52:111-120.
21. *McLeod JG.* (1981): Electrophysiological studies in the Guillain-Barré syndrome. *Ann Neurol* 9 (Suppl): 20-27.
22. *Prineas JW.* (1981): Pathology of the Guillain-Barré syndrome. *Ann Neurol* 9 (Suppl): 6-19.
23. *Prineas JW.* (1971): Demyelination and remyelination in recurrent idiopathic polyneuropathy. An electron microscope study. *Acta Neuropath (Berl)*. 18:34-57.
24. *Dyck PJ, Lais AC, Ohta M, Bastron JA, Okazaki H, and Groover RV.* (1975): Chronic inflammatory polyradiculoneuropathy. *Mayo Clin Proc* 50:621-637.
25. *Lewis RA, Sumner AJ, Brown MJ, and Asbury AK.* (1982): Multifocal demyelinating neuropathy with persistent conduction block. *Neurology* 32:958-964.
26. *Prineas JW, and McLeod JG.* (1976): Chronic relapsing polyneuritis. *J. Neurol Sci* 27:427.
27. *Pollard JD, and Selby G.* (1978): Relapsing neuropathy due to tetanus toxoid. *J. Neurol Sci* 37:113-125.
28. *Austin JH.* (1958): Recurrent polyneuropathies and their corticosteroid treatment with five year observation of a placebo-controlled case treated with corticotropin, cortisone and prednisone. *Brain* 81:157-194.
29. *Bradley WG.* (1974): Disorders of Peripheral Nerves. Bradley WG. (Ed). Blackwell Scientific Publications, Oxford. p. 181.
30. *Dalakas MC, and King Engel W.* (1981): Chronic relapsing (dysimmune) polyneuropathy: Pathogenesis and treatment. *Ann Neurol* 9 (Suppl): 134-145.
31. *Adams D, Festenstein H, Gibson JB, Hughes RAC, Jaraquemada J, Papasteriadis C, Sachs J, and Thomas PK.* (1979): HLA antigens in the chronic relapsing idiopathic inflammatory polyneuropathy. *J. Neurol Neurosurg Psychiat* 42:184-186.
32. *Stewart GJ, Pollard JD, McLeod JG, and Wolnizer CM.* (1978): HLA antigens in the Landry-Guillain-Barré syndrome and chronic relapsing polyneuritis. *Ann Neurol* 4:285-289.
33. *Cook SD, and Dowling PC.* (1981): The role of autoantibody and immune complexes in the pathogenesis of Guillain-Barré syndrome. *Ann Neurol* 9 (Suppl): 70-79.
34. *Nyland H, Matre R, and Mork S.* (1981): Immunological characterization of sural nerve biopsies from patients with Guillain-Barré syndrome. *Ann Neurol* 9 (Suppl): 80-86.
35. *Luijten JAFM and Baart de La Faille-Kuyper EJ.* (1972): The occurrence of IgM and complement factor among myelin sheaths of peripheral nerves — an immunohistochemical study of the Guillain-Barré syndrome. *J. Neurol Sci* 15:291-224.
36. *Cook SD, Dowling PC, Murray MR, and Wiltaker JN.* (1971): Circulating demyeli-

- nating factors in acute idiopathic polyneuropathy. *Arch Neurol* 24:136-144.
37. *Feasby TE, Hahn AF, and Gilbert JJ.* (1980): Passive transfer of demyelinating activity in Guillain-Barré polyneuropathy. *Neurology* 30:363.
 38. *Heininger K, Ross HG, Toyka KV, Cleveland S, Besinger VA, and Anzil AP.* (1981): Induction of an experimental neuropathy in the monkey by passive transfer of human Guillain-Barré syndrome with immunoglobulins. (Abstract) Soc for Neurosci, 11th Annual Meeting 7:783.
 39. *Saida T, Saida K, Lisak RP, Brown MJ, Silberberg DH, and Asbury AK* (1982): In vivo demyelinating activity of sera from patients with Guillain-Barré syndrome. *Ann Neurol* 11:69-75.
 40. *Low PA, Schmelzer JD, Dyck PJ, and Kelly JJ.* (1982): Endoneurial effects of sera from patients with acute inflammatory polyradiculoneuropathy: Electrophysiologic studies on normal and demyelinated rat nerves. *Neurology (NY)* 32:720-724.
 41. *Low PA, Schmelzer JD, and Dyck PJ.* (1982): Results of endoneurial injection of Guillain-Barré serum in Lewis rats. *Mayo Clin Proc* 57:360-364.
 42. *Iabal A, Oger JFF, and Arnason BGW.* (1981): Cell-mediated immunity in idiopathic polyneuritis. *Ann Neurol* 9 (Suppl): 65-69.
 43. *Zweiman B, Rostami A, Lisak RP, Moskowitz AR, and Pleasure DE.* (1983): Immune reactions to P2 protein in human inflammatory demyelinating neuropathies. *Neurology* 33:234-236.
 44. *Abramsky O, Webb C, Teitelbaum D, and Arnon R.* (1975): Cell-mediated immunity to neural antigens in idiopathic polyneuritis and myeloradiculitis. *Neurology (Minneapolis)* 25:1154-1159.
 45. *Sheremata W, Colby S, Karkhanis Y, and Eylar EH.* (1975): Cellular hypersensitivity to basic myelin (P2) protein in the Guillain-Barré syndrome. *Canad J. Neurol Sci* 2:87-90.
 46. *Arnason BGW, Winkler GF, and Hadler NM.* (1969): Cell-mediated demyelination of peripheral nerve in tissue culture. *Lab Invest* 21:1-10.
 47. *Seil FJ.* (1977): Tissue culture studies of demyelinating disease: a critical review. *Ann Neurol* 2:345-355.
 48. *Searles RP, Davis LE, Hermanson S, and Forelich CJ.* (1981): Lymphocytotoxic antibodies in Guillain-Barré syndrome. *Lancet* I:273.
 49. *Stevens JG, Pepose JS, and Cook ML.* (1981): Marek's disease: a natural model for the Landry-Guillain-Barré syndrome. *Ann Neurol* 9 (Suppl): 102-106.
 50. *Johnson RT.* (1982): Parainfections neurological syndromes. In: *Viral Infections of the Nervous System*. Johnson RT. (Ed) Raven Press, NY. pp. 169-202.
 51. *Dowling PC, and Cook SD.* (1981): Role of infection in Guillain-Barré syndrome: Laboratory confirmation of herpes viruses in 41 cases. *Ann Neurol* 9 (Suppl): 44-55.
 52. *Evans R, and Alexander P.* (1976): Mechanism of extracellular killing of nucleated mammalian cells by macrophages. In: *Immunobiology of the Macrophage*. Nelson DS (Ed). Academic Press, NY, San Francisco, London. pp. 535-576.
 53. *Griffin FM, Griffin JA, Leider JE, and Silverstein SC.* (1975): Studies on the mechanism of phagocytosis. I. Requirements for circumferential attachment of particle-bound ligands to specific receptors on the macrophage plasma membrane. *J. Exp. Med* 142:1263-1282.
 54. *Griffin FM, Griffin JA, and Silverstein SC.* (1976): Studies on the mechanism of phagocytosis. II. The interaction of macrophages with anti-immunoglobulin IgG-coated bone marrow-derived lymphocytes. *J Exp Med* 144:788-809.
 55. *Peterman AF, Daly DD, Dion FR, and Keith HM.* (1959): Infectious neuronitis (Guillain-Barré syndrome) in children. *Neurology* 9:533-539.
 56. *Drachman DA, Patterson PY, Berlin BS, and Roguska J.* (1970): Immunosuppression and the Guillain-Barré syndrome. *Arch Neurol* 23:385-393.
 57. *Lisak RP, Mitchell M, Zweiman B, Orecchio E, and Asbury AK.* (1977): Guillain-Barré syndrome and Hodgkin's disease: three cases with immunologic studies. *Ann Neurol* 1:72-78.
 58. *Penney MD, Murphy D, Walters G.* (1979): Resetting of osmoreceptor response as cause of hyponatremia in acute idiopathic polyneuritis. *Br Med J* 2:1474-1476.
 59. *Nixon RA.* (1978): Quinine sulfate for pain in the Guillain-Barré syndrome. *Ann Neurol* 4:386-387.
 60. *Stillman JS, and Ganong WF.* (1952): The Guillain-Barré syndrome: report of a case treated with ACTH and cortisone. *N Eng J Med* 246:293-296.
 61. *Swich HM, McQuillen MP.* (1976): The use of steroids in the treatment of idiopathic polyneuritis. *Neurology* 26:205-212.
 62. *Hughes RAC, Newson-Davis J, Perkin GD, and Pierce JM.* (1978): Controlled trial of prednisolone in acute polyneuropathy. *Lancet* 2:750-753.
 63. *Palmer KNV.* (1965): Polyradiculoneuropathy treated with 6-mercaptopurine. *Lancet* 1:733-734.
 64. *Palmer KNV.* (1966): Polyradiculoneuropathy treated with cytotoxic drugs. *Lancet* 1:265.
 65. *Yuill GM, Swinburn WR, and Silversedge LYA.* (1970): Polyneuropathy with azathioprine. *Lancet* 2:750-753.
 66. *Rosen AD, Vastola EF.* (1976): Clinical effects of cyclophosphamide in Guillain-Ba-

- rré Syndrome polyneuritis. *J Neurol Sci* 30:179-187.
67. *Brettle RP, Gross M, Legg NJ, Lockwood M, and Pallis C.* (1978): Treatment of acute polyneuropathy by plasma exchange. *Lancet* 2:1100.
68. *Vanderheyden JE, Kennes B, Bain H, Hubert C, and Neve P.* (1979): Plasma exchange in acute polyneuropathy. *Acta Clin Belg* 34:246.
69. *Rail D, Stark R, Swash M, and Newland AC.* (1980): Improvement in nerve conduction after plasma exchange for Guillain-Barré syndrome. *J Neurol Neurosurg Psychiat* 43:1147.
70. *Mark B, Hurwitz BJ, Olanow CW, and Fay JW.* (1980): Plasmapheresis in idiopathic inflammatory polyradiculoneuropathy. *Neurology* 30:361.
71. *Ropper AH, Shahani BT and Huggins CE.* (1980): Improvement in four patients with acute Guillain-Barré syndrome after plasma exchange. *Neurology* 30:361.
72. *Cook JD, Tindall RAS, Walker J, Kahn A, and Rosenberg R.* (1980): Plasma exchange as a treatment of acute and chronic idiopathic autoimmune polyneuropathy: limited success. *Neurology* 30:361-362.
73. *Valbonesi M, Garelli S, Mosconi L, Zerbi D, and Celano I.* (1981): Plasma exchange as a therapy for Guillain-Barré syndrome with immune complexes. *Vox Sanguinis* 47: 74-78.
74. *Littlewood R, and Bajada S.* (1981): Successful plasmapheresis in the Miller-Fisher syndrome. *Br Med J* 282:778.
75. *Gerard A.* (1981): Successful plasmapheresis in the Miller-Fisher syndrome. *Br Med J* 282:1627.
76. *Durward WF, Burnett AK, Watkins R, and Reid JM.* (1981): Plasma exchange in the Guillain-Barré syndrome. *Br Med J* 283: 794.
77. *Schoonerman F, Janot C, Streiff F, et al* (1981): Plasma exchange in the Guillain-Barré syndrome: ten cases. *Plasma Therapy* 2:117-121.
78. *Rumpl E, Mayr U, Gerstenbrand F, Hackl JM, Rosmanith P, and Aichner F.* (1981): Treatment of Guillain-Barré syndrome by plasma exchange. *J Neurol* 225:207-217.
79. *Irvine AT, and Tibbles J.* (1981): Treatment of Fisher's variant of Guillain-Barré syndrome by exchange transfusion. *Canadian J Neuro Sci* 8:49-50.
80. *Osterman PO, Fagius J, Safwenberg J, Danersund A, Wallin G, and Nordesjo L-O.* (1982): Treatment of the Guillain-Barré syndrome by plasmapheresis. *Arch Neurol* 39:148-154.
81. *Kennard C, Newland AC, and Ridley A.* (1982): Treatment of the Guillain-Barré syndrome by plasma exchange. *J Neurol Neurosurg Psychiat* 45:847-850.
82. *Maisey DN, and Olzak SA.* (1981): Successful plasmapheresis in the Miller-Fisher syndrome. *Br Med J* 282:1159.
83. *De Jager AE, The TH, Smit Sibinga CTH and Das PC.* (1981): Plasma exchange in Gaillain-Barré syndrome. *Br Med J* 282: 794-795.
84. *Griffin JW.* (1982): The Guillain-Barré Study: current status (letter). In: *Guillain-Barré Updae*. Vol 1, N° 3.
85. *Dyck PJ, O'Brien PC, Oviatt KF, Dinapoli RP, Daube Jr, Bartleson JD, Mokri B, Swift T, Low PA, and Windebank AJ.* (1982): Prednisone improves chronic inflammatory demyelinating polyradiculoneuropathy more than no treatment. *Ann Neurol* 11:136-141.
86. *Matthews WB, Howell DA, and Hughes RC.* (1970): Relapsing corticosteroid-dependent polyneuritis. *J Neurol Neurosurg Psychiat* 33:330-337.
87. *Fauci AS, Dale DC, Balow JE.* (1976): Glucocorticosteroid therapy: mechanisms of action and clinical consideration. *Ann Int Med* 84:304-315.
88. *Cupps TR, Fauci AS.* (1982): Management and treatment. In: *The Vasculitides*. Cupp TR and Fauci AS. (Eds). Saunders Company, Philadelphia, PA. pp. 155-172.
89. *Cendrowski W.* (1977): Treatment of polyneuropathy with azathioprine and adrenal steroids. *Acta Med Pol* 18:147-156.
90. *Prusinsk A, Szulc-Kuberska J, and Zawadzki Z.* (1978): A case of chronic Guillain-Barré syndrome treated successfully with azathioprine. *Wiad Lek* 31:1545-1547.
91. *Pentland B, Adams GGW, and Maudsley C.* (1982): Chronic idiopathic polyneuropathy treated with azathioprine. *J Neurol Neurosurg Psychia* 45:866-869.
92. *Walker GL.* (1979): Progressive polyradiculoneuropathy. Treatment with azathioprine. *Aust New Zealand J Med* 9:184-187.
93. *Colin-Jones DG, Heathfield KWG.* (1965): 6-Mercaptopurine in polyradiculoneuropathy *Lancet* 2:739.
94. *Gamstorp I, Aronson S, and Lindquist B.* (1966): Mercaptopurine in polyradiculoneuropathy. *Lancet* 1:99-100.
95. *Heathfield K, and Dallos V.* (1970): Treatment of polyneuropathy with azathioprine. *Lancet* 2:854-856.
96. *Geraint JD.* (1979): Immunotherapy. In: *Clinical Neuroimmunology*. Clifford Rose (Ed). Blackwell Scientific Publishers, Oxford. pp 463-472.
97. *Wolff PS.* (1973): Neutropenia. In: *Current Therapy*. Conn HF (Ed). Saunders Company, Philadelphia, PA p 223.
98. *Dalakas MC, Flaum M, Engel WK, et al* (1980): Successful treatment of polyneuropathy in Waldenstrom macroglobulinemia (WM): Role of dysproteinemia in pathogenesis of the neuropathy. *Neurology* 30: 428.
99. *Pirofsky B, and Bardana EJ.* (1977): Immunosuppressive therapy in rheumatoid diseases. *Med Clin N A* 61 (2): 419-437.

100. *Wahl SM. and Rosenstreich DL. (1976):* Suppression of lymphocyte function by glucocorticosteroids. In: *Mitogens in Immunology*. Oppenheim JJ and Rosenstreich DL. (Eds). Academic Press, NY, pp 537-553.
101. *Engel WK. Cuneo RA. and Levy HB. (1978):* Polyinosinic-polycytidylic acid treatment of neuropathy. *Lancet* 1:503-504.
102. *Bower BD. and Newsholome EA. (1978):* Treatment of idiopathic polyneuritis by a PUFA diet. *Lancet* 1:583-584.
103. *Server AC. Lefkowitz J. Braine H. and McKhann GM. (1979):* Treatment of chronic relapsing inflammatory polyradiculoneuropathy by plasma exchange. *Ann Neurol* 6:258-261.
104. *Levy RL. Newkirk R. and Ochoa J. (1979):* Treating chronic relapsing Guillain-Barré syndrome by plasma exchange. *Lancet* 2: 259-260.
105. *Toyka KV. Augspach R. Paulus W. Gabensee B. and Hein D. (1980):* Plasma exchange in polyradiculoneuropathy. *Ann Neurol* 8:205-206.
106. *Server AC. Stein SA. Braine H. Tandon DS. and McKhann GM. (1980):* Experience with plasma exchange and cyclophosphamide in the treatment of chronic relapsing inflammatory polyradiculoneuropathy. *Neurology* 30:362.
107. *Maas AIR. Busch HFM. and van der Heul C. (1981):* Plasma infusion and plasma exchange in chronic idiopathic polyneuropathy. *N Eng J Med* 305:344.
108. *Gross MLP. and Thomas PK. (1981):* The treatment of chronic relapsing and chronic progressive idiopathic inflammatory polyneuropathy by plasma exchange. *J Neurol Sci* 52:69-78.
109. *Fowler H. Vulpe M. Marks G. Egolf C. and Dau PC. (1979):* Recovery from chronic progressive polyneuropathy after treatment with plasma exchange and cyclophosphamide. *Lancet* 2:1193.
110. *Lockwood MC. Rees AJ. Pearson TA. Evans DJ. Peters DK. Wilson CB (1976):* Immunosuppression and plasma exchange in the treatment of Goodpasture's syndrome. *Lancet* 1:711-716.
111. *Melnick SC. and Flewett TH. (1964):* Role of infection in the Guillain-Barré Syndrome *J Neurol Neurosurg Psychiat* 27:385-407.
112. *Goust JM. Chenais FC. Hammes CG. Fudenberg HH. and Hogan EH. (1978):* Abnormal T-cell subpopulation and circulating immune complexes in the Guillain-Barré Syndrome and multiple sclerosis. *Neurology* 28:421-425.

Thiamine Deficiency Neuropathy, a Reappraisal

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Thiamine deficiency is known to cause beriberi neuropathy among oriental people and alcoholic neuropathy in chronic alcoholics. There is no essential difference between the two. The author experienced many cases of beriberi neuropathy recently.

Beriberi has been described in the ancient documents of ninth century in Japan. The disease had been popular among orient people whose staple diet was white polished rice. Since the machine-milled white rice came to be available, the incidence of beriberi increased markedly. Initially, beriberi was suspected to be caused by some infections or toxic agents. Eijkman (1897)¹ succeeded in setting up the polyneuritis resembling to human beriberi after feeding fowls by polished white rice, being cured by replacing white rice to crude rice. He was also convinced that the peripheral nerves were damaged by some toxic agent in the rice to which the pericarp of the rice was an antidote. In 1911, Funk² extracted a substance from rice polishings, a deficiency of which caused polyneuritis in pigeons. He named the substance vitamin. Thereafter, the concept that beriberi is caused not by the toxic substance but by a deficiency of the substance essential for health is established and many investigations proved that human beriberi is caused by nutritional deficiency of vitamin, namely thiamine. In Japan the beriberi was popular among young peoples who were taking white polished rice and the death rate due to beriberi was 50 in 100,000 populations in

1923³. However the incidence of the disease decreased markedly and had been practically none until a few years ago, since the etiology of beriberi became apparent and the nutritional counterplan was taken place³. However, beriberi neuropathy outburst again in Japan recently⁴.

Clinical, pathological and chemical feature of beriberi neuropathy will be reviewed in this paper.

Recent reappearance of beriberi neuropathy in Japan.

Acute polyneuritis associated with edema and often with cardiac enlargement occurred with increasing incidence in the last few years in this country⁴. The disease affected mostly young males, that is, high school students. Estimation of blood thiamine level and therapeutic effectiveness of thiamine established that the disease was beriberi neuropathy which had been disappeared in Japan. From 1973 to 1976, 371 patients were found on the survey conducted by a research committee of the ministry of public health. The patients were distributed mostly in western Japan. The sex ratio of male to female was 5 to 1 and about 90 per cent of the patients were from 15 to 20 years old⁴. Seventy five percent of the patients occurred in hot season, when the energy consumption and the requirement of thiamine increase, leading to relative deficiency of thiamine. Most of the patients belonged to athletic clubs in high school or were physical workers, who need much of thiamine. It is well known that alcoholic neuropathy occurs in the mid-



Figure 1. — *Edema in the leg. a 16 year-old male.*

dle age and the beriberi neuropathy mostly in young people⁵. In general, the former is popular in European countries and the latter in Orient.

Clinical features

a) Onset of illness

Most patients showed acute or subacute onset, with edema, weakness and paresthesia, prior to the acute onset of polyneuritis, the patients often experienced a vague feeling of general fatigue, loss of appetite,

nausea, palpitation of the heart or dyspnoea. Remissions and exacerbations at various intervals, ranging from 2 months to a year, were occasionally observed. Some patients noted a slight edema along the inner surface of the tibia in summer, which subsided spontaneously in a few days, and the following summer, edema and weakness of the leg became apparent. In another case, edema of the legs occurred during hard work and recovered with the rest, but reappeared with beginning of the work, finally progressing to a severe paralysis after several remissions and exacerbations. At times, the symptoms occurred in conjunction with infectious diseases with fever or with hyperthyroidism, in which the metabolic rate is high and much of thiamine is required. On some occasions, cardiac symptoms as palpitation, dyspnoea and severe edema, suddenly set in.

b) General symptoms

Edema is observed in pretibial portions in almost all cases, with or without a puffiness of the face (Fig. 1). As the edema often subsides easily by the rest of several days, some patients have no edema at the time of their coming to the hospital.

They feel only the strain sensation in the calf muscles. Systolic heart murmurs of grade II to III were usually recognized at the apex. The second pulmonary sound was accentuated. On some occasions, arterial sounds over the inguinal areas were noted. Cardiac dullness was often enlarged in both sides. Frequently, systolic blood pressure was high and diastolic blood pressure was depressed, showing an elevated pulse pressure for example 180/0 mmHg in a young patient.

c) Neurological findings.

Neurological symptoms of beriberi are essentially those of polyneuritis⁶. In recently reappeared beriberi neuropathy in Japan, weakness, loss of tendon reflexes and sensory impairment were usually observed in the legs. In mild cases, there were only paresthesia without objective sensory impairment and loss of tendon reflexes in the leg. Muscle tenderness on pressure and painful cramps of calf muscles were common. Transient neuralgia in the legs was noticed in the early stage of the disease. Muscle

weakness was prominent in the distal legs. Dorsal flexion of the foot was more affected than plantar flexion. Sensations were impaired in all modalities, predominantly in distal extremities. On rare occasions, paresthesia was noticed around the lips or navel. Muscular atrophies were observed on the legs in the cases of prolonged course. In general, muscle weakness was more remarkable than sensory disturbances, compatible to motor predominant type of neuropathy.

At times, cranial nerve involvements, as bilateral facial palsy or hoarseness due to vagal nerve palsy, were observed, as have been reported previously⁷. Deafness hypoglossal nerve palsies and amblyopia, which had been described in beriberi⁷, were not noticed in the present series of reappeared beriberi. No sphincter disturbance was noticed. Hyperactive tendon reflexes which had been described previously⁶ were rare in the present cases. In the most severely affected case, a 20 years old male, who had severe weakness of four extremities, bilateral facial palsy and sensory loss in distal four extremities and trunks under the upper thoracic, patellar reflex became hyperactive during the recovery stage, indicating concomitant involvement of the pyramidal tract.

Laboratory findings

Routine laboratory findings, including blood cell count, urinalysis, total protein, liver functions, LE reaction, CPK and plasma electrophoresis were all within normal limits. Chest X-ray films showed cardiac enlargement in approximately half of the present series examined in the hospital (Fig. 2A). On some occasions, electrocardiograms showed biphasic T wave and ST depression in the thoracic leads, or disturbance of auriculoventricular conduction^{4,8}. Ultrasonocardiogram disclosed ventricular dilatation in these cases⁸. In the cases of cardiac involvement, cardiovascular hemodynamics measured by catheterization revealed high output cardiac failure showing marked increase in cardiac index, pulmonary arterial pressure and pulmonary arterial wedge pressure, and decrease in systemic and pulmonary vascular resistance^{8,9,10}. The circulation time was shortened.

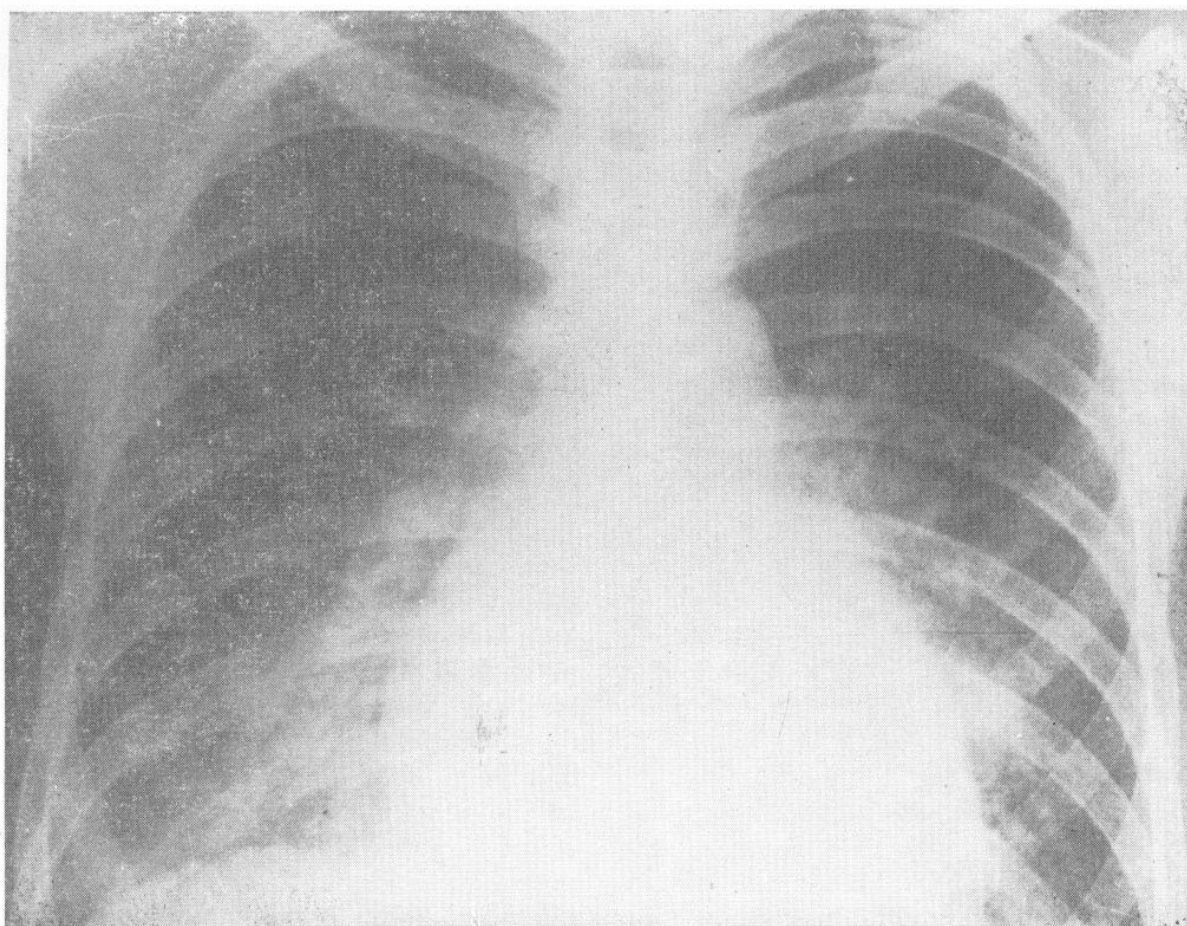


Figure 2. — *Cardiac enlargement. a 18 year-old male.*

ned. Myocardial edema and, on some occasions, degeneration of muscle fibers were observed by myocardial biopsies⁸⁾. Blood thiamine level and thiamine excretion in urine were reduced in most of the patients⁴⁾¹¹⁾. Loading of 5 mg of thiamine often resulted in a less increase in the urinary excretion, compared with normal cases⁴⁾¹¹⁾.

Lactic acid and pyruvic acid were elevated, specially after glucose administration and exercise¹²⁾. The blood transketolase activity, which is the most reliable index of thiamine deficiency were also decreased in most of the patients examined¹³⁾¹⁴⁾.

CSFs were mostly normal, contrary to that of Guillain-Barré syndrome. Electromyograms were of neurogenic changes, with denervation potentials and large action potentials. Electromyographic abnormalities were found frequently in the asymptomatic upper extremities. Maximum conduction velocities (MCVs) in posterior tibial nerve, examined in 25 cases in our clinic, sho-

wed slight prolongation; 30 to 40 m per second, in 3 cases who had severe signs of polyneuritis, and were faster than 41 m per second in the others¹⁵⁾. It was noteworthy that MCVs were only slightly reduced, compared with the severity of the motor palsy. These findings might be due to the fact that beriberi neuropathy is essentially the axonal degenerations, and the segmental demyelinations in which the MCVs reduce markedly⁶⁾¹⁷⁾, are uncommon.

Sural nerve

The author performed sural nerve biopsies in 11 cases.

Light microscopy There was a considerable loss of myelinated fibers and collapsed myelins in the osmium fixed cross sections. The severity of these changes corresponded to the degree of sensory loss in the legs in every cases (Fig. 3).

Teased fibers Lineal rows of myelin ovoids over the total length of the fibers were abundant in all cases (Fig. 4A) On the other hand, segmental demyelinations

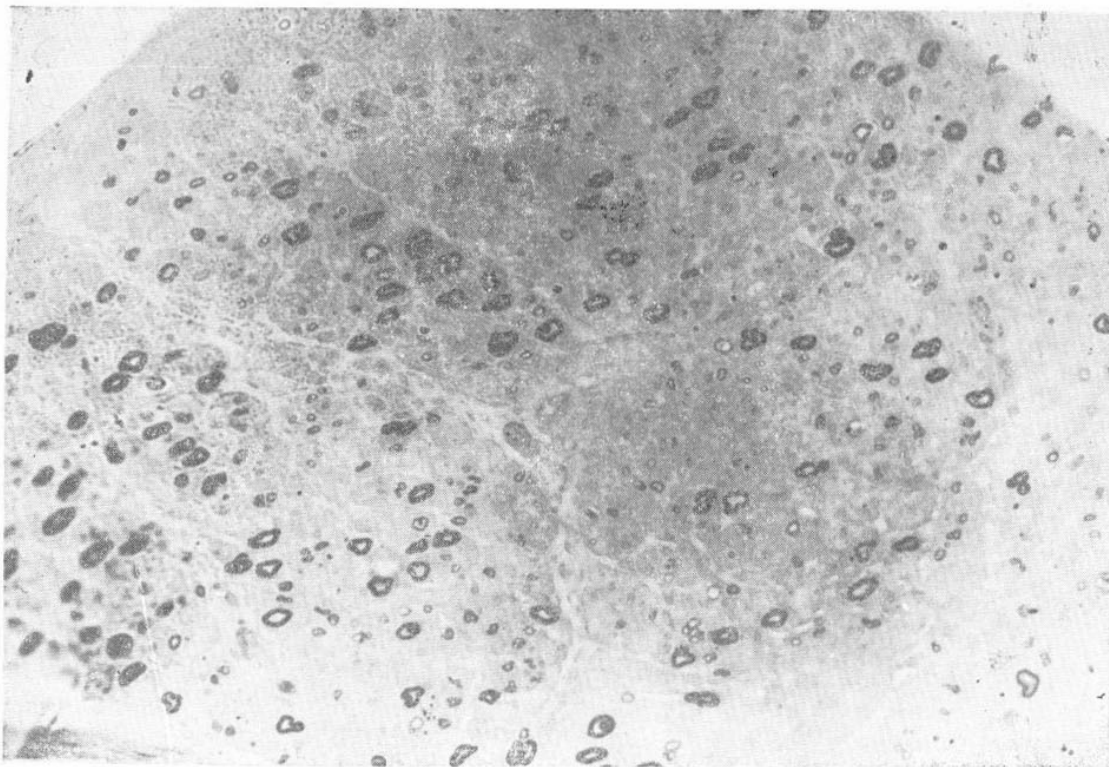


Figure 3. — Sural nerve. Loss of large myelinated fibers. $\times 150$.

were scant (Fig. 4B). The relationship between internodal length and fiber diameter indicated myelinated fibers with disproportionately short internodes, suggesting axonal degeneration and regeneration¹⁸⁾.

Electron Microscopy Sural nerve biopsy specimens taken at the onset of disease presented frequently the early changes of axonal degenerations, showing irregular accumulation of tubular or vesicular structures in the axons, the myelin of which were preserved (Fig. 5). Some myelinated fibers contained floccular and electron-dense materials or glycogen granules. In addition, there were nonspecific changes of axonal degeneration in all cases, most of whom had been treated by thiamine at the biopsy. These changes were the followings, disorderly arrangement or rarefaction of neurofilaments, axoplasm containing accumulation of degenerated mitochondria, vesicles, and small myelin figures, myelinated fibers in which axons were replaced by homogenous dense material, and Schwann cell cytoplasm with collapsed myelin but no axon. The lamellar structure of myelin was often preserved even in fiber with degenerated axon. Occasionally, demyelinated axons and remyelinated fibers with thin myelin sheath

and redundant basement membrane were observed. Active degeneration of unmyelinated axons was occasionally found, but these changes were slight compared to those of large myelinated fibers.

There were a number of clusters of Schwann cell processes in all biopsy specimens. The clusters in untreated patients contained no definite profiles of regenerated axons, whereas those in the treated patients had many axons, some not yet individually enveloped by Schwann cell cytoplasm. Clusters of thin myelinated axons were also abundant in the treated cases.

Comment on sural nerve pathology In thiamine deficient rats, unusual accumulation of flattened sacs or tubuli in the axoplasm have also been recognized within the intramuscular nerves and the terminal axoplasmic expansions of neuromuscular junction²⁰⁾, as were seen in human beriberi neuropathy. These findings may be characteristic of the early changes in thiamine deficient states. The pattern of degeneration observed has been that of dying-back neuropathy in experimental animal²⁰⁾ as well as in man⁶⁾.

With the teased fiber method, main feature was of axonal degenerations. Segmen-

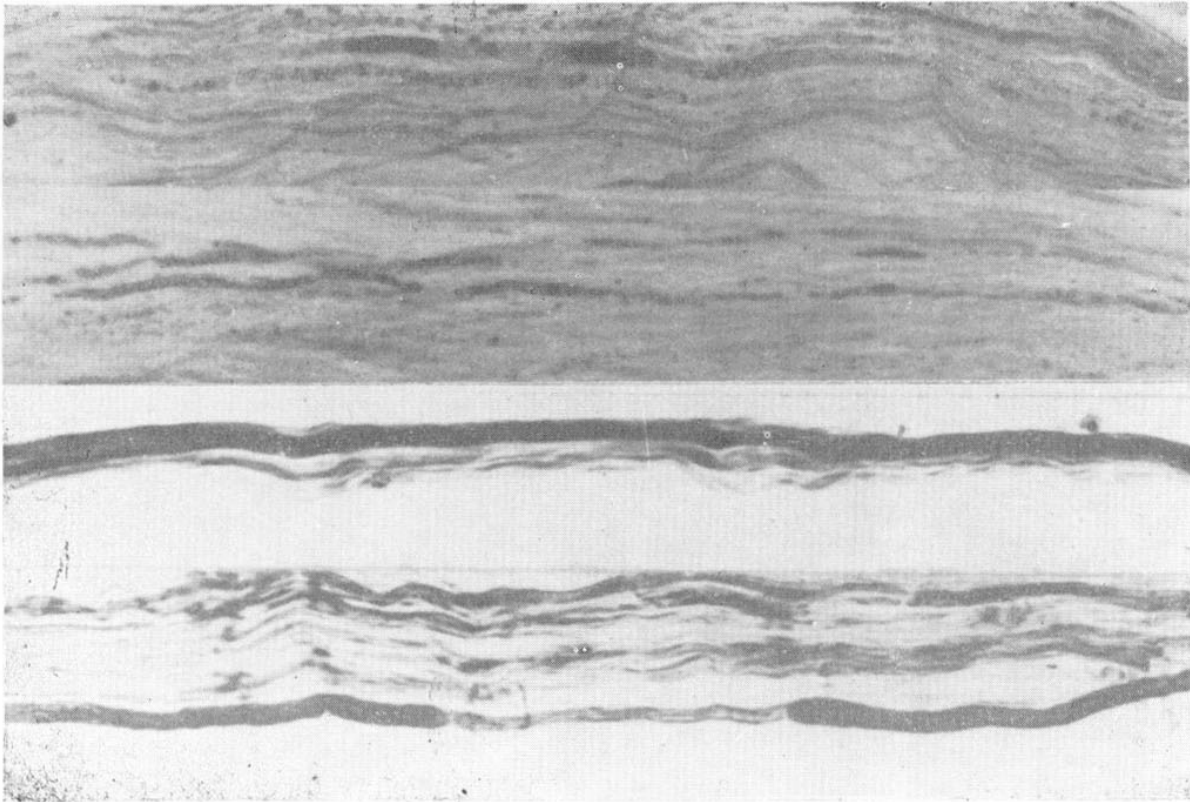


Fig. 4. — *Teased fiber. Axonal degenerations and a segmental demyelination (Lower most).*

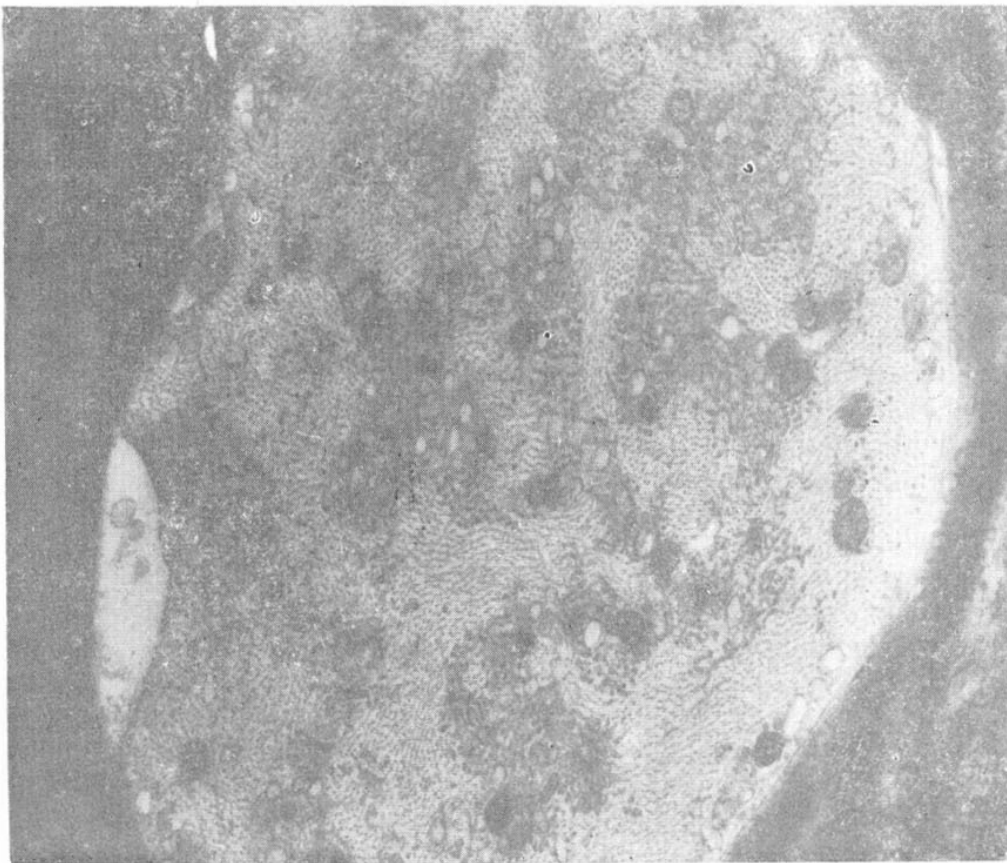


Figure 5. — *Irregular accumulations of sacs and tubular structures in the axon, $\times 16,000$.*

tal demyelination was exceptional, and might be secondary to the axonal degeneration, as has been described by Dyck et al²¹⁾ in uremic neuropathy. Recently, Ohnishi et al²²⁾ observed the clustered segmental demyelination on teased fibers in beriberi neuropathy and recognized that most of the segmental demyelination occurring in beriberi neuropathy are the secondary changes of axonal degeneration. The reason why the reduction of MCVs was slight in beriberi neuropathy, might be correlated with the axonal degenerations. In the neuropathies of segmental demyelination, such as Guillain-Barré syndrome¹⁶⁾, Charcot-Marie-Tooth disease and Déjérine-Sottas disease¹⁷⁾, MCVs is reduced markedly. In neuropathies of axonal degeneration, the reduction of MCV is slight²³⁾.

The mechanism of the nerve damage in beriberi neuropathy remain uncertain. Thiamine plays an important role in oxidative metabolism²⁴⁾, the depression of which impairs fast axoplasmic transport. Thiamine also had a direct effect to functioning of the excitable membrane of neurons²⁵⁾.

Course and treatment

With thiamine therapy, edema subsided in a few days, cardiac enlargement in a few weeks and muscular weakness in several months. Most if the patients recovered completely by the thiamine therapy in the present series. Hyporeflexia or muscular weak-

ness remained in a few cases, in whom the beginning of the therapy were delayed.

Nutritional problem

No patients showed emaciation, anemia, or other signs of malnutrition. They were all well nourished and had good muscular development. However, their staple food consisted of white polished rice, in addition to large amounts of "instant noodles" and processed foods which contain only a small amount of vitamin B₁. They were also taking large quantities of soft drink or coffee, which contain much of sugar. They often disliked milk, meat and fish, and took a small amount of subsidiary diets, fresh vegetables, peas, eggs, potatoes etc. Consequently their diets were consisted of high carbohydrate, low protein and vitamin B₁. Their caloric intakes were normal or over, as were given in the table 1. Some patient had been taking normal quantity of vitamin B₁, 1.10 mg per day with high carbohydrate intake, 1253 g, leading to relative deficiency of thiamine that is 0.18 mg of thiamine to 1.000 caloric (normal: 0.33 mg to 1.000 caloric). Contrary to the beriberi of old-time in orient, being often due to poor diet, the recently reappeared beriberi in Japan was caused by imbalance of nutrition, though being "rich" in caloric. Today's reappearance of beriberi in Japan give warning to the "instant" or processing foods.

case	age	sex	energy (cal)	protein (g)	carbohydrate (g)	V. B ₁ (mg)
M M	17	M	3,432	95.9	619.8	0.98
A N	16	M	4,654	97.6	941.4	0.74
T M	15	M	2,452	53.1	361.3	0.28
Y T	19	F	2,998	66.4	605.8	0.66
A N	37	M	6,264	124.3	1252.8	1.10

Table 1. — Nutritional analysis of beriberi patients.

SUMMARY

Thiamine deficiency neuropathy was reviewed with special reference to the recently reappeared beriberi in Japan. Clinically edema, weakness of legs, and sensory disturbance in distal extremities were most prominent features. Cardiac involvement; systolic murmur, accentuation of second pulmonary sound, cardiac enlargement and sometimes acute cardiac failure, were seen

in approximately half of the cases. Peripheral neuropathy was of motor predominant type. Axonal degeneration was prominent, and segmental demyelination seemed to be secondary to the axonal degeneration. Maximum conduction velocity reduced slightly. Nutritional problems concerning foods among oriental people whose staple foods are white polished rice, were discussed.

RESUMEN

La neuropatía por deficiencia en Tiamina fue estudiada con referencia especial al beriberi que se hizo presente en el Japón. Los síntomas y signos más prominentes desde el punto de vista clínico fueron edema, debilidad en las piernas, disturbios sensitivos en el sector distal de las extremidades. En aproximadamente la mitad de los casos se comprobó complicación cardíaca, soplo sistólico, acentuación del segundo tono pulmonar, aumento del área cardíaca y a veces

insuficiencia cardíaca aguda. La neuropatía periférica fue predominantemente de tipo motor. La degeneración axonal fue prominente y la desmielinización segmental parecía ser secundaria a la degeneración axonal. La máxima velocidad de conducción estaba ligeramente reducida. Se discutió el problema nutricional en relación con los alimentos de la población oriental cuyo alimento principal es el arroz blanco pulimentado.

RÉSUMÉ

La polynévrite déficiente de thiamine a été rapporté, spécialement en ce qui concerne du bériberî névrite, réparue récemment en Japon. Cliniquement, oedème, faiblesse du pied, trouble sensorielle en extrémité distale ont été les symptômes cardinales. Les symptômes cardiaque, comme le bruit de souffle du cour, accentuation du second bruit pulmonale, élargement cardiaque, ou, en quelque temps, décompensation du cour

ont été observé chez à peu près demis de cas. La névrite périphérique était prédominant de type motorice. Dégénération axonale étaient prominent et les démyélinisations segmentaires étaient parue comme le hangement secondaire. La vitesse de conduction nerveux était edue légèrement. Le problèmes de la nourriture de Japon, consisté du riz polié, sont discuté.

ZUSAMMENFASSUNG

Die avitaminotischen Polyneuritis wurde mit besonderer Beri-Beri besprochen. In fast sämtlichen Fällen, liessen sich Ödem, Lähmung der unteren Extremitäten und Sensibilitätsstörungen feststellen. Die kardiovaskulären Symptome, z. B. systolisches Geräusch, akzentierter Zweiten Pulmonalton und Herzdilation, fanden sich etwa zur Hälfte der Kranken. Akute Herzinsuffizienz

wurde manchmal in den Kranken wahrgenommen. Beim Polyneuritis handelten sich um motorische Störungen hauptsächlich. Die Axonaldegeneration entsprach als die primäre Veränderung und es erscheint, dass die Segmentale-degeneration nachfolgend auftrat. Die Ernährungsfrage über die immer mit den polierten Reis genährten Japaner wurden behandelt.

REFERENCES

1. *Eijkman, C.*: Eine beriberiähnliche Krankheit der Hühner. *Virchows Arch.* 148: 523, 1897.
2. *Funk, C.*: On the chemical nature of the substance which cures polyneuritis in birds induced by a diet of polished rice. *J. Physiol. (Lond.)* 43: 395, 1911.
3. *Abe, T.*: Clinical problems of vitamins in present Japan. *Jap. J. Med.* 5: 153, 1966.
4. *Takahashi, K., Kitagawa, T. & Shimao, M.*: Acute polyneuritis associated with edema. *Jap. J. Med.* 15: 214, 1976.
5. *Erbsloh, F. & Abel, M.*: Deficiency neuropathies, Hand book of Clinical Neurology. Edited by Vinken, P.J., Bruyn, G.W., New York, American Elsevier, 1970, vol. 7, chap. 23.
6. *Pekelharing, C.A. & Winkler, C.*s Mittheilung über die Beri-Beri. *Dtsch. Med. Wochenschr.* 13: 845, 1887.
7. *Victor, M.*: Polyneuropathy due to nutritional deficiency and alcoholism. In "Peripheral Neuropathy". Edited by Dyck P.J., Thomas, P.K. and Lambert, E.H. Saunders Co. 1975, p. 1031.
8. *Munakata, J. et al.*: Hemodynamics of the beriberi heart disease, as observed in a typical case. *J. Jap. Soc. Int. Med.* 66: 656, 1977.
9. *Jeffrey, F.E. & Abelman, W.H.*: Recovery from proved Shoshin beriberi. *Am. J. Med.* 50: 123, 1971.
10. *Kozam, R.L., Esguerra, O.E. & Smith, J.J.*: Cardiovascular beriberi. *Am. J. card* 30: 418, 1972.
11. *Melnick, D. & Oser, B.L.*: Physiological availability of the vitamins. *Vitamin & Hormones*. 5: 39, 1947.
12. *Morwitt, M.K. & Kreisler, O.*: The determination of early thiamine deficient states by estimation of blood lactic acid and pyruvic acids after glucose administration and exercise. *J. Nutr.* 37: 411, 1949.
13. *Akbarian, M. & Dreyfus, P.M.*: Blood transketolase activity in beriberi heart disease. *JAMA* 203: 77, 1968.
14. *Arima, H. et al.*: Reappearance of beriberi Japan Med. J. 2736: 23, 1976.
15. *Takahashi, K.*: An electrophysiological study on beriberi neuropathy. *Neurol. Med. (Tokyo)* 5: 357, 1976.
16. *Humphrey, J.G.*: Motor nerve conduction studies in the Landry-Guillain-Barré syndrome. (acute ascending polyneuropathy). *Electroencephalogr. Clin. Neurophysiol.* 17: 96, 1964.
17. *Mavor, H. & Libman, I.*: Motor nerve conduction velocity measurement as a diagnostic tool. *Neurology (Minneapolis)* 12: 733, 1962.
18. *Fullerton, P.M., Gilliat, R.W., Lascelles, R.G. et al.*: The relation between fiber diameter and internodal length in chronic neuropathy. *J. Physiol.* 178: 26, 1965.
19. *Takahashi, K.*: Anoxal degeneration in beriberi neuropathy. *Arch. Neurol.* 33: 836, 1976.
20. *Prineas, J.*: Peripheral nerve changes in thiamine-deficient rats. An electron microscope study. *Arch. Neurol.* 23: 545, 1970.
21. *Dyck, P.J., Johnson, W.J., Lambert, E.H. et al.*: Segmental demyelination secondary to anoxal degeneration in uremic neuropathy. *Mayo clin. Proc.* 46: 400, 1971.
22. *Ohnishi, A., Shimizu, N. & Ikeda, M.*: Clustered segmental demyelination in beriberi neuropathy. *Neurol. Med. (Tokyo)* 7: 227, 1977.
23. *McLeod, J.G., Prineas, J.W. & Walsh, J.C.*: The relationship of conduction velocity to pathology in peripheral nerves. A study of the sural nerve in 90 patients. In "New developments in electromyography and clinical neurophysiology", (edited by Desmedt, J.E.), Karger, Basel, 1973.
24. *Ochs, S. & Ranish, N.*: Metabolic dependence of fast axoplasmic transport in nerve. *Science*, 167: 878, 1970.
25. *Itokawa, K.*: Is calcium deficiency related to Thiamin dependent neuropathy in pigeon? *Brain Research*. 94: 475, 1975.

Acquired Demyelinating Neuropathies

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Recent epidemiologic, clinical, pathological, electrophysiological, and immunological studies have increased the available knowledge concerning demyelinating neuropathies. This presentation will discuss two major types of demyelinating neuropathy: (1) acquired inflammatory demyelinating neuropathy (Guillain-Barré syndrome and chronic inflammatory demyelinating polyradiculoneuropathy), and (2) demyelinating neuropathy associated with dysimmunoglobulinemia.

1. *Acquired Inflammatory Demyelinating Neuropathies*

Acquired demyelinating inflammatory neuropathies constitute approximately 40% of all adult polyneuropathies (Prineas, 1970). They may occur in association with infections, vaccinations, malignant lymphoproliferative disorders, or with no apparent cause. The clinical features and temporal course of these neuropathies are quite variable with acute, subacute, relapsing-remitting, or chronically progressive forms being seen. An acute, monophasic, symmetrical polyneuropathy, with flaccid, areflexic proximal or distal weakness, cranial nerve paresis, as well as minor sensory and autonomic involvement is commonly referred to as the Guillain-Barré syndrome (GBS) (Asbury, 1981). Other acute cases with predominantly cranial nerve, sensory, or autonomic dysfunction may be variants of GBS (Asbury, 1981). Occasionally, patients with what appears initially to be acute GBS have an atypical course with one or more relapses (Arnason, 1975). Relapses may be related to steroid therapy during the acute

illness (Hughes, Kadlubowski and Hubschmidt, 1981), may occur spontaneously (Wiederholt, Mulder and Lambert, 1964), or with vaccinations (Pollard and Selby, 1978; Segal, Ziegler and Couch, 1978). A more insidiously progressive neuropathy, with many features of GBS, has also been described, which may in some instances be associated with remissions and exacerbations. This entity has received a variety of names but has aptly been termed chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) by Dyck et al (1975, 1982). Some patients with acute or chronic demyelinating neuropathy have monoclonal gammopathy or other serum dysproteinemias, although most do not. The relationship between CIDP and GBS has been debated for many years. Differences in temporal profile and response to therapy have been the basis for considering the acquired demyelinating neuropathies as separate entities in many classifications. However, these neuropathies also have much in common, sharing the following clinical features: (1) segmental demyelination in the presence of invading mononuclear cells; (2) slow nerve conduction velocities; and (3) elevated CSF proteins (Arnason, 1975, Dyck et al, 1975; 1982). Recent studies suggest they may also share a common immune-mediated mechanism of tissue injury and may all respond to some form of immunoregulatory therapy, such as steroids, immunosuppression, or plasmapheresis. Therefore, variability in clinical course and temporal profile in the acquired demyelinating neuropathies may reflect differences in inciting

factors, or host response rather than different pathogenetic mechanisms. For example, a similar spectrum of acute, relapsing, and chronic disease can be seen in experimental allergic neuritis, the putative animal model of GBS and CIDP (Pollard, King and Thomas, 1975).

A. Guillain-Barré Syndrome

Acute inflammatory demyelinating polyradiculoneuropathy, GBS, is an acute to subacute paralytic disease of the peripheral nervous system with characteristic clinical, electrophysiological, pathological, and immunological features.

Epidemiology: The annual incidence rate of GBS in geographically widespread, distinct populations, ranges from 0.6 to 1.9 cases per 100,000 population (recently reviewed by Schonberger et al, 1981). GBS incidence rates in the United States are 38% higher in males than females and 58% higher in whites than blacks (Schonberger et al, 1981). Although individuals can be affected in any decade, several studies have shown a higher incidence of GBS with increasing age. In contrast, a New York-New Jersey survey of 176 GBS patients also showed a clear age peak in young patients, aged 16 to 25, with a second lesser peak between ages 45 to 60 (Dowling, Menonna and Cook, 1977). In this study, the younger age group commonly had evidence of an associated infection with cytomegalovirus (CMV), Epstein-Barr virus (EBV), or Mycoplasma pneumonia (Dowling and Cook, 1981). Some studies have revealed seasonal clustering of GBS, often with summer and autumnal peaks, whereas others have not (Baoson et al, 1981; Dowling and Cook, 1981).

Although many uncontrolled case reports have linked GBS with various inciting factors, or associated diseases, such as antecedent vaccinations, surgical procedures, serum sickness and neoplasms, the only significant risk factors for GBS documented by case-control studies are A/New Jersey influenza vaccine, and antecedent respiratory, gastrointestinal or febrile illnesses (Schonberger et al, 1981). Two-thirds of patients with GBS have such an antecedent illness within eight weeks before onset of neurological symptoms, with a peak interval of

two weeks (Schonberger et al, 1981). In most instances the infectious agent responsible for these illnesses has not been identified.

The role of vaccine in triggering GBS deserves further comment. A significant excess of GBS over the expected rates was noted following the 1976-1977 A/New Jersey influenza ("swine flu") vaccination program in the United States (Schonberger et al, 1981). The period of increased risk was concentrated primarily within the 5 week period after vaccination, although it lasted for approximately 9 or 10 weeks. In addition, numerous reports of GBS following rabies and other vaccines have appeared in the literature (Arnason, 1975). The close temporal relationship between administration of vaccine and onset of the neurological disorder suggests that vaccines in some way induce the neurological syndrome. However, present available data suggest that GBS is not a risk inherent in every vaccine. For example, an increased incidence of GBS was not detected following the closely observed 1978-1979 United States influenza vaccine program (Schonberger et al, 1981).

Pathology: The pathology of the GBS is quite distinctive consisting of inflammatory segmental demyelination in the presence of mononuclear cell infiltrates (reviewed by Prineas, 1981). Lesions are randomly scattered throughout the peripheral nervous system involving motor, sensory and autonomic nerves. Histologically, circumscribed areas are seen in which myelin is generally lost, in association with invading lymphocytes and macrophages. In severely involved nerves, more widespread damage occurs with axonal injury and resultant Wallerian degeneration. Recovery is generally associated with remyelination.

Clinical Features: The most prominent clinical feature in GBS is the rapid onset of flaccid, areflexic weakness which is usually, but not always, symmetrical (reviewed by Arnason, 1975; Asbury, 1981). Weakness ranges from minimal paresis to total paralysis of all voluntary muscles, necessitating assisted ventilation. Weakness may be proximal, or distal, most often beginning in the legs. Deep tendon reflexes disappear

early in affected muscles but rarely may remain detectable. Symptoms and signs of motor weakness develop rapidly over several days, and cease to progress by 2 weeks in 50 percent, 3 weeks in 80 percent and 4 weeks in 90 percent of patients.

Distal pain and paresthesias may be present, but sensory abnormalities are usually less marked than the weakness. However, some patients may have prominent distal sensory loss and rarely this may be present without weakness. Approximately 50 percent of patients have cranial nerve involvement most commonly facial diplegia, although any motor cranial nerve may be affected.

Autonomic nerve dysfunction manifested as tachy— or bradyarrhythmias, hypertension, hypotension, inappropriate ADH, and vasomotor abnormalities may occur (Posner et al, 1967; Lichtenfeld, 1971; Arnason, 1975; Asbury, 1981) and can cause sudden death. Usually sphincter function is normal, but transient bladder paralysis may occur during the evolution of symptoms. Evidence of mild central nervous system (CNS) involvement including extensor plantar responses may be seen in up to 10 percent of patients, and rarely more prominent CNS findings occur (Dyck et al, 1975; Asbury, 1981).

The usual course of GBS is that of rapidly progressive neurological dysfunction, followed by a plateau period of variable duration and ultimate recovery in most instances. In two large series, approximately 20 percent of patients required ventilatory assistance, 5 percent expired, and only 60 percent recovered fully (Dowling, Menonna and Cook, 1977; Hughes, Kadlubowski and Hubschmidt, 1981).

Laboratory Studies: CSF — During the first few days of neurological illness CSF protein levels are often normal; however, they are elevated in 90 percent of patients after the first week of symptoms and may remain elevated for long periods of time, even after clinical improvement (Arnason, 1975; Asbury, 1981). Transient CSF oligoclonal immunoglobulin bands have been described in the CSF of 40 percent of GBS patients, as well as increases in IgM, IgA and IgG in 25, 35 and 63 percent of patients respectively (Link, 1973; Link, Wa-

hren and Norrby, 1979). Typically, less than 10 mononuclear cells/mm³ are found in the CSF, but rarely up to 50 mononuclear leucocytes/mm³ are present (Arnason, 1975; Asbury, 1981).

Electrophysiological Studies: Slowing of motor and sensory conduction is seen in 90 percent of GBS patients (recently reviewed by McLeod, 1981). Because of the patchy distribution of demyelinating lesions, the likelihood of finding abnormalities is greater if multiple nerves are studied. Marked slowing of nerve conduction velocities or abnormally prolonged distal latencies consistent with demyelination are found in 50 percent of patients. The application of F wave studies may assist in detecting proximal nerve or root lesions.

Blood Studies: Several abnormalities in the peripheral blood or serum of GBS patients have been described. Increased numbers of circulating primitive lymphocytes or immunoblasts actively synthesizing DNA may be present during the acute phase of the disorder (Cook and Dowling, 1968; Behan et al, 1970; Cook, Dowling and Whitaker, 1970a). Decreased total T cells (including a T cell subset which forms rosettes with lymphoblastoid cell lines) and increased B cells have also been described in GBS (Glouster et al, 1978).

Elevated levels of IgM, IgA and IgG are found in the serum of some GBS patients (Cook, Dowling and Whitaker, 1970b; Link, 1973). In a recent study of 162 patients with GBS by Dowling et al (in press), 27 percent were found to have elevated IgM, 13 percent increased IgA, and 42 percent abnormal levels (high or low) of IgG, although no relationship between disease severity and serum immunoglobulin levels was found. Oligoclonal bands have been detected in serum and CSF in 21 percent of GBS patients (Link, Wahren and Norrby, 1979).

Treatment: At the present time there is no proved therapy for lessening disability, stopping progression or hastening recovery in GBS patients. Treatment is therefore symptomatic, consisting of supportive care with particular attention to ensuring adequate ventilation, and preventing complicating illnesses associated with prolonged bed

rest, autonomic dysfunction and bulbar weakness. Tracheostomy and assisted ventilation are required in 10 to 23 percent of patients, and the observed mortality rate of 2.4 to 5.6 percent (Hughes, Kadlubowski and Hubschmidt, 1981) is usually secondary to respiratory failure and related complications, autonomic disturbances and pulmonary emboli.

The use of steroids, although attractive on theoretical grounds, is controversial (recently reviewed by Hughes, Kadlubowski and Hubschmidt, 1981). Although isolated case reports have purportedly shown beneficial effects, two controlled studies which have been carried out using steroids or adrenocorticotrophin (ACTH) have given conflicting results. Swick and McQuillen (1976) administered ACTH to seven GBS patients, and placebo to eight others. The duration of the disease was significantly shortened from nine months in the placebo group to 4.4 months in the ACTH group. While this study was interpreted by its authors as showing a beneficial effect of steroid therapy in GBS, a subsequent larger controlled study came to the opposite conclusion. In a randomized trial by Hughes et al (1978) 21 patients with acute GBS were treated with 60 mg of prednisone daily for one week, followed by 40 daily for four days, then 30 mg daily for the next three days. Nineteen GBS patients served as a control group. No evidence of more rapid improvement was seen in the steroid-treated group and, in fact, there were three relapses in the steroid-treated group, but none in the controls. Based on the results of these two studies, steroids have not to date been shown to be of clear benefit in GBS. However, dose, route of administration and duration of therapy may all be important variables which need to be fully assessed in GBS before the true efficacy of steroid therapy is known (Dowling, Bosch and Cook, 1980).

As with steroids, isolated case reports of patients with GBS responding to immunosuppressants have also appeared in the literature. In one uncontrolled study, Rosen and Vastola (1976) used high-dose cytoxan in a group of 15 patients with GBS and noted a possible beneficial effect in some pa-

tients. At present, the limited scope and uncontrolled nature of these studies preclude accurate assessment of immunosuppressive therapy in GBS.

In 1978, Brett et al. noted striking clinical improvement in a patient with GBS who underwent plasmapheresis. Since that time, a large number of similar reports have appeared in the literature. Compilation of this literature shows rapid improvement in 24 of 28 GBS patients who underwent plasmapheresis. The best response often occurred when plasmapheresis was initiated within the first two weeks of onset of neurological symptoms, whereas the few failures occurred most often in patients undergoing treatment later in their illness. Although these results are uncontrolled, the remarkable rate of improvement seen in many of these patients is unlike the spontaneous rate of improvement seen in most GBS patients. Randomized, controlled studies presently being carried out in the United States and Great Britain should give the definitive answer concerning plasmapheresis. Until that time, since no other clearly effective therapy is available, it would seem justifiable to consider early plasmapheresis in any GBS patient who is severely ill or has a rapidly progressive course.

Possible Mechanism of Tissue Injury in Guillain-Barré Syndrome

Because of its similar clinical, and pathological features to experimental allergic neuritis (EAN), and its occurrence after various inciting factors including infectious diseases and vaccinations, GBS has been considered to be an immune-mediated disease of peripheral nerve (Arnason, 1975). However, the precise relationship between the initiating event which precedes the neurological symptoms and the host immune response which appears to cause demyelination has not been defined. Possible mechanism for demyelination in GBS include cell-mediated immunity, autoantibodies, circulating immune complexes, or direct infection of nerve (Arnason, 1975; Cook and Dowling, 1981). These considerations have been recently reviewed by Zito, Cook and Dowling (1982).

B. *Chronic Inflammatory Demyelinating Polyradiculoneuropathy*

Much less is known about the epidemiology of CIDP than GBS. This is probably because the disorder, with its various presentations, has been confused with other acquired and hereditary neuropathies and has only recently been characterized clinically and pathologically as a discrete nosological entity. Several large series or reviews of the literature by Dyck et al (1975; 1982), Prineas and McLeod (1976), Oh (1978), and Dalakas and Engel (1981a) provide most of the clinical and epidemiologic data on CIDP. Males are affected more than females (1.5 to 2:1). The disease can occur at any time from early childhood to the seventh decade, and in the Mayo Clinic study, the greatest number of cases were noted in the fifth and sixth decades (Dyck et al, 1975). HLA-linked genetic factors may influence susceptibility to CIDP in that HLA-AW30, AW31, DRW₃ and DW₃ haplotypes are more commonly seen in this disorder than controls (Stewart et al, 1978; Adams et al, 1979; Dalakas and Engel, 1981a). The role of an inducing factor in initiating CIDP, or precipitating relapses, is unclear. Prineas and McLeod (1976) elicited a history of a non-specific upper respiratory tract infection within a month of the onset of neurological symptoms in 10 of 23 patients with CIDP. In reviewing 54 cases of CIDP from the literature, Oh (1978) also found evidence of an antecedent infection in 14 patients. Although not citing specifics, Dyck et al (1975) state there is often a history of a preceding infection, immunization, or receipt of biologic material within a few weeks or months of onset, or a period of worsening. In contrast to these studies, Dalakas and Engel (1981a) noted no preceding illness which coincided with the onset of the neuropathy or induction of relapses in their 23 patients. Unlike GBS, no specific infectious agent has been convincingly linked to CIDP at this time. However, relapses of CIDP have been temporally related to vaccines in several instances. It would appear that an antecedent or associated illness such as an overt infection or vaccination may induce CIDP or relapses of this neu-

ropathy, but perhaps less commonly than in GBS.

Clinical Features: Patients with CIDP generally present with either an insidiously progressive, stepwise progressive, or relapsing-remitting symmetrical sensorimotor neuropathy (Dyck et al, 1975, 1982; Prineas and McLeod, 1976; Oh, 1978; Dalakas and Engel, 1981a). Weakness, which is often the most prominent feature of CIDP may be predominantly distal or involve both proximal and distal limb muscles, and occurs about equally in the upper and lower extremities. Muscle wasting may be less severe than expected from the duration and severity of paralysis. Respiratory muscles are involved in about 10 percent of patients. Cranial nerve paresis is not as common as in GBS but is present in 10 to 25 percent of patients, causing facial paresis and weakness of the tongue, palate, and extraocular muscles. Deep tendon reflexes are invariably depressed or absent at some stage of the illness. Sensory impairment is almost always present and is predominantly distal, involving all modalities. Rarely, a predominantly sensory presentation may be seen. Autonomic dysfunction, or minor CNS abnormalities, are seen in up to 10 percent of patients. Peak disability is from 3 weeks to 2 years after onset, but is usually reached after a 6 to 12 month period (Dyck et al, 1975; Dalakas and Engel, 1981a). Dyck et al (1975) have reported that in 49 percent of their cases, the course was progressive in an insidious or stepwise fashion, and that in 34 percent, the course was relapsing.

Laboratory Findings: CSF proteins are elevated at some time in the course of CIDP in 90 percent of patients, and protein levels above 100 mg percent (up to 600 mg percent) are frequently seen (Dyck et al, 1975). Although the CSF is usually acellular, a low grade pleocytosis consisting primarily of mononuclear cells may be found in about 10 percent of patients (Dyck et al, 1975). A single band in the IgG region on agarose gel electrophoresis of CSF has been described in 14 of 15 CIDP patients by Dalakas and Engel (1981a), which persists regardless of the phase of disease activity.

Complete blood count (CBC), sedimentation rates, serum protein electrophoresis,

serum immunoelectrophoresis, and serum immunoglobulins have been found to be normal in most series, although Dyck et al, (1975) has reported increased gamma globulins in 16 percent of CIDP patients.

Slow nerve conduction velocities are a characteristic finding in CIDP (Dyck et al, 1975; Prineas and McLeod, 1976; Oh, 1978; Dalakas and Engel, 1981a). Severe slowing of motor and sensory conduction times, often below 30 m/sec, or delayed latencies, are found in 90 percent of patients. A poor correlation exists between disease severity and motor nerve conduction velocities, although some patients show slight improvement in nerve conduction with clinical remission.

Immunology: Relatively few immunologic studies have been carried out comparing CIDP patients to adequately matched controls and direct evidence for an immune mechanism of tissue injury in CIDP is less substantial than in GBS. However, as in GBS, provocative direct and indirect evidence for involvement of the immune response in causing tissue injury exists, perhaps through some combination of CMI, antibody, and immune complexes (Cook et al, 1971; Zito, Cook and Dowling, 1982). The clear response of most patients to some form of immunoregulatory therapy is consistent with this hypothesis.

Pathology: Pathologic studies of peripheral nerves and roots in CIDP show segmental demyelination usually, but not invariably, in the presence of mononuclear cell infiltrates, and stripping of myelin by invading macrophages (Prineas and McLeod, 1976). Occasionally, similar lesions are present in the CNS (Dyck et al, 1975). As with GBS, a variable number of fibers undergoing Wallerian degeneration may also be found. Additionally, onion bulb formation reflecting repeated episodes of demyelination and remyelination may be a prominent feature of CIDP (Thomas and Lascelles, 1967; Webster et al, 1967; Prineas, 1971).

Therapy: In 1958, Austin originally described a case of relapsing polyneuropathy remarkably responsive to steroids on multiple occasions. Since that time, it has been generally recognized that steroids are often

effective in treating CIDP. However, only one case-controlled study on the effectiveness of steroids has been carried out. Dyck et al, (1982) treated 28 patients with prednisone or placebo for a 3 month period. The prednisone-treated group showed a small, but significant, improvement in neurological disability, sensory threshold, hand strength and various nerve conduction measurements as compared to the control group. In a large uncontrolled study, Dalakas and Engel (1981a) treated 25 CIDP patients with steroids alone, and the majority improved. They emphasized that a lag period usually of 1 to 4 weeks, but occasionally up to 5 months, occurred from onset of therapy to the first sign of improvement. They recommended high doses of steroids for about 1 year, then cautious tapering to avoid "pharmacorelapses", and long-term, low maintenance doses to prevent spontaneous relapses.

A number of authors, in uncontrolled studies, have reported therapeutic benefit with cyclophosphamide, and other immunosuppressive drugs (Palmer, 1966; Dalakas and Engel, 1981a). More recently, some enthusiasm has been engendered for plasmapheresis as an important new therapeutic modality in CIDP (Levy, Newkirk and Ochoa, 1979; Server et al, 1979). In a short period of time, a large number of case reports have appeared in the literature describing dramatic improvement in many patients with CIDP following plasmapheresis. Nerve conduction times, distal latencies, and amplitude of action potentials have been noted to improve with plasmapheresis in some patients. Unfortunately, cessation of plasmapheresis is often associated with deterioration in the neuropathy, and it is likely that maintenance of the beneficial response will require simultaneous administration of steroids and/or immunosuppressant drugs in some patients.

In summary, a number of effective therapies are available for treating patients with CIDP. All share a common mechanism in having a powerful effect on the immune response, thereby supporting the hypothesis that CIDP is an immune-mediated polyneuropathy.

2. *Peripheral Neuropathy and Dysimmunoglobulinemia*

Peripheral neuropathy has been reported in association with various dysimmunoglobulinemic states including multiple myeloma, macroglobulinemia, solitary plasmacytoma, cryoglobulinemia, diffuse hypergammaglobulinemia, amyloidosis, and benign dysproteinemias. The incidence of peripheral neuropathy with these dysimmunoglobulinemic states is variable and depends on the clinical, electrophysiological, and neuropathological methods of investigation used to detect nerve dysfunction. In myeloma, for example, peripheral neuropathy is generally reported in 3-5 percent of patients (Silverstein and Doniger, 1963; Currie et al, 1970); however, an incidence of 13 percent is noted in prospective studies (Walsh, 1971) and reaches 40-60 percent when subclinical cases are included based on sensitive nerve conduction (Walsh, 1971) and neuropathological studies (Hesslevik, 1969). Also the incidence of peripheral neuropathy may be related to the specific type of dysimmunoglobulinemia; for example, neuropathy is reported to occur more frequently with osteosclerotic myeloma than with other types of myeloma (Kelly et al, 1981).

The etiology of peripheral nerve dysfunction in dysimmunoglobulinemic states is often unclear and multiple causative factors have been suggested. These factors include: (1) serum hyperviscosity, (2) amyloidosis, (3) direct nerve infiltration by tumor cells, (4) toxic-metabolic factors, (5) nutritional factors, and (6) immunological factors. The presumed multifactorial etiology of peripheral neuropathy in dysimmune states is probably responsible for the heterogeneous nature of the clinical features (signs, symptoms, course, and response to therapy) and pathologic features reported in these neuropathies.

Within this heterogeneous group of neuropathies associated with dysimmunoglobulinemia, recent studies suggest that there is a more homogeneous subgroup of demyelinating peripheral neuropathy. Chronic, progressive demyelinating sensorimotor peripheral neuropathy is described in association with various dysimmunoglobulinemic states including myeloma, macroglobulinemia,

and the benign gammopathies (Kahn, Riches and Kohn, 1980; Latov et al, 1980; Dalakas and Engel, 1981b). In general, the clinical features of this neuropathy are similar to those of other acquired, chronic demyelinating peripheral neuropathies. These features include: (1) insidious onset (which may antedate the symptomatic onset and/or diagnosis of the dysimmune state); (2) symmetrical sensorimotor deficits with distal weakness and stocking-glove sensory abnormalities, usually most marked in the feet; (3) slowly progressive course with distal to proximal extension of sensorimotor deficits; (4) usual sparing of cranial nerve and respiratory functions; (5) elevated CSF protein levels (with other CSF studies normal); (6) slowed motor and sensory nerve conduction velocities; (7) demyelination of peripheral nerve in biopsy specimens.

The treatment of dysimmunoglobulinemic neuropathies is usually two-fold. First, treatment directed against the specific neoplastic process (e.g., multiple myeloma) using standard treatment modalities (such as radiotherapy and chemotherapy) may provide improvement of the neuropathy. For example, certain patients with solitary sclerotic myeloma and neuropathy have significant improvement of the neuropathy after local radiotherapy to the plasmacytoma (Kelly et al, 1981). Second, treatment that decreases or removes the abnormal serum protein (such as steroids, immunosuppressants, or plasmapheresis) may also cause clinical improvement of the peripheral nerve disorder (Latov et al, 1980). This type of therapy may be particularly helpful in patients with "benign" dysimmunoglobulinemia and neuropathy.

Relationship of Acquired Inflammatory Demyelinating Neuropathy and Dysimmunoglobulinemic Neuropathy

GBS and CIDP are generally considered closely related conditions based on their clinical, pathological, and immunological findings. These interrelationships have been discussed above in the sections on GBS and CIDP. Even more intriguing is the relationship between demyelinating dysimmunoglobulinemic neuropathy and the inflam-

matory demyelinating polyradiculoneuropathies (GBS and CIDP). Certain clinical features usually distinguish these conditions including: (1) occurrence of GBS and CIDP in association with recent infections or the administration of vaccinations; (2) occurrence of dysimmunoglobulinemic neuropathy in patients with overt symptoms of multiple myeloma, macroglobulinemia, or other paraproteinemic states; (3) the acute monophasic course in GBS and the multiple monophasic episodes in the relapsing form of CIDP (in contrast to the chronic progressive course of dysimmunoglobulinemic neuropathy); (4) prominent cranial nerves involvement and proximal body involvement often with respiratory insufficiency in GBS and at times in CIDP; (5) predominantly motor neuropathy of GBS.

Although the clinical features mentioned above generally differentiate dysimmune neuropathy from GBS and the relapsing form of CIDP clinical overlap may occur among these neuropathies. For example, isolated patients with GBS have been reported in association with dysimmunoglobulinemic neuropathies. In a review of dysproteinemic neuropathies, Waldenström (1970) mentioned the occurrence of myeloma and the polyradiculitis of the GBS type in 6 or 7 cases; however, the details of these cases were not presented. Read, Van Hegan and Mathews (1978) presented a patient with benign IgG paraproteinemia and an acute GBS which showed spontaneous improvement over months. One myeloma patient reported by Kelly et al (1981) had a severe, predominantly motor neuropathy with a monophasic course initially progressive over 2 months, proximal weakness with respiratory insufficiency, and bilateral facial palsies. Also of interest is the report of Lisak et al (1977) describing a patient with Hodgkin's disease, GBS, and an abnormal serum paraprotein. Therefore, although uncommon, certain patients with dysimmunoglobulinemic neuropathy have been noted to have features that are usually seen in GBS, such as cranial nerve involvement, proximal weakness with respiratory insufficiency, and even acute onset with spontaneous improvement.

The greatest clinical similarity among

the acquired demyelinating neuropathies appears to be between the progressive form of CIDP and dysimmunoglobulinemic neuropathy. In addition to the general features of demyelination, both these types of neuropathy usually have insidious onset and slowly progressive course, predominantly affect distal extremities with sensorimotor polyneuropathy, and often respond to immunoregulatory therapies. The difficulty distinguishing between progressive CIDP and dysimmune neuropathy on the basis of clinical findings is apparent in the literature reports. Dyck et al (1975) in their review of chronic inflammatory polyradiculoneuropathy included one patient with an abnormal spike in the gamma globulin fraction on serum protein electrophoresis and an hypercellular bone marrow. In another large series of chronic polyneuritis, Prineas and McLeod (1976) reported two patients with features suggestive of dysimmunoglobulinemic states. The first (case 22) had hepatosplenomegaly, hemolytic anemia, elevated ESR, raised serum gamma and alpha 2 globulins, and lymphocytic infiltration of the spleen. The second (case 23) had an elevated serum gamma globulin level and marked lymphocytic infiltration of the bone marrow. From these and other reports, it is apparent that the progressive form of CIDP may be clinically identical to demyelinating dysimmunoglobulinemic neuropathy. This striking resemblance has led Asbury (1980) and others to suggest that when evaluating patients with acquired demyelinating neuropathies of uncertain cause, a careful search for paraproteinemia should be made.

The similar clinical, pathological, and immunological features of GBS, CIDP, and paraproteinemic neuropathy suggest that they may be closely related and may share a common immune-mediated mechanism of peripheral nerve demyelination. At present, the specific immunological abnormality responsible for the myelin destruction is unknown. However, based on the immunological findings to date (recently reviewed by Zito, Cook and Dowling, 1982), one important mechanism may be the occurrence of autoantibodies directed against peripheral nerve myelin.

The differences in clinical course that distinguish GBS, CIDP, and dysimmunoglobulinemic neuropathy may reflect differences in the inciting factor or differences in the host immune response. The acute monophasic course of GBS may be due to a transients inducing event or transient host immune dysfunction, whereas the relapsing form of CIDP may reflect the repeated occurrence of such abnormalities. The chronic course of progressive CIDP and dysimmunoglobulinemic neuropathy may involve continuing immune stimulation or persistent host immune dysfunction. Of course other non-immune factors may also be important.

Despite the currently limited understanding of demyelinating peripheral nerve diseases, certain important clinical implications are apparent. When evaluating patients with chronic, acquired neuropathy of undetermined etiology, studies should be done to assess whether or not the neuropathy is demyelinating in nature. Important studies include: (1) nerve conduction studies; (2) CSF analysis; and (3) nerve biopsy. If a patient is found to have an ac-

quired, demyelinating neuropathy, a careful search should be made for clinical and laboratory evidence of a dysimmunoglobulinemic state, using such studies as serum and urine protein electrophoresis and immunoelectrophoresis. If a paraproteinemia is found, any underlying neoplasm should be treated aggressively in an attempt to lower or remove the abnormal protein which may lead to improvement of the neuropathy. Patients with chronic, acquired demyelinating neuropathy with or without paraproteinemia, should receive a trial of steroids or other immunoregulatory therapy in an attempt to counter the possible immune-mediated peripheral nerve demyelination.

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SUMMARY

The clinical, pathological, and immunological features of the major types of acquired demyelinating neuropathies are reviewed. The Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) are distinct clinicopathological entities which may share a common immune-mediated mechanism of tissue injury and may all respond to some form of immunoregulatory

therapy, such as steroids, immunosuppressants, or plasmapheresis. The peripheral neuropathy associated with dysimmunoglobulinemic states, such as multiple myeloma, may in some instances be a demyelinating neuropathy with many features similar to the acquired inflammatory demyelinating neuropathies. Current concepts for evaluation and treatment of these neuropathies are presented.

RESUMEN

Son considerados los aspectos clínicos, patológicos e inmunológicos de los tipos más complejos de neuropatías desmielinizantes adquiridas. El síndrome de Guillain-Barré (SGB) y la polirradiculoneuropatía desmielinizante inflamatoria crónica (PDIC) son entidades clínico patológicas distintas que tienen en común un mecanismo inmunomediado de daño tisular y pueden responder a alguna forma de terapia inmunorregu-

ladora del tipo de esteroides, inmunosupresores o plasmaferesis. La neuropatía periférica asociada a un estado desinmunoglobulinémico, tal como el mieloma múltiple, puede en algunas ocasiones ser una neuropatía desmielinizante con muchos aspectos similares al de las neuropatías desmielinizantes inflamatorias adquiridas. Son presentados conceptos difundidos para la evaluación y tratamiento de estas neuropatías.

RÉSUMÉ

On considère les aspects cliniques, pathologiques et immunologiques des types les plus complexes de neuropathies démyélinisantes acquises. Le syndrome de Guillain-Barré (SGB) et la polyradiculoneuropathie démyélinisante inflammatoire chronique (PDIC) sont des entités cliniques pathologiques distinctes qui ont en commun un mécanisme immuno-provoqué de destruction tissulaire et peuvent répondre à une certaine forme de thérapie immunorégula-

trice du genre des stéroïdes, immunosuppressive ou plasmaphérese. La neuropathie périphérique associée à des états de désimmunoglobulinémie tels que le myélome multiple, peut dans certains cas, être une neuropathie démyélinisante en divers aspects similaires de celui des neuropathies démyélinisantes inflammatoires acquises. On présente des concepts émis pour l'évaluation et le traitement de ces neuropathies.

ZUSAMMENFASSUNG

Die klinischen, pathologischen und immunologischen Bilder der mehr komplexen erworbenen demyelinisierenden neuropathischen Komplexe werden in Betracht gezogen. Das Syndrom von Guillain-Barré (SGB) und die Polyradiculoneuropathie demyelinisierende mit chronischer Inflammation (FDIC) sind distinte klinisch pathologische Einheiten, die einen immuno-gemessenen geweblichen Schaden haben und die auf irgend eine Form von immunoregulieren de Therapie vom Typ der Esteroiden,

Immunosuppressoren oder Plasmaphoresen ansprechen können. Die periphere Neuropathie assoziiert an den desimmunoglobulizierten Zustand, wie er ist beim multiplen Myelom, kann in bei einigen Gelegenheiten eine desmyelinisierende Neuropathie sein mit vielen ähnlichen Aspekten wie bei den erworbenen entzündlichen Neuropathien. Es werden Konzepte, verbreitet, vorgewiesen für die Evolution und der Behandlung dieser Neuropathien.

REFERENCES

1. Adams, D., Festenstein, H., Gibson, J.B., Hughes, R.A.C., Jaraquemada, J., Papasteriadis, C., Sachs, J. & Thomas, P.K. (1975) HLA antigens in chronic relapsing idiopathic inflammatory polyneuropathy. *Journal of Neurology, Neurosurgery and Psychiatry*, 42, 184-186.
2. Arnason, B.G.W. (1975) Pathogenesis of acute inflammatory polyradiculoneuropathy. In *Peripheral Neuropathy* (Ed.) Dyck, P.J., Thomas, P.K. and Lambert, E.H. pp. 1137-1148. Philadelphia, London, Toronto: Saunders.
3. Arnason, B.G.W., Winkler, G.F. & Hadler, N.M. (1969) Cell mediated demyelination of peripheral nerve in tissue culture. *Laboratory Investigation*, 21, 1-10.
4. Asbury, A.K. (1981) Diagnostic considerations in Guillain-Barré Syndrome. *Annals of Neurology*, 9 (Suppl.), 1-5.
5. Asbury, A.K. & Lisak, R.P. (1980) Demyelinative neuropathy and myelin antibodies. *New England Journal of Medicine*, 303 (editorial), 638-639.
6. Austin, J.H. (1958) Recurrent polyneuropathies and their corticosteroid treatment. *Brain*, 81, 157-192.
7. Baoxan, Z., Yinghang, W., Huifen, H. & Xiugin, L. (1981) Acute polyradiculitis (Guillain-Barré syndrome): an epidemiological study of 156 cases observed in Beijing. *Annals of Neurology*, 9 (Suppl.), 146-148.
8. Behan, P.O., Lamarche, J.B., Feldman, R.G. & Sheremata, W.A. (1970) Lymphocyte transformation in the Guillain-Barré syndrome. *Lancet*, 1, 421.
9. Brettell, R.P., Gross, M., Legg, N.J., Lockwood, M. & Pallis, C. (1978) Treatment of acute polyneuropathy by plasma exchange. *Lancet*, 2, 1100.
10. Chazot, G., Bergen, B., Carrier, H., et al, (1976) Manifestations neurologiques des gammopathies monoclonales. *Revue Neurologique (Paris)*, 132, 195-212.
11. Cook, S.D. & Dowling, P.C. (1968) Neurologic disorders associated with increased DNA synthesis in peripheral blood. *Archives of Neurology*, 19, 583.
12. Cook, S.A. & Dowling, P.C. (1981) The role of autoantibody and immune complexes in the pathogenesis of Guillain-Barré syndrome. *Annals of Neurology*, 9 (Suppl.), 70-79.
13. Cook, S., Dowling, P.C. & Whitaker, J.N. (1970a) The Guillain-Barré syndrome. Relationship of circulating immunocytes to di-

- sease activity. *Archives of Neurology*, 22, 470-474.
13. Cook, S.D., Dowling, P.C. & Whitaker, J. (1970b) Serum immunoglobulins in the Guillain-Barré syndrome. *Neurology*, 20, 403.
 14. Cook, S.D., Dowling, P.C., Murray, M.R. & Whitaker, J.N. (1971) Circulating demyelinating factors in acute idiopathic polyneuropathy. *Archives of Neurology*, 24, 136-144.
 15. Currie, S., Henson, R.A., Morgan, H.G. & Poole, A.J. (1970) The incidence of the non-metastatic neurologic syndromes of obscure origin in the reticuloses. *Brain*, 93, 629-640.
 16. Dalakas, M.C. & Engel, W.K. (1981a) Chronic relapsing (dysimmune) polyneuropathy: pathogenesis and treatment. *Annals of Neurology*, 9, (Suppl.), 134-145.
 17. Dalakas, M.C. & Engel, W.K. (1981b) Polyneuropathy with monoclonal gammopathy: studies of 11 patients. *Annals of Neurology*, 10, 45-52.
 18. Dowling, P.C. & Cook, S.D. (1981) Role of infection in Guillain-Barré syndrome: laboratory confirmation of herpesviruses in 41 cases. *Annals of Neurology*, 9 (Suppl.), 44-55.
 19. Dowling, P.C., Menonna, J.P. & Cook, S.D. (1977) Guillain-Barré syndrome in Greater New York-New Jersey. *Journal of the American Medical Association*, 238, 317-318.
 20. Dowling, P.C., Bosch, V.V. & Cook, S.D. (1980) Possible beneficial effect of high dose intravenous steroid therapy in acute demyelinating disease and transverse myelitis. *Neurology*, 30, 33-36.
 21. Dowling, P.C., Bosch, V.V. & Cook, S.D. Serum immunoglobulins in Guillain-Barré syndrome. *Journal of the Neurological Sciences*, in press.
 22. Dyck, P.J., Lais, A.C., Ohta, M., Bastron, J.A., Okazaki, H. & Groover, R.V. (1975) Chronic inflammatory polyradiculoneuropathy. *Mayo Clinic Proceedings*, 50, 521-537.
 23. Dyck, P.J., O'Brien, P.C., Oviatt, K.F., Dinapoli, R.P., Daube, J.R., Bartleson, J.D., Mokri, B., Swift, T., Low, P.A. & Windebank, A.J. (1982) Prednisone improves chronic inflammatory demyelinating polyradiculoneuropathy more than no treatment. *Annals of Neurology*, 11, 136-141.
 24. Goust, J.M., Chenais, F.C., Hames, C.G., Fudenberg, H.H. & Hogan, E.L. (1978) Abnormal T cell subpopulation and circulating immune complexes in the Guillain-Barré syndrome and multiple sclerosis. *Neurology*, 28, 421-425.
 25. Hesselvik, M. (1969) Neuropathological studies on myelomatosis. *Acta Neurologica Scandinavica*, 45, 95-108.
 26. Hughes, R.A.C., Kadlubowski, M. & Hubschmidt, A. (1981) Treatment of acute inflammatory polyneuropathy. *Annals of Neurology*, 9 (Suppl.), 125-133.
 27. Hughes, R.A.C., Newsom-Davis, J., Perkin, G.D. & Pierce, J.M. (1978) Controlled trial of prednisolone in acute polyneuropathy. *Lancet*, 2, 750-753.
 28. Iqbal, A., Oger, J.J.-F., Arnason, B.G.W. & Noronha, A.B.C. (1981) Absence of antibodies to P₂ protein in idiopathic polyneuritis. *Neurology*, 31 (4, Pt. 2), 156.
 29. Kahn, S.N., Riches, P.G. & Kohn, J. (1980) Paraproteinemia in neurological disease: incidence, associations, and classification of monoclonal immunoglobulins. *Journal of Clinical Pathology*, 33, 617-621.
 30. Kelly, J.J., Kyle, R.A., Miles, J.M., O'Brien, P.C. & Dyck, P.J. (1981) The spectrum of peripheral neuropathy in myeloma. *Neurology*, 31, 24-31.
 31. Latov, N., Sherman, W.H., Nemni, R., Gallassi, G., Shyong, J.S., Penn, A.S., Chess, L., Olarte, M.R., Rowling, L.P. & Osserman, E.F. (1980) Plasma-cell dyscrasia and peripheral neuropathy with a monoclonal antibody to peripheral-nerve myelin. *New England Journal of Medicine*, 303, 618-621.
 32. Levy, R.L., Newkirk, R. & Ochoa, J. (1979) Treating chronic relapsing Guillain-Barré syndrome by plasma exchange. *Lancet*, 2, 259-260.
 33. Link, H. (1973) Immunoglobulin abnormalities in Guillain-Barré syndrome. *Journal of the Neurological Sciences*, 18, 11-23.
 34. Link, H., Wahren, B. & Norrby, E. (1979) Pleocytosis and immunoglobulin changes in cerebrospinal fluid and herpes virus serology in patients with Guillain-Barré syndrome. *Journal of Clinical Microbiology*, 9, 305-316.
 35. Lisak, R.P., Mitchell, M., Zweima, B., Orrechio, E. & Asbury, A.K. (1977) Guillain-Barré syndrome and Hodgkin's disease: three cases with immunological studies. *Annals of Neurology*, 1, 72-78.
 36. McLeod, J.G. (1981) Electrophysiological studies in the Guillain-Barré syndrome. *Annals of Neurology*, 9 (Suppl.), 20-27.
 37. Oh, S.J. (1978) Subacute demyelinating polyneuropathy responding to corticosteroid treatment. *Archives of Neurology*, 35, 509-516.
 38. Palmer, K.N.Y. (1966) Polyradiculoneuropathy treated with cytotoxic drugs. *Lancet*, 1, 265.
 39. Pollard, J.D. & Selby, G. (1978) Relapsing neuropathy due to tetanus toxoid. *Journal of the Neurological Sciences*, 37, 113-125.
 40. Pollard, J.D., King, R.H.M. & Thomas, P.K. (1975) Recurrent experimental allergic neuritis. *Journal of the Neurological Sciences*, 24, 365-383.
 41. Posner, J.B., Ertel, N.H., Kossmann, R.J. & Scheinberg, L.C. (1967) Hyponatremia in acute polyneuropathy. *Archives of Neurology*, 17, 530-541.
 42. Prineas, J. (1971) Demyelination and remyelination in recurrent idiopathic polyneuropathy. An electron microscope study. *Acta Neuropathologica (Berlin)*, 18, 34-57.
 43. Prineas, J.W. (1981) Pathology of the Gui-

- llain-Barré syndrome. *Annals of Neurology*, 9 (Suppl.), 6-19.
44. *Prineas, J.W. & McLeod, J.G.* (1976) Chronic relapsing polyneuritis. *Journal of the Neurological Sciences*, 27, 427-458.
 45. *Read, D.J., Van Hegan, R.I. & Mathews, W.B.* (1978) Peripheral neuropathy and benign IgG paraproteinemia. *Journal of Neurology, Neurosurgery and Psychiatry*, 41, 215-298.
 46. *Rosen, A.D. & Vastola, E.F.* (1976) Clinical effects of cyclophosphamide in Guillain-Barré polyneuritis. *Journal of the Neurological Sciences*, 30, 179-187.
 47. *Schonberger, L.B., Hurwitz, E.S., Katona, P., Holman, R.C. & Bregman, D.J.* (1981) Guillain-Barré syndrome: its epidemiology and associations with influenza vaccine. *Annals of Neurology*, 9 (Suppl.), 31-38.
 48. *Segal, M., Ziegler, D.Y. & Couch, J.R.* (1978) Recurrent Guillain-Barré syndrome following influenza vaccine. *Neurology*, 28, 725-726.
 49. *Server, A.C., Lefkowitz, J., Braine, H. & McKhann, G.M.* (1979) Treatment of chronic relapsing inflammatory polyradiculoneuropathy by plasma exchange. *Annals of Neurology*, 6, 258-261.
 50. *Silverstein, A. & Dóniger, D.E.* (1963) Neurologic complications of myelomatosis. *Archives of Neurology*, 9, 534-544.
 51. *Stewart, G.J., Pollard, J.D., McLeod, J.G. & Wolnizer, C.M.* (1978) HLA antigens in the Landry-Guillain-Barré syndrome and chronic relapsing polyneuritis. *Annals of Neurology*, 4, 285-289.
 52. *Swick, H.M. & McQuillen, M.P.* (1976) The use of steroids in the treatment of idiopathic polyneuritis. *Neurology (Minneapolis)*, 26, 205-212.
 53. *Thomas, P.K. & Lascelles, R.G.* (1967) Hypertrophic neuropathy. *Quarterly Journal of Medicine*, 36, 223-238.
 54. *Waldenstrom, J.* (1970) Dysproteinemic neuropathies. In *Handbook of Clinical Neurology*, Vol. 8, (Ed.) Vinken, P.J. & Bruyn, G.W., pp. 72-76. Amsterdam: North-Holland.
 55. *Walsh, J.C.* (1971) The neuropathy of multiple myeloma: An electrophysiological and histological study. *Archives of Neurology*, 25, 404-414.
 56. *Webster, H. de F., Schroder, J.M., Asbury, A.K. & Adams, R.D.* (1967) The role of Schwann cells in the formation of "onion bulbs" found in chronic neuropathies. *Journal of Neuropathology and Experimental Neurology*, 26, 276-299.
 57. *Wiederholt, W.C., Mulder, D.W. & Lambert, E.H.* (1964) The Landry-Guillain-Barré Strohl syndrome or polyradiculoneuropathy: historical review, report on 97 patients, and present concepts. *Mayo Clinic Proceedings*, 39, 427-451.
 58. *Zito, G., Cook, S.D. & Dowling, P.C.* (1982) Immunologic Diseases of the Human Peripheral Nervous System. In *Clinics in Immunology and Allergy: Immunoneuropathology*, (Ed.) Waksman, B. Vol. 2 pp. 309-331. Saunders: London.

A Polio-like Syndrome in Adults Following Acute Hemorrhagic Conjunctivitis

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A new type of epidemic conjunctivitis, which is characterized by a very short incubation period and prominent subconjunctival hemorrhage, first broke out in Ghana (West Africa) in 1969.⁽¹⁾ The epidemic wave swiftly spread to the neighbouring countries, and in 1971 a pandemic occurred in Africa, Asia and Europe.⁽²⁾ In the same year, patients who developed polio-like neurological symptoms following this new epidemic conjunctivitis, which is now generally called "Acute Hemorrhagic Conjunctivitis (AHC)" were observed by neurologists in India⁽³⁾⁽⁴⁾ and Taiwan.⁽⁵⁾ The causative virus of AHC was first isolated in Japan by Kono et al.,⁽⁶⁾ who also studied its neurovirulent properties by inoculating AHC virus into the spinal cord and thalamus of cynomolgus monkeys and successfully reproduced motor paralysis similar to that occurring in human cases.⁽⁷⁾

Until the end of 1977, 128 cases of neurological complication following AHC have been observed in Taiwan, India, Thailand, Senegal and Japan. It has been agreed that the essential clinical manifestations represent a form of radiculomyelitis, being very similar to those of acute poliomyelitis, but the age incidence is almost confined to adulthood.⁽⁵⁾⁽⁸⁾⁽⁹⁾⁽¹⁰⁾

AHC AND AHC VIRUS

AHC is highly contagious and its spread is rapid. The usual mode of transmission is by person-to-person contact through hand or objects contaminated by eye discharge.

The outbreaks frequently occur in poor hygienic communities such as large families, schools, dormitories and eye clinic in tropical or subtropical countries⁽²⁾.

AHC affects both sexes and people of all ages, except for a low incidence in infants. It is more prevalent among the age group of young adults, and children under the age of 10 are less frequently affected⁽²⁾.

The incubation period is very short, being usually between 18 and 36 hours. The onset is acute, reaching the peak within several hours. Bilateral involvement is common, but it usually starts in one eye and spread to the fellow eye within one day. The initial ocular symptoms include lid swelling, redness of eyes, photophobia, discharge, burning or itching sensation, foreign body sensation and ocular pain. Constitutional symptoms may appear in some patients as mild pyrexia, malaise, headache and upper respiratory problems. Preauricular lymphadenopathy may occur in the early phase.

Subconjunctival hemorrhage, the most characteristic sign of the disease, varies from pinpoint petechiae to large blotches occupying the entire area of the bulbar conjunctiva. The hemorrhage is often facilitated and enlarged by rubbing the eyes. Edema and congestion of the palpebral conjunctiva are also frequent. Involvement of the cornea is usually transient and mild.

The ocular manifestations begin to subside from the fourth to fifth day from the onset, and complete recovery usually takes

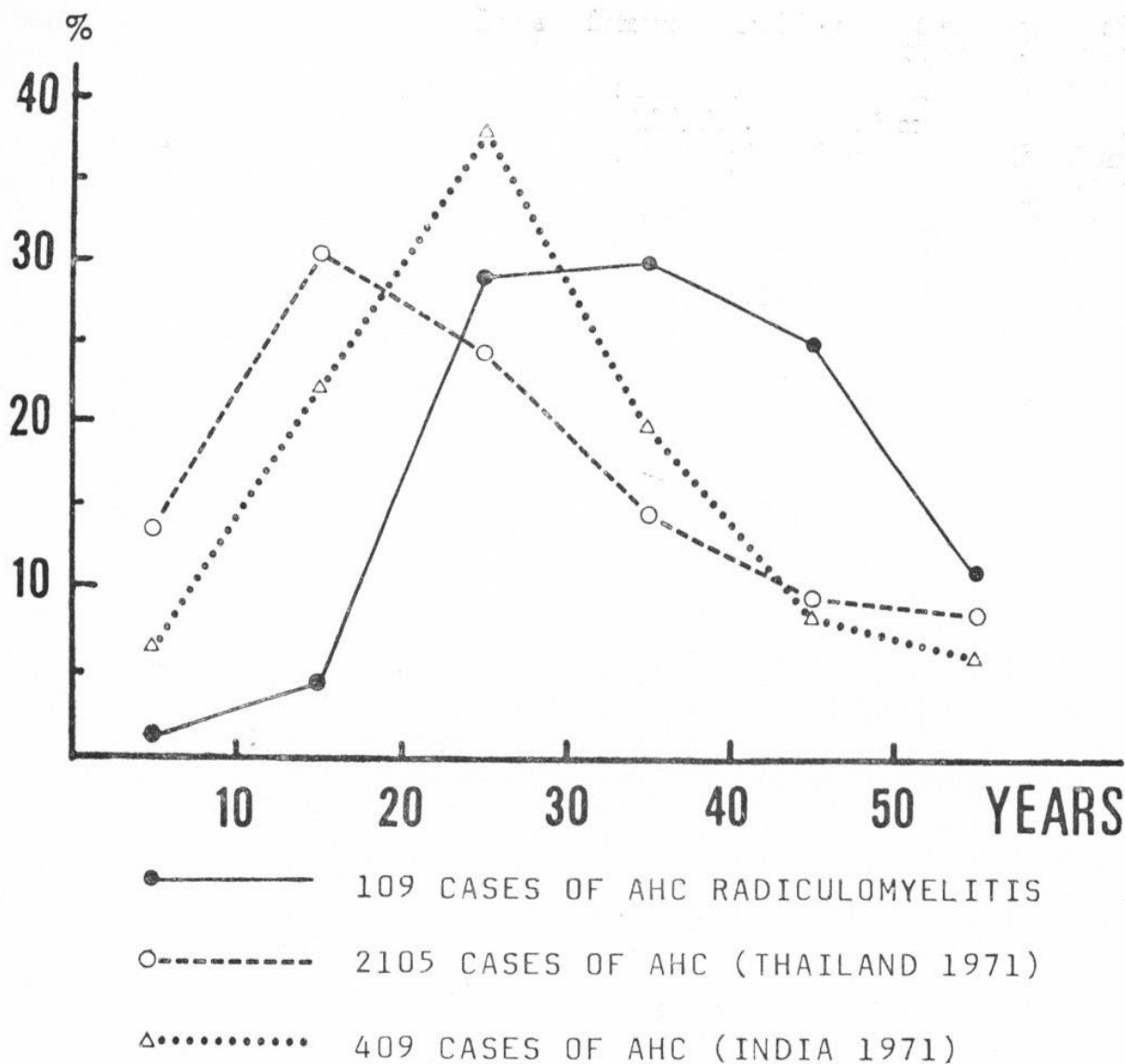


Fig. 1. — Comparison of age distribution between AHC radiculomyelitis and AHC.

place by the seventh to tenth day, even in the absence of any treatment. Thus, AHC itself is a benign disease, running a self-limited clinical course, except for neurological complication which may follow in a small proportion of the patients.

The causative agent of AHC is a new member in the enterovirus subgroup of picornaviruses, but it is not neutralized by antisera against known enteroviruses.⁽⁶⁾ After the first isolation of the virus in Japan, the similar virus has been isolated and identified in other parts of the world; the virus is now classified as "Enterovirus type 70 (EV 70)" by the W.H.O. Enterovirus Reference Centre.⁽¹¹⁾

It has been known that EV 70 has some properties which are different from other

enteroviruses. It is a naturally occurring and temperature-sensitive virus, and the optimal temperature for growth in tissue culture is as low as 33° C, which is much lower than that required for the growth of other enteroviruses⁽¹²⁾. This explains that the virus adapts well in the conjunctiva where the temperature is much lower than that of the internal organs of the body. Unlike ordinary enteroviruses, AHC virus is shed little in throat secretion and stools. Of many strains of EV 70, the J670/71 strain, which was isolated by Kono et al. in Japan⁽⁶⁾, has been used as the standard strain of AHC virus. Its neurovirulent properties were observed in human cases,⁽¹³⁾⁽¹⁴⁾⁽¹⁵⁾ as well as in experimental monkeys; the neurovirulence of this strain appeared

to be comparable to that of live attenuated poliovirus vaccine⁽⁷⁾.

AHC has become one of the common infectious eye diseases in Asian and African countries. The exact number of patients affected with AHC is unknown, however, it is likely that at least 10 million people were affected in 1969-1971 pandemic, and still more people have been infected every year since.

INCIDENCE OF AHC RADICULOMYELITIS

Compared with enormous number of AHC cases in various parts of the world, the number of patients with radiculomyelitis following AHC (AHC radiculomyelitis) appears to be very small and they have been reported by neurologists from certain geographical areas: 55 cases have been observed in Taiwan (1971-1977), 29 cases in India (1971),⁽⁸⁾⁽⁹⁾ 29 cases in Thailand (1974),⁽¹⁵⁾ 8 cases in Senegal (1970)⁽¹⁶⁾ and 1 case in Japan (1977)⁽¹⁷⁾. It is very likely that there have been in fact more cases of AHC radiculomyelitis, but they have been unrecognized or diagnosed as other diseases because the link between AHC and radiculomyelitis following it has not been widely known to practicing physicians, especially since the patients with the former consulted ophthalmologists and those with the latter were seen by neurologists or internists, and at different times. This view is well supported by observations in India and Taiwan where cases of AHC radiculomyelitis were all diagnosed in places where there were neurologists who had noticed the association between the two⁽⁵⁾⁽⁸⁾.

Both the annual and monthly incidence of cases with AHC radiculomyelitis goes parallel with the magnitude of the epidemic of AHC in each year. In Taiwan, about 2/3 of the patients with radiculomyelitis were affected in the June-October period, during which AHC was also more prevalent⁽⁵⁾.

It has been agreed by most investigators that AHC radiculomyelitis is mostly confined to adulthood⁽⁵⁾⁽⁸⁾⁽¹⁵⁾. Of a total of 109 cases, in which the ages were described, only 3 cases were under the age of 20. Between the ages 20 and 50 the cases were

evenly distributed. Fig. 1 compares the age distribution of cases with AHC radiculomyelitis with of two large series of AHC patients⁽²⁾. It shows that the proportion of patients with AHC alone are either in the 10-20 or 20-30 year-old age group; whereas the higher proportions of patients with radiculomyelitis are rather evenly distributed in the age groups between 20 and 50. In contrast with the above, post-epidemic serological studies on healthy populations showed that the positive rate of presence of antibody to EV 70 was highest in children under the age of 10, and it decreased significantly with increasing age⁽¹⁸⁾.

From the observations described above, it is very likely that infants and children have a higher rate of AHC infection but many of them are asymptomatic, or the symptoms are milder compared with those in adults. Thus, the susceptibility of the host and the vulnerability of the tissues to AHC infection appear to increase with age, and this tendency is more conspicuous in the patients with neurological complication.

Males are about 2.5 times more frequently affected than females; it simply reflects the higher morbidity rates of AHC in males⁽⁵⁾.

CLINICAL MANIFESTATIONS OF AHC RADICULOMYELITIS

Based on the observations of patients with neurological complication following AHC in Taiwan⁽⁵⁾ and on those reported in other countries,⁽⁹⁾⁽¹⁰⁾⁽¹³⁾⁽⁷⁶⁾ the clinical manifestations of this syndrome are described as follows.

Latent period

AHC usually has subsided when the patients develop neurological symptoms. The latent period between the onset of AHC and that of neurological symptoms varies from five days to eight weeks, being between one and five weeks in the majority (Fig. 2).

Prodromal symptoms

After the latent period, the majority of patients develop some kind of constitutional upset before the onset of neurological symptoms. Such constitutional symptoms consist of mild to moderate pyrexia, general malaise, headache, dizziness and sometimes

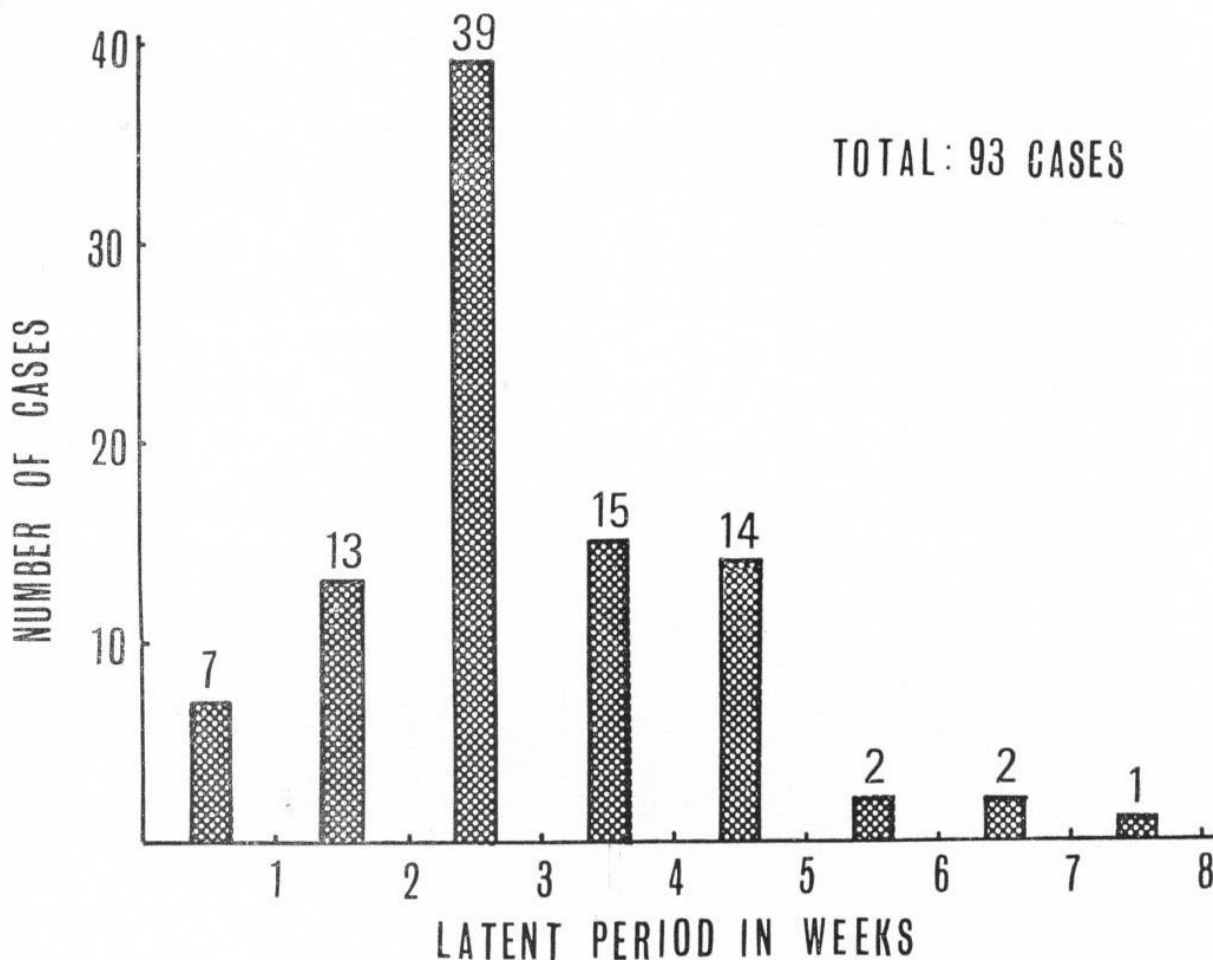


Fig. 2. — Latent period between onset of AHC and onset of motor weakness in 93 cases of AHC radiculomyelitis.

vomiting, which usually last for one or a few days. In some patients, however, these symptoms are entirely absent.

Initial neurological manifestations

The patients start their neurological symptoms either with subjective sensory phenomena or motor weakness, or both. The sensory phenomena often precede the onset of motor weakness, but they may occur together with or after the motor paralysis. In some cases, the initial sensory phenomena are absent. Transient difficulty in passing urine may occur in rare instances⁽⁵⁾.

The character and severity of sensory symptoms vary greatly from case to case. These are complained as regional aching pain in muscles, burning pain, radiating pain in a limb or limbs, nuchal pain or lower backache. In severe cases, lancinating radicular pain may spread down from the neck or the lower back to one more limbs. Burning pain or aching in muscles may so-

metimes be severe enough to cause extreme discomfort or to disturb night sleep. Aching pain or cramping pain is often prominent in the muscles where severe motor weakness ensues. Nuchal pain is sometimes accompanied by neck stiffness which suggests the presence of meningeal involvement. Objective sensory loss is seldom present and is mild and transient⁽⁵⁾⁽⁹⁾. The initial sensory phenomena usually last for several days and gradually subside within one or two weeks.

The onset of motor weakness is often acute, muscle tone is usually flaccid and the deep reflexes are diminished or absent in the affected muscles. Occasionally there are cases showing hyperactive tendon reflexes and presence of pathological reflexes in some limbs, especially when they are examined at the early stage of the motor paralysis⁽⁵⁾⁽¹⁰⁾⁽¹³⁾. These pyramidal signs are usually seen only in the acute stage, and

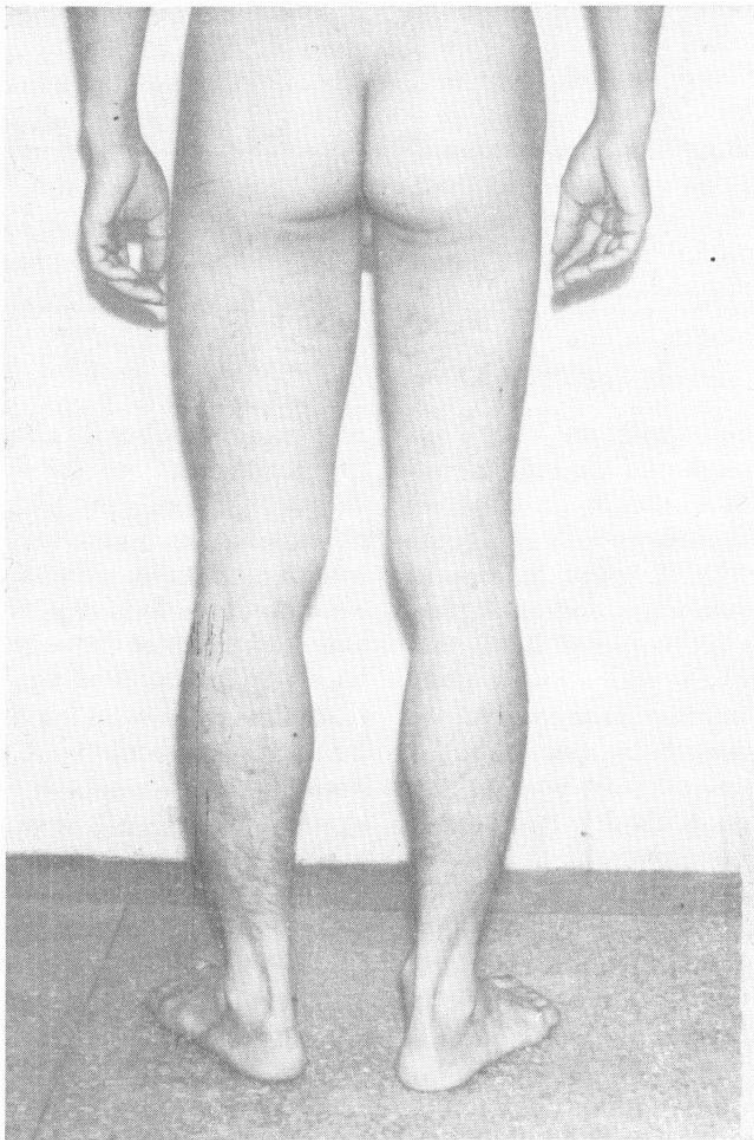
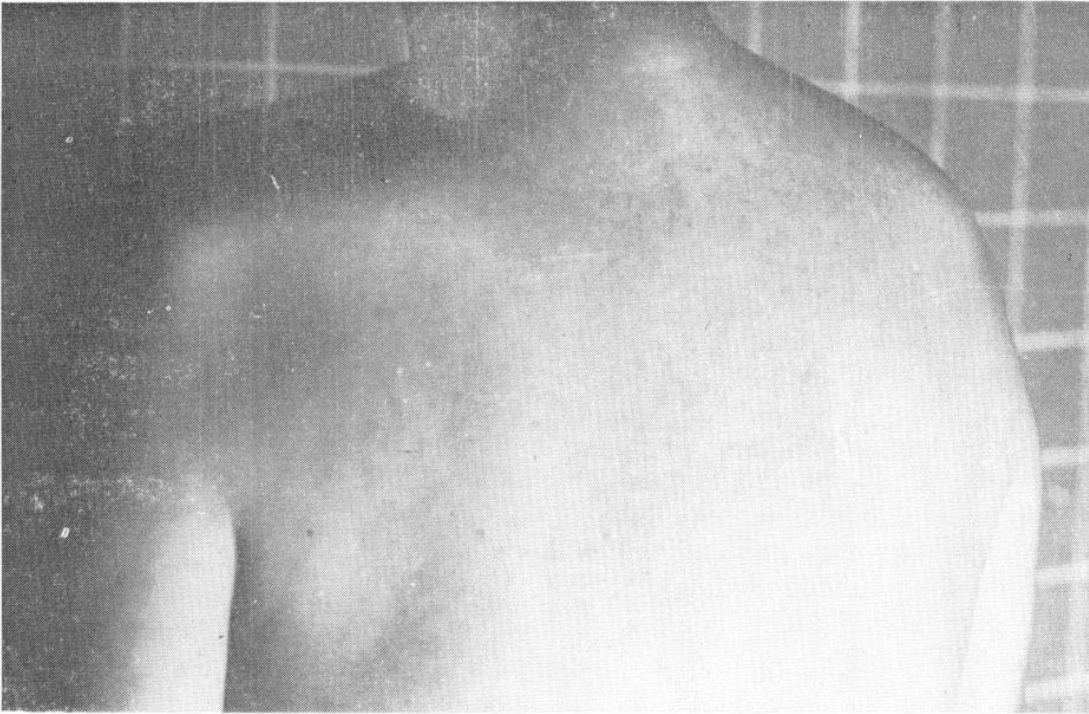


Fig. 3. — Muscular atrophy in AHC radiculomyelitis. (A) Prominent wasting in muscles around the left shoulder on the 34th day of severe motor weakness. (B) Atrophy in the right thigh, 80 days after the onset of moderate motor weakness in the right lower limb.

rarely persist for more than two weeks.

Motor paralysis

Flaccid paralysis in one or more limbs is the most outstanding feature throughout the whole clinical course. The onset is usually acute and may be quite abrupt. The motor weakness often starts in the proximal muscles of the limbs and those related to the hip and shoulder joints. The muscles in the lower limbs are more frequently affected at first. Further spread to other parts does not show a constant pattern. The motor weakness reaches to the maximum within a few days to two weeks.

Involvement of muscles in the limbs is often at random and asymmetrical. The muscles in the lower limbs are more frequently affected than the upper limbs. Of a total of 257 limbs affected in 107 patients (55 cases observed in Taiwan and 52 cases collected from reports in other countries), 73 were in the upper limbs and 184 were in the lower limbs, thus the lower limbs were about 2.5 times more frequently affected than the upper limbs. Table 1 clearly shows that the proximal muscles are more frequently and often more severely affected than the distal.

The distribution of the motor weakness according to the number and parts of the affected limbs are shown in Table 2. Of the 107 cases, only one limb was affected in 15 cases (14%), two limbs were involved in 50 cases (46.7%), three limbs in 26 cases (24.3%), and all four limbs were affected 16 cases (15%). Mild weakness of respiratory muscles may be seen in severe tetraplegic patients during the acute phase of paralysis.

The paralysed muscles are cold and flaccid, and the deep reflexes are markedly diminished or abolished in them. In moderately or severely affected muscles, muscular wasting becomes apparent in the second or third week; the degree of atrophy usually corresponds to the severity of paralysis (Fig. 3). Transient fasciculation on

exertion may be noted in mildly or moderately weak muscles during the progression of motor paralysis. In the chronic phase, more sustained fascicular twitches in the wasted muscles are seen in some patients.

The pattern of distribution of flaccid paralysis, the early development of muscular wasting, and the absence of sensory loss during the paralytic stage of illness indicate that the principal site of involvement is in the anterior horn cells of the spinal cord. During the acute phase of paralysis, however, involvement of the motor nerve roots may also contribute to some extent to the motor paralysis.

Cranial nerve involvement

Six patients who developed involvement of cranial nerves unassociated with motor paralysis of the limbs were reported by ophthalmologists in India in the 1971 pandemic of AHC,⁽¹⁹⁾⁽²⁰⁾ and one case was observed in Taiwan. The incubation period between the onset of AHC and that of cranial nerve involvement is often shorter than that of cases with limb paralysis, being within one or two weeks. These cases developed either palato-pharyngeal or facial palsy, or both, which ran a benign clinical course. Involvement of cranial nerves in addition to the symptoms of limb paralysis was observed in only 2 cases from Taiwan⁽⁵⁾. It still remains unknown whether the palato-pharyngeal and facial palsies represent involvement of the motor cranial roots or their nuclei in the brain stem.

Clinical course and prognosis

The initial symptoms other than motor paralysis usually subside within one to two weeks. After passing through the acute phase of motor paralysis, muscular weakness remains stationary for a varied length of time before recovery takes place. In mildly affected muscles, the recovery of function usually starts within a few weeks, leaving no muscular wasting. In moderately or severely paralysed muscles, the recovery is delayed and muscular atrophy ensues. Per-

MEAN VALUES

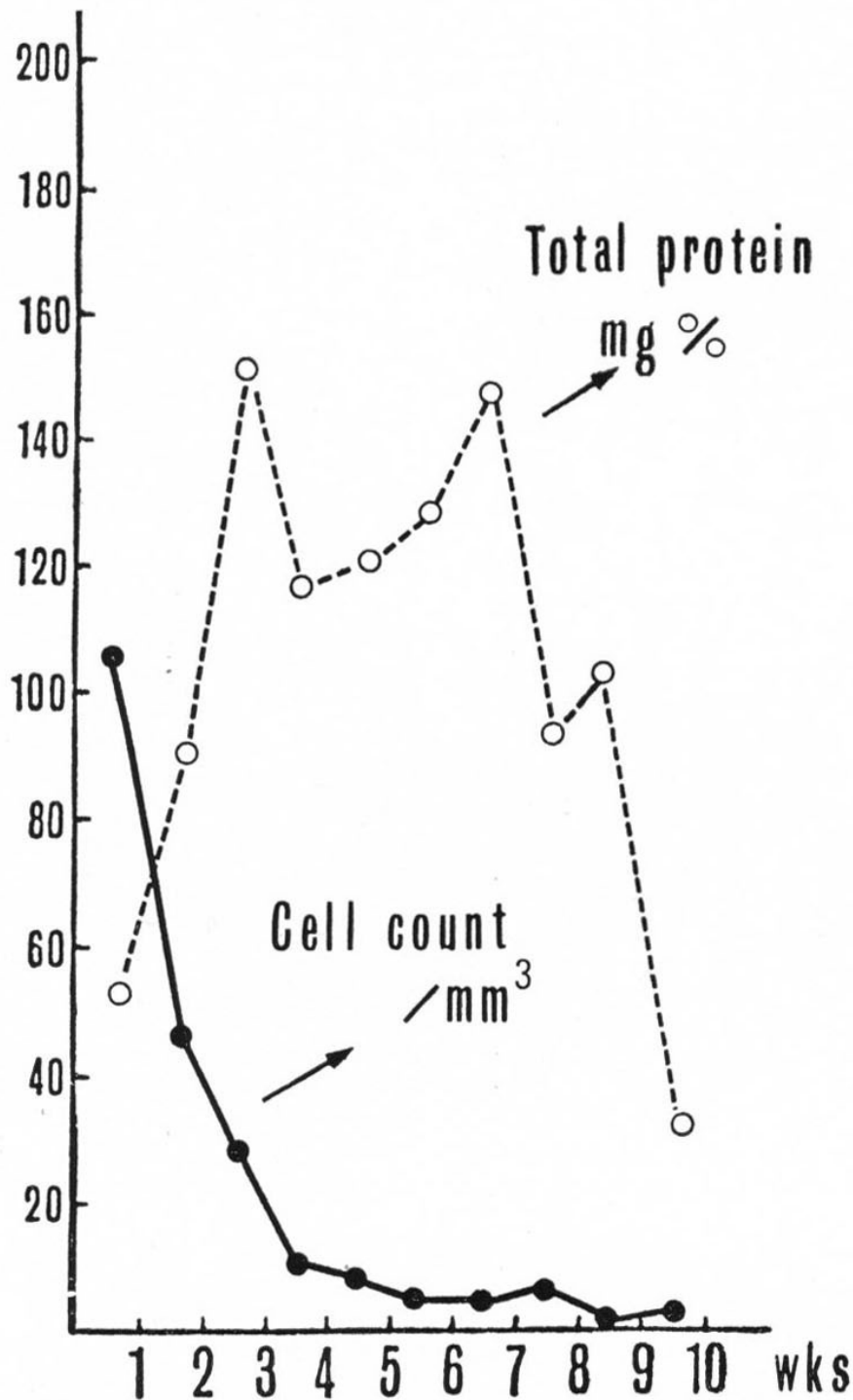


Fig. 4. — Mean values of cell count and total protein level in CSF in different stages of AHC radiculomyelitis (63 specimens from 36 patients in the Taiwan series).

manent loss of function and prominent atrophy may be seen in completely paralysed muscles. Profound bilateral proximal paralysis of the lower limbs causes the most severe incapacitation. Up to the present, none of the reported patients with

neurological complication have had a fatal outcome.

LABORATORY FINDINGS

Cerebrospinal fluid (CSF) findings

The pressure, sugar and chloride levels

of the CSF are usually normal. The cell count and total protein levels vary with the stage of the disease. The cell count (mostly lymphocytes) is raised in the majority of patients when the CSF is examined within the first three weeks from the onset of neurological symptoms. Those specimens which show a high count above 51 cells per mm³ are all taken in the first or second week. The pleocytosis is no more seen from the sixth week. Elevation of the total protein is not a striking feature during the first week, but it becomes more prominent in the second or third week, and may remain so as long as the seventh week or later. The sequence of changes of cell count and total protein is shown in the two curves of mean values based on 63 CSF specimens collected from 36 patients in the Taiwan series (Fig. 4). The changes in CSF at various stages of the illness are very similar to those seen in poliomyelitis.

Electrodiagnostic tests

In completely paralysed muscles, there may be an absence of electrical activity during the acute phase. Polyphasic motor unit potentials on weak voluntary contraction, and reduced interference pattern on maximal effort, are noted in partially paralysed muscles. Fibrillation potentials and positive sharp waves at rest usually become apparent in the affected muscles from the third or fourth week onwards. Both the motor and sensory nerve conduction velocities are usually normal in the affected limbs.

All the findings above are in keeping with the view that the main site of involvement responsible for the motor paralysis is at the level of the anterior horn cells or the ventral roots.

DIAGNOSIS

Clinical diagnosis

A clinical diagnosis of AHC radiculomyelitis can be made without difficulty when an adult patient is found to have a polio-like motor paralysis in one or more limbs which has been preceded by a history of AHC in the recent past. Occurrence of such patients in the seasons of epidemic outbreaks of AHC in the tropical or subtropical regions may facilitate the diagnosis. The characteristic features of EV 70 infec-

tion should be borne in mind in establishing the diagnosis of AHC and its neurological complications, since subconjunctival hemorrhage can occur in conjunctivitis due to other agents.

Differential diagnosis

The clinical manifestations of AHC radiculomyelitis and acute poliomyelitis are so much alike that, in the absence of a history of AHC, the differential diagnosis on clinical grounds alone is difficult. However, an age incidence strongly confined to adulthood in AHC radiculomyelitis is in distinct contrast with that of poliomyelitis, in which children are predominantly affected in most parts of the world, especially in places where hygienic conditions are poor and exposure of the inhabitants to poliovirus usually occurs very early in life. For confirmatory diagnosis in both diseases, virological and serological tests are essential.

When the patient develops relatively symmetrical flaccid paralysis in the limbs, differentiation from Guillain-Barré syndrome (GBS) during the acute stage may be difficult. However, early development of muscular wasting in the affected muscles, frequent pleocytosis in the CSF in the early stage of paralysis and normal nerve conduction velocity in AHC radiculomyelitis are the features differing from those in GBS.

Paralytic brachial neuritis (neuralgic amyotrophy) may simulate rare cases of AHC radiculomyelitis only involving one or both upper limbs, but there are usually no constitutional symptoms and the CSF is normal.

Virological and serological diagnosis

Isolation of EV 70 from eye swabs cannot be applied with success because AHC has usually subsided at the time when neurological symptoms appear. Since the virus is shed very little in throat secretion and feces, attempt to isolate EV 70 from these materials is usually futile; whereas in poliomyelitis, isolation of poliovirus from these specimens can often be achieved with success.

Serological diagnosis by using virus neutralization test or hemagglutination-inhibition test are the only practical and available means of confirmation for cases with

neurological complications. Generally speaking, a titer equal to or above 1:16 is of diagnostic value for AHC virus infection, but it only indicates that the patient has had EV 70 infection in the past. However, a fourfold or greater rise in antibody titers between paired sera, which has been observed in some patients, can be regarded as confirmative evidence for the virus being the causative agent of the observed paralytic symptoms⁽¹⁴⁾⁽¹⁵⁾. On the other hand, the diagnosis of AHC radiculomyelitis can be excluded if no detectable antibody to EV 70 is shown. Differentiation between AHC radiculomyelitis and poliomyelitis can be achieved by comparing the neutralizing activity of the antibodies to EV 70 and to poliovirus in 7S and 19S fractions of immune globulins. In patients with AHC radiculomyelitis, Kono et al. observed that neutralizing antibody to EV 70 was detected in both 19S and 7S fractions, whereas the antibodies to the 3 types of poliovirus were confined to the 7S fraction of the sera⁽¹⁵⁾. Thus the demonstration of neutralizing antibody to EV 70 in the 19S fraction of IgM confirmed that the infection by EV 70 occurred recently, and that both AHC and the paralytic phenomena were caused by the same virus.

POSSIBLE MECHANISM OF NEUROLOGICAL COMPLICATIONS

As EV 70 adapts well at 33°C, it grows in the conjunctiva causing AHC. Preauricular lymphadenopathy in the second or third day of AHC in the majority of patients indicates that the virus must have moved from the conjunctiva to the lymph nodes. Most of the patients recover from the infection within two weeks; however, in some susceptible patients, neurological symptoms may occur after a certain period of latency.

It is likely that some strains of EV 70 are more neurovirulent than others either through its specific affinity to nerve tissue or by changing to a temperature-resistant mutant which can grow at a higher temperature in the body, including the central nervous system. It has been found that there are some temperature-resistant wild strains of EV 70 which can grow at 39°C⁽²¹⁾.

This may explain why cases with neurological complication have been found only in some places, and in some particular outbreaks of AHC, although AHC is widely distributed in many parts of the world. By analogy with the pathogenesis of poliomyelitis, some host factors such as excessive physical exercise and fatigue, injections or inoculations, and other stresses to the body may contribute to precipitate or to determine the site and severity of the motor paralysis following AHC⁽¹⁰⁾. The age incidence of AHC radiculomyelitis being mostly confined to adulthood is in great contrast to that of poliomyelitis. The susceptibility of the host and the vulnerability of the nervous system to EV 70 infection vary from person to person, and they appear to increase with age. These host factors may explain the rarity of the cases with neurological complication compared with the enormous number of AHC patients and the age-specific phenomenon of this neurological syndrome.

The preparalytic symptoms of AHC radiculomyelitis perhaps represent the occurrence of viremia, during which the virus spreads widely in the body tissues. The initial neurological manifestations such as subjective sensory phenomena, nuchal pain, neck stiffness, headache and pleocytosis in the CSF, are very likely due to irritation of the spinal nerve roots and leptomeninges. The white matter of the spinal cord may be involved in some patients in the early stage. The asymmetrical flaccid motor paresis or paralysis, the pattern of distribution of weak muscles, and the early development of muscular wasting, all indicated that the involvement of the anterior horn cells in the spinal cord is mainly responsible for such paralytic phenomena. The clinical findings described above are indeed very reminiscent of the patterns of poliomyelitis, being also compatible with the histopathological findings in experimental monkeys inoculated with EV 70⁽⁷⁾.

PREVENTION AND TREATMENT

Although AHC itself is a benign eye disease, the paralytic neurological complication which may occur in some adult patients is often serious enough to incapacitate

tate them. Thus, effective public health measures to prevent and control the outbreaks in prevalent seasons and countries are of primary importance for the elimination of both AHC and its hazardous neurological complications.

Since eye clinics are often the source of spreading the virus, patients with AHC must be treated separately from other patients. Improvement of individual and environmental sanitary condition can reduce the chance of infection and its spread.

Until the present, no specific therapy has

been available to prevent the progression of motor weakness once it appears. Administration of corticosteroids has been reported to be effective in relieving sensory phenomena which have been refractory to other drugs, but its therapeutic effect on paralytic symptoms is questionable. Physiotherapy must be started as soon as the aching and root pains subside, and the progression of motor paralysis stops. The use of crutches or orthopedic braces may facilitate ambulation of the cases with severe paralysis in the lower limbs.

SUMMARY

A polio-like syndrome has been found to occur in some patients following acute hemorrhagic conjunctivitis (AHC) caused by a newly discovered virus, which is now classified as Enterovirus type 70 (EV 70). Until the end of 1977, a total of 128 cases with neurological complication of AHC have been observed in Taiwan, India, Thailand, Senegal and Japan. The neurological manifestations are very similar to those of poliomyelitis, but the age incidence is almost confined to adulthood. The salient initial neurological symptoms are radicular pains and flaccid paralysis which develop from 5 days to 8 weeks after the onset of AHC. Symptoms and signs indicating involvement of the meninges, cranial nerves and the white matter of the spinal cord are noted in some patients in the early stage. Asymmetrical flaccid paralysis in one or more limbs is the most outstanding feature during the whole clinical course. The lo-

wer limbs are more frequently and often more severely affected than the upper limbs, and weakness in the proximal muscles is usually more severe than that in the distal. Muscular wasting ensues in the severely affected muscles 2-3 weeks after the onset of limb paralysis. Pleocytosis is noted in the early stage of paralysis in the majority of patients, and the total protein level is usually raised from the second week onwards. A 4-fold rise of neutralizing antibody titers against EV 70 between paired sera has been noted in some patients with neurological complication. Differential diagnosis from acute poliomyelitis and other diseases simulating this neurological syndrome has been discussed. Effective public health measures to control the outbreaks of AHC in prevalent seasons and countries are of primary importance for the elimination of this hazardous neurological complication.

RESUMEN

Se ha observado en algunos pacientes la aparición de un síndrome similar a la polio como consecuencia de una conjuntivitis aguda hemorrágica (CAH) causada por un virus que ha sido clasificado como Enterovirus tipo 70 (EV 70). Hasta fines de 1977 un total de 128 casos con complicación neurológica de la CAH fueron observados en Taiwan, India, Tailandia, Senegal y Japón.

Las manifestaciones neurológicas son muy similares a las de la poliomiелitis, pero la

edad de incidencia de la afección ocurre casi siempre en la adultez.

Los síntomas neurológicos iniciales son dolores radiculares y parálisis flácida los cuales se desarrollan de 5 días a 8 semanas después del comienzo de la CAH.

En algunos pacientes al comienzo del proceso se observan síntomas y signos que indican afección de las meninges, nervios craneales y la sustancia blanca de la médula espinal. Parálisis flácida asimétrica en uno o varios miembros es la nota clínica más

aparente durante toda la evolución del proceso.

Los miembros inferiores son afectados más frecuentemente y con mayor severidad que los miembros superiores y la debilidad en los músculos proximales es habitualmente de mayor gravedad que en los músculos distales.

Atrofia muscular se hace presente en los músculos severamente afectados de dos o tres semanas después del comienzo de la parálisis de los miembros. En la mayoría de los pacientes se observan en el comienzo de la parálisis una Fleocitosis y el nivel total de proteínas habitualmente está eleva-

do a partir de la segunda semana del proceso.

En algunos pacientes con esta complicación neurológica se ha comprobado un aumento manifiesto de titular de anticuerpos centralizados contra el EV 70.

Se ha discutido el diagnóstico diferencial entre poliomiélitis aguda y otras enfermedades que simulan este síndrome neurológico. Medidas efectivas públicas de salud para controlar la irrupción de CAH en estaciones y países en las que prevalece, son de primordial importancia para obtener la eliminación de esta complicación perniciosa neurológica.

ZUSAMMENFASSUNG

Ein polio-ähnliches Syndrom, ausgelöst durch einen neuen Virus, Enterovirus Typ 70 (EV 70), nach einer akuten hämorrhagischen Konjunktivitis (AHK), wird beschrieben. Bis Ende 1977 sind in Taiwan, Indien, Senegal und Japan insgesamt 128 Fälle von AHK mit solchen neurologischen Komplikationen beobachtet worden.

Die neurologischen Erscheinungen sind der Polio sehr ähnlich, beschränken sich aber fast ausschliesslich auf Erwachsene. Die anfänglichen Symptome, nämlich Radikulargie und Erschlaffungs-lähmungen, treten nach 5 Tagen bis 8 Wochen der AHK auf. In einigen Fällen zeigen sich auch Symptome, welche auf eine Mitbetroffenheit der Hirnhaut, der kranialen Nerven und der Medullarspinalis schliessen la-

ssen. Assymetrische Erschlaffungs-lähmungen in einzelnen oder mehreren Gliedern sind das auffälligste klinische Merkmal. Die unteren Extremitäten sind häufiger und meistens schwerer betroffen, die Schwächung der Proximalmuskulatur im allgemeinen ausgeprägter. Muskelatrophie tritt 2-3 Wochen nach den Lähmungen auf. Vielfach zeigt sich eine Pleozytose in den frühen Phasen der Lähmungen, und eine Erhöhung der Totalproteine macht sich gewöhnlich von der zweiten Wochen an bemerkbar. Bis zu einer vierfachen Erhöhung an Antikörpern EV70 sind festgestellt worden. Der Autor erörtert ebenfalls die differenzierte Diagnose des Syndrome sowie die erforderlichen gesundheitsbehördlichen Massnahmen.

RÉSUMÉ

On a décrit récemment un nouveau syndrome neurologique ressemblant à la poliomyélite et qui survient après une conjonctivite hémorragique aiguë (CHA) due à un Entérovirus type 70 (EV 70) nouvellement isolé. Jusqu'à maintenant (décembre 1977) 128 cas en ont été observés à Taiwan, en Inde, en Thaïlande, au Sénégal et au Japon. Si les manifestations neurologiques de cette affection sont très semblables à celles de la poliomyélite, en revanche celle-ci n'atteint pratiquement que des adultes. Ce syndrome neurologique apparaît de 5 jours à 8 semaines après le début de la

CHA et s'annonce principalement par des douleurs radiculaires avec paralysie flasque. Dans certains cas on observe également des signes méningés précoces et une atteinte des nerfs crâniens et de la substance médullaire blanche. Le signe cardinal de l'affection, et cela pendant toute sa durée, est la présence d'une paralysie flasque asymétrique d'un ou de plusieurs membres. Les membres inférieurs sont plus fréquemment et gravement atteints que les membres supérieurs, avec prédominance des troubles dans les muscles proximaux. Deux à trois semaines après le début des paralysies ap-

paraît une fonte musculaire dans les régions les plus atteintes. Dès l'installation des paralysies on observe dans la plupart des cas une pléiocytose du liquide céphalo-rachidien avec augmentation des protéines totales dès la seconde semaine. On a pu démontrer par-

fois une élévation jusqu'à quatre fois la normale des anticorps EV 70. L'auteur discute également dans ce travail le diagnostic différentiel de l'affection, ainsi que les mesures de Santé Publique qui doivent être prises pour l'enrayer.

TABLE 1.

Comparison of severity of motor weakness between proximal and distal muscles in 55 cases of AHC radiculomyelitis in Taiwan series.

Both proximal and distal	52
More severe in proximal	33
Equally severe in both	15
More severe in distal	4
Proximal only	3
Distal only	0
Total	55 cases

TABLE 2

Distribution of motor weakness in the limbs (107 cases of AHC radiculomyelitis from 5 countries).

In one limb only	
one upper limb	
one lower limb	
In two limbs	
two upper limbs	
two lower limbs	
two limbs on one side	

two limbs, one on each side	
In three limbs	
two upper limbs + one lower limb	
one upper limb + two lower limbs	
In four limbs	
Total number of cases	N° of cases (%)
	15 (14.0)
2 (1.0)	
13 (12.1)	
	50 (46.7)
2 (1.9)	
41 (38.3)	
3 (2.8)	
4 (3.7)	
	26 (24.3)
2 (1.9)	
24 (22.4)	
	16 (15.0)
	107 (100.0)

REFERENCES

1. Chatterjee, S., Quarcoopome, C.O. and Apenteng, A.: Unusual type of epidemic conjunctivitis in Ghana. *B. J. Ophthalmol.*, 54:628-630, 1970.
2. Kono, R.: Apollo 11 disease or acute hemorrhagic conjunctivitis: a pandemic of a new enterovirus infection of the eyes. *Am. J. Epidemiol.*, 101:383-390, 1975.
3. Bharucha, E.P. and Mondkar, V.P.: Neurological complications of a new conjunctivitis. *Lancet*, 2:970, 1972.
4. Wadia, N.H., Irani, P.F. and Katrak, S.M.: Neurological complications of a new conjunctivitis. *Lancet*, 2:970-971, 1972.
5. Hung, T.P., Sung, S.M., Liang, H.C., Landsborough, D. and Green, I.J.: Radiculomyelitis following acute haemorrhagic conjunctivitis. *Brain*, 99:771-790, 1976.
6. Kono, R., Sasagawa, A., Ishii, K., Sugiura, S., Ochi, M., Matsumiya, H., Uchida, Y., Kamayama, K., Kaneko, M. and Sakurai, N.: Pandemic of new type of conjunctivitis. *Lancet*, 1:1191-1194, 1972.
7. Kono, R., Uchida, N., Sasagawa, A., Akao, Y., Kodama, H., Mukoyama, J. and Fujiwara, T.: Neurovirulence of acute haemorrhagic conjunctivitis virus in monkeys. *Lancet*, 1:61-63, 1973.
8. Wadia, N.H., Irani, P.F. and Katrak, S.M.: Lumbosacral radiculomyelitis associated with pandemic acute haemorrhagic conjunctivitis. *Lancet*, 1:350-352, 1973.
9. Bharucha, E.P., Mondkar, V.P. and Kulkarni, S.A.: Postconjunctival myeloradiculopathy. *Neurol. India*, 22:79-82, 1974.
10. Phuapradit, P., Roongwithu, U., Limsukon, P., Boongird, P. and Vejajiva, A.: Radiculomyelitis complicating acute haemorrhagic conjunctivitis. A clinical study. *J. Neurol. Sci.*, 27:117-122, 1976.
11. Mirkovic, R.R., Kono, R., Yin-Murphy, M., Sohler, R., Schmidt, N.J. and Melnick, J.L.: Enterovirus type 70; the etiologic agent of pandemic acute haemorrhagic conjunctivitis. *Bull. Wld. Hlth. Org.*, 49:341-346, 1973.
12. Miyamura, K., Yamazaki, S., Tajiri, E. and

- Kono, R.: Growth characteristic of acute hemorrhagic conjunctivitis (AHC) virus in monkey kidney cells. I. Effect of temperature on viral growth. *Intervirology*, 4:279-286, 1974.
13. Kono, R., Miyamura, K., Tajiri, E., Shiga, S., Sasagawa, A., Irani, P.F., Katrak, S.M. and Wadia, N.H.: Neurologic complications associated with acute hemorrhagic conjunctivitis virus infection and its serologic confirmation. *J. Inf. Dis.*, 129:590-593, 1974.
 14. Green, I.J., Hung, T.P. and Sung, S.M.: Neurologic complications with elevated antibody titer after acute hemorrhagic conjunctivitis. *Am. J. Ophthalmol.*, 80:832-834, 1975.
 15. Kono, R., Miyamura, K., Tajiri, E., Sasagawa, A., Phuapradit, P., Roongwithu, N., Vejajiva, A., Jayavasu, C., Thongcharoen, P., Wasi, C. and Rodprassert, P.: Virological and serological studies of neurological complications of acute hemorrhagic conjunctivitis in Thailand. *J. Inf. Dis.*, 135:706-713, 1977.
 16. Kono, R., Miyamura, K., Tajiri, E., Robin, Y. and Girard, P.: Serological studies of radiculomyelitis occurring during the outbreak of acute hemorrhagic conjunctivitis in Senegal in 1970. *Jap. J. Med. Biol.*, 29(2): 91-94, 1976.
 17. Kuroiwa, Y., Tsuji, S., Murai, Y. and Shibasaki, H.: A case of poliomyelitis syndrome following acute hemorrhagic conjunctivitis, the first Japanese case. *Neurol. Med. (Tokyo)*, 7:87-88, 1977.
 18. Kono, R., Sasagawa, A., Miyamura, K. and Tajiri, E.: Serologic characterization and sero-epidemiologic studies on acute hemorrhagic conjunctivitis (AHC) virus. *Am. J. Epidemiol.*, 101:447-457, 1975.
 19. Bujarboura, D., Dutta, L.C. and Dutta, N.N.: Epidemic conjunctivitis. *Orient. Arch. Ophthalmol.*, 10:58-63, 1972.
 20. Saxena, R.C., Bhatia, M. and Chaturved, U.C.: Recent epidemic conjunctivitis in Lucknow. A clinical study. *Orient. Arch. Ophthalmol.*, 10:253-257, 1972.
 21. Miyamura, K., Sasagawa, A., Tajiri, E. and Kono, R.: Growth characteristic of acute hemorrhagic conjunctivitis (AHC) virus in monkey kidney cells. II. Temperature sensitivity of the isolates obtained at various epidemic areas. *Intervirology*, 7:192-200, 1976.

Acute Autonomic Neuropathy

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The acute and subacute autonomic neuropathies consist of a variety of disorders which selectively affect the peripheral autonomic nervous system over a period of days to weeks. Most peripheral neuropathies affect motor sensory and autonomic fibers to varying degrees. We will focus on a group of rare neuropathies which have as their primary manifestation abnormalities of the autonomic nervous system.

Clinical Presentation

Autonomic neuropathies usually affect both sympathetic and parasympathetic fibers. Concomitant involvement of both systems has been referred to as pandysautonomia¹. A few autonomic neuropathies are characterized by selective and often localized involvement of adrenergic or cholinergic systems. Examples of disorders which selectively affect cholinergic fibers or ganglia include: Hirschsprung's disease, Adie's syndrome, inherited cholinergic dysautonomia, and the cholinergic dysautonomia associated with Botulinum B intoxication and Eaton-Lambert syndrome. The autonomic nervous system is a diffuse network which innervates numerous organs. As a result the signs of symptoms of autonomic neuropathy may be widespread². They typically include a mixture of problems referable to sympathetic and parasympathetic dysfunction³. The most common problems include: 1. Pupillary and lid abnormalities, including blurred vision, photophobia, presbyopia and ptosis secondary to Horner's syndrome⁴. 2. Circulatory dysfunction, including orthostatic dizziness and syncope due to orthostatic hypotension, and paroxysmal

and supine hypertension⁵. 3. Lacrimation problems, including dry eyes and lack of overflow tears⁶. 4. Gastrointestinal dysfunction, including dry mouth due to decreased salivation, and motility disorders of the upper and lower gastrointestinal tract⁷. 5. Sexual dysfunction, including male erectile and ejaculation failure and retrograde ejaculation⁸. 6. Respiratory dysfunction, primarily sleep apnea⁹. 7. Bladder dysfunction, such as spastic or flaccid neurogenic bladder^{10,17}. 8. Sweating disturbance, including heat intolerance secondary to anhidrosis, and hyperhidrosis in uninvolved areas¹². The most common and often the most disabling presenting problem of acute and subacute autonomic neuropathies is orthostatic hypotension¹³. The orthostatic hypotension may be worse post-prandially and may be associated with supine hypertension. The second most common problem, which occasionally may precede signs of orthostatic hypotension, is blurred vision due to pupillary disturbance¹⁴. Several possible combinations of pupillary abnormalities may exist due to variable involvement of sympathetic and parasympathetic innervation. These include fixed anisocoria to light at far and near gaze, tonic pupils, light-near dissociation, no dilation in darkness and irregular iris sphincter margin secondary to segmental denervation. Evidence on examination for pyramidal, extrapyramidal or cerebellar dysfunction usually means the patient has patient has Shy-Drager Syndrome, which refers to one or more degenerative disorders characterized by prominent autonomic dysfunction due to involvement of pre-ganglio-

nic and/or post-ganglionic autonomic neurons in addition to central nervous system involvement¹⁵. A subgroup of patients with acute and subacute autonomic neuropathy have pure cholinergic dysautonomia¹⁶. The presenting problems are usually fixed, unreactive pupils to light and atonic bladder and bowel. Orthostatic hypotension is uncommon in this group.

Differential Diagnosis

The differential diagnosis of an autonomic neuropathy includes inherited¹⁷ and acquired disorders^{18,19} (see Table # 1). The acute and subacute autonomic neuropathies refer to acquired disorders which are not present from birth, are typically self-limited and often partially or completely remit spontaneously. As previously

PERCENTAGE CHANGE IN SYSTOLIC B.P.

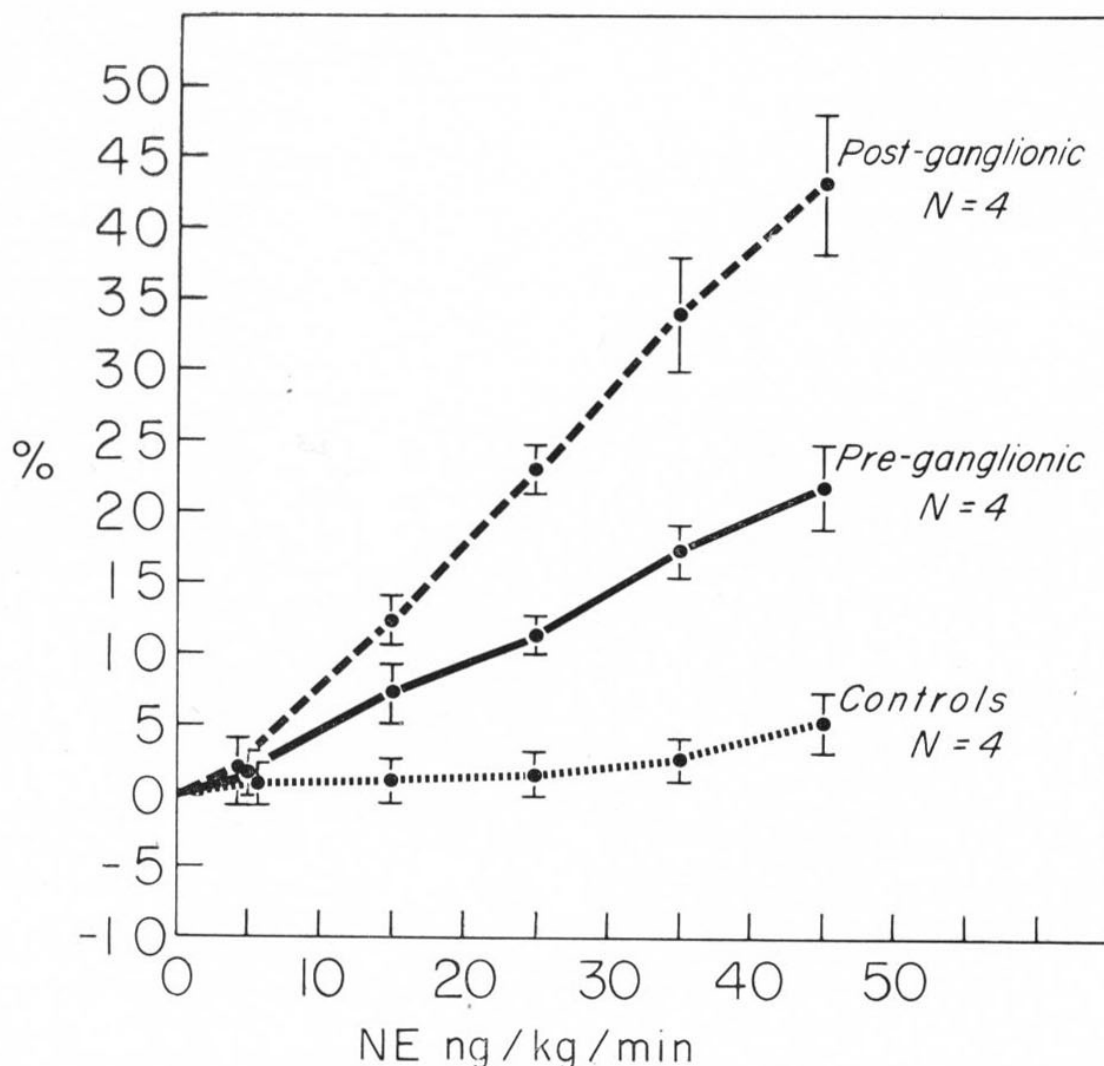


Fig. 1 — Response of patients with pre-ganglionic and post-ganglionic neurogenic orthostatic hypotension to dilute intravenous norepinephrine.

mentioned, signs of central nervous system dysfunction may indicate Shy-Drager syndrome²⁰. Some patients with Shy-Drager syndrome will have autonomic dysfunction as their presenting and only problem. Serial examinations will usually demonstrate signs of central nervous system involvement wi-

thin six to twelve months^{21,22,23}. The diagnosis of autonomic dysfunction due to diabetes mellitus²⁴, uremia^{25,26}, and variegate porphyria^{27,28,29} may be made by documenting the specific metabolic problem with appropriate laboratory tests. Autonomic neuropathy in alcohol associated thiamine

deficiency is made by obtaining a history of alcohol abuse and poor diet, and by finding other systemic evidence for alcohol abuse³⁰. Diagnosis of toxic causes of autonomic neuropathy is dependent on an adequate history and the presence of other specific signs of toxicity³¹. The neuroleptic malignant syndrome may present acutely with autonomic dysfunction but is typically accompanied by a high fever, marked extrapyramidal signs and a history of excessive neuroleptic use³². Vincristine^{33, 34, 35, 36}, diabetic³⁷, thiamine deficient³⁰, and vacor autonomic neuropathies³⁸ are usually seen in association with a diffuse sensory polyneuropathy. Table # 2 lists those autonomic neuropathies which commonly present in an acute or subacute manner over days to weeks.

Autonomic dysfunction may be an initial or late complication in Guillain-Barre Syndrome³⁹. Orthostatic hypotension is the most frequent initial autonomic problem; both sympathetic and parasympathetic hypoactivity and hyperactivity may be seen⁴⁰. The most common autonomic problems in a series of Guillain-Barre patients are reviewed in Table # 3⁴¹. A prospective study of autonomic disturbances in Guillain-Barre found a majority had at least two abnormalities on autonomic function testing⁴². Autonomic dysfunction is usually less prolonged than motor dysfunction, but is associated with a higher incidence of mortality^{43, 44, 45, 46}.

An acute autonomic neuropathy has been reported as a remote effect of carcinoma. The presenting problem in the four cases reported was orthostatic hypotension^{47, 48, 49, 50}. Sweating and lacrimation problems were also noted. Autonomic dysfunction preceded signs of cancer in three of four patients. In one case autonomic dysfunction improved with tumor removal and recurred with tumor regrowth⁵⁰.

Acute pandysautonomia associated with collagen vascular disease is uncommon⁵¹. The few reported cases have usually had signs of mononeuritis multiplex or a diffuse sensory polyneuropathy^{52, 53, 54}. Sjogren's syndrome associated with autoimmune disease may be differentiated from autonomic neuropathy by salivary gland biopsy which

will demonstrate infiltration and destruction of the gland in the former condition and a normal gland in the latter.

Ingestion of the rodenticide Vacor has been reported to produce an acute autonomic neuropathy associated with insulin dependent diabetes mellitus⁵⁵. Ingestion occurs most commonly in children as accidental poisoning and in adults as a suicide attempt. Neurological involvement in vacor poisoning may include an encephalopathy, myoclonus and a sensorimotor polyneuropathy⁵⁶. The most common autonomic disturbances are reviewed in Table # 4. The autonomic problems tend to be chronic if the patient survives and may be the last of the neurologic problems to improve⁵⁷.

Acute and subacute autonomic dysfunction have been occasionally reported with chronic use of a variety of medications (see Table # 5)^{58, 59}. In most cases, cessation of the medication resulted in complete improvement.

Clostridial toxin ingestion is a rare cause of acute autonomic dysfunction which is confined to cholinergic disturbances. Jenzer et al.⁶⁰ reviewed an outbreak of Botulinum B ingestion in which 20 % of those affected had cholinergic autonomic dysfunction in the absence of muscle weakness (see Table # 6). Neurologic examination revealed only subtle pupillary abnormalities and abnormal Schirmer tests. There was complete resolution of findings in all cases within three months. Jenzer has suggested that some cases of acute autonomic neuropathy presumed to be idiopathic or autoimmune in etiology may actually be Botulinum B intoxication. Other clostridial toxins have been reported to cause autonomic disturbances, though not as isolated phenomena⁶¹. Kerr et al.⁶² reported two cases of systemic tetanus complicated by orthostatic hypotension and systemic hypertension with absent baroreceptor reflex. Both cases had associated ileus and bladder dysfunction.

Approximately 17 cases of acute autonomic neuropathy of the idiopathic type have been reported^{13, 14, 16, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73}; we have seen two more cases⁷⁴. None of these cases have died and most have had a partial or full recovery. The clinical characteristics of 19 known cases of acute ac-



Fig. 2A — Normal control. Falck-Hillarp catecholamine histofluorescence of perivascular catecholamine containing granules (muscle biopsy).

quired autonomic neuropathy are summarized in table # 7. The most prominent problem in all cases was orthostatic hypotension. Four cases were noted to have increased CSF protein in the absence of pleocytosis, which suggests that some cases may

represent part of the spectrum of the Guillain-Barre syndrome⁷⁵. At least 2 cases had serologic evidence for associated infectious mononucleosis. Three cases had associated sensory polyneuropathy. In four cases the autonomic dysfunction was restric-

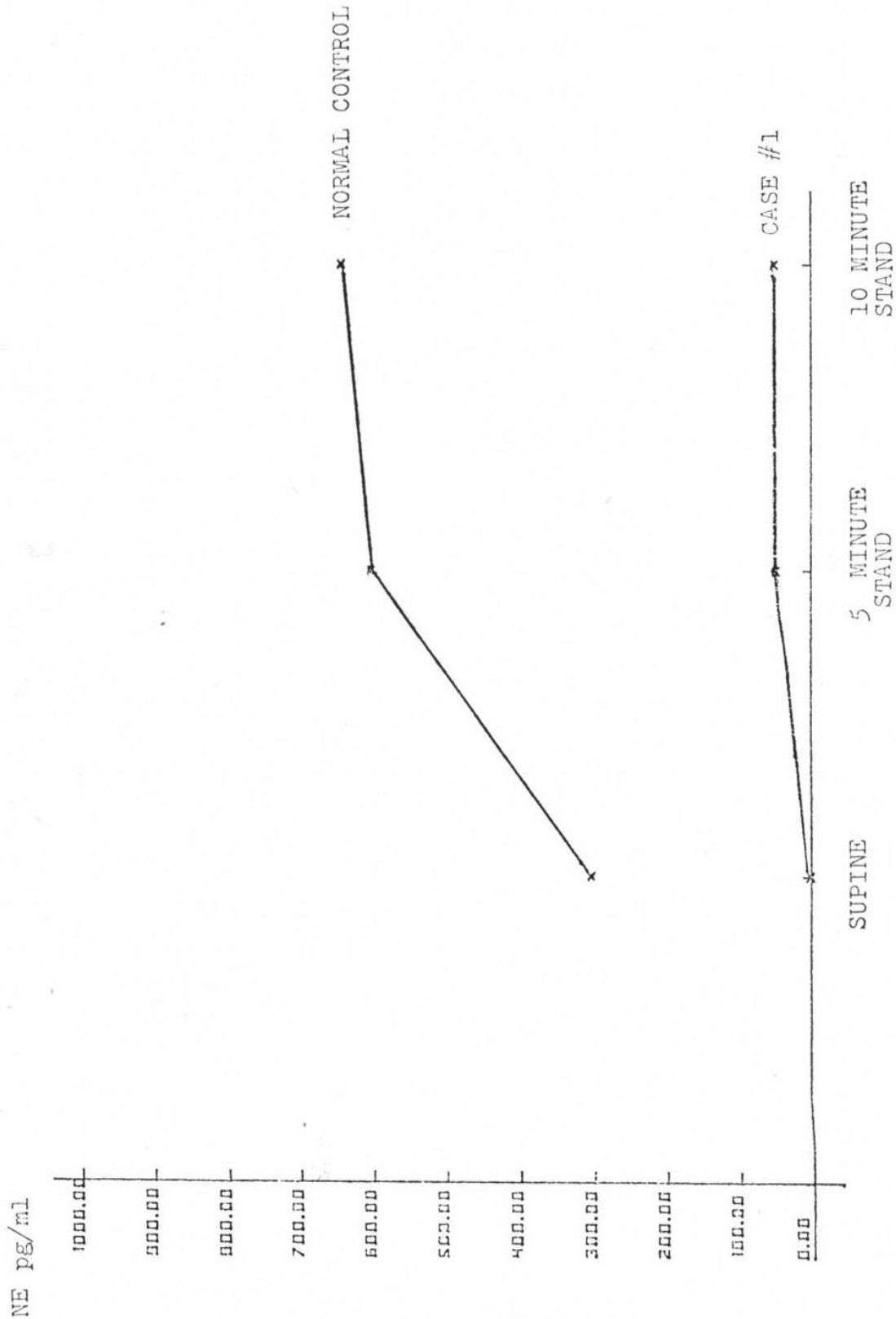


Fig. 2B — Acute idiopathic autonomic neuropathy. Falck-Hillarp catecholamine histofluorescence. No fluorescing granules are noted (muscle biopsy).

ted to cholinergic abnormalities. These patients did not present with orthostatic hypotension but with gastrointestinal and bladder

motility problems. Treatment in acute autonomic neuropathy of the idiopathic type is symptomatic. There is no evidence

Figure 3: Plasma norepinephrine in a patient with severe orthostatic hypotension due to
vapor autonomic neuropathy.



to suggest that steroid treatment alters the course of the disorder which is usually, though not always, self-limited.

Evaluation

A variety of physiologic tests are availa-

ble to document autonomic failure involving the circulatory system. These include tilt table testing, valsalva maneuver, resting R-R interval variation and cold-pressor responses^{76,77,78,79,80}. Pharmacologic tests

include intravenous or intra-arterial infusion of dilute direct sympathomimetics to look for the presence and degree of supersensitivity. Infusion of indirect sympathomimetics with concomitant measurement of norepinephrine release can quantitate the amount of catecholamine available in peripheral sympathetic nerve endings. Figure # 1 demonstrates the blood pressure response to intravenous infusion of dilute norepinephrine in patients with orthostatic hypotension of pre-ganglionic and post-ganglionic origin. The supersensitive blood pressure response is much higher in patients with peripheral autonomic neuropathy^{81,82}. Peripheral catecholamine depletion in autonomic neuropathy may be demonstrated by examination of peripheral catecholamine stores in sympathetic nerve terminals with catecholamine histofluorescence or electron microscopy^{83,84}. Figure # 2 illustrates catecholamine depletion by histofluorescent study of perivascular adrenergic fibers in a patient with acute autonomic neuropathy of the idiopathic type. Low et al.⁸⁵ have recently reported absence of the catecholaminergic synthetic enzyme Dopamine-Beta-Hydroxylase in sural nerve in a patient with acute autonomic neuropathy. Ziegler et al. have correlated low resting plasma norepinephrine levels which fail to rise on standing with post-ganglionic autonomic dysfunction in orthostatic hypotension^{86,87,88,89,90}. Figure # 3 demonstrates extremely low plasma norepinephrine levels in a patient with severe orthostatic hypotension due to vagal autonomic neuropathy. Table # 8 summarizes pharmacologic evaluation of neurogenic orthostatic hypotension^{91,92}.

Evaluation of pupillary abnormalities includes measurement of pupillary diameter in darkness and light and with accommodation⁹³. Quantitation of pupillary response is improved with pupillometry. Pharmacologic testing is performed with direct and indirect sympathomimetics and with a direct parasympathomimetic. It is important to note that abnormalities of lacrimation can result in false positive supersensitive responses to a dilute neurotransmitter due to failure of reflex tearing to flush the pharmacologic agent through the nasolacrimal duct. Table # 9 summarizes the res-

ponse of the pupil to various pharmacologic agents in different forms of autonomic denervation⁹⁴. Slit lamp evaluation in Adie's syndrome invariably demonstrates segmental constriction to light which is presumably due to segmental cholinergic denervation of the iris sphincter.

Treatment

Orthostatic hypotension, which is the most common problem in acute autonomic neuropathy, has two different forms of treatment; physical and pharmacologic. Physical forms of treatment include elevation of the upper part of the trunk and head at night. This apparently increases renin release and blood volume⁹⁵. Counter pressure stockings applied to the legs and lower part of the body decrease venous pooling in the legs⁹⁶. Pharmacologic treatments attempt to increase circulating blood volume to act as direct or indirect sympathomimetics and to increase arterial and venous tone directly. Fludrocortisone acetate is the most commonly used agent for treating orthostatic hypotension of all types^{97,98}. The most prominent effect is sodium retention with expansion of plasma volume. Serum catecholamine levels are not affected but pressor responsiveness to infused epinephrine is increased. This suggests that fludrocortisone increases receptor sensitivity to catecholamines. The initial dose is 0.1 mgm daily which may be gradually increased. Side effects of fludrocortisone include recumbent hypertension, congestive heart failure and hypokalemia⁹⁹. Sodium chloride tablets up to 8 gm. per day may also be added to increase plasma volume. Other therapeutic approaches have been suggested but have not been widely utilized. Ephedrine, a primarily indirect sympathomimetic, has limited effectiveness for post-ganglionic autonomic neuropathies in which little or no catecholamine stores are present peripherally¹⁰⁰. Indomethacin has been suggested to be of help due to its potential effects on prostaglandins but conflicting results have been reported with its use^{101,102}. Monoamine oxidase inhibitors in conjunction with tyramine have been tried but may lead to paroxysmal hypertension¹⁰³. Propanolol has been tried therapeutically with the rationale that it may prevent adre-

nergic mediated vasodilation resulting in unopposed vasoconstriction¹⁰⁴. L-dopa, a precursor to both dopamine and norepinephrine, has had limited use with variable results¹⁰⁵. Atrial tachypacing has been reported to help orthostatic hypotension in a few cases^{106,107}.

Ergot alkaloids are the most promising of the various pharmacologic agents suggested to be useful in the treatment of orthostatic hypotension, though clinical data is limited to case reports, and ergot toxicity has been reported with its use^{38,108}. Dihydroergotamine appears to be the safest of the ergot alkaloids, but is not available as an oral preparation¹⁰⁸.

Table #1

AUTONOMIC NEUROPATHY

Congenital:

Familial Dysautonomia

Hereditary Sensory Neuropathy with Anhidrosis

Congenital Cholinergic Dysautonomia

Hirschsprung's Disease

Porphyria

Fabry's Disease

Multiple Endocrine Neoplasia Type 2b

Familial Amyloidosis

Acquired:

Metabolic:

Diabetes Mellitus

Uremia

Amyloidosis

Alcohol associated Thiamine Deficiency

Idiopathic:

Shy-Drager Syndrome

Parkinson's Disease

Olivo-Ponto-Cerebellar Degeneration

Holmes Adie Syndrome

Idiopathic Orthostatic Hypotension

Neoplastic:

Autonomic Neuropathy as Remote Effect of Carcinoma

Eaton-Lambert Syndrome

Toxic:

Botulinum B

Tetanus

Vacor

Vincristine

Perihexilene Maleate

Neuroleptic Malignant Syndrome

Inflammatory:

Leprosy

Chagas Disease

Guillain-Barre Syndrome

Autoimmune:

"Acute Idiopathic Autonomic Neuropathy"

Autonomic Neuropathy associated with

Connective Tissue Disease

Table #2

ACUTE AUTONOMIC NEUROPATHY

Guillain-Barre Syndrome

Autoimmune

Vacor

Botulism B

Idiopathic

Porphyria (Variegate)

Diabetes Mellitus

Remote Effect of Carcinoma

Table #3

Guillain-Barre Associated Autonomic Disturbances

Hypertension 61 %

Orthostatic Hypertension 43 %

Abnormalities of Sweating 25 %

Sphincter Disturbances 30 %

Electrocardiogram

Abnormalities 64 %

Table #4

Vacor Associated Autonomic Disturbances

Orthostatic Hypotension without Reflex

Tachycardia

Pupillary Abnormalities

Urinary Retention

Ileus

Table #5

Medications Which Cause Transient
Autonomic Dysfunction

1. Sympatholytic Agents

2. Parasympatholytic Agents

3. Phenothiazine Derivatives

4. Tricyclic Antidepressants

5. Monoamine Oxidase Inhibitors

Table #6

Clostridial Botulinum B Associated
Autonomic Disturbances

Blurred Vision 100 %

Dry Mouth 100 %

Constipation 67 %

Dizziness 67 %

Table #7

ACUTE ACQUIRED AUTONOMIC NEUROPATHY

Author	Case	Age	Sex	Abnormalities				Therm
				GI	GU	PUP	CV	
Thomashefsky	1	6	F	+	+	+	—	—
Anderson	2	19	F	+	+	+	—	+
Young	3	49	M	+	+	+		+
Goulon	4	46	M	+	+	+	+	—
Wischer	5	47	F	+	+	+	+	+
Appenzeller	6	6	M	+		+	+	
Hopkins	7	28	F	+	—	+	+	—
Hopkins	8	12	F	+	+	+	—	+
Yahr	9	13	F	+	—	+	+	+
Okada	10	37	M	+	—	+	+	+
Okada	11	43	M	+	—	+	+	+
Yee	12	39	M	+	+	+	+	+
Colan	13	9	M	+	+	+	+	+
Dyck	14	46	F	+	+	+	+	+
Harik	15	9	M	+	+	+	—	+
Fujii	16	23	F	+	+	+	+	+
Low	17	79	F	+	+	+	+	—
Gudesblatt	18	21	F	+	+	+	+	—
Rubenstein	19	40	F	+	+	+	+	+

Table #8

NEUROPHARMACOLOGICAL EVALUATION OF
AUTONOMIC DYSFUNCTION

	DEFECTIVE MECHANISM	
	CENTRAL	PERIPHERAL
Plasma Norepinephrine		
supine	normal	low
erect	no change	no change
Blood Pressure		
Response to Infused NE		
gain threshold	increased normal	increased low
Response to Infused Tyramine		
plasma NE BP	normal elevated	depressed elevated

Table #9

PUPILLARY DISTURBANCES WITH AUTONOMIC DYSFUNCTION

	2.5% Methacholine	1% OHAmph	1% EPI	10% Cocaine	1/6% Pilocarpine
Normal	NR	D	NR	D	NR
Sympathetic Defect					
central	NR	D	NR	slD	NR
pre-ganglionic	NR	D	slD	NR	NR
post-ganglionic	NR	NR	promD	NR	NR
Parasympathetic Defect	C	D	NR	D	C

Pupillary Responses

D = Dilate sl = slight
 C = Constrict prom = prominent
 NR = No response

SUMMARY

The acute and subacute autonomic neuropathies consist of a variety of disorders which selectively affect the peripheral autonomic nervous system over a period of days to weeks. Most peripheral neuropathies affect not only motor and sensory fibers but autonomic fibers as well to varying degrees. This review focuses on a group of rare neu-

ropathies which have as their primary manifestation abnormalities of the autonomic nervous system. The varying presenting objective and subjective phenomenon and the differential diagnosis are discussed. Methods of evaluating autonomic dysfunction and treating orthostatic hypotension are reviewed.

RESUMEN

Las neuropatías autonómicas subagudas consisten en una variedad de desórdenes que afectan en forma selectiva el sistema nervioso autonómico periférico durante un período que oscila entre días y semanas. La mayoría de las neuropatías periféricas afectan no sólo fibras motoras y sensitivas, sino que también en un grado variable fibras autonómicas. Este estudio se refiere a un gru-

po de raras neuropatías que muestran como primera manifestación anormalidades en el sistema nervioso autonómico. Son considerados los variados fenómenos subjetivos y objetivos que se presentan el diagnóstico diferencial. Son estudiados métodos para evaluar la disfunción autonómica y tratamiento de la hipotensión ortostática.

RÉSUMÉ

Les neuropathies autonome acute et subacute comprend plusieurs sortes de maladies qui atteignent en preference le système peripheral nervous allant de quelques jours a quelques semaines. Le plupart des neuropathies peripheral atteint non seulement les fibres motor et sensory mais aussi les fibres autonomiques a des degres diffe-

rents. Cet article met en relief un groupe de neuropathies que se manifestent par l'autonomique système. Les differents diagnostique problemes et possibilités sont discutés. Les methodes d'évaluation du problème autonome et le traitement hypotension orthostatique sont discutés.

ZUSAMMENFASSUNG

Die akuten und subakuten autonomen Neuropathien setzen sich aus einer Vielfalt von Krankheitsbildern zusammen, die, über eine Zeitspanne von Tagen oder Wochen, spezifisch das periphere autonome Nervensystem befallen. Die meisten peripheren Neuropathien betreffen nicht nur motorische und sensorische Fasern, sondern in verschiedener Intensität auch autonome Fasern. Dieser Bericht befasst sich speziell mit

einer Gruppe seltener Neuropathien, die Beeinträchtigung des autonomen Nervensystems als ihre hauptsächliche Manifestation aufweisen. Die verschiedenen subjektiven Beschwerden und objektiven Befunde und ihre Differentialdiagnose werden diskutiert, und die Methoden zur Erfassung autonomer Dysregulation werden dargestellt.

REFERENCES

1. Appenzeller O.: Pure pandysautonomia - a newly discovered syndrome. *Calif. Med.* 1972; 117:18-23.
2. Bannister, R.: Degeneration of the autonomic nervous system. *Lancet* 1971; 1:175-9.
3. Editorial: The diagnosis of autonomic dysfunction. *Lancet* 1976; 1:1115-6.
4. Bronster D.J., Rudolph S., Shanzer S.: Pupillary light-near dissociation in cranial arteritis. *Neuro-Ophthalm* 1983; 3:65-70.
5. Ewing D.J.: Cardiovascular reflexes and autonomic neuropathy. *Clin. Sci. Mol. Med.* 1978; 55:321-7.
6. Gabella G.: Studies of the Autonomic Nervous System, London, Chapman Hall 1976; pp. 48-60.
7. Christie D.L., Knauss T.A.: Gastrointestinal manifestations of "acquired dysautonomic" syndrome. *J. Pediatr.* 1979; 94:625-8.
8. de Groat W.C., Booth A.M.: Physiology of male sexual function. *Ann. Intern. Med.* 1980; 92 (part. 2): 329-31.
9. Eisele J.H., Cross C.E., Rausch D.C.: Abnormal respiratory control in acquired dysautonomia. *N. Engl. J. Med.* 1971; 285:366-8.
10. de Groat W.C., Booth A.M.: Physiology of the urinary bladder and urethra. *Ann. Intern. Med.* 1980; 92 (part 2): 312-315.
11. Bradley W.E.: Autonomic neuropathy and the genitourinary system. *J. Urol.* 1978; 119:299-362.
12. Heath P.D., Moss C., Cartledge N.E.: Ross syndrome and skin changes. *Neurol.* 1982; 32:1041-2.
13. Young R.R., Asbury A.K., Corbett J.D., Adams R.D.: Pure pandysautonomia with recovery; description and discussion of diagnostic criteria. *Brain* 1975; 90:613-36.
14. Yee R.D., Trese M., Zee D.S.: Ocular manifestations of acute pandysautonomia. *Amer. Jour. Ophtha.* 1976; 81:740-4.
15. Shy G.M., Drager G.A.: A neurological syndrome associated with orthostatic hypotension: a clinical pathologic study. *Arch. Neurol.* 1960; 2:511-27.
16. Harik S.I., Ghandour M.H., Farah F.S.: Postganglionic cholinergic dysautonomia. *Ann. Neurol.* 1977; 1:393-6.
17. Thrush D.C.: Autonomic dysfunction in four patients with congenital insensitivity to pain. *Brain* 1973; 96:591-600.
18. Rubinstein A.E., Yahr M.D., Mytilineou C., Sivak M., et al.: Orthostatic hypotension in the Holmes-Adie syndrome. *Mt. Sinai J. Med.* 1980; 47:57-61.
19. Cohen A.S., Benson, M.D.: Amyloid Neuropathy (Chapter 53) in Dyck P.J., Lambert E.H., ed.: *Peripheral Neuropathy*. 1975, W.B. Saunders, Phila. Pa.
20. Thomas J.E., Schirger A.: Idiopathic orthostatic hypotension: A study of its natural history in 57 neurologically affected patients. *Arch. Neurol.* 1970; 22:289-93.
21. Low P.A., Thomas J.E., Dyck P.J.: The splanchnic autonomic outflow in Shy Drager syndrome and idiopathic orthostatic hypotension. *Ann. Neurol.* 1978; 4:511-4.
22. Schober R., Langston J.W., Forno L.S.: Idiopathic orthostatic hypotension: biochemical and pathological observations in 12 cases. *Europ. Neurol.* 1975; 13:177-88.
23. Chokroverty S., Barron K.D., Katz F.H.: The syndrome of primary orthostatic hypotension. *Brain* 1969; 92:743-68.
24. Duchon L.W., Anjorin A., Watkins P.J.: Pathology of autonomic neuropathy in diabetes mellitus. *Ann. Intern. Med.* 1980; 92 (part 2): 301-3.
25. Kersh E.S., Kronfield S.J., Unger A.: Autonomic insufficiency in uremia as a cause of hemodialysis induced hypotension. *N. Engl. J. Med.* 1974; 290:650-3.
26. Tyler H.R.: Uremic neuritis and the autonomic system. *N. Engl. J. Med.* 1974; 290: 685-6.
27. Stewart P.M., Hensley W.J.: An acute attack of variegated porphyria complicated by severe autonomic neuropathy. *Aust. N.Z. J. Med.* 1981; 11:82-3.
28. Ridley A.: Porphyric neuropathy (Chapter 46) in Dyck P.J., Lambert E.H., ed.: *Peri-*

- pheral Neuropathy. 1975, W.B. Saunder, Phil. Pa.
29. *Becker D.M., Kramer S.*: The neurological manifestations of porphyria: A review. *Medicine* 1977; 56:411-23.
 30. *Low P.A., Walsh J.C., Huang C.Y.*: The sympathetic nervous system in alcoholic neuropathy: A clinical and pathological study. *Brain* 1975; 98:357-64.
 31. *Fraser D.M., Campbell I.W., Miller H.C.*: peripheral and autonomic neuropathy after treatment with perhexilene maleate. *Brit. Med. J.* 1977; 2:675-6.
 32. *Caroff S.N.*: The neuroleptic malignant syndrome. *J. Clin. Psych.* 1980; 41:79-83.
 33. *Casey E.B., Jelliffe A.M., LeQuessne P.M.*: Vincristine neuropathy: clinical and electrophysiological observations. *Brain* 1973; 96:69-86.
 34. *Carmichael S.M., Eagleton L., Ayers C.R.*: Orthostatic hypotension during vincristin therapy. *Arch. Intern. Med.* 1976; 196:290-3.
 35. *Rosenthal S., Kaufman S.*: Vincristin neurotoxicity. *Ann. Intern. Med.* 1978; 80:733-7.
 36. *Kaplan R.S., Wiernik P.H.*: Neurotoxicity of antineoplastic drugs. *Seminars* 1982; 9:103-130.
 37. *Ewing D.J., Campbell I.W., Clarke B.F.*: The natural history of diabetic autonomic neuropathy. *Quart. J. Med.* 1980; 49:95-108.
 38. *Mindel J.S., Rubinstein A.E., Franklin B.*: Ocular ergotamine tartrate toxicity during treatment of vacor induced orthostatic hypotension. *Amer. J. Ophth.* 1981; 92:492-6.
 39. *Levy R.L.*: Panautonomic dysfunction and guillain bare syndrome. *JAMA* 1980; 243:1895-6.
 40. *Birchfield R.I., Shaw C.M.*: Postural hypotension in the Guillain-Barre syndrome. *Arch. Neurol.* 1964; 10:149-57.
 41. *Lichtenfield P.*: Autonomic dysfunction in the Guillain-Barre syndrome. *Am. J. Med.* 1971; 50:772-80.
 42. *Tuck R.R., McLeod J.G.*: Autonomic dysfunction in the Landry-Guillain-Barre syndrome. *Clin. Exp. Neurol.* 1978; 15:197-203.
 43. *Matsuyama H., Haymatieu W.*: Distribution of lesions in the Landry-Guillain-Barre syndrome with emphasis on involvement on the sympathetic system. *Acta Neuropathologica* 1967; 8:230-41.
 44. *Edmonds M.E., Sturrock R.D.*: Autonomic neuropathy in the Guillain-Barre syndrome. *Brit. Med. J.* 1979; 2:668.
 45. *Tuck R.R., Pollard J.D., McLeod J.G.*: Autonomic neuropathy in experimental allergic neuritis. *Brain* 1981; 104:187-208.
 46. *Goulon M., Novilhart F., Babinet P.*: La dysautonomie des polyradiculoneurites. *Aigues Primitives. Rev. Neurol.* 1975; 131:95-119.
 47. *Chiappa K.H., Young R.R.*: A case of paraneoplastic pandygaunomia. *Neurol.* 1973; 23:423.
 48. *Thomas J.P., Shields R.*: Associated autonomic dysfunction and carcinoma of the pancreas. *Brit. Med. J.* 1970; 14:32.
 49. *Carr-Locke D.*: Autonomic neuropathy and inappropriate secretion of antidiuretic hormone: occurrence in a patient with Brochogenic carcinoma. *JAMA* 1979; 241:2298.
 50. *Vasudevan C.P., Suppiah P., Udoshi M.*: Reversible autonomic neuropathy and hypertrophic osteoarthopathy in a patient with brochogenic carcinoma. *Chest* 1981; 79:479-81.
 51. *Victor D.J., Green W.R., Stark W.J., Walsh F.B.*: A non-permanent tonic pupil in rheumatoid arthritis. *Can. D. Sciences Neurol.* 1977; 4:209-12.
 52. *Edelman J., Gubbay S.S., Zilko P.J.*: Acute pandysautonomia due to mixed connective tissue disease. *Aust. N.Z.J. Med.* 1981; 11:68-70.
 53. *Edmonds M.E., Jones T.C., Saunders W.A.*: Autonomic neuropathy in rheumatoid arthritis. *Brit. Med. J.* 1979; 2:173-5.
 54. *Gudesblatt M.S., Goodman A.D., Rubinstein A.E., Bender A.N.*: Autonomic Neuropathy in autoimmune disease. *Neurology* 1987; 33 (4) Suppl. 2:72.
 55. *Pont A., Rubino J.M., Bishop D.*: Diabetes mellitus and neuropathy following vacor ingestion in man. *Arch. Intern. Med.* 1979; 139:185-7.
 56. *LeWitt P.A.*: The neurotoxicity of the erat poison vacor: A clinical study of 12 cases. *N. Engl. J. Med.* 1980; 302:73-77.
 57. *Gallarosa A.G., Spyker D.A., Carnow R.T.*: Diabetes mellitus associated with autonomic and peripheral neuropathy after vacor rodenticide poisoning: A review. *Clin. Toxicol.* 1981; 18:441-9.
 58. *Hines S., Houston M., Robertson D.*: The clinical spectrum of autonomic dysfunction. *Am. J. Med.* 1981; 70:1091-6.
 59. *Wichser J., Vijayan N., Dreyfus P.M.*: Dysautonomia-its significance in neurologic disease. *Calif. Med.* 1971; 117:28-37.
 60. *Jenzer G., Numenthaler M., Ludin H.P.*: Autonomic dysfunction in botulism B: A clinical report. *Neurol.* 1975; 25:150-3.
 61. *Kerr J.H., Travis K.W., O'Rourke R.A.*: Autonomic complications in case of severe tetanus. *Am. J. Med.* 1974; 57:303-10.
 62. *Corbett J.L., Spalding J.M.K., Harris P.J.*: Hypotension in tetanus. *Brit. Med. J.* 1973; 2:423-8.
 63. *Young R.R., Asbury A.K., Adams A.D.*: Pure pandysautonomia with recovery. *Trans. Amer. Neurol. Assn.* 1969; 355-7.
 64. *Thomashefsky A.J., Horowitz S.J., Feingold M.H.*: Acute autonomic neuropathy. *Neurol.* 1972; 22:251-5.
 65. *Anderson O., Lindberg J., Modigh K.*: Subacute dysautonomia with incomplete recovery. *Acta Neurol Scan* 1972; 48:510-9.
 66. *Appenzeller O., Kornfeld M.*: Acute pandysautonomia: Clinical and morphologic study. *Arch. Neurol* 1973; 29:334-9.
 67. *Hopkins A., Neville B., Bannister R.*: Autonomic neuropathy of acute onset. *Lancet*

- 1974; 1:769-71.
68. *Yahr M.D., Frontera A.T.*: Acute autonomic neuropathy: its occurrence in infectious mononucleosis. *Arch. Neurol.* 1975; 32:132-3.
69. *Fujii N., Tabira T., Shibushak H.*: Acute autonomic neuropathy associated with elevated Epstein-Barr virus antibody titer. *J. Neurol. Neurosurg. Psych.* 1981; 45:656-661.
70. *Okada F., Yahashita I., Suwa N.*: Two cases of acute pandysautonomia. *Arch. Neurol.* 1975; 32:146-51.
71. *Colan R.V., Snead O.C., Oh S.J.*: Acute autonomic and sensory neuropathy. *Ann. Neurol.* 1982; 12:78.
72. *Low P.A., Dyck P.J., Lambert E.M.*: Acute pandysautonomia. *Ann. Neurol.* 1982; 12:78.
73. *Low P.A., Dyck P.J., Lambert E.H., Brimjoin W.S., Trautman J.C.*: Acute panautonomic neuropathy. *Ann. Neurol.* 1983; 13:412-7.
74. *Gudesblatt M.S., Rubinstein A.E.*: (unpublished observations).
75. *Appenzeller O., Arnason B.G., Adams R.D.*: Experimental autonomic neuropathy: An immunologically induced disorder of reflex vasomotor function. *J. Neurol. Neurosurg. Psych.* 1965; 28:510-5.
76. *Braham J., Sadeh M., Garova-Pinhas I.*: Skin wrinkling on immersion of hands: a test of sympathetic function. *Arch. Neurol.* 1979; 36:113-4.
77. *Editorial*: Diagnosis of autonomic neuropathy. *Brit. Med. J.* 1978; 2:910-11.
78. *Ewing D.J., Campbell I.W., Clarke B.F.*: Assessment of cardiovascular effects in diabetic autonomic neuropathy and prognostic implications. *Ann. Intern. Med.* 1900; 92 (part 2): 308-11.
79. *Watkins P.J., Mackay J.D.*: Cardiac denervation in diabetic neuropathy. *Ann. Intern. Med.* 1980; 92 (part 2): 304-7.
80. *Khurana R.K., Watibiki S., Hebel J.R.*: Cold face test in the assessment of trigeminal-brainstem-vagal functions in humans. *Ann. Neurol.* 1980; 7:144-9.
81. *Bannister R., Sever P., Gross M.*: Cardiovascular reflexes and biochemical responses in progressive autonomic failure. *Brain* 1977; 100:327-44.
82. *Bannister R., Davies B., Holly E.*: Defective cardiovascular reflexes and supersensitivity to sympathomimetic drugs in autonomic failure. *Brain* 1979; 102:163-76.
83. *Petito C.K., Black B.*: Ultrastructure and biochemistry of sympathetic ganglia in idiopathic orthostatic hypotension. *Ann. Neurol.* 1978; 4:6-17.
84. *Black I.B., Petitto C.K.*: Catecholamine enzymes in the degenerative neurological disease idiopathic orthostatic hypotension. *Science* 1976; 192:910-2.
85. *Low P.A., Walsh J.C., Huang C.Y.*: The sympathetic nervous system in diabetic neuropathy: A clinical and pathological study. *Brain* 1975; 98:341-56.
86. *Ziegler M.G., Kopin I.J., Lake C.R.*: The sympathetic nervous system defect in primary orthostatic hypotension. *N. Engl. J. Med.* 1977; 296:293-7.
87. *Ziegler M.R., Lake C.R., Kopin I.J.*: Deficient sympathetic nervous response in familial dysautonomia. *N. Engl. J. Med.* 1976; 94:630-3.
88. *Kontos H.A., Richardson D.W., Norrell J.E.*: Norepinephrine depletion in orthostatic hypotension. *Ann. Intern. Med.* 1975; 82:336-41.
89. *Kopin I.J., Lake C.R., Ziegler M.R.*: Plasma levels of norepinephrine. *Ann. Intern. Med.* 1978; 88:671-80.
90. *Cryer P.E., Silverberg A.B., Santiago J.V.*: Plasma catecholamines in diabetes: the syndromes of hypoadrenergic and hyperadrenergic postural hypotension. *Am. J. Med.* 1978; 64:407-16.
91. *Polinsky R.J., Kopin I.J., Ebert M.H.*: Pharmacologic distinction of different orthostatic hypotension syndromes. *Neurol.* 1981; 31:1-7.
92. *Abbruzzese J.L., Griffin J.N.*: Clinical conference: postural hypotension. *Johns Hopkins Med. J.* 1981; 148:127-31.
93. *Smith S.E., Smith S.A., Brown P.M.*: Pupillary signs in diabetic autonomic neuropathy. *Brit. Med. J.* 1978; 2:924-7.
94. *Maloney W.F., Younge B.R., Moyer N.J.*: Evaluation of the causes and accuracy in pharmacologic localization in Horner's syndrome. *Am. J. Ophthalmol.* 1980; 90:394-402.
95. *Kallay K., Benscouth P.*: Idiopathic orthostatic hypotension: pathophysiological observations with special reference to the renal handling of sodium. *Cardiology* 1976; 61 (Suppl. 1): 168-80.
96. *Sheps S.G.*: Use of an elastic garment in the treatment of orthostatic hypotension. *Cardiology* 1976; 61 (Suppl. 1): 145-67.
97. *Thomas J.E., Schirger A., Fealey R.D.*: Orthostatic hypotension. *Mayo Clin. Proc.* 1981; 566:117-25.
98. *Schatz I.J., Miller M.J., Frome B.*: Corticosteroids in the management of orthostatic hypotension. *Cardiology* 1976; 61 (Suppl. 1):280-9.
99. *Chobanian A.V., Volicer L., Tift C.P.*: Mineralocorticoid induced hypotension in patients with orthostatic hypotension. *N. Engl. J. Med.* 1979; 301:68-73.
100. *Schatz I.J.*: Current management concepts in orthostatic hypotension. *Arch. Intern. Med.* 1980; 140:1152-4.
101. *Kocher M.S., Itskovitz H.D.*: Treatment of idiopathic orthostatic hypotension with indometracin. *Lancet* 1978; 1:1011-4.
102. *Bannister R., Davies B., Sever P.*: Indometracin for Shy-Drager syndrome. *Lancet* 1978; 1:1312.
103. *Nanda R.N., Johnson R.H., Keogh H.J.*: Treatment of neurogenic orthostatic hypotension with a monoamine oxidase inhibitor and tyramine. *Lancet* 1976; 2:1164-7.
104. *Chobanian A.V.*: Use of propranolol in the

- treatment of idiopathic orthostatic hypotension. Clin. Res. 1977; 25:513A.
105. *Steiner J.A., Low P.A., Huang C.Y.*: L-Dopa and the Shy-Drager syndrome. Med. J. Aust. 1974; 2:1336.
 106. *Moss A.J., Glaser W., Topol E.*: Atrial tachypacing in the treatment of a patient with primary orthostatic hypotension. N. Engl. J. Med. 1980; 302:1456-7.
 107. *Goldberg M.R., Robertson R.M., Robertson D.*: Atrial tachypacin for primary orthostatic hypotension. N. Engl. J. Med. 1980; 303: 885-6.
 108. *Sturmer E.*: Pharmacologic basis of the treatment of orthostatic disorders with ergot alkaloids. Cardiology 1976; 61 (Suppl. 1): 290-301.

Polyneuropathy During Perhexiline Maleate Therapy

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Since the initial report by Hirshleifer⁽¹⁵⁾ in 1969, perhexiline maleate (P.M.) has been widely and successfully used in the treatment of angina pectoris. Minor side effects, predominantly dizziness headache and nausea, are frequent during the first month of treatment, particularly with high doses. Weight loss, anorexia and impotence are less common and usually occur with prolonged treatment⁽²⁵⁾. Abnormalities of lipid metabolism with increased triglycerides⁽¹⁸⁾ and of liver function tests⁽²⁸⁾ are frequent. Hypoglycemia⁽¹²⁾ and acute toxic hepatitis⁽¹⁴⁾ are uncommon but can be very serious.

The first report of peripheral neuropathy during P.M. therapy was published in 1973⁽¹⁾ and since then the number of case reports has rapidly increased. At a recent meeting on P.M., Laplane et al. (1976)⁽¹⁷⁾ discussed 35 cases which had been either published^(5,6,7,20,32) or notified to the pharmaceutical firm. This figure is certainly inferior to the actual number of cases since most cases now seen in neurological departments are no longer published. Nevertheless, the incidence of peripheral neuropathy remains probably low compared to the wide diffusion of the drug.

P.M. neuropathy is most unusual for a drug induced neuropathy in that it is a polyradiculoneuropathy, i.e. a diffuse demyelinating polyneuropathy with increased CSF protein⁽⁷⁾.

Modes of evolution

Symptoms develop slowly 3 weeks to 3

years after starting treatment. High doses of P.M. are usually responsible: doses of 300 mg/daily are encountered in 70% of cases, but the neuropathy can occur with doses of 200 mg and even of 150 mg daily. There is no relationship between the time and mode of onset and the daily dose⁽¹⁷⁾.

Symptoms gradually increase as long as the drug is administered.

15 days at least after the withdrawal of the drug, symptoms start to improve. They decrease slowly and disappear in a very variable length of time (a few weeks to more than two years), but it is too early yet to be sure that all cases will make a total recovery. There is no relationship between the rapidity of onset of the neuropathy and the rate of improvement.

Clinical picture

The first symptoms are paresthesiae and weakness in the legs with difficulties in walking. These symptoms are almost invariably accompanied by a prominent weight loss.

Paresthesiae usually affect the legs first, then the hands in a "glove and stocking" distribution. Facial and trunkal paresthesiae are very uncommon. Paresthesiae consist of unpleasant and sometimes painful sensations of tingling, pins and needles, burning, coldness, numbness or "deadness".

Weakness also affects the legs first and then spreads to the upperlimbs. Weakness and loss of proprioceptive sensation explain the high incidence and the great variety of gait troubles at the early stage of the disease^(7,17).

The clinical picture is that of a diffuse, usually symmetrical, proximal and/or distal sensory-motor polyneuropathy.

There is a wide variation in the severity of muscular weakness. In the mildest cases, the weakness affects predominantly the hip girdle musculature, in a "pseudo-myopathic" way⁽⁹⁾. More often, the distal musculature is also involved, and when the disease is more severe, proximal and then distal muscles of the upper limbs become involved (2/3 of cases)⁽¹⁷⁾. Trunkal muscles may be affected whereas cranial nerves are usually spared. Muscle wasting may appear extremely rapidly and fasciculations are seen in some cases⁽⁷⁾.

Tendon reflexes are absent in almost all cases (31 out of 33)⁽¹⁷⁾. Ankle and Knee jerks are the earliest to be affected but in many cases all the tendon jerks are lost or much reduced. Only rarely (2 cases out of 33) are the reflexes absent in the upper limbs and present in the lower limbs⁽¹⁷⁾.

Muscular weakness and loss of tendon jerks are usually symmetrical but some degree of asymmetry can be seen. In one case there was a bilateral symmetrical proximal weakness in the lower limbs and a weakness limited to left proximal group (deltoid, serratus anterior, and biceps brachialis) in the upper limbs⁽²⁷⁾. In another case, weakness was limited to the anterior tibial muscles and peronei on the left and to the distal muscles of the right hand; all tendon reflexes but the left knee jerk were absent⁽¹⁰⁾.

Sensory symptoms occur in nearly all cases (33 out of 35)^(7,17). All forms of sensation are usually affected although proprioceptive sensation is most commonly impaired. We have seen only one case in which sense of position, appreciation of passive movement, appreciation of vibration, tactile discrimination and stereognosis were normal⁽³²⁾. Two such cases have recently been published in the french literature^(2,3). Superficial pain and appreciation of temperature are less frequently impaired. The lower limbs tend to be involved first and the impairment is most marked in the distal parts of the limbs.

Papilloedema is present in about 20% of cases, usually without any impairment of

vision^(7,17). Nevertheless one case has been described with a gross papilloedema and a loss of vision leading to an atrio-ventricular shunting; CSF protein was extremely high: 8,35 g/l⁽³³⁾. Whenever there is a papilloedema, CSF protein is always increased above 1g/l and papilloedema seems to be related to an impairment in CSF resorption, as it is supposed to be in Guillain Barré syndrom.

Neurologic examination is usually otherwise normal. However some cases of peripheral neuropathies have been associated with dysarthria and deafness⁽¹¹⁾, Parkinsonism⁽⁵⁾, mental disturbances and cerebellar signs⁽²⁾. The presence of an action tremor in the absence of any extrapyramidal or cerebellar sign, is fairly common^(3,7). It is similar to that observed in other forms of peripheral neuropathies, such as some cases of Guillain Barré syndrom and of familial neuropathies.

A case of proximal myopathy has been recently reported in the absence of peripheral nerve involvement⁽³¹⁾. This only case is very unusual in its rapidity of onset (2 weeks after starting the treatment) and in its association with a generalised rash.

General examination usually discloses a weight loss which can sometimes be extremely severe: 36 Kg in one of our cases⁽⁷⁾. The cause of this weight loss is still unknown: a diuretic effect and a loss of appetite have been incriminated⁽¹³⁾.

Liver damage was the next most frequent side effect. Most patients (more than 2/3) showed some abnormalities of liver function tests, predominantly an increase in serum transaminase levels and a decrease in bromsulphthalein (BSP) excretion^(7,17). In some cases, liver damage is more severe and leads to a subacute toxic hepatitis^(1,14) or even to a cirrhosis⁽²³⁾.

Other side effects may be present: an increase in erythrocyte sedimentation rate is common⁽⁷⁾, an increase in triglycerides is less common, and a hypoglycemia is very rare.

Cerebrospinal fluid

An increase of the total protein content is extremely frequent (27 out of 28 cases)⁽¹⁷⁾. Though usually moderate (0,52 to

1 g/l), the rise in CSF protein may be extremely marked (up to 17 g/l.)⁽³³⁾. Globulin content and electrophoresis, glucose and chlorides are normal. Cells are usually absent but in about a third of cases there is a moderate increase in the number of lymphocytes (up to 20 cells per mm³).

Electromyography (EMG)

The EMG changes in P.M. neuropathy are in no way specific, representing those seen commonly in peripheral neuropathy. The main abnormality is a reduction of motor unit activity with frequent interference patterns. Fibrillation is scanty and polyphasic units are frequent.

In a study of 23 cases of P.M. neuropathies, Bouche (1977)⁽⁴⁾ found 1) fibrillation potentials and large motor unit action potentials in 3 cases 2) an interference pattern with increased frequency of action potentials in 11 cases 3) of which with polyphasic units 3) an interference pattern alone in 9 cases, 4 of which with polyphasic units. The same findings have recently been observed in 4 other cases⁽³⁾.

Motor and sensory nerve conduction velocity is almost invariably impaired^(7,17). This reduction may be very marked, with velocities sometimes as low as 10 m/sec. Ulnar nerve motor conduction velocity was decreased in 22 out of 23 cases, and common peroneal in 17 out of 21 cases. Terminal latencies are increased in most patients. In only one case was there no impairment of either the conduction velocity or the terminal latency. The global action potential velocity is reduced in all 10 cases which have been studied⁽⁴⁾.

The slowing of conduction velocity is related to segmental demyelination and bears no prognostic value. On the contrary, the presence of fibrillations at test, which is related to axonal degeneration, carries a bad prognosis. In one such case, there has been very little improvement one year after the drug was discontinued⁽⁴⁾. There is usually a delay between the clinical improvement and the increase in nerve conduction velocities as commonly seen in Guillain Barré syndrome.

Attempts have been made to detect peripheral nerve involvement before the onset

of symptoms: Penther (1977)⁽²⁴⁾ has found in 13 cases out of 18, a slowing of nerve conduction in the absence of peripheral neuropathy and he suggests that the measurement of H wave latency could have a good predictive value. On the contrary, Bouche out of 20 asymptomatic patients taking about 200 mg daily for 3 months to 2 years, could not find a significant decrease in motor conduction velocity^(4,17).

The only patient who had a slowed conduction was also diabetic. H Wave latency was normal in all 10 cases studied. In our opinion, the measurement of nerve conduction velocity has no predictive value as to whether the patient is going to develop a peripheral neuropathy or not. It is easier and probably safer to make an early detection of the first clinical symptoms i.e. paresthesiae and, if they occur, to reduce or stop the drug.

Pathology

Under light microscope, the pathological findings are 1) a muscular denervation atrophy with groups of small fibres with dark clustered nuclei 2) a decrease in the number of large myelinated fibres. In only one case, quantitative studies showed a decrease in the total number of myelinated fibres⁽²²⁾. Longitudinal sections and teased preparations show evidence of segmental demyelination⁽²⁰⁾. Immunofluorescences fails to reveal deposits of specific globulins⁽³⁾. There is no lymphoid cellular infiltration.

Electron microscopy confirms the predominant schwannian degeneration with a few onion bulbs formation. A minor degree of wallerian degeneration is seen in some cases in addition to segmental demyelination⁽²²⁾. Evidence of a process repair with remyelination is often noticed, leading to the presence of lesions of varying ages. The most striking feature is the presence in the nerve of polymorphous membrane bound inclusions^(7,8,20,22). These inclusions are abundant in Schwann cells and are also seen in fibrocytes, endothelial and pericytic cells. They are also found in other tissues, such as muscle (in muscular cells as well as in endothelial and pericytic cells) and skin (in endothelial, smooth muscle and Sweat gland cells⁽²²⁾). These inclusions are

polymorphous: some resemble multilamellated bodies others have a regular, crystalline like pattern on which small dense particles are often superimposed; a few others have a dense homogenous appearance^(20,22).

Discussion

In the initial cases, peripheral neuropathy was attributed to P.M. because of 1) the absence of other cause, 2) the occurrence during treatments by P.M. which was the only drug shared in common by all patients 3) the progressive deterioration as long as the drug was given, 4) the presence of a weight loss which is a known side effect of the drug 5) the improvement after the withdrawal of the drug⁽⁷⁾. The responsibility of the drug has now been widely confirmed by the accumulation of cases^(2,3,9,10,11,20,27,32,33).

The clinical picture is strikingly uniform: it is that of a polyradiculoneuropathy since it includes 1) a diffuse sensorimotor neuropathy, 2) a predominantly demyelinating lesion, as shown by the decrease in nerve conduction velocity and the histological pattern, 3) an increased CSF protein level, with a moderate or absent hypercytosis. This polyradiculoneuropathy differs from Guillain-Barré Syndrom in that it is slowly progressive and improves only when the drug is stopped. It bears a resemblance to some chronic inflammatory polyradiculoneuropathies and to some of the neuropathies associated with paraproteinemias, dysproteinemias, diabetes, cancers, systemic lupus erythematosus, sarcoidosis and malignant reticulosos. On the contrary, P.M. neuropathy differs widely from neuropathies due to other drugs such as disulfiram, isoniazid, nitrofurantoin, vincristine and diphenylhydantoin. The majorities of these neuropathies are characterised by a predominant axonal degeneration due either to a direct toxic effect of the drug (vincristine) or to a vitamin deficiency such as pyridoxine deficiency in isoniazid neuropathy⁽¹⁹⁾. The importance of demyelination in P.M. neuropathy suggests a completely different mechanism.

The exact mechanism of the P.M. induced neuropathy is at present unknown:

— The severe demyelination, with rela-

tive axonal preservation, resembles that of diphtheritic neuropathy and suggests a toxic or metabolic disturbance in Schwann cells. If this is the case, it is possible that the drug toxicity is increased by a perturbation in its metabolism. The major biotransformation takes place in the liver and consists of a hydroxylation leading to mono (M_1 and M_3), and dihydroxylated (D_1 D_2 D_3) metabolites. Excretion occurs via urine and feces with approximate half lives ranging from 3-12 days after a single dose⁽³⁴⁾. More recent studies have shown the existence of 2 different populations: the "normal" and the "slow" metabolizers⁽³⁵⁾. The slow metabolizers are characterised by:

- 1) a plasmatic PM/ M_1 ratio >2
- 2) a urinary M_1/M_3 ratio $<0,4$
- 3) a highly increased half life, sometimes as high as several months. 15 to 20% of the North american population are "slow" metabolizers. This proportion is not known for the french population, but it is interesting to note that, among 21 cases of PM induced neuropathies, there were 70% "slow" metabolizers⁽²⁹⁾. Furthermore, most of those who were "normal" metabolizers had drug levels in the blood which exceeded by far the therapeutical levels (ranging from 0,50 to 2 $\mu\text{g/ml}$). These high levels were due either to excessive doses or to hepatic or renal insufficiency. In these last two cases, P.M. half-life was longer than 10 days⁽²⁹⁾. These results suggest that P.M. neuropathy is induced by an excessive drug level due either to physiologically slow metabolism or to an overdosage and/or an hepatic or renal insufficiency.

— The prominent demyelination together with the presence of polymorphous inclusions suggest a disturbance of lipid metabolism close to that observed in some experimentally induced lipid storage diseases^(21,30). This disturbance seems to be confirmed by recent biochemical studies of liver and peripheral nerve samples. These studies showed 1) in liver, an accumulation of phospholipid and in one case, of gangliosides⁽¹⁶⁾ 2) in peripheral nerve, an accumulation of gangliosides but no increase in phospholipids⁽²⁶⁾. Thus phospholipid modifications are different in liver and peripheral nerve whereas ganglioside pertur-

bations are found in both tissues; this suggests that ganglioside storage is the most specific biochemical disturbance observed in liver damage and in peripheral neuropathies induced by P.M. Whether this perturbation of lipid metabolism is induced by the drug itself or reveals an inborn lipid storage di-

sease unmasked by the drug, is at present unknown.

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SUMMARY

Since the initial report by Hirshleifer, perhexiline maleate has been widely and successfully used in the treatment of angina pectoris.

The first report of peripheral neuropathy during perhexiline maleate therapy was published in 1973.

Symptoms develop slowly 3 weeks to 3 years after starting treatment. The first symptoms are paresthesias and weakness in the legs with difficulties in walking. These symptoms are almost invariably accompanied by a prominent weight loss.

Sensory symptoms occur in nearly all cases. All forms of sensation are usually affected although proprioceptive sensation is most commonly impaired.

Papilloedema is present in about 20% of cases, usually without any impairment of vision.

General examination usually discloses a weight loss which can sometimes be extremely severe.

Liver damage was the next most frequent side effect.

In cerebrospinal fluid an increase of the total protein content is extremely frequent.

The EMG changes in perhexiline maleate neuropathy represent those seen commonly in peripheral neuropathy.

Motor and sensory nerve conduction velocity is almost invariably impaired. It is safe to make an early detection of the first clinical symptoms if they occur to reduce or stop the drug.

Anatomically the severe demyelination with relative axonal preservation resembles that of diphtheritic neuropathy and suggests a toxic or metabolic disturbance in Schwann cells.

Perhexiline maleate neuropathy is induced by an excessive drug level due either to physiologically slow metabolism or to an overdosage and or an hepatic or renal insufficiency. Gangliosid storage is the most specific biochemical disturbance observed in liver damage and in peripheral neuropathies induced by Perhexiline maleate.

RESUMEN

Desde la comunicación inicial realizado por Hirshleifer perhexiline maleate ha sido usada en muchos casos y con éxito en el tratamiento del angor pectoris.

El primer comunicado de la existencia de una neuropatía periférica durante la terapia con perhexiline maleate fue publicado en 1973.

Los síntomas se van desarrollando lentamente de 3 semanas a 3 años de comenzar el tratamiento. Los primeros síntomas son parestesias y debilidad en las piernas con dificultades para caminar. Estos síntomas

son casi invariablemente acompañados por una prominente pérdida de peso.

Síntomas sensitivos ocurren en casi todos los casos. Todas las formas de sensaciones son habitualmente afectadas, siendo la sensibilidad propioceptiva la que se afecta con más frecuencia.

Se hace presente un edema de papila en el 20% de los casos aunque sin que la visión esté perturbada.

El examen general habitualmente evidencia una pérdida de peso, la cual a veces es muy severa.

El daño hepático es el que le sigue en frecuencia como efecto pernicioso.

Con mucha frecuencia se observa un aumento en el nivel de proteína en el líquido céfaloorraquídeo.

Las modificaciones EMG en neuropatía de perhexiline maleate representan aquellas vistas por lo general en la neuropatía periférica.

La velocidad de conducción nerviosa motora y sensitiva se muestra casi siempre afectada.

Es muy importante por la seguridad que brinda hacer una detección temprana de los primeros signos clínicos. Si ellos ocurren

para reducir o no emplear la droga. Anatómicamente la demielinización severa con una relativa prenervación axonal se asemeja a la que ocurre en la neuropatía diftérica y sugiere un disturbio tóxico o metabólico en las células de Schwann.

La neuropatía de perhexiline maleate es inducida por un excesivo nivel de droga debido sea a un metabolismo fisiológico lento o a una sobredosificación y/o a una insuficiencia renal o hepática. Depósito de gangliosido es el disturbio bioquímico más específico observado en el daño hepático y en las neuropatías periféricas inducidas por perhexilene maleate.

RÉSUMÉ

Depuis la première communication faite par Hirshleifer, le perhexiline maleate a été employé dans de nombreux cas et avec succès dans le traitement de l'angor pectoris. La première communication relative à l'existence d'une neuropathie périphérique au cours de la thérapie avec le perhexiline maleate a été publiée en 1973.

Les symptômes se développent lentement, de 3 semaines à 3 ans après le début du traitement. Les premiers symptômes sont parasthésie et faiblesse dans les jambes avec difficulté pour marcher. Ces symptômes sont presque toujours accompagnés de perte de poids.

Des symptômes sensitifs apparaissent dans presque tous les cas. Toutes les formes de sensations sont habituellement affectées, la sensibilité proprioceptive étant celle qui apparaît le plus souvent.

On remarque un oedème de la papille dans 20% des cas sans que la vision soit perturbée.

Un examen général met en évidence une perte de poids parfois très sévère. L'altération du foie est ce qui apparaît ensuite en

fréquence comme pernicieuse. On observe aussi, souvent, une augmentation dans le taux de protéines dans le liquide céphalo rachidien.

Les modifications EMG en neuropathie, dues à la perhexiline maleate, sont de neuropathie périphérique.

La vitesse de conduction nerveuse et sensitive est presque toujours affectée. Il est très important, à cause de la sécurité qu'elle donne, de faire une détection rapide des premiers signes cliniques. Anatomiquement la démyélinisation sévère, avec une relative préservation axonale, ressemble à celle qui se produit dans la neuropathie diphtérique et suggère un trouble toxique ou métabolique dans la gaine de Schwann.

La neuropathie du perhexiline maleate est produite par un excès de drogue dû soit à un métabolisme physiologique lent ou à une trop forte dose et/ou à une insuffisance rénale ou hépatique. Un dépôt de ganglioside est le trouble biochimique le plus spécifique dans l'affection hépatique et dans les neurones périphériques atteints par le perhexiline maleate.

ZUSAMMENFASSUNG

Seit der Initialkommunikation von Hirshleifer, Perhexilin maleate ist in vielen Fällen und mit Erfolg bei der Behandlung von Angina pectoris angewandt worden. Der erste Bericht von der Existenz einer peripheren Neuropathie während der Behan-

dlung mit Perhexilin maleate wurde 1973 mitgeteilt.

Die Symptome entwickeln sich langsam zwischen 3 Wochen bis 3 Jahren seit Beginn der Behandlung. Die ersten Symptome sind Parestesie und Schwäche in den Bei-

nen mit Schwierigkeiten zu gehen. Diese Symptome sind unveränderlich begleitet von einem prominenten Gewichtsverlust. Sensitive Symptome finden sich in fast allen Fällen. Alle Formen von Sensationen sind gewöhnlich affektiert, wobei die proprioceptive Sensibilität die am häufigsten affektierte ist.

Es bildet sich ein Ödem der Pupille in 20% der Fälle, auch ohne dass die Vision geschädigt ist.

Die Generaluntersuchung zeigt gewöhnlich einen Gewichtsverlust, der oftmals sehr ernst ist.

Der Leberschaden ist der mit Häufigkeit als perniziöser Effekt folgt.

Sehr oft bemerkt man eine Erhöhung des Proteinniveaus in dem Liquido encephalo-rachidico.

Die Modifikationen EMG bei Neuropathien durch Perhexilin maleata zeigen die im allgemeinen bei peripheren Neuropathien vorhandenen. Die Geschwindigkeit

der motorischen und sensitiven Konduktion ist fast immer affektiert.

Es ist sehr wichtig für die Sicherheit eine frühe Detektion der ersten klinischen Anzeichen zu machen, wenn diese sich zeigen, um die Droge zu reduzieren oder nicht anzuwenden. Anatomisch gleicht die schwere Demyelinisation, mit einer relativen Präervation axonal, der bei der diabetischen Neuropathie und suggeriert ein toxisches oder suerabolisches Stören in den Schwannschen Zellen.

Die Neuropathie von Perhexilin maleata ist durch eine exsive Höhe der Droge induziert in Folge eines langsamen physiologischen Metabolismus oder wegen einer Überdosierung und/oder einer renalen oder hepatischen Insuffizienz. Deposition von Gangliosiden ist die Störung biochemischer Art, die am spezifischsten beim Leberschaden und bei den peripherischen Neuropathien durch Perhexilin maleata beobachtet wurde.

REFERENCES

1. Abaza A., Cattani D., Aziza Cl., Pappo E.: Effets secondaires mais réversibles à la prise de perhexiline. *Nouv. Presse méd.* 1973, 2, 2820.
2. Arnott G., Masingue M., Berenchein-Forrier S., Hache J-C., Boulenger-Beaussart L., Michaux F.: Polyradiculonévrite, manifestations cérébelleuses, tremblement parkinsonien, oedème papillaire et hémorragies au fond d'oeil au cours d'un traitement par le maléate de perhexiline. *Lille médical*, 1977, 22: 168-170.
3. Bady B., Boisson D., Bouillat G., Gouttard F., Carrier H.: Aspects cliniques et électromyographiques des neuropathies périphériques survenant au cours des traitements par le maléate de perhexiline. *Apport de 4 nouveaux cas dont un avec étude histologique.* *Lyon médical*, 1977, 237: 301-307.
4. Bouche P.: To be published.
5. Bourrat Ch., Viala J.J., Guastala J.P.: Neuropathie périphérique après absorption prolongée de maléate de perhexiline. Deux cas. *Nouv. Presse méd.* 1975, 4: 2528.
6. Bousser M-G., Bouche P., Brochard C., Herremans G.: Sept neuropathies périphériques après traitement par le maléate de perhexiline. *Nouv. Presse méd.* 1976, 5: 652-653.
7. Bousser M-G., Bouche P., Brochard C., Herremans G.: Neuropathies périphériques au maléate de perhexiline; à propos de 7 observations. *Coeur et Méd. int.* 1976, 15: 181-188.
8. Castaigne P., Laplane D., Escourolle R., Hauw J-J., Mussini J-M.: Etude des lésions nerveuses périphériques observées au cours de traitements prolongés par le maléate de perhexiline. *Rev. Neurol. (Paris)* 1976, 132: 431.
9. Dereux J-F.: Polynévrite au maléate de perhexiline. *Rev. Neurol. (Paris)* 1977, 133: 139-141.
10. Dress D., Boudesseul B., Morin P., Hamel M., Vergnaud M., Lechevalier B.: Neuropathies au maléate de perhexiline (3 observations). *J. Méd. Caen*, 1976, 11: 115-117.
11. Epstein H.: Polyneuropathy during perhexiline maleate therapy. *South Afric. med. J.* 1977, 51 (7): 189.
12. Feldman G.: Hypoglycémie et perhexiline. *La nouvelle Presse Méd.* 1974, 3, N° 41-43, 2580.
13. Grand A., Sepulchre Ph.: Amaigrissement et maléate de perhexiline. *Nouv. Presse méd.* 1974, 3: 1505.
14. Herne N., Raillat A., Marion J., Le Gall F., Chagnon A.: Hépatite toxique subaiguë et maléate de perhexiline. *Nouv. Presse Méd.* 1976 5: 2164.
15. Hirshleifer I.: Perhexiline maleate in the treatment of angina pectoris. *Curr. Therap. Res.* 1969, 11 (3): 99-105.
16. Lageron A., Poupon R., De Saint-Maur P-P., Levy V-G.: Liver ganglioside storage after perhexiline maleate. *Lancet*, 1977, 1: 483.
17. Laplane D., Bousser M-G., Bouche P., Touboul P-J.: Les neuropathies périphériques dues au maléate de perhexiline. *Proc. In-*

- ternat. Symposium on perhexiline maleate. Excerpta medica. 1976. To be published.
18. *Lemaire M.*: Maleate de perhexiline et lipides sériques. Thèse Méd. Lille, 1976.
19. *Lequesne P.M.*: Iatrogenic neuropathies. In Handbook of clinical Neurology, ed. Vinken P.J. and Bruyn G.W., 1970, North Holland.
20. *Lhermitte F., Fardeau M., Chedru F., Mallecourt J.*: Polyneuropathy after perhexiline maleate therapy. Brit. Med. J. 1976, 1: 1256.
21. *Lüllmann H., Lüllmann-Rauch R., Wassermann O.*: Drug-induced phospholipidoses. Crit. Rev. Toxicol. 1975, 4: 185-218.
22. *Mussini J-M., Hauw J-J., Escourolle R.*: Etude en microscopie électronique des lésions nerveuses, musculaires et cutanées déterminées par le maléate de perhexiline. Acta Neuropath. (Berlin) 1977, 38: 53-59.
23. *Pelletier M., Lambert R., Paliard P., Bory R.*: Hépatite toxique subaigüe après traitement par maléate de perhexiline. Nouv. Presse Méd. 1976, 5: 1070.
24. *Penther Ph.*: Personal communication.
25. *Pilcher J., Chandrasekhar K.P., Russel Rees J., Boyce M.J., Peirce T.H., Ikram H.*: Long term assessment of perhexiline maleate in angina pectoris. Postgrad. Med. J., 1973, 49, (suppl. 3), 115-118.
26. *Pollet S., Hauw J-J., Escourolle R., Bauman N.*: Peripheral nerve lipidic abnormalities including ganglioside storage in perhexiline maleate therapy. Lancet, 1977, 1: 1258.
27. *Pouget-Abadie J-F., Becq-Giraudon B., Gil R., Marin J., Sudre Y.*: Un cas de polyradiculonévrite après traitement prolongé par le maléate de perhexiline. Sem. Hop. Paris, 1976, 52: 2173-2174.
28. *Rees J.R.*: The action of perhexiline maleate in patients with angina and its effect on liver function. Arq. Bras. Cardiol. 1973, 26 (1), 108-112.
29. *Singlas E.*: To be published.
30. *Stern J.*: The induction of ganglioside storage in nervous system cultures. Lab. Invest. 1972, 26: 509-514.
31. *Tomlinson I.W., Rosenthal F.D.*: Proximal myopathy after perhexiline maleate treatment. Brit. Med. J. 1977, 1: 1319-1320.
32. *Touboul P-J.*: Neuropathies périphériques au maléate de perhexiline: à propos de 10 observations. Thèse. Université de Paris VI. Faculté Pitié-Salpêtrière. Paris 1976.
33. *Vorilhon P.*: Contribution à l'étude des complications neurologiques provoquées par le maléate de perhexiline. Thèse. Université de Clermont-Ferrand, 1976.
34. *Wright G.L., Zeiger A.V., Leeson G.A., Lang J-F.*: The absorption, excretion, and metabolism of perhexiline maleate by the human. Postgrad. Med. J. 1973, 49 (suppl. 3): 8-15.
35. *Wright G-J.*: Personal communication, 1976.

Experimental Immunology of Guillain - Barré Syndrome

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Disorders of putative or proven autoimmune pathogenesis may have some of the following features: A monophasic, polyphasic or chronic progressive clinical course; Co-occurrence of two or more autoimmune disorders in the same patient; Familial tendency; Precipitation of disease appearance or relapse by infection or by vaccination; Clinical presentation and symptomatology may be manifested by different syndromes; Beneficial effect of immunosuppressive therapy; Histological evidence for immune response in target organ(s). All these characteristics are present, at least in part, in Guillain-Barré syndrome (GBS). Although etiology and pathogenesis are unknown, cumulative evidence implies that GBS is an immune mediated disease of the peripheral nervous system (PNS).

Immune mediated tissue damage may occur by cellular and/or humoral pathways mainly by two mechanisms: 1) response directed against target organ(s) antigens or towards other antigens who have cross antigenicity with tissue components, or 2) activation of an immunological reaction by deposition of antigen-antibody complexes in target organ tissue. Myasthenia gravis is an example of a human autoimmune disease caused by autoantibodies. The acetylcholine receptor (AChR) antigen is characterized, antibodies against it are present in patients serum and not in controls, and they have been demonstrated in the end plate region which is the pathological site of the disease.

Myasthenia gravis is transferable with anti-AChR antibodies, and immunization with AChR protein produces an experimental animal model. The beneficial effect of plasmapheresis, steroids and immunosuppression has been proven (17). In GBS such sequence of evidence is still far from complete and pathogenesis is not fully understood.

The evidence that the clinical-pathological entity of GBS is immune mediated is based on clinical consideration, histological picture, laboratory findings and experimental models.

Fifty to 70 % of patients describe antecedent infections involving mainly the respiratory and gastrointestinal tracts (38). Viral (measles, mumps, rubella, influenza A & B, Epstein-Barr and other herpes viruses) as well as mycoplasma, salmonella typhoid, lysteria, brucella and other infections may be associated with GBS (97). So are several vaccinations like rabies and swine flu (98). The second week following onset of infection was the peak period of emergence of symptomatology in an epidemiological study done by Hurwitz et al (49). The link between infection, mainly viral or antiviral vaccination and pathogenesis of GBS remains unknown. Nevertheless, such sequence has also been described in other putative autoimmune disorders. In another acute neurological disease, namely acute disseminated postinfectious encephalomyelitis (ADE), acute demyelination occurs in the

central nervous system (CNS) following viral infection, usually by the same agents associated also with GBS (measles, rubella, mumps, infectious mononucleosis etc) (44,59). A similar illness is a complication of vaccination against smallpox and rabies (59). Viruses cannot be demonstrated or be grown from the brains of patients with ADE and the disease is considered as an immune mediated disorder (44,59). During the acute phase of GBS there is an increased incidence of glomerulonephritis, mainly subclinical (19,109), sometimes caused by deposition of immune complexes in renal glomeruli and tubuli basement membrane. Association of GBS with other diseases of putative autoimmune pathogenesis has been reported. These include spontaneous and drug-induced systemic lupus erythematosus (52,89), Hashimoto's thyroiditis (79) and myasthenia gravis (83). In a retrospective study performed in our department we found 7 out of 51 patients (14 %) who had an associated autoimmune disorder (1). GBS was also reported in immune suppressed patients who had Hodgkin's and non-Hodgkin's lymphoma (26,63) or other malignant conditions (54). Three to five percent of GBS patients have relapse(s) (86) appearing after a symptom-free interval of a few weeks and up to 20-30 years in rare instances.

Patients sometimes present with unusual clinical features which make diagnosis difficult. Auxillary studies, namely electrodiagnosis and sural nerve biopsy, as well as follow up, are then needed to establish the diagnosis of GBS. Despite restrictive criteria for diagnosis set forth in 1978 by the Ad Hoc NINCDS Committee (13) there are quite different clinical syndromes which are considered as variants of GBS; The syndrome of ophthalmoplegia, ataxia and areflexia (the Miller Fisher syndrome) (42); The syndrome of sensory loss and areflexia (101); Polyneuritis cranialis; Chronic demyelinating inflammatory polyneuropathy (CDIP). In CDIP the same symptomatology as in GBS develops over months and years in a steady progressive, stepwise or progressive relapsing form. Laboratory, electrodiagnostic and histopathological findings are sometimes indistinguishable from

the findings in acute GBS (34). Peak incidence is in the fifth and sixth decades, and prognosis is less favourable than in GBS. In one series (40) 53 patients were followed for a mean of 7.4 years. Only 4 % recovered while 28 were confined to bed or a wheelchair and 11 % died. CDIP patients have a particular HLA association (HLA-AL B8 and DRW 3) which is encountered in other putative autoimmune disorders (102). Whether all these clinical syndromes have a common pathogenesis is unknown and there is no reliable diagnostic marker shared by them.

In 1949, Haymaker and Kernohan (45) described autopsy findings in 50 patients with GBS. They concluded that the PNS was consistently affected, findings being localized around nerve roots. No pathology was detected in the CNS. In 1969 Asbury, Arnason and Adams (12) reported that inflammatory cells were present from the earliest stages of disease in the nerves of 19 patients who died of GBS. Myelin destruction was confined to loci of nerve roots which were infiltrated by the inflammatory cells. Since then microscopic and ultrastructural studies of both autopsy material and nerve biopsies obtained from patients with GBS confirmed the observation that primary demyelination occurs only in tissues harbouring the inflammatory cells (20,53,80, 82). Today GBS is regarded as a neuropathy consisting of inflammatory lesions scattered throughout the PNS where segmental demyelination occurs in the presence of lymphocytes and macrophages (81). Hence the synonymous term of demyelinating inflammatory polyradioculoneuropathy (DIP). This immunopathological picture is similar in many respects to that observed in other dysimmune disorders and in delayed hypersensitivity type reaction.

Several experimental models in animals which simulate human GBS have been induced. The most extensively investigated model is experimental allergic neuritis (EAN). It was first described in 1955 by Waxman and Adams (115,116) who produced a monophasic inflammatory disease of peripheral nerves in rabbits, mice or guinea pigs by immunizing the animals with peripheral nerve emulsified in complete

Freund's adjuvant. Clinically, EAN is an acute disease of animals appearing 2 weeks following immunization and consisting of ataxia and ascending limb weakness. In monkeys symptomatology also involves cranial nerves (118). Progression to paralysis occurs from as soon as a day or two up to more than a week. In non-fatal cases symptomatology progression is arrested after a week and is followed by gradual clinical recovery. Both chronic and relapsing forms of EAN may follow immunization (18,118). The CSF in EAN contains elevated protein level and no or little cellular response. The pathological picture is that of lymphocytic and macrophage inflammatory reaction with segmental demyelination. The sequential development of the tissue damage has been investigated (11,15,16,32,35,56,115). Ten to 12 days after immunization and 2-3 days before onset of symptomatology, lymphocytes infiltrate PNS venules. This is followed by passage of cells into the nerve parenchyma and transformation into larger lymphocytes. Their cytoplasm shows abundant free ribosomes arranged as multiple rosettes, a structure characteristic of enhanced protein synthesis. Increased mitotic activity can also be visualized. Lymphocyte migration is accompanied by monocytes which invade the peripheral nerve and are transformed into macrophages which become the prominent inflammatory cells in the tissue. They invade axons, stripping the myelin lamellae away from the Schwann cells and the myelin in contact with the macrophages may undergo bubbly disintegration. The vesiculated myelin together with fragments of seemingly intact myelin are ingested by phagocytic cells. Schwann cells survive myelin destruction, appear activated and become the mainstay of repair. They show increased granular endoplasmic reticulum and abundant ribosomes and form new, though thinner, layers of myelin lamellae. This sequence of histological events is similar in all respects to human GBS (81).

The components of the peripheral nerve capable of inducing EAN were isolated, purified and characterized. Two basic proteins were found in myelin of bovine, rabbit, guinea pig and human peripheral nerves. The one migrates in gel electrophoresis si-

ilarly to myelin basic protein (MBP) of the CNS and may be identical with it. It was denoted P_2 or P_2L by London (65), and by Abramsky and London (2,4) or P_1 by Brostoff and Eylar (23). Following immunization with complete Freund's adjuvant it induces in laboratory animals both EAN in the PNS and the analogous disease of the CNS, namely, experimental allergic neuritis (EAE). The other MBP called P_1 by London (65) and P_1L by Abramsky and London (3,4) or P_2 by Brostoff et al (22) is a specific PNS neuritogenic protein (NP) and produces only EAN in PNS without any clinical or pathological evidence of lesions in the CNS. Their molecular weight is around 12,200 and 14,000 respectively (2). Adjuvants are necessary for rapid and constant production of EAN. It is of interest that EAN produced by injection of isolated P_1L (P_2) is usually rather mild (3) when compared to the EAN provoked by whole peripheral nerve myelin. It was speculated that production of the allergic response may be initiated by NP but requires reaction against antigenic determinants of other PNS components. Brostoff et al (24) reported that a peptide containing amino acids 1 to 20 from the amino terminal of P_2 is neuritogenic in rabbits and encephalotogenic in guinea pigs (25). EAN induced by bovine P_2 was enhanced when combined with gangliosides from the same source (70, 108), indicating that gangliosides may serve as a natural adjuvant in the production of EAN.

The evidence that GBS is caused by cell mediated immunity (CMI) is still conflicting. When lymphocytes are present in the CSF of patients with GBS they are predominantly T cells (62). Employing different techniques (lymphocyte transformation, macrophage migration inhibition factor assay) several authors reported presence of lymphocytes in peripheral blood of GBS patients which were sensitized to crude extracts of peripheral nerve myelin (18,27, 55,84). NP could induce proliferation of lymphocytes obtained from peripheral blood of GBS patients (5,61,71,100). Arnason et al (6,10) showed that peripheral blood lymphocytes from the majority of patients suffering from GBS (and not controls or

patients with other neurological disorders) are capable of attacking and destroying myelin *in vitro*. The chronology of pathological events in GBS also supports the hypothesis that CMI may be responsible for peripheral nerve myelin damage in GBS. The main criticism against this rests on the following points: 1) Inability of some investigators to reproduce some of the results mentioned above (51,62,120). 2) Lack of specificity of findings i.e. - presence in other disorders (84). 3) Some of the results may not imply active CMI (51).

It is generally accepted that the pathogenic mechanism in EAN is one of CMI. All the findings described in GBS are also present in EAN, namely - *in vivo* sensitivity to peripheral nerve myelin antigen, destruction of this myelin in tissue cultures by lymphocytes from EAN-ill animals and chronology of events in damaged nerves (8). Yet, in addition, it is possible to transfer EAN either by lymphocytes immunized with peripheral nerve myelin antigen or by lymphocytes taken from animals with EAN (3,9,14,48). This is crucial evidence that EAN is a cell mediated disorder and is another point in favour of CMI causing also GBS.

Studies on humoral factors in GBS and EAN are more problematic. Antibodies directed against different components of the PNS - neurons, axons, Schwann cells and myelin, have been demonstrated by several authors (37,68,72,87,112). Nevertheless, they were present only in some patients during the acute phase of their disease, and could be found, though to a lesser extent, both in controls and in patients with other neurological and systemic disorders. By removing the Fc fragment of IgG Nyland and Aarli (72) succeeded in increasing the specificity of the IgG binding to peripheral nerve tissue, namely - this was present only in sera obtained from GBS patients and not controls. The Fab fragments in the IgG, the one which presumably bound to peripheral nerve tissue, is responsible for the antibody-antigen link while the Fc portion does connect in a non specific way (114). Antibodies directed against possible PNS antigens involved in pathogenesis of GBS such as P₂ or galactocerbroside (GalC)

could not be detected in significant amount in serum from GBS patients (51,62,120). Several studies have demonstrated the presence of antibodies along myelin of peripheral nerves obtained from biopsies of GBS patients (66,99,113). *In vivo*, sera of GBS patients and EAN-ill animals have the capacity to cause demyelination of PBS cultures (7,31,39,117,119), but not a peripheral demyelinating disease when injected into animals systemically (110).

When serum, obtained from animals with whole peripheral-nerve-induced EAN, was injected directly into peripheral nerve of experimental animals *in vivo*, Saida and colleagues could induce acute demyelination in the nerve evident both clinically and electrophysiologically (90,94). The histological picture, however differs conspicuously from GBS and EAN. During the early phases of disease there is no or very little cellular infiltrate in PNS tissue (90,94,105), a characteristic finding in GBS. Several works suggested that anti GalC antibodies are of major importance in the pathogenesis of demyelination in this model (64,91,105). GalC is a constituent of myelin lipids both in the peripheral and the central nervous systems. Indeed, the injection of anti-GalC directly into the peripheral nerve induced the same model disorder (91). Histologically, changes in tissue include splitting and vesiculation of myelin with local edema followed by appearance of macrophages. Remarkably enough, lymphocytes are absent. Although animals immunized with CNS or PNS nerve tissue produce antibodies to GalC (58), attempts to produce EAN employing GalC as antigen were unsuccessful. In 1979 Saida et al (92) reported that repeated immunization of rabbits with GalC in complete Freund's adjuvant induced a demyelinating disorder affecting only the PNS within 6 weeks to one year following immunization. Histopathologically disease is mainly confined to loci in the rabbit PNS where the blood-nerve barrier is defective - the dorsal root ganglia and the nerve roots next to them (95). All these experiments indicate that GalC induced neuritis is an antibody mediated phenomenon. Whether this model is relevant to human GBS remains an open question.

Subsequently, serum obtained from GBS patients was injected intraneurally to experimental animals. In several works this caused local demyelination (41,93,104). Severity however, as measured by conduction block and histopathological examination was less than in EAN or CalC induced neuritis. Mononuclear infiltration was present but to a lesser extent and in a different distribution. This could not be reproduced in other works (30,96,110) and serum from controls produced the same phenomenon although to a lesser degree (93). Thus, whether GBS serum contains specific demyelinating factors, antibodies or other, is not yet clear.

Circulating immune complexes have been detected in GBS patients (36,43,47,107, 110) and they may be responsible in part for renal impairment in these patients. Again they were present only in part of the sera obtained from GBS patients and in controls as well. The demyelinating nature of the disease and its histopathological features do not favour an immune complex mediated disorder. When this type of pathogenetic mechanism is presumed, as in polyarteritis nodosa and serum sickness, mononeuritis multiplex is seen and tissue damage is due to ischemia-infarction (29,50). The relevance of the presence of immune complexes to pathogenesis of GBS is therefore unknown. Whether they induce direct nerve injury, trigger an immunological response to nerve tissue, or by breaking the blood-nerve barrier pave the way to cell-mediated or antibody induced demyelination (76), or whether they are just epiphenomena is still unsettled.

Plasmapheresis was reported to improve the clinical course of GBS and chronic relapsing inflammatory polyneuropathy (21, 60,74,86,111) and others. Nevertheless, within the time this treatment can be effective most untreated patients will improve spontaneously. That makes any evaluation of the efficacy of plasmapheresis impossible until the results of the present randomized controlled trial of this treatment on a large number of patients will be published. If plasmapheresis turns out to be effective in GBS this may aid the understanding of disease pathogenesis. The removed circulatory

demyelinating factor can be an antineural antibody but other blood-born factors must also be considered. Plasmapheresis can remove circulatory antigen-antibody immune complexes and immune regulatory or cytotoxic factors released by T cells as well as lymphotoxic antibodies to suppressor T cells is observed in rheumatoid arthritis and systemic lupus erythematosus (69,103).

Two natural occurring demyelinating disorders of the PNS are recognized. Coonhound paralysis is a disease affecting hunting dogs 7 to 14 days after they have been bitten by a raccoon (33,46). There may be one bout or dogs can suffer a relapse either spontaneously or following a second bite. Despite trials no infective agent could be discovered. Pathologically findings are indistinguishable from human GBS and EAN in dogs. Marek's disease (MD) occurs in chickens infected with MD virus - a lymphotropic herpesvirus (28,67). The virus can be detected in peripheral nerves of infected chickens and in PNS cultures of infected birds. It is confined to satellite cells, nonmyelinating Schwann cells and lymphocytes (77). The detection of the virus is extremely difficult. Explantation and in vitro cultivation of peripheral nerves and dorsal ganglia provides a stimulus which induces appearance of viral antigens and capsids suggesting that infection in the animal is latent rather than active. The pathologic lesions in MD are similar to those present in EAN (57). Lymphocytes in the demyelinating lesions in MD predominantly T cells (88) and elimination of B lymphocytes by surgical removal of the bursa of Fabricius does not protect against disease, but in fact favours it (75). Therefore disease seems to be cell mediated but the antigen(s) that T cells are reacting to are unknown. Virus associated membrane antigens have been demonstrated on lymphocytes latently infected with MD virus (85) as well as Epstein-Barr virus (106). Lymphocytes then can attack Schwann cells harboring the virus with secondary "bystander" non-specific demyelination, or virus antigens may cross-react with a myelin component and lymphocytes sensitized against viral antigens misdirect destruction to myelin. The relevance of MD to human GBS is intri-

guing since two other herpes viruses, namely Epstein-Barr virus and cytomegalovirus

precede GBS in a significant number of cases (38).

SUMMARY

Disorders of putative or proven autoimmune pathogenesis may have some of the following features: Amonophasic, polyphasic or chronic progressive clinical course; CO-occurrence of two or more autoimmune disorders the same patient; Familial tendency; Precipitation of disease appearance or relapse by infection or by vaccination.

All these characteristics are present, at least in part, in Guillain-Barré syndrome (GBS). Cumulative evidence implies that GBS is an immune mediated disease of the peripheral nervous system (PNS) and tissue damage may occur by cellular and/or humoral pathways.

The link between infection, mainly viral or antiviral vaccination and pathogenesis of GBS remains unknown.

During the acute phase of GBS there is an increased incidence of glomerulonephritis sometimes caused by deposition of immune complexes in renal glomeruli and tubuli basement membrane.

Association of GBS with other diseases of putative autoimmune pathogenesis has been reported.

Autopsy findings in 50 patients with GBS showed that the PNS was consistently affected, findings being localized around nerve roots. No pathology was detected in the central nervous system (CNS).

Today GBS is regarded as a neuropathy consisting of inflammatory lesions scattered throughout the PNS where segmental demyelination occurs in the presence of lymphocytes and macrophages.

Several experimental models in animals which simulate human GBS have been induced. The most extensively investigated model is experimental allergic neuritis (EAN). Both chronic and relapsing forms of EAN may follow immunization. The sequence of histological events is similar in all respects to human GBS. Two basic proteins were found in myelin of animals and human peripheral nerves, EAN induced by bovine protein was enhanced when combined with gangliosides from the same source, indicating that gangliosides may serve as a natural adjuvant in the production of EAN.

Peripheral blood lymphocytes from the majority of patients suffering from GBS are capable of attacking and destroying myelin in vitro.

It is crucial evidence that EAN is a cell mediated disorder and this is a point in favor of cell mediated immunity (CMI) causing also GBS.

Several studies have demonstrated the presence of antibodies along myelination of peripheral nerves obtained from biopsies of GBS patients. Serum obtained from GBS patients was injected intravenously to experimental animals. In several works this caused local demyelination. Circulating immune complexes have been detected in GBS patients and they may be responsible in part for renal impairment in these patients.

If plasmapheresis turns out to be effective in GBS this may aid the understanding of disease pathogenesis.

RESUMEN

Desórdenes de supuesta o probada patología autoinmune, pueden tener algunas de las siguientes características: un curso clínico monofásico, polifásico o crónico progresivo; la existencia en el mismo paciente de dos o más desórdenes autoinmunes; tendencia familiar; precipitación de la enfermedad o de la recaída por infección o por

vacunación.

En el síndrome de GUILLAIN-BARRE (SGB) las características señaladas están presentes, por lo menos parte de ellas. Evidencias se acumulan que implican que el SGB es una enfermedad mediada por la inmunidad del sistema nervioso periférico (SNP) y el daño tisular puede originarse

por vía celular o tumoral.

El vínculo que puede existir entre una infección principalmente viral o una vacunación antiviral y la patogenia del SGB aún no ha sido aclarado.

Durante la fase aguda del SGB se hace presente una creciente incidencia de glomerulonefritis, a veces originada por la deposición de complejos de inmunidad en los glomerulos renales y en las membranas basales tubulares.

Se han mencionado casos de asociación del SGB con otras enfermedades de posible patogenia de autoinmunidad.

Los hallazgos observados en la autopsia de 50 pacientes afectados de SGB pusieron en evidencia daño en el SNP localizado alrededor de las raíces nerviosas. En el sistema nervioso central (SNC) no se comprobaron cambios patológicos.

Actualmente el SGB es considerado como una neuropatía constituida por lesiones inflamatorias difundidas en el SNP, en las que se aprecia desmielinización segmentaria con la presencia de linfocitos y macrófagos.

Experimentalmente se ha logrado en animales obtener modelos que reproducen el SGB del ser humano. El modelo que ha merecido más estudio es la neuritis alérgica experimental (NAE).

El proceso inmunitario puede originar formas de evolución crónica o a recaídas en NAE. En la histología el carácter evolutivo es similar a lo que acontece en el SGB del hombre. Dos tipos de proteínas básicas han sido observados en la mielina de los nervios

periféricos de los animales y seres humanos. La NAE promovida por proteína de bovino resultó acrecentada cuando se le agregó gangliósidos del mismo origen, lo cual indica que los gangliósidos pueden promover una contribución natural en la gestación de la NAE.

Los linfocitos de la sangre periférica provenientes de la mayoría de los pacientes que sufren del SGB son aptos para agredir y destruir la mielina *in vitro*.

Existe una clara evidencia de que la NAE es un disturbio mediado por células, lo cual es un argumento en favor de que el SGB es también causado por una inmunidad mediada por células (IMC).

Diversos estudios biopsicos han demostrado la existencia de anticuerpos en la mielina de los nervios periféricos en pacientes con el SGB.

En distintas investigaciones se ha observado una desmielinización local, inyectando en animales experimentales en los nervios, suero recogido de pacientes con el SGB.

En pacientes con el SGB se ha comprobado en la circulación complejos de inmunidad, que pueden ser causales en parte del sufrimiento renal que a veces presentan.

Si la plasmáferesis resulta siendo efectiva en el SGB, esto puede resultar un argumento para definir la patogenia de la enfermedad.

La enfermedad de MAREK (EM) se origina en gallinas infectadas con el virus EM que es un virus herpético linfotrópico.

R É S U M É

Des désordres de pathogénie prouvée ou supposée d'origine auto-immune, peuvent avoir quelques unes des caractéristiques suivantes: une évolution clinique monophasique, poliphasique, chronique ou progressive; l'existence chez le même individu de deux ou plus de deux désordres auto-immune; la tendance familiale; l'accélération de la maladie ou de la rechute par infection ou vaccination.

Dans le syndrome de GUILLAIN-BARRE (SGB) ces caractéristiques sont présentes ou du moins quelques unes d'entre elles. Des évidences s'accumulent qui indiquent

que les SGB est une maladie dans laquelle le système nerveux intervient par son immunité et la lésion tissulaire peut avoir son origine par médiation cellulaire ou tumorale.

La relation qui peut exister entre une infection principalement virale ou une vaccination antivirale et la pathogénie du SGB n'a pas encore été dilucidée.

Il existe une incidence croissante de glomérulonéphrite au cours de la phase aigüe du SGB, quelques fois provoquée par la localisation dans les glomérules ou dans les membranes basales tubulaires, d'éléments

d'immunisation.

On a mentionné des cas d'association du SGB avec d'autres maladies de possible pathogénie autoimmune.

Les trouvailles observées dans les autopsies de 50 malades affectés du SGB ont mis en évidence des lésions du SNP localisées autour des racines nerveuses. Il n'a pas été trouvé de lésions dans le système nerveux central.

Actuellement le SGB est considéré comme une névropathie constituée par des lésions inflammatoires diffuses du SNP, dans lesquelles on observe une démyélinisation segmentaire avec la présence de lymphocytes et de macrophages.

Chez l'animal, on a obtenu de manière expérimentale des modèles qui reproduisent le SGB de l'homme. Le modèle le plus étudié est la névrite allergique expérimentale (NAE).

Le processus immunitaire peut donner des formes d'évolution chronique ou à rechute en NAE. L'histologie a un caractère évolutif similaire à celui du SGB de l'homme. Deux types de protéines ont été observées dans la myéline des nerfs périphériques des animaux et des humains. La NAE provoquée par des protéines bovines a été aggravée par la présence de glucosides du même origine, ce qui suggère que les glucosides peu-

vent avoir une naturelle contribution dans la gestation de la NAE.

Les lymphocytes du sang périphérique qui proviennent de la grande majorité de malades qui souffrent du SGB sont aptes pour attaquer et détruire la myéline in-vitro.

Il est évident que la NAE est un trouble dans lequel les cellules interviennent, ce qui est un argument à faveur de que le SGB est aussi provoqué par une immunité à médiation cellulaire (IMC).

Diverses études et biopsies ont démontré l'existence d'anticorps dans la myéline des nerfs périphériques chez des malades porteurs du SGB.

Diverses études ont observé une démyélinisation locale, si l'on injecte dans les nerfs d'animaux de laboratoire, du sérum de patients porteurs du SGB.

Chez des porteurs du SGB on a trouvé dans la circulation des complexes d'immunité qui peuvent être en partie, responsables des lésions rénales qui se présentent parfois.

Si la plasmaphorèse est efficace dans le SGB, ceci peut être un argument pour définir la pathogénie de la maladie.

La maladie de MAREK (MM) se voit chez des poules infectées par le virus MM lequel est un virus herpétique lymphotrope.

ZUSAMMENFASSUNG

Störungen angenommener oder erprobter autoimmuner Pathogenie können einige der folgenden Charakteristika haben: Einen klinisch monophasischen, polyphasischen oder chronisch-progredienten Kurs; die Existenz beim selben Patienten von zwei oder mehr Störungen autoimmuner Art; familiäre Tendenz; Präzipation der Krankheit oder Rückfall durch Infektion oder Vakzination.

Beim Syndrom von GUILLAIN BARRE (SGB) sind die angezeigten Charakteristika vorhanden, wenigstens Teile davon. Augenscheinlich häufen sie sich an und schließen ein, dass die SGB eine Krankheit ist verursacht durch die Immunität des peripheren nervösen Systems (SNP) und der Gewebeschaden kann sich bilden durch

Zellulären oder tumoralen Weg.

Die Beziehung, die bestehen kann zwischen einer Infektion hauptsächlich durch Virus oder einer Antivirussimpfung und der Pathogenie der SGB ist noch nicht geklärt worden.

Während der akuten Phase der SGB macht sich bemerkbar eine Neigung zu einer Glomerulonephritis, manchmal verursacht durch die Deposition von Komplexen von Immunität bei den renalen Glomerulus und in den basalen tubulären Membranen.

Es werden Fälle erwähnt von Assoziation der SGB mit anderen Krankheiten einer möglichen Pathogenie der Autoimmunität.

Die Befunde bei der Autopsie von 50 Patienten, erkrankt an SGB, ergaben das Vorhandensein von Schäden im SNP, lo-

kalisiert an den nervösen Wurzeln. Beim nervösen Zentralsystem haben sich keine pathologischen Änderungen ergeben.

Aktuell wird der SGB betrachtet als eine Neuropathie hervorgerufen durch entzündliche Verletzungen verstreut im SNF, bei denen man eine Desmyelinisation im Segment mit der Anwesenheit von Lymphozyten und Makrophagen.

Experimental hat man bei Tieren Modelle erzielt, die den SGB des Menschen verursachen. Das Modell hat ein stärkeres Studium bei der allergischen experimentellen Neuritis (NAE) verdient.

Der immunitäre Prozess kann Formen der Evolution hervorrufen chronischer Art oder Rückfall zu NAE. In der Histologie ist der Charakter der Evolution gleich dem SGB des Menschen. Zwei Typen von basischen Proteinen sind beobachtet worden bei dem Myelin der peripherischen Nerven der Tiere und Menschen. Die NAE verursacht durch Protein von Rindern ergab sich vermehrt, Wenn man Gangliosiden desselben Ursprungs zusetzte, was anzeigt, dass die Gangliosiden eine natürliche Kontribution bei der Entwicklung der NAE beitragen können. Die Lymphozyten vom peripherischen Blut, erhalten von der Mehrheit der

Patienten die an SGB leiden, sind geeignet, um das Myelin *in vitro* anzugreifen und zu zerstören.

Es besteht ein klarer Beweis, dass die NAE eine Störung ist hervorgerufen durch Zellen, was ein Argument ist zu Gunsten dessen, dass SOB ebenfalls verursacht ist durch eine Immunität von Zellen (DC).

Verschiedene biopsische Studien haben die Existenz von Antikörpern an dem Myelin der peripherischen Nerven von Patienten mit SGB. ergeben.

Bei verschiedenen Investigationen hat man eine Desmyelinisation lokal beobachtet, wenn man bei den Experimentaltieren in die Nerven Serum, erhalten von Patienten mit SGB, eingespritzt hat.

Bei Patienten mit SGB hat man bewiesen bei der Zirkulation Komplexe von Immunität, die die Ursache sein können teilweise des Nierenleidens, das sie manchmal haben.

Wenn die Plasmaferesis effektiv bei SGB ist, könnte dies ein Argument sein für die pathogenische Definition der Krankheit.

Die Krankheit von MAREK (KM) entsteht bei Hennen, die mit dem Virus KM infiziert sind, das ein lymphotroper herpetischer Virus ist.

REFERENCES

1. *Abramsky, O., Korn-Lubetzki, I., Teitelbaum, D.*: Association with autoimmune disease and cellular immune response to the neuritogenic protein in Guillain-Barré syndrome. *Trans Amer Neurol Assoc.* 105, 350 (1980).
2. *Abramsky, O., London, Y.*: Purification and partial characterization of two basic proteins from human peripheral nerve. *Biochem Biophys Acta*, 393, 556 (1975).
3. *Abramsky, O., Teitelbaum, D., Arnon, R.*: Experimental allergic neuritis induced by a basic neuritogenic protein (P₁L) of human peripheral nerve origin. *Eur J Immunol.* 7, 213 (1977).
4. *Abramsky, O., Teitelbaum, D., Webb, C., Arnon, R.*: Neuritogenic and encephalotogenic properties of the peripheral nerve basic proteins. *J Neuropathol Exp Neurol.* 34, 36 (1975).
5. *Abramsky, O., Webb, C., Teitelbaum, D., Arnon, R.*: Cell-mediated immunity to neural antigens in idiopathic polyneuritis and myeloradiculitis. *Neurology (Minneapolis)* 25, 1154 (1975).
6. *Arnason, B.G.W.*: The inflammatory lesion in idiopathic polyneuritis compared to that in experimental allergic neuritis. In: *Proceedings Sixth International Congress of Neuropathologists*. Paris, Masson & Cie, p. 691 (1970).
7. *Arnason, B.G.W.*: Idiopathic polyneuritis (Landry-Guillain-Barré-Strohl syndrome) and experimental allergic neuritis: A comparison. *Res Publ Assoc Res Nerv Ment Dis* 49m 156 (1971).
8. *Arnason, B.G.W.*: Acute inflammatory demyelinating polyradiculoneuropathy. In: *Peripheral Neuropathy*, Dyck, P.J., Thomas, P.K., Lambert, E.H., Bunge, R. eds. p. 2050, W.B. Saunders Company 1984.
9. *Arnason, B.G.W., Chelmicka-Scorc, H.*: Passive transfer of experimental allergic neuritis in Lewis rats by direct injection of sensitized lymphocytes into sciatic nerves. *Acta Neuropathol (Berl)* 22, 1 (1972).
10. *Arnason, B.G.W., Winkler, F.F., Hadler, N. N.*: Cell-mediated demyelination of peripheral nerve in tissue culture. *Lab Invest* 21, 1 (1969).
11. *Asbury, A.K., Arnason, B.G.*: Experimental allergic neuritis: a radio-autographic study.

12. *J Neuropathol Exp Neurol* 27, 581 (1968).
13. *Asbury, A.K., Arnason, B.D., Adams, R.D.*: The inflammatory lesions in idiopathic polyneuritis. Its role in pathogenesis. *Medicine (Baltimore)* 48, 173 (1969).
14. *Asbury, A.K., Arnason, B.D., Karp, H.R., McFarlin, D.E.*: Criteria for diagnosis of Guillain-Barré syndrome. *Ann Neurol* 3, 565 (1978).
15. *Aström, K.E., Waksman, B.H.*: The passive transfer of experimental allergic encephalomyelitis and neuritis with living lymphoid cells. *J Pathol Bacteriol* 83, 459 (1962).
16. *Aström, K.E., Webster, H.D., Arnason, B.G.*: The initial lesion in experimental allergic neuritis: a phase and electron microscopic study. *J Exp Med* 128, 462 (1968).
17. *Ballin, R.H.M., Thomas, P.K.*: Electron microscope observations in demyelination and remyelination in experimental allergic neuritis. Part I. Demyelination. *J Neurol Sci* 8, 1 (1968).
18. *Behan, P.O., Currie, S.*: Clinical neuroimmunology pp 130-142, W.B. Saunders Company Ltd. 1978.
19. *Behan, P.O., Lamarche, J.B., Feldman, R.G., Sheremato, W.A.*: Lymphocyte transformation in the Guillain-Barré syndrome. *Lancet* 1, 421 (1970).
20. *Behan, P.O., Lowenstein, L.M., Stilmant, M., Sax, D.S.*: Landry-Guillain-Barré-Strohl syndrome and immune complex nephritis. *Lancet* 1, 850 (1973).
21. *Bonnaud, E., Vital, C., Cohere, G., Castaing, R., Loiseau, P.*: Recurrent and relapsing polyneuritis. Four cases with ultrastructural studies of the peripheral nerves. *Pathol Eur* 9, 109 (1974).
22. *Brett, R.P., Gross, M., Legg, N.J. et al.*: Treatment of acute polyneuropathy by plasma exchange. *Lancet* 2, 1100 (1978).
23. *Brostoff, S.W., Burnett, P., Lampert, P., Eylar, E.H.*: Isolation and characterization of a protein from sciatic nerve myelin responsible for experimental allergic neuritis. *Nature (New Biol)* 235, 210 (1972).
24. *Brostoff, S.W., Eylar, E.H.*: The proposed amino acid sequence of the P₁ protein of rabbit sciatic nerve myelin. *Arch Biochem* 153, 590 (1972).
25. *Brostoff, S.W., Levit, S., Powers, J.M.*: Induction of experimental allergic neuritis with a peptide from myelin P₂ basic protein. *Nature* 268, 752 (1977).
26. *Brostoff, W.S., Powers, J.M., Weiss, M.J.*: Allergic encephalomyelitis induced in guinea pigs by a peptide from the NH₂ terminus of bovine P₂ protein. *Nature* 285, 103 (1980).
27. *Cameron, D.G., Howel, D.A., Hutchinson, J.L.*: Acute peripheral neuropathy in Hodgkin's disease: report of a fatal case with histologic features of allergic neuritis. *Neurology (Minneapolis)* 8, 575 (1958).
28. *Caspari, E.A., Currie, S., Walton, J.N., Field, E.J.*: Lymphocyte sensitization to nervous tissue and muscle in patients with Guillain-Barré syndrome. *J Neuro Neurosurg Psychiatry* 34, 179 (1971).
29. *Churchill, A.E., Biggs, P.M.*: Agent of Marek's disease in tissue culture. *Nature* 215, 528 (1967).
30. *Conn, D.L., Dyck, O.J.*: Angiopathic neuropathy in connective tissue diseases. In: *Peripheral Neuropathy*, Dyck, P.J., Thomas, P.K., Lambert, E.H., Bunge, R. eds. W.B. Saunders Company, pp. 2027 (1984).
31. *Cook, S.D., Dowling, P.C.*: The role of autoantibody and immune complexes in the pathogenesis of Guillain-Barré syndrome. *Ann Neurol* 9 (suppl) 70 (1981).
32. *Cook, S.D., Dowling, P.C., Murray, M.R., Whitaker, J.N.*: Circulating demyelinating factors in acute idiopathic polyneuropathy. *Arch Neurol* 24, 136 (1971).
33. *Cragg, B.D., Thomas, P.K.*: Changes in nerve conduction in experimental allergic neuritis. *J Neurol Neurosurg Psychiatry* 27, 106 (1964).
34. *Cummings, J.G.F., Haas, D.C.*: Coonhound paralysis. An acute idiopathic polyradiculitis in dogs resembling the Landry-Guillain Barré syndrome. *J Neurol Sci* 4, 51 (1967).
35. *Dalakas, M.D., Engel, W.K.*: Chronic relapsing (dyimmune) polyneuropathy: pathogenesis and treatment. *Ann Neurol* 9 (suppl) 134 (1981).
36. *DalCanto M., Wisniewski, H.M., Johnson, A.B., Brostoff, S.W., Raine, C.S.*: Vesicular disruption of myelin in autoimmune demyelination. *J Neurol Sci* 24, 313 (1975).
37. *Dowling, P.C., Cook, S.D.*: Circulating complexes in neurologic disease. *J Neuropathol Exp Neurol* 31, 161 (1972).
38. *Dowling, P.C., Cook, S.D.*: Antibodies to dorsal root ganglia in Guillain-Barré syndrome. *Neurology (Minneapolis)* 23, 423 (1973).
39. *Dowling, P.C., Cook, S.*: Role of infection in Guillain-Barré syndrome: laboratory confirmation of herpesvirus in 41 cases. *Ann Neurol* 9 (suppl) 44 (1981).
40. *Dubois-Dalcq, M., Buyse, G., Gorce, F.*: The action of Guillain-Barré serum on myelin. A tissue culture and electron microscopic analysis. *J Neurol Sci* 13, 67 (1971).
41. *Dyck, P.J., Lois, A.C., Otha, M. et al.*: Chronic relapsing polyradiculoneuropathy. *Mayo Clin Proc* 50, 621 (1975).
42. *Feasby, T.E., Hahn, A.F., Gilbert, J.J.*: Passive transfer studies in Guillain-Barré polyneuropathy. *Neurology (Ny)* 32, 1159 (1982).
43. *Fisher, M.*: An unusual variant of acute idiopathic polyneuritis (syndrome of ophthalmoplegia, ataxia and areflexia). *N Engl J Med* 255, 57 (1956).
44. *Goust, J.M., Chenais, F., Carnes, J. et al.*: Abnormal T cells subpopulations and circulating immune complexes in the Guillain-

- Barré syndrome and multiple sclerosis. *Neurology* 28, 421 (1978).
44. Harter, D.H., Choppin, P.W.: Possible mechanisms in the pathogenesis of "postinfectious" encephalomyelitis. In: Rowland L. P. (Ed): *Immunological disorders of the nervous system*. Baltimore, The Williams & Wilkins Company, p. 342 (1971).
 45. Haymaker, W., Kernohan, J.W.: The Landry-Guillain-Barré syndrome. A clinicopathologic report of fifty fatal cases and a critique of the literature. *Medicine (Baltimore)* 28, 59 (1949).
 46. Homes, D.F., deLahunta, A.: Experimental allergic neuritis in the dog and its comparison with the naturally occurring disease, coonhound paralysis. *Acta Neuropathol (Berl)* 30, 329 (1974).
 47. Hughes, R.A.C.: Acute inflammatory polyneuropathy. In: *Clinical Neuroimmunology* Rose, F.C., ed., Oxford, Blackwell Scientific publications p. 170 (1979).
 48. Hughes, R.A.C., Gray, I.A., Kodlowski, M.: Immune response in experimental allergic neuritis. *Neurology* 30, 408 (1980).
 49. Hurwitz, E.S., Holman, R.C., Nelson, D.B., Schonberger, L.B.: National surveillance for Guillain-Barré syndrome: January 1978 March 1979. *Neurology (NY)* 33, 150 (1983).
 50. Iqbal, A., Arnason, B.G.W.: Neuropathy of serum sickness. In: *Peripheral Neuropathy*, Dyck, P.J., Thomas, P.K., Lambert, E.H., Bunge, R. eds. W.B. Saunders Company p. 2044 (1984).
 51. Iqbal, A., Oger, J.J.F., Arnason, B.G.W.: Cell-mediated immunity in idiopathic polyneuritis. *Ann Neurol* 9 (suppl) 65 (1981).
 52. Johnson, R.T., Richardson, E.P.: The neurological manifestations of systemic lupus erythematosus. *Medicine* 47, 337 (1968).
 53. Julien, J., Vital, G., Lagueny, A., Darriet D., Brechenmacher, C.: Guillain-Barré syndrome and Hodgkin's disease - ultrastructural study of peripheral nerve. *Neurol Sci* 45, 23 (1980).
 54. Klingon, G.H.: The Guillain-Barré syndrome associated with cancer. *Cancer* 18, 157 (1965).
 55. Knowles, M., Saunders, M., Currie, S., Walton, H.N., Field, E.H.: Lymphocyte transformation in the Guillain-Barré syndrome. *Lancet*, 2, 1168 (1969).
 56. Lampert, P.W.: Mechanism of demyelination in experimental allergic neuritis. *Electron microscopic studies*. *Lab Invest* 20, 127 (1969).
 57. Lampert, P., Garrett, R., Powell, H.: Demyelination in allergic and Marek's disease virus-induced neuritis. *Acta Neuropathol* 40, 103 (1977).
 58. Leibowitz, S., Hughes, R.A.C.: *Immunology of the nervous system*. Edward Arnold (Publishers) Ltd., London, p. 113 (1983).
 59. Leibowitz, S., Hughes, R.A.C.: *Immunology of the nervous system*. London, Edward Arnold (Publishers) Ltd. p. 169 (1983).
 60. Levy, R.L., Newkirk, R., Ochoa, J.: Treatment of chronic relapsing Guillain-Barré syndrome by plasma exchange. *Lancet* 2, 241 (1979).
 61. Lin, J.T., Rowe, V., Brostoff, S.W., Abdou N.I.: Lymphocyte studies in a patient with chronic relapsing polyradiculoneuropathy. *Neurology* 32, 1227 (1982).
 62. Lisak, R.P., Brown, M.J., Summer, A.K.: Abnormal serum factors in Guillain-Barré syndrome. *Ital J Neurol Sci* 3, 265 (1983).
 63. Lisak, R.P., Mitchell, M., Zweiman, B., Orrechio, E., Asbry, A.K.: Guillain-Barré syndrome and Hodgkin's disease: three cases with immunological studies. *Ann Neurol* 1, 72 (1977).
 64. Lisak, R.P., Saida, T., Kennedy, P.G.E. et al: EAE, EAN and galactocerebroside sera bind to oligodendrocytes and Schwann cells. *J Neurol Sci* 48, 287 (1980).
 65. London, Y.: Ox peripheral nerve myelin membrane. Purification and partial characterization of two basic proteins. *Biochem Biophys Acta* 249 188 (1971).
 66. Luitjen, J.A.F.M., Baart de la Faille-Kuyper, E.H.: The occurrence of IgM and complement factors along myelin sheaths of the peripheral nerve - an immunohistochemical study of the Guillain-Barré syndrome. *J Neurol Sci* 15, 219 (1972).
 67. Marek, J.: Multiple Nervenentzündung (polyneuritis) bei Hühnern. *Dtsch Tierärztl Wochenschr* 15, 417 (1907).
 68. Melnick, S.C.: Thirty-eight cases of the Guillain-Barré syndrome: an immunological study. *Brit J Med* 1, 368 (1963).
 69. Morimata, C., Abe, T., Toguchi, T. et al: Studies of antilymphocyte antibody of patients with active SLE. *Scand J Immunol* 10, 213 (1979).
 70. Nagai, Y., Uchida, T., Takeda, S., Ikuta F.: Restoration of activity for induction of experimental allergic peripheral neuritis by a combination of myelin basic protein P₂ and gangliosides from peripheral nerve. *Neurosci Lett* 8, 247 (1978).
 71. Nomura, K., Hamaguchi, K., Ohno, R., Negishi, T., Yamashita, T., Uyemura, K.: Cell mediated immunity in experimental allergic neuritis and human demyelinating neuritis. *Excerpta Medica, APCS 22, 6th Asian and Ocean Congress of Neurology* Tape p. 135 (1983).
 72. Nyland, H., Aarli, J.A.: Guillain-Barré syndrome: demonstration of antibodies to peripheral nerve tissue. *Acta Neurol Scand* 58, 35 (1978).
 73. Nyland, H., Naess, A.: Lymphocytes subpopulations in blood and cerebrospinal fluid from patients with acute Guillain-Barré. *Eur Neurol* 17, 247 (1978).
 74. Osterman, P.O., Fagius, J., Safwenberg, J. et al: Treatment of the Guillain-Barré syndrome by plasmapheresis. *Arch Neurol* 39, 148 (1982).

75. *Payne, L.N., Rennie, M.*: Lack of effect of bursectomy on Marek's disease. *J Natl Cancer Inst* 45, 387 (1970).
76. *Reik, L. Jr.*: Disseminated vasculomyelinopathy: An immune complex disease. *Ann Neuro* 7, 291 (1980).
77. *Pepose, J.S., Stevens, J.G., Cook, M.L. et al*: Marek's disease as an animal model for the Landry-Guillain-Barré syndrome. Latent infection restricted to neuronal supporting cells and accompanied by specific immune response to peripheral nerve and myelin. *Am J Pathol* 103, 309 (1981).
78. *Pollard, J.D., King, R.H., Thomas, P.K.*: Recurrent experimental allergic neuritis. An electron microscopic study. *J. Neurol Sci* 24, 365 (1975).
79. *Potz, G., Neundorfer, B.*: Polyradicular neuritis and Hashimoto thyroiditis. *J Neurol* 210, 283 (1975).
80. *Prineas, J.W.*: Acute idiopathic polyneuritis. An electron microscope study. *Lab Invest* 26, 133 (1972).
81. *Prineas, J.W.*: Pathology of the Guillain-Barré syndrome. *Ann Neuro* 9 (suppl) 6, 1981.
82. *Prineas, J.W., McLeod, J.G.*: Chronic relapsing polyneuritis. *J Neurol Sci* 27, 427 (1976).
83. *Regev, I., Bornstein, N., Carasso, R., Vardi Y.*: Acute polyneuropathy combined with myasthenia gravis. *Acta Neurol Scand* 65, 681 (1982).
84. *Rocklin, R.E., Sheremata, W.A., Feldman, R.G., Kies, M.W., David, J.R.*: Cellular response in Guillain-Barré syndrome and multiple sclerosis. *N Eng J Med* 284, 803 (1971).
85. *Ross, L.J.N.*: Anti-viral T-cell-mediated immunity in Marek's disease. *Nature* 268, 644 (1977).
86. *Ropper, A.H., Shahani, B.T.*: Diagnosis and management of acute areflexic paralysis with emphasis on Guillain-Barré syndrome. In: *Peripheral Nerve Disorders*, Asbury A. K., Gilliatt, R.W. eds. Butterworth & Co (Publishers) Ltd., p. 21 (1984).
87. *Rosenberg, R.N., Aug, M.H., Tindall, R.S. A. et al*: Idiopathic polyneuropathy associated with cytotoxic antineuroblastoma serum. *Neurology (Minneapolis)* 25, 1101 (1975).
88. *Rouse, B.T., Wells, R.J.H., Warner, N.L.*: Proportion of T and B lymphocytes in lesions of Marek's disease: theoretical implications for pathogenesis. *J Immunol* 110, 534 (1973).
89. *Sahenk, Z., Mendell, J.R., Rossio, J.L., Hurtubise, P.*: Polyradiculopathy accompanying procainamide induced lupus erythematosus: evidence for drug enhanced sensitization to peripheral nerve myelin. *Ann Neurol* 1, 378 (1977).
90. *Saida, K., Saida, T., Brown, M.J. et al*: Antiserum mediated demyelination in vivo - a sequential study using intraneural injection of experimental neuritis serum. *Lab Invest* 39, 449 (1978).
91. *Saida, K., Saida, T., Brown, M.J. et al*: In vivo demyelination induced by intraneural injection of antigalactocerbroside serum - a morphologic study. *Am J. Path* 95: 99 (1979).
92. *Saida, T., Saida, K., Dorfman, S. et al*: Experimental allergic neuritis induced by sensitization with galactocerbroside. *Science* 204, 1103 (1979).
93. *Saida, T., Saida, K., Lisak, R.P. et al*: In vivo demyelinating activity of sera from patients with Guillain-Barré syndrome. *Ann Neuro* 11, 69 (1982).
94. *Saida, T., Saida, K., Silberberg, D.H. et al*: Transfer of demyelination with experimental allergic neuritis serum by intraneural injection. *Nature (London)* 272, 639 (1978).
95. *Saida, T., Saida, K., Silberberg, D.H. et al*: Experimental allergic neuritis induced by galactocerbroside. *Ann Neuro* 9 (suppl) 87 (1981).
96. *Server, A.C., Lefkowitz, J., Braine, H. et al*: Treatment of chronic relapsing inflammatory polyradiculoneuropathy by plasma exchange. *Ann Neuro* 6, 258 (1979).
97. *Schaumburg, H.H., Spencer, P.S., Thomas, P.K.*: Disorders of peripheral nerves, p. 27 F.A. Davis Company, Philadelphia, 1983.
98. *Schonberger, L.B., Hurwitz, E.S., Katona, P., Holman, R.C., Bregman, D.J.*: Guillain-Barré syndrome: its epidemiology and association with influenza vaccination. *Ann Neuro* 9 (suppl) 31, 38 (1981).
99. *Schott, B., Chazot, G., Kopp, N. et al*: Subperineural space and immunoglobulin deposits in inflammatory and dysglobulinemic neuropathies. In: *Peripheral neuropathies*, Canal, N., Pozza G. eds. Elsevier, Amsterdam, 1978.
100. *Sheremata, W., Colby, S., Karkhanis, Y., Eylar, E.H.*: Cellular hypersensitivity to basic myelin (P₂L) protein in the Guillain-Barré syndrome. *Can J Neurol Sci* 2, 87 (1975).
101. *Sterman, A.B., Schaumburg, H.H., Asbury, A.K.*: The acute sensory neuropathy syndrome: a distinct clinical entity. *Ann Neuro* 7, 354 (1980).
102. *Stewart, G.J., Pollard, J.D., McLeod, J.G., Wolnizer, C.M.*: HLA antigens in the Landry-Guillain-Barré syndrome and chronic relapsing polyneuritis. *Ann Neuro* 4, 285 (1978).
103. *uskas, Callerz, R.T., McDowell, J. et al*: Direct evidence for loss of human suppressor cells during active autoimmune disease. *Proc Natl Acad Sci USA* 75, 5150 (1978).
104. *Summer, A.J., Said, G., Idy, I. et al*: Demyelination conduction block produced by intraneural injection of human Guillain-Barré serum into rat sciatic nerve. *Neurology (Ny)* 32(2)A106 (1982).
105. *Sumner, A.J., Saida, K., Saida, T., et al*: Acute conduction block associated with ex-

- perimental antiserum-mediated demyelination of peripheral nerve. *Ann Neuro* 11, 469 (1982).
106. *Svedmyr, E., Jondal, M.*: Cytotoxic effector cells specific for B cell lines transformed by Epstein-Barr virus are present in patients with infectious mononucleosis. *Proc Nat Acad Sci USA* 72, 1622 (1975).
 107. *Tachovsky, T.G., Koprowsky, H., Lisak, R. P. et al*: Circulating immune complexes in multiple sclerosis and other neurological disease. *Lancet* 2, 997 (1976).
 108. *Takeda, S., Ikuta, F., Nagai, Y.*: Neuropathological comparative studies on experimental allergic neuritis (EAN) induced in rabbits by P₂ proteinganglioside complexes. *J Exp Med* 50, 453 (1980).
 109. *Talamo, T.S., Borochoviz, D.*: Membranous glomerulonephritis associated with the Guillain-Barré syndrome. *Am J Cl Pathol* 78, 563 (1982).
 110. *Tandon, D.S., Griffin, J.W., Drachman, D. E. et al*: Studies on the humoral mechanisms of inflammatory demyelinating neuropathies. *Neurology* 30, 362 (1980).
 111. *Toyka, K.V., Augspach, R., Paulus, W. et al*: Plasma exchange in polyradiculoneuropathy. *Ann Neurol* 8, 205 (1980).
 112. *Tse, K.S., Arbesman, C.E., Tomasi, T.B. Jr., Tourville, D.*: Demonstration of antimyelin antibodies by immunofluorescence in Guillain-Barré syndrome. *Clin Exp Immunol* 8, 881 (1971).
 113. *Lis, J.M.J., Jennekens, P.G.L.*: Plasma proteins in human peripheral nerve. *J Neurol Sci* 34, 329 (1977).
 114. *Van Oss, C.J.*: The immunoglobulins. In: *Principles of Immunology*, Rose N.R., Milgrom, F., van Oss C.J. eds., p. 122, Macmillan Publishing Co. Inc. New York, 1973.
 115. *Waxman, B.H., Adams, R.D.*: Allergic neuritis: experimental disease of rabbits induced by peripheral nervous tissue and adjuvants. *J Exp Med* 102, 213 (1955).
 116. *Waxman, B.H., Adams, R.D.*: A comparative study of experimental allergic neuritis in the rabbit, guinea pig and mouse. *J Neuropathol Exp Neurol* 15, 293 (1956).
 117. *Winkler, G.F.*: In vitro demyelination of peripheral nerve induced with sensitized cells. *Ann NY Acad Sci* 122, 287 (1965).
 118. *Wisniewski, H.M., Brostoff, S.W., Carter, H., Eylar, E.H.*: Recurrent experimental allergic polyganglioradiculoneuritis. Multiple demyelinating episodes in rhesus monkey sensitized with rabbit sciatic nerve myelin. *Arch Neurol* 30, 347 (1974).
 119. *Yonezawa, T., Robbins, N., Ishihara, Y., Iwanami, H., Nakatani, Y.*: In vitro demyelination produced by sera from Landry-Guillain-Barré syndrome. *Proc 6th Int Congr Neuropath.*, Paris Masson & Cie p. 688 (1970).
 120. *Zwieman, B., Rostami, A., Lisak, R.P., Moskowitz, A.R., Pleasure, D.*: Immune reaction to P₂ protein in human inflammatory neuropathies. *Neurology* 33, 234 (1983).

A History of Stroke

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The first adequate account of stroke or apoplexy appeared in the Hippocratic writings. Apoplexy in Greek meant "struck with violence" and implied, in addition, being struck by lightening or a thunderbolt with resulting paralysis of some part or all parts of the body. According to Hippocrates, the causes of apoplexy were varied but generally related to the heating of the blood vessels of the head which thereby attracted phlegm or caused the flow of black bile into the head. In the Hippocratic aphorism these are several references to apoplectic attacks.

During the spasms, the loss of speech for a long time is unfortunate: if present for a short time it proclaims a paralysis of the tongue, of the arm or of parts situated on the right side.

This is the earliest Greek reference to the loss of speech occurring with paralysis on the right side of the body. In the Hippocratic aphorism there are parts which imply apoplexy and many modern concepts are expressed, such as "persons are most subject to apoplexy between the ages of forty and sixty" and "Unaccustomed attacks of numbness and anesthesia are signs of impending apoplexy". A probable subarachnoid hemorrhage is also described in his aphorisms.

When persons in good health are suddenly seized with pains in the head, and straightway are laid down speechless, and breathe with stertor, they die in seven days, un-

less fever comes on.

Aretaeus believed that "should indeed the apoplexy be severe", the patient is as good as dead, particularly in the aged, for "they cannot survive the greatness of the illness combined with the misery of advanced life". Aretaeus attributed the attack to congestion of the flow of blood. He also implied that there may be a deficiency of blood to the involved part, saying that the blood is diverted from the diseased region to the healthy part: "thither the revolution is made from the parts affected". This is the first implication, although vague, that ischemia may be responsible at times for apoplexy. To Aretaeus, apoplexy was an acute disease different in some ways from paralysis.

Apoplexy is a paralysis of the whole body, of sensation, of understanding and of motion; wherefore to get rid of a strong attack of apoplexy is impossible, and of a weak not easy.

He also noted the unilateral characteristics of apoplexy in his statement, "In smaller attacks of apoplexy, it is necessary to consider whether the paralytic seizure be on the left or on the right side".

Paul of Aegina followed Hippocrates and Aretaeus in forming his conceptions of apoplexy.

When the common origin of the nerves is affected and from it all the other parts of the body have lost their motion and sensibility, the affection is called apoplexy, by which the leading energies are impaired:

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but if the obstruction is in either side, it is called hemiplegia and paralysis; and if the injury is seated in any one part, it is called an affection of that part and hence Hippocrates says, "His leg was seized with apoplexy".

Wherefore apoplectics lie speechless, motionless, and insensible, without fever. The precursors of this affection are sudden and acute pain of the head, distention of the jugular veins, vertigo, flashes, as it were of light in the eyes, an inordinate coldness of the extremities, palpitation and difficult motion of the whole body.

Celsus differentiated apoplexy from paralysis by observing that in apoplexy the whole body is paralyzed while the effects of paralysis are local.

Apoplexy to Galen and his predecessors was merely a clinical conception. Its causation by cerebral hemorrhage or softening was unknown and remained so until the 17th Century. Consequently, Galen followed Hippocrates in attributing apoplexy to an accumulation of phlegm in the arteries of the brain which obstructed the passage of the animal spirits from the ventricles.

Galen was also the originator of another error regarding the cerebral circulation. He discussed in detail the blood supply of the brain and adopted the Alexandrian idea of animal spirits and the rete mirabile, a network of blood vessels on the base of the brain in animals. Galen considered this network essential for functioning of the brain. He must have observed the rete at the base of the brain of an ox which he dissected. The rete mirabile does not appear in man and this error caused much confusion for centuries. Both Vesalius and Leonardo da Vinci followed the ancient classical traditions also drew the rete mirabile. In da Vinci's sketch, he seems to have superimposed the rete on the human brain despite the fact that he could not have observed it there. Galen elaborated and extended the Alexandrian theory of animal spirits and their production in cerebral blood vessels. He paid more attention to the blood vessels of the brain than to other structures because he considered their function important. Galen described the carotid arteries and some of the intracranial branches,

as well as the venous sinuses. It was not until the 17th Century when the hexagonal circle of the base of the brain in man replaced the notion of the rete mirabile.

Although a few additional clinical features had been presented during the Middle Ages and Renaissance, little was added to the ancient descriptions and concepts of apoplexy. In the 17th Century, Wepfer made the first correlations between apoplexy and hemorrhage. Other early descriptions of this disease were given by Bayle (1677), Nymman (1670), Mistichelli (1709), Chandler (1785), and Kirkland (1792).

In his play, "Henry IV", Shakespeare gives some notions of apoplexy in the 17th Century:

Falstaff: And I hear moreover, his highness is fallen into this same whoreson apoplexy.

Chief Justice: Well, heaven mend him! I pray let me speak with you.

Falstaff: This apoplexy is, as I take it, a kind of lethargy, an't to please your lordship; a kind of sleeping in the blood, a whoreson tingling.

Chief Justice: What tell you me of it? Be it as it is.

Falstaff: It hath its original from much grief, from study and perturbation of the Brain. I have read the cause of its effects in Galen.

Although Thomas Willis was one of the foremost contributors to neurology, the structure for which he is eponymously remembered was actually described by several others before him. The arterial circle of vessels at the base of the human brain was first mentioned as such in 1561 by Gabriel Fallopius, a pupil of Vesalius. Fallopius described the union and later division of the vertebral arteries and the union of the anterior rami (corresponding to our anterior communicating arteries) to the carotid arteries. Only part of the posterior communicating artery was mentioned and it had only an indirect connection with the external branch (corresponding to our middle cerebral artery) of the carotid artery. Fallopius' description resembles one side of the arterial circle shown in the drawing

by Casserio, a professor at Padua and one of Harvey's teachers. Casserio (1632) first illustrated the circle of Willis probably as early as 1616 showing the complete union of the posterior communicating artery only on one side.

The arterial circle next appeared in the anatomical work of Johann Vesling, a professor of anatomy and surgery at Padua. In Vesling's plate (1647), the posterior cerebral arteries are absent and the basilar artery divides into two large posterior communicating arteries.

It can easily be seen that the circle of Willis was not first observed by Willis. His own studies (1664), however, were the product of careful observation and experimentation. Willis also showed the existence of the blood vessels within the substance of the brain by injecting solutions of dark colored dye into the peripheral vessels and noting the appearance of dark spots on the surface of the brain. His anatomical injection of the cerebral blood vessels are second only to the great Dutch anatomist, Ruysch (1724). Willis did not, in fact, claim the description of the circle of himself. He acknowledged previous anatomical studies. He was, however, along with Wepfer, the first to recognize the clinical importance of the circle. Willis records the clinical history of two patients where he suggests that the anatomical anastomoses prevented apoplexy or paralysis. One patient had occlusion of both the right carotid and vertebral artery but did not have apoplexy during life. Willis reasoned that the remaining large vessels running to the arterial circle to the base of the brain were able by the way of their "mutual conjoinings" to "supply or fill the channels or passages of all the rest".

Willis was also the first to recognize that lesions in the region of the internal capsule produce hemiplegia. Willis wrote that in post-mortem examinations of patients afflicted with "long and severe paralysis... these bodies were less firm, discolored... and the striae much obliterated". He was referring here to "the internal capsule".

In the 17th Century, studies of apoplexy were carried out by Gregor Nymman (1670) of Whittenberg. Using Varolio's

method of dissection, he published the first monograph on apoplexy. Although his hypothesis of the cause of apoplexy is intertwined with their erroneous 17th Century concepts of the movement of vital spirits, Nymman did recognize that an apoplectic attack would occur with the closure of vessel or passageways that bore vital spirits to the brain.

The most significant advance in the investigation of apoplexy came with the precise studies of the brilliant Johann Jacob Wepfer of Schaffhausen. Wepfer, a remarkable practitioner and physician to the Duke of Wurtemberg, performed meticulous studies (1658) of the cerebral blood vessels in the brains of patients with apoplexy. He dissected and traced the carotid and vertebral arteries from their origin to the formation of the circle of Willis. He was the first to illustrate the siphon of the carotid arteries and gave a good description of the course of the middle cerebral artery in the Sylvian fissure and of other cerebral arteries including the circle of vessels at the base of the brain.

That apoplexy was often due to cerebral hemorrhage was little known until Wepfer's *Treatise on Apoplexy* which passed through five printings from 1658 to 1724. Wepfer described four cases of cerebral hemorrhage of varying severity from subarachnoid bleeding at the base of the brain to massive intracerebral hemorrhage. Wepfer applied Harvey's concept of circular blood flow through the body recognizing flow through the carotid and vertebral vessels with egress through the dural sinuses and jugular veins. He recognized that anything capable of preventing the influx of blood to the brain from the cerebral arteries and its return through the jugular veins was capable of producing apoplexy. Obstruction of the internal carotid artery or the vertebral artery by compression or by the occlusion or narrowing of the lumen by corpora fibrosa (small fibrous bodies) in the wall of these vessels would prevent insufficient blood from entering the brain.

Wepfer declared that those most liable to apoplexy were the obese whose face and hands were livid and those whose pulse was constantly irregular. This is the first

implication that hypertensive individuals or patients with cardiac disease are more liable to apoplexy. Wepfer recognized that the clinical picture in apoplexy varied and that the brain cannot be deprived of its nourishment for even a short time. He further recorded that some patients are immediately deprived of all senses while others may recover from an attack in relatively a short time; still others will have a hemiplegia if one side of the brain alone is involved. The nature of the attack, he held, depends on the amount and degree of arterial obstruction.

Although Wepfer was the first to recognize that apoplexy often resulted from cerebral hemorrhage, he was not definite in his opinion that the location of the lesion was on the opposite side. As a rule, Wepfer looked for the lesion on the same side. Morgagni in the 18th Century claimed for his master, Valsalva, the credit for demonstrating that in a hemiplegia the lesion should be looked for on the opposite side of the brain. The actual demonstration of the mechanism of paralysis on the opposite side of the lesion in apoplexy, however, was made by Mistichelli. In his book on apoplexy, Mistichelli speaks of the crossed relationship as a well recognized fact and endeavors to explain his views of the anatomy of the brain, particularly the decussation of the pyramids. The occurrence of atherosclerosis of blood vessels had been recognized as early as Da Vinci but Francois Bayle was among the first to relate it to apoplexy. Bayle gave a description of the calcification of plaques seen in the cerebral vessels.

In his study of the pathology of the nervous system, Morgagni provided one of the earliest works in neuropathology. The first book of his "Disorders of the Head" was divided into fourteen letters or chapters. The first consisted of pain in the head and the next four are on apoplexy which Morgagni divides into three classes: serous apoplexy, sanguinous apoplexy, and apoplexy that is neither serous or sanguinous. It is in these chapters that Morgagni first presents the pathological evidence that the lesion in apoplexy is on the side opposite to the paralysis.

Morgagni believed that the extravasation of blood was from an aneurysmal state of the arteries, but added that he did not conceive them as true aneurysm. Blood vessels that ramify to the brain, he noted, characteristically had delicate coats; when they became moderately enlarged, they could suddenly rupture. The soft substance of the brain yielded to the impulse of the blood, thus forming the apoplexy and laceration at the same time. If the power of the heart and arteries did not languish the laceration increased and with it the disease increased. This in turn formed smaller or larger cavities from the ruptured vessels, depending on the diameter of the vessel, the size of the rupture, the degree of congestion and the laxity of the brain itself. These cavities might be in the substance of the brain, might rupture into the ventricles or outwardly upon the surface of the brain.

Morgagni also described cavities in the deeper parts of the brain, lined by a tough substance or membrane. These, he considered, were originally produced by extravasation of blood in attacks of apoplexy in which the patient had survived. This was the first clear elaboration of the findings in apoplexy since the pioneer descriptions of Wepfer in the 17th Century.

The 18th Century notions on apoplexy largely reflected the experience of previous observers; apoplexy was still classed merely as a sudden deprivation of all sensation and motion with the exception of the heart and thorax. Apoplexy included lethargy and coma, and covered practically all conditions of unconsciousness and semiconsciousness from any cause. This resulted in endless disputes as to treatment by bleeding, counter-irritation and so forth. The situation is exemplified by William Cullen, who placed apoplexy in "Of comata, or the loss of voluntary motion" in his section "Of Neuroses or Nervous Disease". Cullen distinguished apoplexy from palsy in that the former was an affection "of the whole powers of sense and of voluntary motion". Apoplexy was different from syncope in that with apoplexy there is a "continuance of respiration and the action of the heart".

In the 18th Century, the English pathologist, Matthew Baillie, in the last chapter

of his *Morbid Anatomy* (1793) on "Diseased Appearances of the Brain and its Mechanisms" includes a section on cerebral hemorrhage.

It is very common in examining the brain of persons who are considerably advanced in life, to find the trunks of the internal carotid artery upon the side of the sella turcica very much diseased, and this disease extends frequently more or less into the small branches. The disease consists in a bony or earthy matter being deposited in the coats of the arteries, by which they lose part of their contractile and distensible powers as well as their tenacity. The same sort of diseased structure is likewise found in the basilar and its branches.

The vessels of the brain under such circumstances of disease, are much more liable to be ruptured than in a healthy state. Whenever blood is accumulated in unusual quantity, or the circulation is going on in them with unusual vigor, they are liable to this accident, and accordingly in either of these states ruptures frequently happen. Were the internal carotid arteries and the basilar artery not subject to the diseased alterations of structure which we have described, effusions of blood within the cavity of the cranium, where there has been no previous external injury, would be very rare.

Baillie thus pointed out that cerebral hemorrhage was due to disease of the blood vessels of the brain but did not recognize the vascular disease as a cause of brain softening.

Portal (1781, 1811) wrote that there was no way of distinguishing between hemorrhage and "serous" apoplexy from a clinical point of view. Serous or nonhemorrhagic apoplexies were considered to be of a circulatory origin and caused by vascular engorgement. The first suggestion that cerebral embolism could cause apoplexy is found in van Swieten's (1754) commentaries on Boerhaave.

It has been established by many observations that these polyps occasionally attach themselves as excrescences to the columnae carneae of the heart, and perhaps then separate from it and are propelled, along with the blood, into the pulmonary artery

or the aorta, and its branches. . . . were they thrown into the carotid or vertebral arteries, could disturb—or if they completely blocked all approach of arterial blood to the brain—utterly abolish the functions of the brain.

In the works (1802) of the great London practitioner, William Heberden, there is a description of transient cerebral vascular insufficiency, which often precedes complete paralysis.

A faltering and inarticulation of the voice, drowsiness, forgetfulness, a slight delirium, a dimness of sight, or objects appearing double, trembling, a numbness gradually propagated to the head, a frequent yawning, weakness, a distortion of the mouth, a palpitation, a disposition to faint; some, or most of these have preceded a palsy for a few minutes, or for some hours, or even for a few days; in a weakness of the limb, or of one side, has been many months, or a few years, gradually increasing to a perfect loss of one side or a hemiplegia. I have known a sleepiness and duplicity of objects with violent pains and tightness of the head for two days, then the senses and voice were lost on the third and the man expired. A numbness of the hand has come on the first day, and on the second a faltering of the voice, and a palsy on the third.

One of the most unusual 18th Century contributions to cerebral vascular disease was the case of Gaspard Vieusseux, a Swiss physician. He suffered from what conforms in some aspects to be a lateral medullary syndrome. He recorded his symptoms himself and they were presented by Marcet to the medical and surgical society of London on December 18, 1810. Vieusseux had suffered pain and analgesia on the left side of his face and a left facial paresis in addition to vertigo, vomiting, dysarthria, dysphagia, ptosis of the left eyelid, and anhydrosis on the left. On the right trunk he had analgesia and thermoanesthesia; his left extremities were weak. After improvement, Vieusseux did well for over five years until he was suddenly seized with a great debility of the left side with giddiness and palsy of the mouth and tongue. This clinical case of a lateral medullary syndrome

appeared 85 years before Wallenberg's classic description.

At the turn of the 19th Century, apoplexy was classified by Pinel and others as a form of cerebral neurosis. This was a reflection of the lack of contemporary knowledge concerning the pathology of apoplexy and of unwillingness to accept hemorrhage, as described by Wepfer, as the single cause of the symptom complex considered to be apoplexy. Most medical writers admitted that hemorrhage might cause apoplexy, but only the vaguest conjectures were advanced to explain what the cause was when no hemorrhage could be found.

The definition of apoplexy was so broad and vague that an impracticable latitude in morbid findings was allowed. Furthermore, the postmortem difference between infarction and hemorrhage was still unknown since the pathological substratum of thrombosis and infarction was not elucidated until the middle of the 19th Century. Early 19th Century works on apoplexy include those by Gay (1807), Montain (1811), Richelmi (1811), Portal (1811), Rochoux (1814), Rostan (1823), and Granier (1826).

The first idea that anemia of the brain rather than vascular congestion might be the cause of apoplexy is to be found in the work of John Cheyne (1812). He wrote that the affection produces an excitement of the arteries of the brain which may lead to "interrupted circulation and absorption of the brain". Although he did not specifically conclude that cerebral anemia was the cause of apoplexy, he described pathological cases of cerebral infarction and of cerebral hemorrhage. Cheyne pointed out that in those who survive "a stroke of apoplexy" for a considerable time, there may be found in the brain a cavity filled with serum which is rusty yellow in color and which may stain the substance of the brain in the neighborhood of the rupture. He further postulated that the cavities are lined by a membrane "which obtains the power, not only of absorbing the red particles of the blood, but of secreting a fluid which is of a nature perhaps less irritating than the original extravasation". This work contained Cheyne's conception of the role of

the cerebral circulation in apoplexy and the pathological findings in this condition. Included in this work are five plates illustrating various forms of apoplexy that were engraved from the drawings of the specimen in Charles Bell's museum. These include the earliest illustration of a subarachnoid hemorrhage and examples of cerebral infarction.

In the first separate work on Neurology in the early part of the 19th Century, John Cooke, who was a physician at the London Hospital wrote a *Treatise on Nervous Diseases*. The first volume of Cooke's (1820-1823) work contains his 1819 Croonian lectures on apoplexy, in which he summarized the contemporary concept of apoplexy. Although he had little new to add to the subject, these lectures contain one of the best sources of information on the history of apoplexy. Apoplexy was considered by Marshall Hall (1836) to be a form of "congestion and hemorrhage in the encephalon" with little differentiation of the types of attacks. In the treatment of apoplexy Hall recommended blood-letting, purges and counter-irritants, measures that had been in vogue for nearly two hundred years. Romberg (1853), too, added nothing on apoplexy, which he included among the various "cerebral paralyses" in his section on the "Neuroses of Motility".

The first useful clinical classification of apoplexy was introduced by the French anatomist Antoine Etienne Renaud Augustin Serres, physician to the Hôpital de la Pitié. He (1819, 1823-1824) believed that apoplexies were of two types, those with and those without paralysis, and that these occurred in a ratio of four to one, respectively. In the majority of cases (those with paralysis) the brain was involved. In the latter group, without paralysis, the meninges rather than the brain were affected. Clinically the patient showed general lassitude, obtundation, bradycardia, slow respiration and reduction of other functions. This group probably referred to patients without focal findings, such as may occur in meningeal versus massive intracranial hemorrhage, and in contrast to individuals with paralysis, from focal cerebral infarction. Serres' classification became generally accepted in the early part

of the century. He later (1822) reported a case of cerebellar apoplexy, shortly before Parker (1845) observed a case of pontine apoplexy.

Another early 19th Century writer was John Abercrombie who published a work, "Pathological and Practical Researches on Diseases of the Brain and Spinal Cord" in 1828. The second part of this work is on the apoplectic affections. This includes discussion of the current concepts of cerebral circulation as well as description of the clinical course and various pathological findings. In an analysis of more than forty cases of apoplexy, Abercrombie (1828) went into great detail concerning various aspects of the disorder. Clinically, apoplexy was put into three classes by Abercrombie. The first primary apoplexy, occurs when the patient is suddenly struck down, deprived of sense and motion, as in a deep sleep. Convulsions may occur and there may be rigid contraction of the muscles of the extremities of one side with relaxation of the other. In such state of profound stupor the patient may die after various intervals from a few minutes to several days, or he may recover perfectly without any bad consequences of the attack remaining; or he may recover from the coma, with paralysis of one side. This paralysis may disappear in a few days, it may subside gradually or it may be permanent. Other functions, such as speech, may be affected in the same manner. Clinically, this class probably included intracerebral hemorrhage and most cases of massive cerebral infarction. Primary apoplexy from a pathological point of view resolved itself into three divisions: apoplexy with extravasation of blood, apoplexy with serous effusion and apoplexy without any morbid appearance obvious in the brain. Abercrombie considered the latter category to be simple apoplexy.

The second class of apoplexy as described by Abercrombie is the form in which the disease begins with a sudden pain in the head. The patient becomes pale and faint, generally vomits and often falls. He may or may not be paralyzed, but is usually not. Recovery generally occurs, although coma and death may supervene. Most cases of subarachnoid hemorrhage from a

ruptured aneurysm will fall within this group. In Abercrombie's third class of apoplexy, the patient is suddenly deprived of the power of one side of his body and of speech, without stupor. The patient usually recovers, but become stuporous. In many cases the recovery is gradual at the end of several weeks or months and the patient may remain well for several years, unless he is cut off by a fresh attack. This group most likely encompassed cases of cerebral vascular insufficiency or vascular occlusion.

Abercrombie describes the various clinical symptoms of the patients in his three classes of apoplexy, as well as the variety of pathological findings in the disease. Besides Cooke's review of the disorder, Abercrombie's work was the most significant advance in the study of apoplexy since that of Morgagni. In addition to his clinicopathological case presentations, Abercrombie also discussed the notion of the etiology of apoplexy, suggesting the following as possible causes of apoplexy: spasm of the vessels, interruption of the circulation, narrowing or contraction of the arteries and rupture of diseased vessels or aneurysms producing hemorrhage. He noted the frequent occurrence, especially in elderly people, of small opaque osseous rings constricting the lumen in the principal arteries of the brain, and further noted that the inner coat of the artery might be thicker. Abercrombie recognized that the rupture of diseased arteries was an important cause of apoplexy. In the early part of the century, however the role of vascular occlusion as a cause of apoplexy was not yet firmly established.

From the pathological studies that had been made at this time, a crude notion of the relationship between the lesion and the clinical findings was formulated. Serres, Foville, Pinel and others believed that paralytic affections of the arms with or without rigidity were due to lesions of the thalamus and posterior part of the brain. Lesions of the corpus striatum including the internal capsule were thought to cause paralysis of the leg. Although these concepts of cerebral localization were in error, they were the first crude attempts at some form of localization of function within the brain. Also, before the clinicopathological studies of

Charcot and others, these were the earliest attempts at correlating clinical signs in patients with involvement of a specific area in the brain found at postmortem.

By 1840, John Hughes Bennett (Hope, et al., 1840) distinguished four forms of apoplexy. First was the transient type, which had been described by Abercrombie where the symptoms last less than a day. "Primary apoplexy" was a form in which there was either death or a slow recovery from the affection. "Ingravescent apoplexy" was characterized by partial recovery, succeeded by a relapse. The last form, "paraplexic apoplexy" had been described by a relapse. The last form, "paraplexic apoplexy" had been described by Hippocrates and was considered to be synonymous with paraplegia, which at this time meant paralysis anywhere in the body. Paraplexic apoplexy was apoplexy complicated by paralysis. Bennett believed that increased intracranial pressure was the basic cause of apoplexy.

The role of disease of the arteries in the production of apoplexy had been suggested by Morgagni and was illustrated by Bright (1831, 1836). In a color plate of the basilarvertebral system on the "under part of the cerebellum, the pons varolii and the medulla oblongata", Bright showed that the vertebral and basilar arteries and "the arteries proceeding from them are in a highly diseased state, their coats having become studded with cartilagenous patches... by this disease the diameter of the vessels is rendered irregular". Bright also illustrated the external surface and coronal section in a case of acute softening of the brain which involved most of the territory of the middle cerebral artery. The various sites of cerebral hemorrhage are shown in other plates. To Bright, inanition or deficiency of the cerebral circulation was as follows:

... a very powerful cause of many derangements in which the brain and nervous system bear a prominent part: it shows itself in that general want of power which depends on an insufficient supply of nourishing and stimulating blood to the brain. It may arise from excessive depletion; in which case it may be but a temporary effect, having amongst its symptoms, inten-

se headache, a sense of ringing in the ears, deafness, confused vision, or total blindness, syncope, and convulsion.

The relationship of anemia of the brain to apoplexy was set forth in a series of experiments of ligation of the carotid artery. This was first performed by Cooper (1836) and repeated in 1842 by Sedillot. Chevers (1845) made the earliest comprehensive review of the effects on the cerebral circulation of obliteration of the carotid arteries. The fact that alterations in the cerebral circulation might be related to "cerebral accidents" or apoplexy was brought out in the clinical and experimental studies of Burrows. Although first suggested by Cheyne, it was Burrows (1846) who gathered strong evidence on the relationship between cerebral anemia and apoplexy. He was the first to point out that the effects of cerebral anemia could be produced not only by obvious anemia itself but also by a diminution in vascular pressure insufficient to drive blood through the brain. Burrows was also aware that cardiac and apoplectic symptoms may occur simultaneously. At the same time softening of the brain from "obliteration of the arteries" was described and distinguished pathologically from cerebral hemorrhage by Carswell (1838), Cruveilhier (1835-1842), Durand-Fardel (1843), and others.

The concepts of apoplexy in the middle of the 19th Century were reviewed by Copland (1850), Mushet (1866), Lidell (1873) and others. Hughlings Jackson (1875) was among the earliest to be firmly convinced that cerebral vascular occlusion produced softening of the brain and cerebral infarction. In Gower's Manual (1866-1888) specific clinical descriptions of cerebral vascular disorders are given, including basilar artery disease.

The next most significant advance in the study of apoplexy came in the elucidation of areas of vascular supply of the brain and in the demonstration of the common sites of lesions in the brain following vascular occlusion and hemorrhage. This was largely carried out by Henry Duret (1873, 1874) in Charcot's laboratory at the Salpêtrière. Duret studied more than two hundred cases to formulate his classification of cere-

bral softening and hemorrhage from an anatomical point of view. He mapped the areas of distribution of the anterior, middle and posterior cerebral arteries, as well as the penetrating branches to the basal ganglia and brain stem. He demonstrated the subarachnoid arterial anastomosis by tying three of the principal arteries of the circle of Willis and injecting the fourth. With Charcot he described the lenticulostriate artery, styling it the "artery of cerebral hemorrhage". The usual sites of infarction and hemorrhage in the lateral and medial ganglionic areas were described, as well as their variations. Although the role of vascular occlusion in the production of cerebral infarction had been demonstrated by Virchow (1856) and by Cohnheim, Duret and Charcot first used the pathological lesions so produced to demonstrate the nature and evolution of cerebrovascular disease. The details of their work are clearly presented in the 1883 English translation of Charcot's lectures on localization of cerebral and spinal diseases.

At the same time as Duret was performing his studies in Paris, Otto Heubner, professor of medicine at Leipzig, carried out a similar investigation of the anatomy of the vascular supply of the brain. Heubner (1874) demonstrated by injection the subarachnoid arterial anastomoses, which he believed had an important role in the distribution of blood via a complex canal network. He also described the recurrent arterial branch from the anterior cerebral artery to the anterior limb of the internal capsule, as well as syphilitic arteritis; both of these discoveries were named for him.

Other investigations of the cerebral vasculature were performed; the most important being those of Beevor (1907, 1908-1909). The definitive modern studies of the arterial supply of the brain and the distribution of Sylvian infarcts were performed by Foix (1923, 1925, 1927) and his associates and by Pfeiffer (1928).

During the 19th Century it was generally accepted that cerebral hemorrhage resulted from rupture of diseased cerebral arteries. Charcot (1866) and Bouchard (1872), however, put forth the hypothesis that apoplectic hemorrhages were due to mi-

nute dilatations on the cerebral blood vessels. These were called "miliary aneurysms" and were considered to cause the hemorrhage, which in no way was considered to be related to atherosclerosis of the cerebral blood vessels. The subject was discussed by Liouville (1871) and the role of miliary aneurysms in cerebral hemorrhage continued to be contested even into the 20th Century.

The concept that the occlusive disease of the extra-cranial blood vessels could be responsible for neurological symptoms was first put forth by Chiari (1905). He emphasized the frequency of atherosclerosis in the region of the carotid bifurcation, believing that such lesions cause cerebral symptoms from atheromatous embolization. Ramsay Hunt (1914) gave the first definitive description of the role of the carotid artery occlusion in the production of vascular lesion of the brain and the symptoms so produced. Early modern scientific studies of the role of atherosclerosis in vascular disease were by Faber (1912) and on cerebral arteriosclerosis itself by Wolkoff (1933). Hypertensive encephalopathy was described by Oppenheimer and Fishberg (1928); Binswanger (1917) suggested that chronic progressive subcortical encephalitis was due to atherosclerosis, and Spielmeyer (1928) was among the first to recognize the effects of transient cerebrovascular insufficiency.

The occurrence of meningeal apoplexy or subarachnoid hemorrhage was recognized by Morgagni, who implied the existence of intracranial aneurysms. A ruptured aneurysm in a case of apoplexy had been reported by Biumi in 1765, but it was Gilbert Blane who gave the best clinical picture and autopsy finding of a "case of aneurysms of the carotid arteries". The patient had been under Blane's care and John Hunter performed the autopsy. The first illustration of a subarachnoid hemorrhage from an aneurysm is in Cheyne's (1812) book of apoplexy. Other cases were subsequently described by Blackall in 1813, Serres in 1819, Jennings in 1832 and Brinton in 1852. Bright's (1831) atlas contains a picture of a small mycotic aneurysm that "by its bursting had produced effusion of blood upon the surface of the brain and

consequent apoplexy".

The role of the cerebral circulation in normal brain metabolism and in disease states was greatly clarified during the Nineteenth Century. One of the fundamental doctrines of circulatory physiology was postulated by Alexander Monro secundus (1783). From his experience in brain anatomy, Monro deduced that the cranium is a rigid box completely filled with incompressible contents.

For being englosed in a case of bone, the blood must be continually flowing out of the veins that room may be given to the blood which is entering by arteries. For, as the substance of the brain, like that of other solids of our body is nearly incompressible, the quantity of blood within the head must be the same or nearly the same at all times whether in health or disease.

Monro's concepts were confirmed by the experimental work of George Kellie (1824). Kellie had noted that the brains of animals killed by exsanguination still contained blood, except where he had broken the integrity of the skull by trephining before death. The Monro-Kellie hypothesis thus postulated that the volume of the blood in the brain does not change.

This concept was shown to be not entirely valid, however, by the experimental work of George Burrows physician to St. Bartholomew's Hospital, London, who performed one of the first definitive studies of the physiology of the cerebral circulation. In his Lumleian Lecture of 1843-1844, Burrows concluded that he had demonstrated that the amount of blood in the brain can vary and that this may be responsible for clinical signs. Burrows' work (1846) was a milestone in the study of cerebral vascular physiology.

The Monro-Kellie doctrine therefore pertained only to the constancy of the blood volume of the brain, while Burrows showed that the cerebrospinal fluid volume would vary with alterations in intracranial contents. The production and absorption of cerebrospinal fluid was sufficiently slow under normal circumstances, so that the Monro-Kellie doctrine generally held as far as alteration taking place in the adult with an intact skull over a short period of time.

Many other investigators applied the Monro-Kellie doctrine, converting the craniovertebral cavity into an oncometer to measure changes in the intracranial pressure, which were interpreted as an alteration in intracranial volume occurring with changes in blood flow.

Sir Astley Paston Cooper, a leading London surgeon, performed a remarkable experiment (1836) to demonstrate that loss of consciousness was due to anemia of the brain. After tying off the carotid arteries of a rabbit, Cooper then compressed the vertebral arteries with his thumbs.

Respiration almost directly stopped; convulsive struggles succeeded; the animal lost consciousness and appeared dead. The pressure was removed and it recovered with a convulsive inspiration. It laid upon its side, making violent convulsive efforts, breathed laboriously and its heart beat rapidly. In two hours it had recovered but its respiration was laborious.

This important experiment was one of the first demonstrations of the effects of circulatory arrest and anoxia on the brain.

Frans Cornelius Donders was the first investigator to study the cerebral circulation in a living animal by observation of pial vessels through a sealed glass window in the calvarium. Donders, a professor at Utrecht and a pioneer ophthalmologist, observed (1850) variations in the caliber of pial vessels in different states especially during asphyxia, in which these vessels were significantly dilated. He was followed by Angelo Mosso of Turin, who performed one of the earliest studies of human cerebral circulation. Mosso (1881) recorded changes in the volume of intracranial contents by sealing a tambour system to the scalps of patients with cranial defects and continuously recording the alteration produced under varying physiological conditions. The changes in cerebral blood flow which he inferred from his measurements were often quite accurate.

The regulation of the cerebral circulation was further elucidated in the experiments of Roy and Sherrington (1890). Using a delicate recording apparatus, the measured changes in the vertical diameter of the brain in the open cranium. They found that un-

der many experimental conditions the blood supply of the brain varied directly with the blood pressure in the systemic arteries. They also observed that during asphyxia and following the intravenous infusion of strong acids, a marked expansion of the brain occurred which was independent of the arterial blood pressure. Stimulation of the vasomotor nerves, they discovered, affected intrinsic control, and anemia caused vasoconstriction with an increase in the blood flow. From their many studies they concluded that the variation in caliber of the cerebral vessels was regulated by

...the chemical products of cerebral metabolism contained in the lymph which bathes the walls of the arterioles of the brains... In this reaction the brain possesses an intrinsic mechanism by which its vascular supply can be varied locally in correspondence with local variations of functional activity.

This concept of Roy and Sherrington was subsequently proven to be the basis of the regulation of cerebral circulation. Although Sir Leonard Hill (1896) and Sir W. H. Bayliss (1895) suggested that the cerebral circulation varied directly with the blood pressure in the systemic arteries, their concept, accepted for nearly twenty-five years, was later proven invalid. Cappie (1890)

and Browning (1897) also produced notable monographs on blood circulation in the brain. Bayliss (1902), in studying vasomotor regulation of brain blood flow, was the first to present definitive evidence that changes in intraluminal pressure would cause alterations in tone of the arterial wall.

Studies of the human cerebral circulation were made much less difficult by the demonstration by Abraham Myerson and his colleagues (1927) that cerebral venous blood could be obtained safely and easily through the insertion of a needle into the internal jugular vein. Using this technique changes in cerebral blood flow were estimated by Lennox and Gibbs (1932) by measuring cerebral arteriovenous oxygen, glucose and carbon dioxide difference.

The definitive work on cerebral blood flow was carried out by the utilization of arteriovenous difference and the Fick principle, elaborated by Adolf Fick of Cassel. A pupil of Ludwig, Fick produced works on medical physics and heat production during muscular activity. The application of his (1870) principle that the blood flow of an organ may be determined providing that the oxygen consumption and the arteriovenous oxygen difference are known, was first used to study human cerebral blood flow by Kety and Schmidt.

BIBLIOGRAPHY

1. *Abercrombie, J.*: Pathological and Practical Researches on Diseases of the Brain and the Spinal Cord. Edinburg, Waugh and Innes, 1828.
2. *Baillie, M.*: The Morbid Anatomy of Some of the Most Important Parts of the Human Body. London, J. Johnson and G. Nicol, 1793.
3. *Bayle, F.*: Tractatus de Apoplexia. Toulouse B. Guillemette, 1677.
4. *Bayliss, Sir W. M.*: On the origin from the spinal cord of the vasodilator fibers of the hindlimb, and on the nature of these fibers. J. Physiol (London), 26:173, 1901.
5. *Bayliss, Sir W. M.*: On the local reactions of the arterial wall to changes of internal pressure. J. Physiol (London), 28:220, 1902.
6. *Bayliss, Sir W. M. and Hill, L.*: On intracranial pressure and the cerebral circulation. J. Physiol (London), 18:334, 1895.
7. *Beevor, C.E.*: The cerebral artery supply. Brain, 30:403, 1907.
8. *Beevor, C.E.*: On the distribution of the different arteries supplying the human brain. Phil Trans Roy Soc, (ser. B) 200:1, 1908; 200:9, 1909.
9. *Binswanger, O. and Schazel J.*: Beitrage zur normalen und pathologischen Anatomie der Arterien des Gehirns. Arch Psychiat, 58: 141, 1917.
10. *Bouchard, C.*: A Study of Some Points in the Pathology of Cerebral Hemorrhage. London, Simpkin, Marshall and Co., 1872.
11. *Bright, R.*: Reports of Medical Cases Selected with a View of Illustrating the Symptoms and Cure of Diseases by References to Morbid Anatomy. Diseases of the Brain and Nervous System. London, Longman, 1831, vol. 2.
12. *Bright, R.*: Cases illustrative of the effects produced when the arteries and brain are diseased. Guy's Hosp Rep, 1:9, 1836.
13. *Browning, W.*: The Normal and Pathological Circulation in the Central Nervous System (Myelencephalon), Original Studies. Philadelphia, Lippincott, 1897.

14. *Burrows, G.*: On Disorders of the Cerebral Circulation and on the Connection Between Affections of the Brain and Disease of the Heart. London, Longman, Brown, Green and Longmans, 1846.
15. *Cappie, J.*: The Intracranial Circulation and Its Relation to the Physiology of the Brain. Edinburgh, J. Thin., 1890.
16. *Carswell, R.*: Pathological Anatomy: Illustrations of the Elementary Forms of Disease. London, Longman and Co., 1838.
17. *Casserio, G.*: Tabulae Anatomicae. xxiix. Frankfurt, Daniel Buietius, 1632.
18. *Chandler, B.*: An Inquiry into the Various Theories and Methods of Cure of Apoplexies and Palsies. Canterbury, Simmons and Kirkby, 1785.
19. *Charcot, J.M.*: Lecons sur les maladies du système nerveux faites à la Salpêtrière. Paris. A. Delahaye, 1872-1893.
20. *Charcot, J.M. and Bouchard, A.*: Douleurs fulgurantes de l'ataxie sans incoordination des mouvements; sclérose commençante des cordons postérieurs de la moelle épinière. Gaz Méd. France, (3^{ser.}) 21:122, 1866.
21. *Chevers, N.*: Remarks on the effects of obliteration of the carotid arteries upon the cerebral circulation. London Med Gaz, 1: 1140, 1845.
22. *Cheyne, J.*: Cases of Apoplexy and Lethargy with Observations on Comatose Patients. London, Thomas Underwood, 1812.
23. *Chiari, H.*: Über das Verhalten des Teilungswinkels der Carotis communis bei der Endarteritis chronica deformans. Verh Deutsch Path Ges, 9:326, 1905.
24. *Clarke, E.*: Apoplexy in the Hippocratic writings. Bull Hist Med, 37:301, 1963.
25. *Clarke, E. and O'Malley, C.*: The cerebral circulation. In: The Human Brain and Spinal Cord. Chapt. 13, Berkley Univ. of California Press, 1968.
26. *Clarke, E.*: Cerebrovascular system—historical aspects. In: Radiology of the Skull and Brain, T.H. Newton and D.G. Potts (eds.), Chapt. 42. Mosby, St. Louis, 1974.
27. *Cooke, J.*: A Treatise on Nervous Disease. London, Longman and Co., 1820-1823.
28. *Cooper, Sir A.*: Some experiments and observations on tying the carotid and vertebral arteries, and the pneumogastric, phrenic, and sympathetic nerves. Guy's Hosp Rep, 1:457, 1836.
29. *Copland, J.*: Of the Causes, Nature and Treatment of the Forms, Seats, Complications and Morbid Relations of Paralytic and Apoplectic Diseases. Philadelphia, Lea and Blanchard, 1850.
30. *Cruveilhier, J.*: Anatomie pathologique du corps humain; descriptions avec figures lithographiées et coloriées; des diverses altérations morbides dont le corps humain est susceptible. Paris, J.B. Bailliere, 1835-1842.
31. *Cullen, W.*: Of neuroses, or nervous diseases. Part II. In: First Lines of the Practice of Physic. Edinburgh, William Creech, 1778-1784.
32. *Donders, F.C.*: Die Bewegung des Gehirns und die Veränderungen der Gefäßfüllung der Pia mater, auch bei geschlossen, unausdehnbarem Schädel unmittelbar beobachtet. Nederl Lancet, 1850.
33. *Durand-Fardel, C.L.M.*: Traité du ramollissement du cerveau. Paris, 1843.
34. *Duret, H.*: Sur la distribution des artères nourricières du bulbe rachidien. Arch Physiol Norm Path, 5:97, 1873.
35. *Duret, H.*: Recherches anatomiques sur la circulation de l'encéphale. Arch Phys Norm Path, (2^{ser.}) 1:60, 316, 664, 919 1874.
36. *Faber, A.*: Die Arteriosklerose: ihre pathologische Anatomie, ihre Pathogenese und Aetiologie. Jena, G. Fischer, 1912.
37. *Fick, A.*: Über die Messung des Blutquantums in den Herzventrikeln, Verh Phys Med Ges Würzburg, 2:14, 1870.
38. *Foix, C. and Hillemand, P.*: Les syndromes de l'artère cérébrale antérieure Encephale, 4:209, 1925.
39. *Foix, C. and Hillemand, P.*: Les artères de l'axe encéphalique jusqu'au diencéphale inclusivement. Rev Neurol (Paris), 32:705, 1925.
40. *Foix, C. and Levy, M.*: Les ramollissements Sylvien. Rev Neurol (Paris), 2:1, 1927.
41. *Foix, C. and Masson, A.*: Le syndrome de l'artère cérébrale postérieure. Presse Méd. 32:361, 1923.
42. *Gay, J.A.*: Vues sur le caractère et le traitement de l'apoplexie dans lesquelles on réfute la doctrine du Docteur Portal sur cette maladie. Paris, Gabon, 1807.
43. *Wers, Sir W.R.*: A Manual of Diseases of the Nervous System. London, J. and A. Churchill, 1886-1888.
44. *Granier, J.E.*: Traite sur l'apoplexie, considérée en elle-même, d'après les vues anciennes et modernes et relativement aux maladies qui la simulent, la précèdent l'accompagnent ou lui succèdent. Paris, Bechet Jeune, 1826.
45. *Hall, M.*: Lectures on the Nervous System and Its Diseases. London, Sherwood, Gilbert and Piper, 1836.
46. *Heubner, O.*: Die leutische Erkrankung der Hirnarterien. Leipzig, Vogel, 1874.
47. *Hill, Sir L.E.*: The Physiology and Pathology of the Cerebral Circulation. London, J. and A. Churchill, 1896.
48. *Hooper, R.*: The Morbid Anatomy of the Human Brain; Illustrated by Coloured Engravings of the Most Frequent and Important Organic Diseases to Which That Viscus is Subject. London, printed for the author, 1828.
49. *Hope, J.; Bennett, J.H.; Prichard, J.C.; Taylor, R.M.; and Thomson, T.*: Dissertations on nervous diseases, In Tweedie, A. (ed.): Library of Practical Medicine. Philadelphia, 1840.
50. *Hunt, J.R.*: The role of the carotid arteries in the causation of vascular lesions of the

- brain, with remarks on certain special features of the symptomatology. *Amer J. Med Sci*, 147:704, 1914.
51. *Jackson, J.H.*: A lecture of softening of the brain. *Lancet*, 2:335, 1875.
 52. *Jensen, P.*: Über die Blutversorgung des Hirns. *Arch Ges Physiol*, 103:171, 1904.
 53. *Kellie, G.*: Reflections on the pathology of the brain. *Trans Med Chir Soc Edinburgh*, 1:123, 1824.
 54. *Kety, S.S.*: The cerebral circulation. In: *Circulation of the Blood, Men and Ideas*. Fishman, A.F. and Richards, D.W. (eds.). Chapt. 11, New York, Oxford, 1964.
 55. *Kirkland, T.*: A Commentary on Apoplectic and Paralytic Affections and On Diseases Connected with the Subject. London, W. Dawson, 1792.
 56. *Lennox, W.G., and E.L. Gibbs*: The blood flow in the brain and the leg of man, and the changes induced by alteration of blood gases. *J. Clin Invest*, 11:1155, 1932.
 57. *Lidell, J.A.*: A Treatise on Apoplexy, Cerebral Hemorrhage, Cerebral Embolism, Cerebral Gout, Cerebral Rheumatism and Epidemic Cerebrospinal Meningitis. New York, Wm. Wood & Co., 1873.
 58. *Liquille, H.*: De la généralisation des anévrysmes miliaires. Paris, Germer Bailliere, 1871.
 59. *McHenry, L.C., Jr.*: Garrison's History of Neurology. C.C. Thomas, Springfield, Ill., 1969.
 60. *Meyer, A. and Hierons, R.*: Observations on the history of the circle of Willis, *Med Hist*, 6:119, 1962.
 61. *Mistichelli, D.*: Trattato dell apoplessia. Roma A. De Rossi alla Piazza di Ceri, 1709.
 62. *Monro, A.*: Observations on the Structure and Functions of the Nervous System. Edinburgh, W. Creech, 1783.
 63. *Montain, J.F.F.*: Traité de l'apoplexie. Paris, Brunot-Labbe, 1811.
 64. *Morgagni, G.B.*: De sedibus, et causis morborum per anatomem indagatis libri quinque. Vienna, ex typographica Remondiana, 1761.
 65. *Mosso, A.*: Über den Kreislauf des Blutes im menschlichen Gehirn. Leipzig, Viet, 1881.
 66. *Mushet, W.B.*: A Practical Treatise on Apoplexy (Cerebral Hemorrhage); Its Pathology, Diagnosis, Therapeutics and Prophylaxis. London, John Churchill and Sons, 1866.
 67. *Myerson, A., R.D. Halloran, and H.L. Hirsch*: Technic for obtaining blood from the internal jugular vein and internal carotid artery. *Arch Neurol Psychiat (Chicago)*, 17: 807, 1927.
 68. *Nymman, G.*: De apoplexia tractus, 2nd ed., Wittebergae, J.W. Fincelli, 1670.
 69. *Oppenheimer, B.S. and Fishberg, A.M.*: Hypertensive encephalopathy. *Arch Intern Med*, 41:264, 1928.
 70. *Portal, A.*: Observations sur l'apoplexie. *Mem Acad Sci*, 83:623, 1781.
 71. *Portal, A.*: Observations sur la nature et le traitement de l'apoplexie, et sur les moyens de la prévenir. Paris, Chochard, 1811.
 72. *Richelmi, P.*: Essai sur l'apoplexie, ou pathologie, sémeiotique, hygiène et thérapeutique de cette maladie, considérée dans ses différentes especes. Marseille, Joseph-François Achard, 1811.
 73. *Ridley, H.*: The Anatomy of the Brain Containing its Mechanisms and Physiology; Together with Some New Discoveries and Corrections of Ancient and Modern Authors upon That Subject. London, Sam. Smith, 1695.
 74. *Rochoux, J.A.*: Recherches sur l'apoplexie. Paris, Marvis, 1814.
 75. *Romberg, M.H.*: A Manual of the Nervous Diseases of Man, edited and translated by H. Sieveking, London, The Sydenham Society, 1853.
 76. *Rostan, L.*: Recherches sur le ramollissement du cerveau. Ouvrage dans lequel on s'efforce de distinguer les diverses affections de ce viscere par des signes caracteristiques. Paris, Bechet, 1823.
 77. *Roy, C.S. and Sherrington, C.S.*: On the regulation of the blood-supply of the brain. *J. Physiol (London)*, 11:85, 1890.
 78. *Ruysch, F.*: Opera omnia anatomico-medico-chirurgica. Amsterdam, Janssionio-Waesbergios, 1724.
 79. *Schiller, F.*: Concepts of stroke before and after Verchow. *Med Hist*, 2:115, 1970.
 80. *Serres, A.E.R.A.*: Nouvelle division des apoplexies. *Ann Med Chir*, 1:246, 1819.
 81. *Serres, A.E.R.A.*: New division of apoplexies. *Phil J. Med. Phys Sci*, 7:227, 1823; 8: 89, 1824; 9:53, 304, 1824.
 82. *Spielmeyer, W.*: Vasomotorisch trophische Veränderungen bei zerebraler Arteriosklerose. *Mtschr Psychiat*, 68:605, 1928.
 83. *Swieten, G. van*: Of the apoplexy, palsy and epilepsy, Commentaries Upon the Aphorisms of Dr. Herman Boerhaave. London, John & Paul Knapton, 1754, vol x.
 84. *Vesling, J.*: Syntagma anatomicum, locis plurimum actum, emendatum, novisque iconibus diligenter exornatum. Patavii. Pauli Frambotti Bibliopolae, 1647.
 85. *Virchow, R.L.K.*: Gesammelte Abhandlungen zur wissenschaftlichen Medizin. Frankfurt, Meidinger, 1856.
 86. *Wepfer, J.J.*: Observationes anatomicae, ex cadaveribus eorum, quos sustulit apoplexia, cum exercitatione de ejus loco affecto. Schaffhausen, John. Caspari Suteri, 1658.
 87. *Willis, T.*: Cerebri anatome: cue accessit nervorum descriptio et usus. Londini, J. Fleisher, 1664.
 88. *Wolkoff, K.*: Über Atherosklerose der Gehirnarterien. *Bierr Z Path Anat Allg Path*, 91:515, 1933.

*Napoléon and Josephine
at Malmaison*



On vacation

Napoleón and Josephine at Malmaison

Houses, the same as people, are born to fulfill a destiny, to contain hopes, laughter, dreams and tears.

Many of them live several lives, to end in anonymity, destroyed by time. Some survive sustained by historical events and reach immortality, and that was the case of the Château of Malmaison. Malmaison, Napoleon and Josephine had a date to be accomplished at a given time, to pass together to immortality.

While Napoleon was an adolescent growing in Corsica, surrounded by greenish mountains and a wavy ocean, Josephine was a graceful girl, learning the duties of a future lady in the flowery and enchanting Martinique, the Malmaison had already a long history behind it.

Settled on the slopes of selvatic hills, crisscrossed by streams of clear waters, Malmaison had travelled through the times enduring a hazardous life.

How far in time is Malmaison historically recorded?.

It belonged to the villa of Reuil which was already mentioned in the VIth century. A fisher village was settled on the Seine between Malmaison and Bougival and its owner Charles Martel divided his earnings with the monks, especially those of the Saint Denis Abadie.

In 845 the Normands invaded the place and fought the Royal troops which fled.

After many combats and the spoils that followed them, this place deserved the adjective of Malport or Malmaison, and thus its name was coined.

In a generous gesture Charles the Bald donated in 870 the district of Reuil to the Abbey of Saint Denis.

The place was parcelled according to their convenience, but they maintained their rule above them.

Towards the XIIIth century the fief of Malmaison was established and in the beginning of the next century a Scotch named Onfroy d'Oricpatrie became its owner, who lacking heirs donated this place in 1330 to Guy de Castres. Abbe of Saint Denis who in 1337 turned it to his Community.

This place aroused the interest of Raoul Lamoureux, clerk of the Royal Treasury who bought it in 1376. His son Raoul II sold the Malmaison to some relatives, and this property became the property of different members of the same family, passing from the Auverns, to the Perrots, Barentins, who for a time inherited Malmaison, facts that were recorded in historical documents, regarding this place.

The construction of the main building in moillon access without any sculpted decoration, has a ground floor, first floor and an attic with nine windows. On the roof between two pavillions the roof was covered with slates which dated to the beginning of the XVIIIth century, and it is believed that by that epoch it belonged to Cristopher Perrot, Councillor of the Parliament of Paris and son of the President Claude Perrot.

The entrance was located on the East side and a dry ditch was excavated all around the building.

But this modest building was by no means considered the real Castle of Reuil.

The one that deserved this title was owned by the all powerful Richelieu, whose dwellings gained in beauty and splendor under the direction of Jacques Lemercier.

Important events were carried out and signed in this Castle such as the process and judgement of the Marechal Maurillac and the treaty of the annexation of Colman at France.

The Castle fountains and gardens resembled those of Versailles.

While the modest Malmaison, constructed in 1622 at the same time as the Richelieu castle, it was condescendingly tolerated in its neighborhood.

Richelieu, being Minister of Louis XIII and enjoying great authority, bought from the Abbey of Saint Denis the rights over Reuil and the neighboring fiefs which included Malmaison.

But in 1686, Louis XVI gave the Lordship over this district to the Ladies of Saint Louis who were in charge of the girls of Saint Cyr.

Malmaison continued its voyage through time changing owners from time to time.

While the appointed "Castle of Reuil" whose beauty and splendor were the pride of Richelieu was steadily deteriorating until its very ruins were bought by Massina, at the end of the XVIIIth century.

Charles Perrot Member of the Parliament acquired the Malmaison and after marrying his daughter Marie-Madeline, Jacques Barentin, First President of the Great Council, became the owner of Malmaison in 1685.

His sons and grandsons, Intendants of Orleans, leased these domains to some distinguished personalities.

Since 1742 M. de la Jonchere became its long life tenant, introducing some changes in the building: two attics in the wings of the roof were transformed into pavillions. In 1757 M. de Boulogne general tax collector, rented the Malmaison for a lapse of six years.

Afterwards Mme. Harenc de Presle became its tenant; gatherings at Malmaison of the most cultured people of her time, were held.

Mme. d'Aguessau widow of a council of State bought Malmaison in 1766 and in 1771, this building was acquired by Jacques-Jean le Goulteulx du Moley general collector of Lottery and administrator of the Discount Company, who paid 180.000 pounds for it.

Malmaison became the center of elegant gatherings of highly sophisticated guests, where the best of the nobility were alternating with artists, men of letters, and it was regarded as a pleasant and inspiring place, with beautiful natural surroundings.

But the rumblings of Revolution were filtering into the conversations with a tinge of danger. Premonitions of disaster were felt like menacing thunders.

When the storm shook the pillars of the French aristocracy, the Du Moley could save their lives but by the forces of the circumstances they were obliged to sell Malmaison.

In Croissy neighboring with Malmaison was a creole from Martinique named Marie-François de Louvigne the widow of Jean Baptiste Lamothe-Hostin. There Josephine was invited to spend a vacation while her husband Alezander de Beauharnais was engaged in political and military activities.

From her hostess' house Josephine saw for the first time at the distance the white walls and the slate roof of Malmaison and fell in love with it.

The vacation was abruptly interrupted when she was arrested to follow the same fate as all the aristocracy of her time.

Her husband was beheaded on July 23 of 1794 and a few days later on

August 23 she was liberated and returned to Croissy.

Josephine alone, with two children to take care of, faced a hard aspect of life.

The reign of Terror changed her world and in the new one all the old aristocratic levels were vanishing. In this new world she met the General Napoleon Bonaparte, and married him on May 9, 1796.

Even if Napoleon loved her and steadily carried her toward a luminous future, she felt insecure.

They had separate belongings; their house in the Chantierine street became Napoleon's private property.

Some dark premonitions clouded Josephine's thoughts, when time was slipping by and after several years of marriage, and medical treatment, she failed to give Napoleon an heir.

She feared divorce, especially when Napoleon's brothers and sisters, were insisting on the need that Napoleon had an heir to avoid future troubles to the country. Their attacks were poisoning her life, and she remembered Malmaison as a paradise where she would like to enjoy a peaceful and pleasant existence.

After Napoleon's successful campaign in Italy, Josephine suggested to buy Malmaison as a country house. Napoleon visited the place near the village of Reuil, ten miles down the Seine from Paris.

But he did not obtain an agreement with the Du Moleys who wished a sum superior to Napoleon's offer.

Josephine was in love with Malmaison and decided not to give up her wish to own it so she asked a friend of hers, Mr. Chanonier, an old neighbor of Croissy to serve as a mediator with the Du Moley.

Chanonier carried the message to the Du Moley, who conveyed to her their last offer of 290.000 francs, for the castle. They valued the mirrors in 20.000 francs and the furniture would be estimated by an expert.

They discussed the price and finally Josephine bought the Malmaison.

On April 21, 1799, in front of her notary Mme. Raguideur, she acquired the domain of nineteen farms, on a surface of 260 hectares of wheat, vineyard forests, prairie, and the livestock.

The castle and its dependences, concerning the nine rooms of the "Batiment de l'Horloge (the Clock Building) the four levels of the Tower with its Office of Natural History and the Liberty Pavillion, the orange grove, the green-house, the wine-press, the pidgeon-house, the mill, the aviary, the barn, and the apartment of Mr. Lhuillier, the concierge.

In the notary document it is established that "La presente vente est faite moyennement la somme de 225.000 francs, en deduction dequel prix l'adquereur a presentement paye la somme de 15.000 francs ...". "La citoyenne Bonaparte declare que le 15.000 francs qu'elle vient de payer proviennent de l'emprunt qu'elle en a fait de Jean Lhuillier cultivateur a Reuil".

As could be gathered from this document, Josephine did not hesitate to loan from the concierge the necessary amount of money to pay an advance of 15.000 francs needed to close the purchase of the chateau Malmaison and to be in debt for the rest.

In another document her notary stated that the furniture was bought by Josephine for 37.516 francs in selling her diamonds.

At last Josephine has a home of her own.

Even if the furniture was deteriorated and mediocre, included a collection of curiosities among them a straw stuffed lobster.

This was just a start, Josephine's plans for Malmaison were grand, and some years after, it was transformed significantly.

Napoleon never forgot the affront that she caused him when she made the house-warming of Malmaison in company of the handsome young Lieutenant

Charles in his presence in Egypt. But Josephine exerted such a power over Napoleon that she always obtained his pardon.

The soreness of this fact was still remembered by Napoleon at St. Helene.

Josephine was elated, her new home reminded her of Martinique, her beloved Island where she was born.

She began to spend money without measure, beyond her means, forgetting to pay her suppliers and even her debt with the Du Moleys.

Napoleon acted generously forgetting her treason paying all her debts, and rescuing her from disaster.

Thus the Malmaison was completely acquired on 5 Nevose, 3 Pluviose, 5 Ventose, and VIII.

The castle of Malmaison was living its best times, Josephine continued her way of living, it being impossible to refrain her from spending money. Napoleon always cried, protested and paid.

Josephine, aimed at transforming Malmaison according to her wishes, called to her aid two great artists, Charles Perrier, winner of the first prize in the Rome competition in 1786 and Pierre Fontaine, the winner of the second prize in the competition of 1785.

They were desolated at the sight of Malmaison. They wanted to build a real castle. To reform Malmaison it would constitute for them a nightmare.

They lamented "It is a pity that we cannot have the occasion to have the honor of constructing in this beautiful place of Malmaison a building worthy of a great man whom we admire".

Fontaine lamented in his diary the affliction of having to employ their talents in reforming an "old building".

"It was necessary to reform and rend comfortable a banned mansion whose ruins were falling apart and that was built for ordinary people".

In spite of all the troubles and expenses in repairing Malmaison, the First Consul persisted in giving orders for making this place adequate. He ordered that the dining room ought to be enlarged and that all the small rooms that preceded it be destroyed, that a place for him ought to be made over the drawing room.

"He (the First Consul) let us perceive by his questions and among all the great projects and magnificence that he proposed, that we must submit ourselves to the most severe expense restrictions".

And in spite of all these difficulties the architects transformed Malmaison beyond recognition.

Inside the austere hall, Percier and Fontaine had achieved that the columns placed in an exact proportion appeared as monumentals, this effect was softened by great mobile mirrors which without being silvered would allow the perceptions of the adjoining rooms.

Noisy parrots perched in the hall placed an array of colours and enlivened the atmosphere.

Josephine was specially fond of these birds that reminded her of her native Island, Martinique.

The floor was covered by black and white squared marble, giving the impression of a big chess board.

The visitor, nowadays, may see around, the same busts of marble of the different members of Bonaparte's family as if they were placed there by hands of destiny, to play a historical chess game whose moves will rend them immortal. Now, motionless, placed around the walls, they may see crossing the hall other lives that came to peer into their lives.

The reception apartments were decorated by Jacob Lafitte and Moench whose abilities rendered a beautiful effect, after a considerable effort to adapt the old elements to the consular style whose characteristic was a great profusion of Roman and Pompeyan decorations.



MALMAISON - Entrance



The Rosary, with the Empress Josephine Statue.

The ground floor was modified so that a suite of large rooms may communicate with each other ending on one side in a small gallery and on the other end in a library.

On the first floor are the rooms of the First Consulate, another seven comfortable rooms, and ten on the second one.

A small theater was constructed aside the building and was connected with the gallery by a canvas covered passage.

The park has gained more than a half of extension. In a place where there was a mill before, a stable was constructed for the chariots. Another one at the end of the park with guards for the pickets of cavalry.

The kitchen that was placed underground was transported to one of the farms.

Josephine's personal taste enhanced the gardens, the panorama became beautiful, the streams of waters were directed according to her wish, to rest in ponds or to continue their ways in graceful curves passing under bridges bordered by flowered gardens.

Malmaison was transformed beyond recognition and became the symbol of two powerful personalities, to comply with each one's wishes became a "tour de force" for the architects Fontaine and Percier.

When they finished the planting of the park, Josephine objected because the straight avenues did not please her, she dreamed of a park in the English style. To design an avenue that conducts in a straight way to a point was in her opinion against the best rules of gardening.

It is heartbreaking to read in the Fontaine's diary all the bitterness and humiliation he suffered in planning the garden.

"To talk about order and regularity in the planning of a garden was for her a blasphemy. She wanted only groups of effects, of opposites, and above all of feelings".

They were happy that she conceded the avenue of the entrance and that a tortuous design was spared for the transit of the horses.

Mr. Morel, an old gardener, author of books on gardening, was for them an unwelcome visitor.

He was ready to criticize all the works done, pointing out faults against good taste, everywhere.

Desolated Fontaine remarks "A project of a botanical garden, with greenhouses, barn yard, aviary, tree-nursery and with a pavillion in the center, in whose interior was a Museum, was already presented and was very much praised, one of the greenhouses was already built, but the patriarch of the English gardens did not like it". The greenhouse was rejected.

On September 7, 1801 he wrote in his diary "M. le General Duroc confided to us that the First Consul had appointed M. Lileur from Ville-sur-Arce as intendant of the gardens, and I have heard rumors at Malmaison that the architects did not know anything about gardening, and if Mr. Morel were not so old, he could direct the gardens".

"I didn't answer, I understood from whom the first part of the sentence came and I recognized from the second that our aim was lost".

These bitter words came from an architect recognized as one of the best artists of his time.

In spite of all these disagreements and changes of intendants of the gardens of Malmaison they became world famous by their beauty and the collections of rare plants brought from almost every country of the world.

Thibaut and Vignon built in 1805 a large green house which was named "Little Malmaison" a delightful place scented with the smell of exotic flowers.

It has been referred in a beautiful illustrated book entitled "Gardens of Malmaison" by the world famous Ventenat.

Another exciting book was one entitled "Descriptions of rare plants cultiva-



Berthault and Lenoir: The Temple of Love. Malmaison Park.

ted in *Malmaison and Navarre*, published by the famous botanist Bonpland who accompanied Humbolt on an expedition to America. This book was published in 1813.

He was appointed intendant of the domain of Malmaison in 1809. Josephine who was a wonderful match-maker married him to a creole like her from the Martinique, a widow, who made him very unhappy.

The park remodelled by Berthoult in 1805 reached the peak of its beauty, when he got from Alexandre Lenoir, founder of the Museums of French Monuments, columns that were to embellish the construction of a small ancient temple and the statue of "Love" made by Tassaert; he also furnished different types of statues, the rostral columns and the lovely statue of Neptune that was placed in the "Naumache" on the "Neptune Fountain", and the obelisks placed at the entrance of a stone bridge.



Sculpture of Neptune before at "Naumache" or Fountain of Neptune. Malmaison Park.

*Art from different epochs enhance Malmaison, some ancient, like the Etruscan vases and bronzes, that were mixed with splendid statues of Canova, that shared everybody's admiration with the most celebrated paintings from Pousin, Pat-
 ter, Rembrandt, Le Lovain, etc and were placed in the Big Gallery, bestowing upon it the impression of a museum of high quality.*

At the beginning of 1809 it was incorporated a Music Room under the wise direction of Berthault.

Josephine's love of beauty made her a wonderful collector of the best in Art, and as she was a passionate lover of Nature, she never ended in her persistence in getting the most rare and beautiful plants.

This was a kind of worship because as Sir Thomas Browne said "All things



Bosio: Love throwing an arrow and flying away. Marble 1810. Before at the center of the salon of the Hothouse.

are artificial, for nature is the art of God".

She managed to get by most surprising means the specimens she wanted.

She wrote General Brune Ambassador in Constantinople the following letter dated March 16, 1804.

"Votre situation vous met à portée de me procurer toutes les plants du Levant, et je vous devrai l'avantage et le plaisir d'avoir les plus beaux et le plus curieux jardin de L'Europe" *"Entre les choses precieuses que vous pourriez m'adresser, je citerai les cerises de Cerasontes les glands de chêne Velani, les noisettes de Constantinople, le saule pleureur odorant d'Alep"*.

N'oubliez pas la promesse que vous m'avez faite de faire executer des fouilles en Grece et notamment a Athene par nous procurer des medailles, des marbres et des bronzes antiques".

"Your situation allows you to provide me with all the plants of the East and I would owe you the advantage and the pleasure of having the most beautiful and the most curious garden of Europe".

"Among the precious things you can send me I will mention the cherries of Cerasontes, the acorn of cak Velani the hazelnut of Constantinople, the scented weeping willow from Aleppo".

"Don't forget your promise of ordering that excavations be made in Greece and especially in Athens to obtain for me medals, and antique bronzes".

To another diplomatic in mission in Berlin, and who had sent her notices about the beautiful flowers of Pomerania she sent the following letter:

"On m'a assurée qu'il avait aussi des plantes tres rares dans le jardin de l'electeur de Hesse et dans ceus du Hanovre. Je crois que ses collections ne son pas indignes de vous soins".

"I have been assured that there also exists very rare specimens in the gardens of the Elector of Hesse and also in those of Hanover. I believe that their collection deserves your attention". Mr. de Beauharnais brother of his first husband who was ambassador in Spain knowing her predilection for plants sent her many beautiful specimens that she thanked in a letter dated February 18, 1808, his contribution to beautify her garden *"d'orner Malmaison de nouvelles richesses"* *"Mon seul regret en recevant ces plantes a été de voir que la route en avait endommagé une assez grande partie"* *Je serai charmée aussi de avoir quelques tableaux de Morillos (sic) et de l'Espanolet"*.

"To adorn Malmaison with new richness" *"My only regret in receiving these plants has been to see that a great number of them have been damaged during the voyage"* *I would be also enchanted if I could have some paintings of Morrillos (sic) and of the "Espanolet" Jose V. Ribera.*

Josephine was insatiable in getting beautiful things in all its manifestations paintings, antiques, colorful birds, beautiful and rare plants, incurring sometimes in excesses that aroused commentaries like this:

According to Mademoiselle Avrillon *"The Empress could have built a tremendous palace for what she poured into improvements for that relatively simple country state. "Why, I once saw her pay three thousands francs for a single tulip bulb from Holland"*.

From the Directory days she was critized by the Marquies de Sade who said *"Not all the revenues of all the provinces of France could have satisfied her extravagances"*.

Josephine's search for plants is a never ending task, and her wishes were respected even during wartime. It is interesting to remark that the English ve-

ssels were ordered to let pass the grains, the buds, and branches, coming from the antipodes.

Josephine made a wonderful contribution to the gardening of France, acclimatizing many hundreds of new specimens at Malmaison.

Her collection of roses were very much praised and became famous, more than 250 different kinds of roses flourished at Malmaison among them "Belle sans flatterie". "Beautiful without flattery" and "Cuisse de nymphe emue" "Leg of touched nymph".

In the midst of these natural surroundings, a highly sophisticated life was maintained.

A savory mixture of aristocrats playing at being revolutionaries and of revolutionaries aspiring at being aristocrats.

Malmaison became the favorite place of Napoleon; it was commented that in visiting Malmaison he was as happy as a boy on vacation.

A ball at Malmaison was a most delightful event, Josephine was a model of grace and elegance.

From Paris to Malmaison a stream of carriages came to attend the social event. At one of these balls Josephine startled the attendance by wearing a gown



Girodet: The Apotheosis of the French Heroes, who died for the Country during the Liberty war 1801. Destined for the Salon of Malmaison. Malmaison Museum.



Gerard Ossian evoke the Phantoms at the Tune of the Harp on the Borders of the Lora. 1800-1501.

Destined for the Salon of Malmaison. Malmaison Museum.

created for her by Leroy; it was made of gleaming white satin covered by thousands of very palid pink rose petals. Marie Joseph Rose, as she was baptized was the only beautiful Rose that night.

Theatrical events also took place at Malmaison, which Napoleon enjoyed very much, seeing members of his family and other persons of Malmaison acting in different plays.

Bourrienne and Hortense behaved as consummated actors and were the most brilliant stars of this amateur company.

The theater was in a separate building, and had seats for 200 persons; this was connected with the Long Gallery, a true museum displaying treasures of art pieces among them some of striking beauty coming from Italy and Egypt.

In the so-called little Gallery, today known as the Music Room, streams of music filled Malmaison inviting to dance. Hortense, Josephine's daughter was a great composer and singer.

Josephine, seated at her golden eagle harp was a delightful vision, she excelled and dominated the art to look always beautiful and elegant. Whether seated at the musical instrument, or when led by the Consul she opened the ball.

But not everything was singing and dancing at Malmaison; early in the morning, a multitude of messengers arrived who were standing still with respect, when with rapid steps the little boots of Napoleon resounded rapidly crossing the hall, he received the visitors or messengers in his office library.

It is worthwhile to remark that this place was ordered by Napoleon in July 1800 and was finished on September 23, in spite of all the difficulties that were necessary to obviate.

Only Percier and Fontaine, recognized talents in architecture could transform an inadequate place into a splendid room, to house an armonic and functional library.

The soffit was painted by Moench following the drawing instructions of the architects.

This is a very well preserved room at Malmaison and one of the most admired by the visitors.

Even so, Napoleon objected that the room seemed more like a sacristie than an Office-Library.

But in reality the architects and associates had performed a wonderful achievement that has rendered an elegant place in spite of the fact that they were handicapped by its former construction.

In the corner they made two small arched vaults, one central vault rests on two semicircular vaults. The vaults are separated by arcades that sustain the cornice of mahogany wood. All was performed with perfect geometry.

In the underground of the library was originally situated the kitchen, and mirrors ought to be placed in order to hide the chimney coffer.

All the details were closely studied to obtain a comfortable place with many ornaments and places for books. There were windows which communicate with the garden and brightened the library with its refreshing view.

In the arched vaults of the ceiling could be seen the decoration in medallions with the portraits of Muses or immortals like Dante, Voltaire, Ossian and others.

If Napoleon thought of this place as a sacristie, this impression was enhanced when the northern winds brought the sonorous vibrations of the bells of Reuil to the Angelus with the most beautiful voices.

There Napoleon had moments of profound recollection, reading poetry, history, travel narrations.

Many of them bear his handwriting on the margins.

All the books have under the monogram P.B. (Pagerie-Bonaparte) a seal reading "BIBLIOTHEQUE DE LA MALMAISON". A marble bust of Josephine made by Bosio and placed on the shelf of books, symbolized that she was always first in his thoughts.

There is also a small statue of bronze that depicts the Emperor measuring distances on a plane.

Napoleon loved Malmaison and he used to say that he was as happy there as in the battlefield.

It is significant that he ordered Percier and Fontaine that a Council Room ought to be built adjoining his Library Office.

The room ought to simulate a military tent. It is really the most colorful and original room of Malmaison, no other palace in the world has a room like that.

Percier and Fontaine were the architects and decorators while the furniture was from Jacob Freres and brought from Saint-Cloud.

This room with the appearance of a tent had elegance and military garb. Swords that sustain the curtains and the trophies painted on the doors, completed the adornments and beauty.

In this historical place an active life was held in which participated Mem-



The
Empress'
Bedroom.



The
Council
Room.



The
Library.

bers of the State Council, other consuls and messengers from princes of foreign states.

Under this military tent were celebrated important events such as the conclusion of the treaty of Saint Idelfonse by which Spain returned Louisiana to France; there he negotiated the Concordate, established the peace conditions with Austria and England, and where he planned and organized the Legion of Honor. There he established the first articles of the civil law and elaborated the Instruction Law.

In this very place he discussed projects and rules to be established as Law. Some of his biographers stated that he always posed the same questions "Here is a project".

"Are all the cases foreseen?" "Why didn't you take care of that?"... "This, is it necessary to say?".

But above all he was always concerned "Is that just?... Is that useful"? if the projet had the deserved questions.

He discussed exhaustively every point, looking for the exact equilibrium that means justice.

He liked very much to be informed, to prove his ideas testing them against the others, until the perfect solution was achieved. Josephine was a wonderful hostess and after receiving the news of Marengo, she gave a dinner on the open under the trees, in the park, on October 23 a reception in honor of General Moreau and a breakfast offered to the new sovereigns of Etruria.

Dramatic instances were lived at Malmaison when a conspiracy to assassinate Napoleon was discovered and the Duke d'Enghien, was found guilty. He and others had hired assassins in Paris, and were awaiting the news of Napoleon's death to conduct the royalist armies across the Rhine into Alsace.

The fate was against the thirty years old Duke d'Enghien, the last on the Conde's line.

Even when Josephine pleaded Napoleon to pardon the young aristocrat, Napoleon was inflexible and the Duke was executed.

This was a decision that raised a historical controversy, but even in his last moments at St. Helene, he in his last will and testament declared that this was the only solution left, and he would take the same resolution if under the same circumstances.

Other important events were elaborated at the Council Room, the ratification of the Treaty of Saint Idelfonse and the Peace of Amiens with England (1801) and a very delicate point, the conclusion of the Concordat of 1802 by which the Government of the Republic recognized that the Catholic, Apostolic, and Roman religion was the faith of the majority of the French people, and on the other hand the Holy Father was pleased and expressed that the greatest of the benefits for him, would be that the reestablishment of this creed were also professed by the Consuls of France.

Napoleon wished to have good relations with the Monks who were enemies of France after 1789.

The dining room was enhanced by paintings of Laffite who painted on the doors airy figures of beautiful dancers.

The chairs were of ebony and had nacre incrustated.

We have seen on one of our visits to Malmaison the dining table, with the remnant of a wonderful vermilion dinner set a gift from the City of Paris given to the Emperor on the occasion of his coronation.

Napoleon was very moderate in his meals, many times he lunched alone or accompanied by some interesting people, like scientists, men of letters, and artists in whose company he relaxed from his own preoccupation.

A continued activity would seem foreign to a country manor like Malmaison,

and which through its doors messengers came and went carrying out news and orders.

But sometimes the activity relaxed and then Josephine took her promenade; there was colorful animation of carriages attended by a multitude of pages.

They went through the Park to the woods. They passed near the wonderful places of captivating beauty like the pond of St. Cucufa and the streams of waters with greenish reflections from the trees, they moved through a scented atmosphere of a bucolic gaiety.

Passing through bridges and following the twisting ways of the English gardens the carriages disappeared and joined again and again.

They passed by the Temple of Love admiring all the time the beautiful flower whether in the open or at the internationally famous Malmaison hotgarden with their exotic ones.

Josephine's love of nature was also extended to the animals, and the people passing through the park admired white and black swans gliding on the silky waters of the lake, the jumping kangaroos and the swift gazelles appearing and disappearing through the trees, beautiful birds of colorful feathers many of them brought from Martinique, singing a symphony to life calm llamas, and monkeys shrieking and jumping from tree to tree, gave the park an unusual charm, mixture of Zoo and Botanical Garden.

In the museum of "La Rochelle" there is an embalmed female orangutan who died at Malmaison in 1812.

Malmaison was a curious mixture of beauty and force, beauty shed everywhere by Josephine, imaginative, elegant and an art lover, and force by Napoleon, practical, intelligent and a man of war.

THE EAGLE AND THE SWAN

The eagle and the swan. These two birds so different in their characteristic and form became the symbol of Napoleon and Josephine.

Josephine, soft, graceful, a lover of art and nature and identified herself with the swan majestic in its attitudes, symbol of love, soft, calm gliding on placid waters, reflecting like a mirror its beauty.

Once the city of Amiens wishing to compliment her sent to her as a gift four beautiful white swans that caused her delight.

Everything Josephine possessed was ornated with swans, they were woven into carpets, carved on thrones, chairs and most strikingly even her bed at Malmaison was embellished by golden swans that guarded her sleep, even the last one.

When Napoleon was confronted with the dilemma of choosing an animal that symbolized the new Empire of France or maybe of the world, many advisers proposed different animals each one exalting their most striking characteristics, among them, the Lion, the Elephant, the Eagle and the Cock.

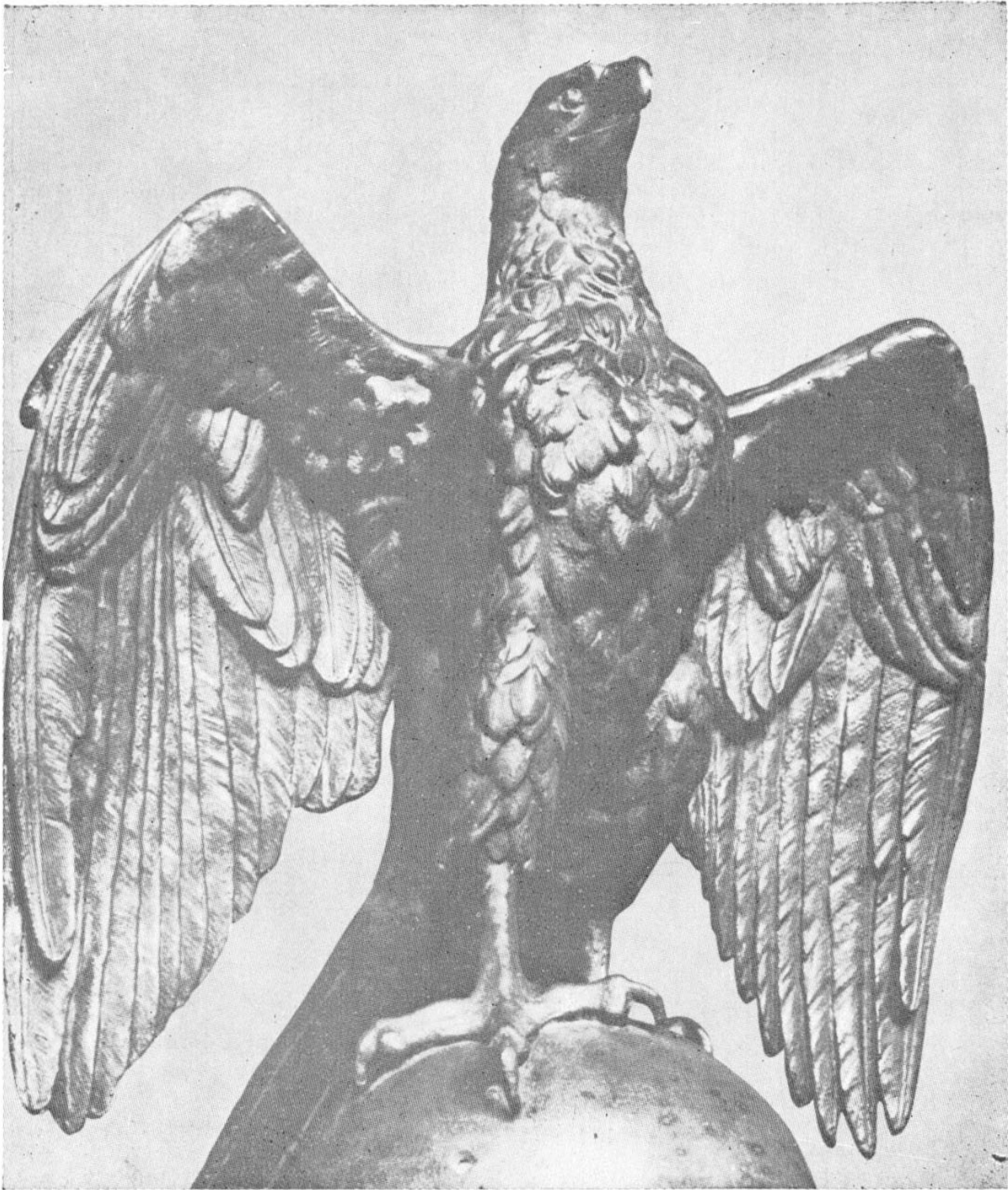
Percier and Fontaine were in charge of all the details concerning the crowning, judged the Lion, king of the animals, arrogant and powerful the best symbol of the new Empire, and then did not hesitate to make a beautiful design with a superb Lion of Judah for the back of the throne to be placed in the Throne Room of the Tulleries Palace.

When the decree was sent to Napoleon to be signed he became furious "A Lion?, No" he cried and crossed the Lion's proposal and wrote over "Aigle déployée" that was his definitive choice.

A bird that reminded him of Charlemagne, ancient Rome and the bas reliefs of the ancient Roman Church of the Saint Apostle.

Nothing more fitting to Napoleon's nature, than an eagle, a bird that can soar high to the summits of the mountains and see afar the object of its wishes.

From now on this bird would be the Empire's symbol. It will be on the sword hilts and sheets, engraved, embroidered, painted, and sculptured on every item of the Imperial Palace.



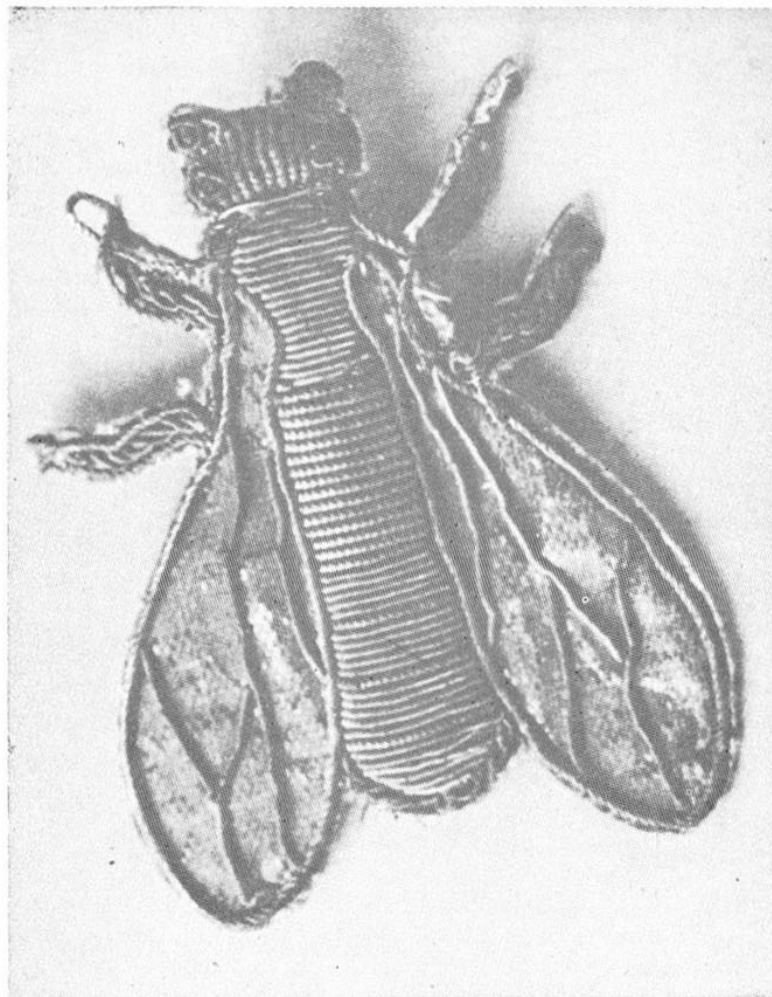
Imperial Eagle with Spread Wings.

For the masts of the flags Napoleon wished an eagle with the wing half folded, with the claws grasping a group of rays.

The eagle was embroidered on the Royal mantle for the coronation day.

But a little insect would also accompany the eagle as a symbol of the Empire. The bee, example of cooperative work, and full obedience to the sovereign.

This small labourer was chosen to fill the void of the "Fleur-de Lys", a flower of heraldic beauty. For centuries the "Fleur-de-Lys" was seen everywhere as a symbol of the Royalty, now this aristocratic characteristic will be substituted by a bee, a symbol of constant activity in benefit of its community and total obe-



Bee. Gold Embroidered to Ornate the Consacrating Garments.

dience to their Queen.

It is interesting to realize how much a stylised bee resembles a "Fleur-de-Lys".

This placed all over the Royal mantle accompanying the Eagle on the coronation day the attendance would believe they were seeing the familiar sign of Royalty.

During her life Josephine had endured sudden changes of fortune; when still adolescent at Martinique a negro sorcerer Euphémie David had predicted that she would be more than a Queen.

This prediction was fulfilled and in 1804 the coronation was carried out and Napoleon and Josephine became Emperor and Empress.

Josephine has shown tact and diplomacy in social relationship, taste in collecting art. She has discovered really good talents in painting and encouraged them by choosing their work.

She kept at Malmaison a collection sent to her in 1803 by the King of the two Sicily.

She received the most striking recent findings from Herculano and Pompeya, bronzes and vases with black figures and among other interesting items a very valuable ancient cameo from the Vatican depicting Cleopatra at the feet of Caesar.

She was the one who ordered the famous painting "The Plagued from Jaffa" due to the magnificent talent of Proud'hon.

Her collection of paintings from the Renaissance were steadily growing as Napoleon sent her as spoils of war, in 1806 she received a wonderful collection of



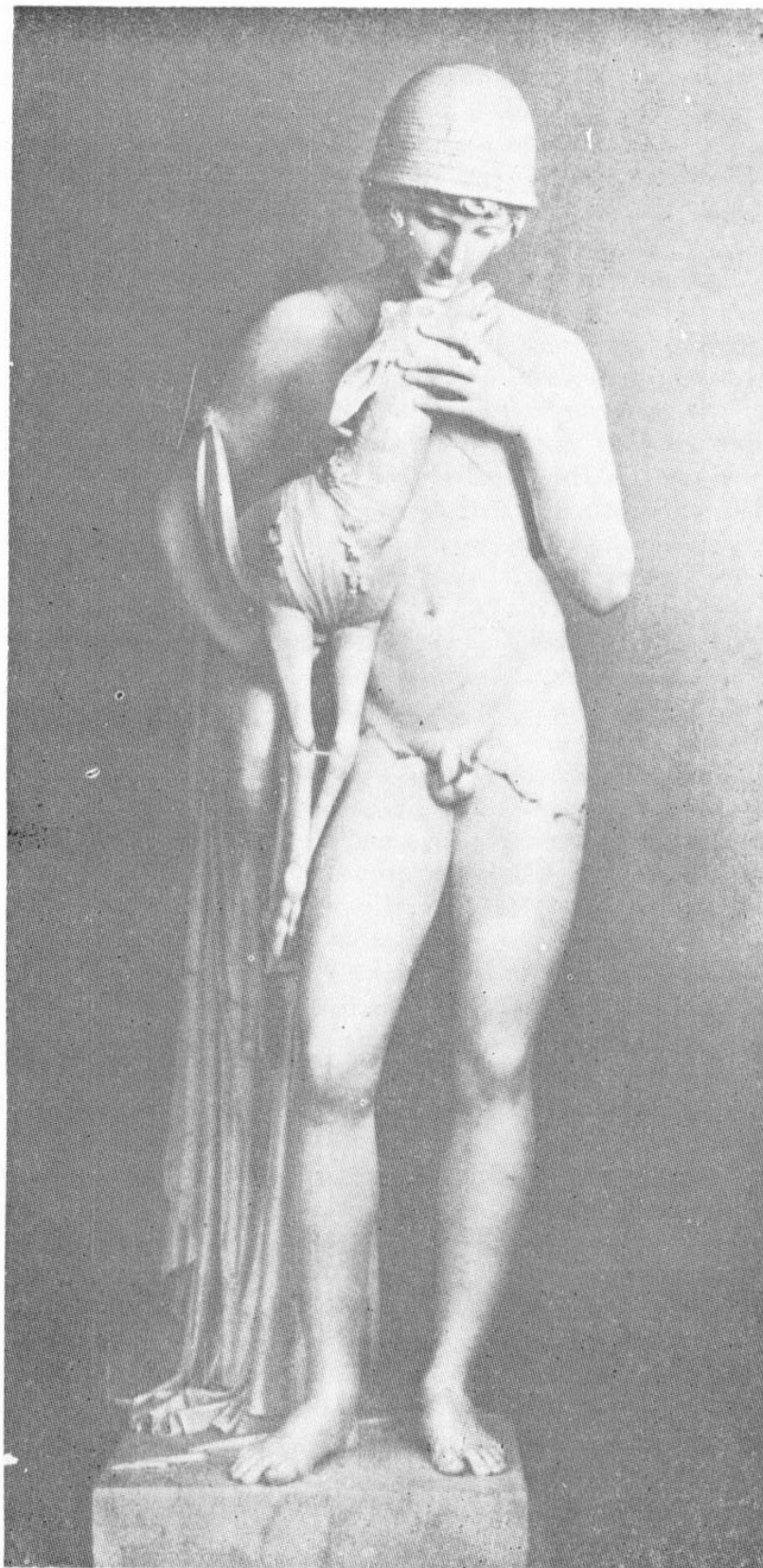
ROBERT LEFEVRE - The Empress Josephine in Coronation Garments.



DAVID - Bonaparte Crossing the Alps at Mont Saint Bernard.



Table of the Marshals, Sèvres porcelaine with gilded bronzes



A.M. Chaudet: Cyparissus crying over his fawn. Ancient collection of Josephine. Leningrad, Ermitage Museum.

Dutch paintings.

There is an injustice to consider Josephine just as a frivolous coquette only concerned in herself.

Casting an appreciative look on her whole life it may be considered that she

has had a very hazardous one. In her adolescence she had an unhappy marriage, the scars of rejection from her former husband, may have exalted her wish to be appreciated as a woman. She endured prison and was confronted with death, and the imminence of being beheaded, she suffered famine as a widow with two children. She learned that charm, elegance, and grace could be a solution to her more afflicting difficulties.

She learned how to alternate with the most fashionable centers of Paris society.

She was a compassionate lady always ready to help people in distress.

She contributed to the improvement and the enrichment of the French Botany with new species of plants, rare flowers and trees. Her collections of paintings bronzes and sculpture made of Malmaison a delightful Museum of Art.

She enhanced the panoramic beauty of its surroundings.

Now at the peak of her glory, being Empress for five years of a powerful France she still had two hidden fears. One was the continuous attempts against Napoleon's life. The other, the fear of divorce.

The last one was justified. She was already 46 years old, and Napoleon 40 and without a child of their own.

The rumors grew louder "Que tardez vous Seigneur, á la repudier?" "Why do you delay in repudiating her?". Being the more hostile those coming from the members of Napoleon's family.

Malmaison became too small for the court and it was left in spite of Josephine.

Josephine only returned when her husband was on the battlefield. However a wonderful feast was held at Malmaison on March 19, 1809, in honor of the King of Saxony. In the theater were played the "Gageure Imprévue" "Unexpected Bet" and "Coquette Corrigée". "Coquette amended", there was a dance at the Great Gallery, and the park was fantastically illuminated by fireworks.

Josephine circulated among the guests, charming and smiling as usual, but inside her heart was crying. By this epoch she was sure of her fate.

Finally it was decided that the divorce was the best solution for the benefit of France; Josephine accepted Napoleon's decision.

On December 15, 1809, they were divorced; the next day Napoleon gave to Josephine all the rights over Malmaison, and on this very day, Josephine left Paris, in a palace's carriage named "l'Opal" a stone of bad luck.

She was depressed and sad her eyes were clouded with tears, returning to a place where they had been so happy; it would seem void without Napoleon after 15 years of marriage.

Soon after, Napoleon was married to Marie Louise of Austria. By this alliance Napoleon thought his dignity as Emperor reinforced.

He was exultant when the next year on May 28, 1811, a child was born to become the King of Rome.

Because of Marie Louise's jealousy, Josephine was exiled to Navarra until the child was born.

Again at Malmaison she carried a quiet life enriching her garden with new specimens aided by Berthault and Bonpland.

Napoleon's rooms constituted for her a sanctuary; everything was left as if he were to return at any time. The clothes were casually left on the chairs, she took personal care of the room and dusted it herself.

She retained the title of Empress, had a small court, they promenaded through the park, and held frequently concerts to break the monotony of a country life.

Napoleon visited her from time to time, paid her debts and even aided her to expand her dominion giving her the necessary amount of money to buy Bois-Preau.

Deep inside he always loved Josephine, and tried that she suffer the least

possible under her new condition, and he asked the people of the court to visit her and to pay her due respects.

Others like Talleyrand and Mme. de Noailles went to see her on their own initiative.

She also found a source of happiness in the children of her daughter Hortense, especially the future Napoleon III now nicknamed "Oui-Oui".

But this calm was disrupted when sad news reached her.

Napoleon invaded Russia on June 1812, the Battle of Borodino, and the French retreat from Moscow, and because the loss and sufferings of the French Army her heart was oppressed by anguish.

Napoleon without Josephine began to lose his good star, In 1813-1814 the War of the Sixth Coalition against France started. And there was a conspiracy against Napoleon in Paris.

These were very trying times, Napoleon needed a son to inherit his Empire, now having one son would he be able to retain his Empire?.

October 16-18 was the French defeat at Leipzig, on March 30 the Capitulation of Paris.

Napoleon was right when he once said "My power depends on my glory, and my glory on my victories".

In April a provisional government headed by Talleyrand was constituted.

Five days after, Napoleon abdicated and Louis XVIII, former Count of Provence, was declared sovereign of France.

Josephine felt very much distressed; again she was in the middle of a social turmoil and political changes. On March 1814 she looked for refuge in her castle of Navarra, but soon, fearful of the fate of her children, Prince Eugene and Queen Hortensia, she returned to Malmaison.

A hostile world was around her, but she found the protection of Tzar Alexander who very spontaneously tried to aid her.

Two Russian guards were posted at the entrance of Malmaison.

Some historians have objected that Josephine had accepted the protection of whom had invaded France, and defeated Napoleon.

But in a letter from Napoleon addressed to Josephine from the exile he advised her to seek the help of the Tzar for her and her children.

He trusted in him, and he was right; he tried by all means to aid them.

The Empress Marie Louise had deserted Napoleon, and returned to Austria in spite of the fact that he pleaded her that she and their son join him at Elba and spare him the pains of knowing that the king of Rome was in the enemy's hands.

Josephine suffered thinking of Napoleon being alone at Elba, and she would be most happy if she could join him.

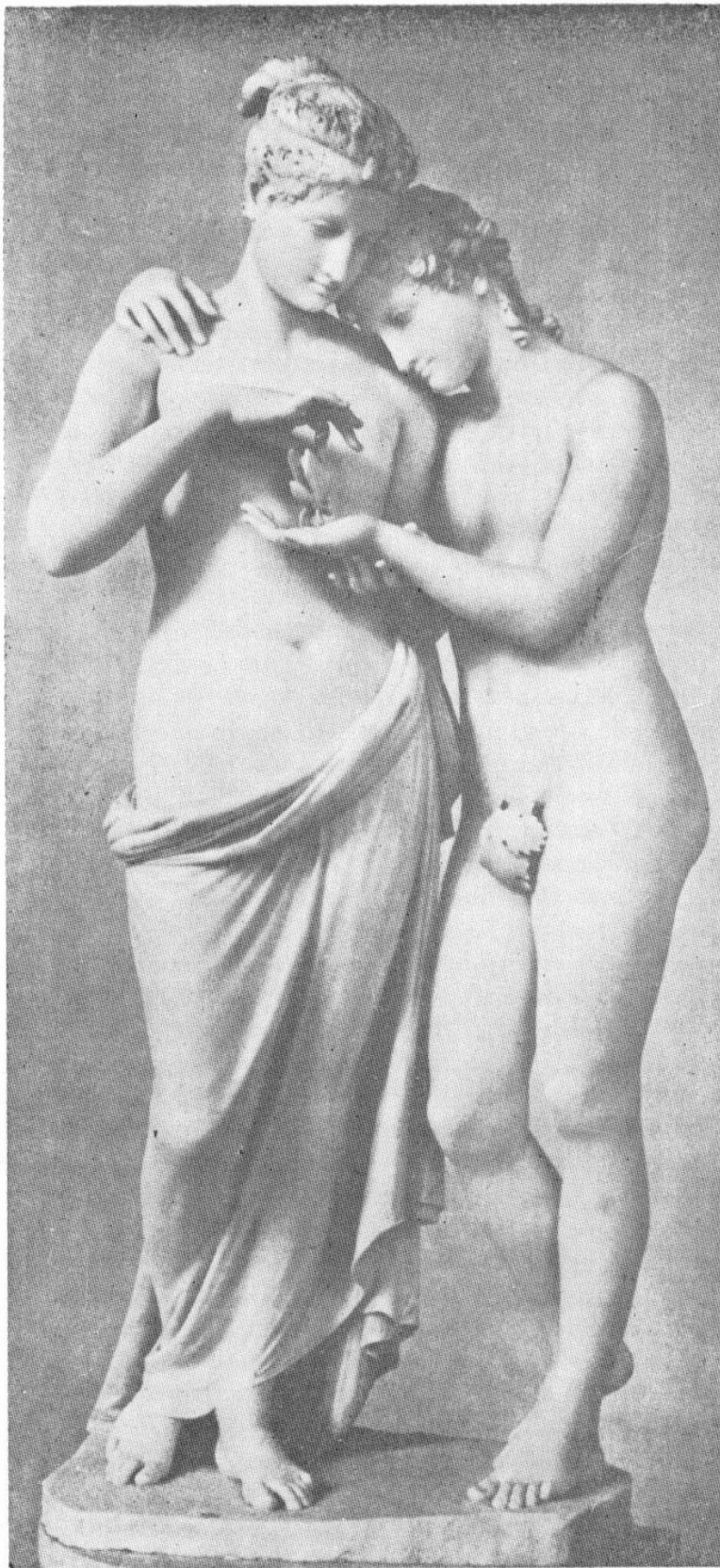
On May 15 Josephine caught a cold after a promenade through the Montmorency Forest; this was carried out in honor of Alexander who came for two days to visit St. Leu Hortense's Chateau.

Exhausted she confessed to Hortense's secretary that she could not conceal her sadness, thinking of Napoleon, abandoned on an island alone, and the uncertainty of a future very unstable for her and her children in spite of the Tzar's promises.

But Josephine was a courageous lady and she continued to receive people like the Great Duke Constantin and the King of Prussia.

On May 24 in spite of the fact that her condition was aggravated she opened the ball in honor of the Imperial visitors with the Tzar and even ventured herself to go into the chill of the garden air wearing a light gown with very pronounced décolletage.

Her health worsened, and she still fought to be on her feet, until she went to bed, that sumptuous bed with her golden swans and red drapes. On May 29,



Canova. Love and Psiquis standing up. Copy in marble. Leningrad Ermitage Museum.

Marie-Joseph-Rose, best known as Josephine, as Napoleon named her closed her eyes for ever.

She died in the middle of difficult times. The death certificate reads "epouse de Napoleon Bonaparte, General en Chef de l'Armée d'Italie, mariée le 8 de Mars 1706 sacrée et couronnés Emperatrice 2 decémbre 1804".

"Wife of Napoleon Buonaparte, General in Chief of Italy's Army consecrated and crowned Empress on December 2, 1804".

During three days more than twenty thousand people flowed from Paris into the hall of Malmaison to see Josephine's body on a catafalque.

Many people loved her and shed tears at the sight of the "Bonne Josephine". The soldiers used to call her "Notre Dame des Victoires".

All the church bells were tolling for her, it was a sad lament which the winds transmitted all along Reuil.

After, she found her eternal rest at the Church of Reuil.

The inventory of Malmaison called the attention about the richness in Art and antiques that were there accumulated.

The Tzar bought the most outstanding painting and sculptures which can still be admired at the Ermitage Museum in Russia.

A curtain of silence fell on Malmaison.

When Napoleon learned the sad news, he shut himself up in a room alone, deeply distressed.

A year later Napoleon made an escape from Elba. He managed to gain again popular favor and he entered victorious into Paris and the sound so precious to his ears "Vive l'Empereur" was shouted by thousands of throats in the streets.

But Josephine was not there to greet him in success, to kiss him tenderly, celebrating his triumph.

Napoleon's thoughts flew to Malmaison and during the "Hundred Days" he asked Hortense, Josephine's daughter, to accompany him to Malmaison.

During the visit he kept saying — "Comme ces lieux me la rapellent, je ne puis me persuader qu'elle n'est pas plus ici" — "How this place reminds me of her. I can't believe that she is not here any more".

Before leaving Malmaison he wished to enter alone to Josephine's bedroom. On leaving it his eyes were full of tears.

Scarcely two months had passed when the disaster of Waterloo occurred. Again fate was against him. Passions and divisions in Paris were used with ability by his enemies, which ended in his second abdication.

He found comfort when Malmaison was assigned to him a first stage in his exile.

He stayed there from June 25 to 29.

Malmaison where he had been at the summit of his glory was now the theater of dramatic episodes, when Napoleon desperately tried to regain at least some of his former power.

General Becker in charge of his security and in reality of his custody, was quite surprised to see Napoleon all dressed up in his uniform of War, and with an air of assurance and confidence in himself, trying to impose again the authority he had always exerted upon others.

He said to the astonished General Beckers "Je vous charge d'aller dire a la Commission du gouvernement le commandement non comme Empereur, mais comme un General dont le nom et la reputation peuvent encore exercer une gran influence sur le sort de la nation. Je promet, foi de soldat de citoyen, et de Français, de partir pour l'Amerique afin d'y accomplir ma destineeé, le jour meme ou j'aurai repoussé l'ennemie".

"I ask you to go and to tell the Commission of the Government a command not as an Emperor, but as a General whose name and reputation may still exert a great influence upon the destiny of the Nation, I promise you, faith of a soldier, of a citizen, and of French man to leave for America, with the aim to accomplish there my destiny, the very day that I could repel the enemy".

It could be understood that this offer was dismissed, and Napoleon ought to be prepared for exile.

The day before his departure before going to bed, he called Frere, first valet

de chambre of Josephine who took note of the following dialogue, whose manuscript is kept at the Museum.

"C'est bien beau Malmaison".

—...Tout me rapolle ici cette pauvre Josephine.

—...Je n'ai pas voulu coucher dans le chambre de cette pauvre Josephine.

—...C'est tres beau Malmaison c'est un beau lieu; Josephine a bien dépensé de l'argent et il n'y a pas de maison; J'ai bien crié contre elle dans le temps, hein?.

—C'est vrai, Sire.

—Mais c'est tres beau.

—Qu'est devenu le portier, un vieux sergent?

—Le père Otté. Il est mort, Sire"

"Les habitants de Reuil sont-ils bien?"

—Qui, Sire, ils aimoient beacoup l'Empetrice

—Elle fesait beaucoup de depense ici?

—Oui, Sire, Elle fesait beaucoup travailler.

—Ah Elle dépensoit plus qu'elle n'avoit...

Elle avoit envie de tout".

"Y a-t-il toujours des moutons?

—Oui, Sire

Josephine trouvoit cela superbe"

"Josephine est dans l'église de Reuil?

—Oui, Sire

—Lui, a-t-on fait un monument?

—Pas encore, Sire..."

"J'ai cru voir l'Empereur s'endormi et je me suis-retiré"

"It is beautiful Malmaison"

—...Everything here reminds me of that poor Josephine"

—...I didn't wish to sleep in the bedroom of that poor Josephine.

—...It is very beautiful Malmaison. It is a beautiful place;

Josephine has well spent the money and she had not a house;

I have shouted enough against her all the time, hah?.

—...It is true Sir

—...But it is very beautiful.

—What has happened to the porter, and old sergeant?

—"The father Otté. He has died Sir"

(Antoine Auteir, an old concierge of the School of Brienne whom Napoleon hired himself for Malmaison, died in 1814)

"The inhabitants of Reuil, are they well?"

—...Yes Sir, they loved the Empress very much.

—...Has she spent very much here?

—...Yes Sir, She gave much to work.

—...Ah She spent more than she could afford...She wished everything"

—...Are there always the muttons?

—...Yes Sir

—...Josephine had located there superb ones"

"Is Josephine at the Church of Reuil?

—...Yes Sir.

—...Has a monument been made for her?

—...Not yet Sir.

"I have believed to see the Emperor sleep, and I left the place".

Next day Napoleon left Malmaison for ever.

Malmaison carried through the times the secret of two lives which elevated

it to historical immortality.

What happened to Malmaison when Josephine was no longer there is a sad story.

Malmaison belonged now to Eugene, Josephine's son, who sold many pieces of art it had.

Napoleon at Saint Helene was very much distressed to know that. He would have liked that Eugene whom he loved and held in high esteem, would have preserved the historical patrimony of his mother.

But Eugene was forced to do it in order to pay a debt of three million francs outstanding. Many of the treasures of art were bought by the Emperor Alexander of Russia and may be seen at the Ermitage Museum in Russia.

The Musée du Louvre enriched its collection of Egyptian and Italian antiquities, claiming or buying Josephine's gathering of about six thousands pieces of art.

Hortense inherited her mother's jewels, one of the most famous collections in Europe.

Eugene who had become Duke of Leuchtemberg, living with his father in law the King of Baviere died in 1824 leaving his wife with many children.

Four years later his widow tried to sell Malmaison and Bois Preau.

The notary Casimir Noel distributed numerous edicts announcing the selling entitled:

"Superb Domaine de la Malmaison lodging of Napoleon and Josephine".

Followed by a flowery description of the beauty and historical value of the place.

A Swedish banker named Hagerman bought Malmaison.

Queen Hortense passing through France in 1831 tried with her son Charles-Louis-Napoleon to visit Malmaison, but their admission was rejected.

She felt the bitterness of the situation, and pressed her face against the entrance's iron railings, trying to recapture the vision of the place of far happier days.

"Il me fut impossible de vaincre d'ordre du nouveau propriétaire... Il était difficile de s'y reconnaître; et pouvais je me croire au même lieu que j'avais laissée si beau ou j'étais aussi cruellement interdite?"

"It was not possible to overcome the order of the new owner... It was difficult to recognize and to believe that this was the same place I left so beautiful, where I was always received with such a joy, the same whose entrance was now for me so cruelly forbidden?"

Hagerman didn't remain for a long time the owner of Malmaison, After selling part of forefront of the park he gave it in 1842 to the Queen Marie Christine of Spain who lived there for twenty two years. She demolished the Grand Gallery and the theater and built a neo-gothic Chapel of doubtful good taste, which was eliminated in 1912.

In 1861 Charles-Louis-Napoleon, transformed in Napoleon III. The little grandson of Josephine nicknamed "Oui-Oui", brought to reality a dream for such a long time cherished by him. He bought Malmaison for a million francs.

He came frequently to visit Malmaison, especially on the anniversary of Josephine and his mother Hortense's death, both of them buried at the Church of Reuil.

Napoleon III brought to life the old château and the joy and the laughter of members of Napoleon and Josephine's family.

By the initiative of the Empress Eugenie the first Napoleonic Museum was there settled in 1867 and part of the mobiliary and portraits were there restored.



Cartellier: The Empress Josephine, Marble, Empress'tomb at the Church of Rueil-Malmaison.

But this placid existence was again disrupted. After the fall of the second Empire by a decree of the provisional Government, Malmaison was declared the State's property, on September 6, 1870.

During the siege of Paris furious combats reached Malmaison and the park and the Château were damaged.

But the stoic Malmaison survived the Prussian attacks, and the fire, but it

found a worse enemy in the IIIrd Republic willing to erase any trace of Napoleon's era.

Malmaison passed from hand to hand during the successive years, its park everytime reduced and the castle had the appearance of a quarter.

Finally a Banker David Osiris-Iffa bought Malmaison for 132.000 francs on August 12, 1896.

After performing some badly needed restorations he gave it to the French Government under the condition to create there a Napoleonic Museum. Many of its former paintings and furniture were again restored.

Opened to the public in 1906, many thousands of people came to its doors from different parts of the world to admire at Malmaison the vestiges of a glorious past when Napoleon indomitable conqueror of proven valour and intelligence, and Josephine of exotic beauty, grace and elegance charmed everyone with the fascination exerted by their unique personalities, and made of Malmaison a Historical place to be remembered.

Prof. Dr. VICTOR SORIANO

• News

1984 HAROLD G. WOLFF, M.D. LECTURE AWARD WON BY BRITISH INVESTIGATORS

By Donald J. Dalessio, M.D.,
Chairman Department of Medicine
Scripps Clinic and Editor of Journal
"HEADACHE"

The Harold G. Wolff, M.D. Lecture Award for 1984 has been won by four British investigators who have found a metabolic abnormality in patients with cluster headache. The investigators were J. de Belleruche, F. Clifford Rose, I. Das and G.E. Cook and the subject of their lecture award was Metabolic Abnormality in Cluster Headache.

The investigators measured the levels of a single chemical, choline, in red blood cells in patients with cluster headache, those with migraine, and those without headache. They found decreased choline levels in patients with cluster headache, both when they were without symptoms and during the actual cluster headache attack. This was not seen in patients with migraine who had normal to elevated levels of choline in their blood.

After treatment with lithium, which alleviated their headaches to some degree, the choline levels in the red blood cells of patients with cluster headache rose to within normal range. It is known that patients taking lithium for whatever reason will increase the amounts of choline in their red blood cells. Possibly, this represents another reason why some patients with cluster headache who take lithium are relieved of their complaints.

The work is important because it demonstrates a specific metabolic abnormality, that is, decreased choline in the red cells, which appears to be associated with cluster headache. This should provide both a biochemical marker and an aid to diagnosis, and perhaps further insights into the abnormalities which may produce cluster headache

SINUS PROBLEMS INFREQUENT CAUSE OF HEADACHE

Report of the Post-Graduate Course for
Physicians, Scottsdale, Arizona,

(continued from NMF Newsletter
Spring 1984, N° 48) by Harold W.
Levine, Editor

Arthur H. Elkind, M.D., Attending Physician, Mt. Vernon Hospital, Mt. Vernon, NY, discussed the subject SINUS HEADACHE, which is probably one of the most frequently used terms, yet a relatively infrequent cause of headache. The over the counter drug market is replete with analgesics and sympathomimetic amines for reduction in sinus headache and pain. Relationships regarding the sinuses, nasal structures and headache remain unsettled and quite controversial. Dr. Elkind observed that chronic sinusitis infrequently causes headache, but patients with chronic headache may have signs of chronic sinusitis.

Infections or inflammations of the paranasal sinuses may cause headache and pain but the distress should parallel the course of an acute febrile illness. Only occasionally may chronic disease as a tumor, chronic infections as fungal or neoplasm persist over months or years present with pain. Furthermore, Dr. Elkind continued, sinus pain is usually accompanied by other signs or symptoms of sinus disease as nasal discharge, epistaxis, ear sensations or fullness, as well as facial swelling.

Patients will often describe a dull and aching type of distress pain but not throbbing. Nausea and vomiting are unusual. The pain often is increased by a dependent position of the head or shaking the head. Increasing venous engorgement may aggravate the pain such as straining or coughing. Use of nasal anaesthetics or vasoconstrictors will often alleviate or reduce the pain. Cold air through the nasal mucous membranes may increase the pain. Headache of frontal sinus origin is often present early in the morning and subsides towards evening. Maxillary sinus headache frequently begins in the early afternoon. Chronic sinus disease generally produces a less severe pain than acute disease.

Dr. Elkind stated that patients with an allergic history may reveal nasal polyposis and changes within the maxillary and ethmoid sinuses as mucosal thickening and opacification. However, whether the symptoms of headache are referable to sinus disease remains to be determined by history and

response to therapy for the allergy. At times a complex therapeutic approach is indicated to treat the local allergy and additional therapy for the headache.

Sinus headache or the headache due to chronic sinus infection is often associated with nasal inflammation and symptoms. Most often the use of the term sinus headache will refer to a vascular form of headache and less often structural sinus disease. The sinus involvement itself usually does not produce much pain or headache. Apparently it is the affected nasal structures with engorgement and inflammation that result in the pain symptoms.

Acute sinusitis most often involves the maxillary sinus. Head movements as bending or straining may aggravate the pain or pressure.

He further reported that chronic headache is infrequently due to disease of mastoid sinuses. Acute infections may result in pain. Rapid changes in atmospheric pressure may result in sinus headache with negative pressure developing within the sinuses.

Distinguishing vascular headaches of the migraine type from sinus headache may seem quite simple but many patients with migraine may include prominent nasal and seemingly paranasal symptoms with their history. The nasal symptoms probably have a vascular origin in the migrainous individual and very often respond to usual migraine therapy. At times nasal vasoconstrictors may be needed, alone, in combination with analgesics and/or antihistamines for maximum relief.

Finally, Dr. Elkind stated that the headache of sinus origin or acute sinusitis is usually associated with constant pain and tenderness over the affected sinus, a deep dull ache, and exaggerated by head movements or straining. As mentioned earlier nasal symptoms are prominent. Therapy is usually directed towards relief of infection or accompanying allergy. Symptomatic relief includes analgesics and nasal vasoconstrictors. More recently the use of local corticosteroids may offer the allergic individual added relief where nasal symptoms are prominent. Therapy of the symptomatic type is similar in both cases where sinus and nasal symptoms are prominent, but the acute sinusitis requires the added therapy directed towards the offending organism or aller-

gy. The migrainous individual requires the added therapy directed towards the basic migraine disorder.

A. David Rothner, M.D., Chief, Section of Child Neurology, The Cleveland Clinic, Cleveland, Ohio, lectured on the **DIAGNOSIS AND MANAGEMENT OF HEADACHE IN CHILDREN AND ADOLESCENTS**. Headache is a frequent symptom in pediatric practice. As many as 25% of children will have experienced significant headache by the age of 15 years. Although the vast majority of headaches in children are not associated with organic structural disease, parents frequently seek a physician's aid, fearing that their child has a brain tumor. In dealing with headaches in children, physicians must consider both the physical and psychologic factors in determining the correct diagnosis and selecting the optimal treatment program.

Dr. Rothner stated that although Hippocrates described migraine more than 25 centuries ago, very few references were made concerning the subject of headaches in children until 1873 when William Henry Day, a British pediatrician, devoted a chapter of his book "Essays on Diseases in Children" to the subject of headaches. He recognized that nonorganic, nonvascular headaches were the most common types in children and stated, "Headaches in the young are for the most part due to bad arrangements in the lives of children". In 1962, Bille reported on the incidence and nature of headaches in 9,000 school children. In 1967, Friedman and Harms wrote the first book on the subject of headaches in children.

Dr. Rothner commented that in Bille's study it was noted that by age seven years, 2.5% of children had frequent nonmigrainous headaches; 1.4% had true migraine; and 35% had infrequent headaches of other varieties. By age 15, 15.7% had frequent nonmigrainous headaches; 5.3% had migraine headaches; and 54% had experienced infrequent nonmigrainous headaches.

He emphasized that a properly obtained history is the key to the correct diagnosis. Questions should be directed to both the child and the parents. Computed tomography (CT) is a safe, rapid, accurate method of evaluating the intracranial contents. It is useful in a wide variety of conditions, in-

cluding malformations, intracranial infections, trauma, neoplasms, and degenerative and vascular disorders. Psychologic tests are useful for individuals with "functional" headaches and when certain stressful circumstances are thought to be precipitating factors in migraine headaches.

In discussing specific headache syndromes Dr. Rothner stated that 2% to 6% of all emergency room visits are due to headaches. Dental disorders and temporomandibular joint (TMJ) dysfunction may cause frontal or temporal headaches. Headache associated with head trauma is related to the specific area of impact and usually resolves within a few days. Occipital neuralgia is a pain localized to the occipital and upper cervical areas. It occurs primarily in adolescents and young adults and is characterized by acute or chronic occipital and suboccipital headaches.

Dr. Rothner continued that migraine is a specific genetic disorder characterized by episodic, periodic paroxysmal attacks of vasoconstriction and vasodilation. By age 15, 5% of adolescents have experienced a migraine attack. In 50% of all individuals who have migraine headaches, the attack starts before the age of 20. In early childhood, boys are affected more frequently than girls, but at puberty and afterward, girls are affected more frequently.

Dr. Rothner emphasized that young patients cannot be relied on to carry their own medication and take it at the start of the headache. If attacks occur more than once a month or are particularly distressing, prophylaxis should be considered. Cyproheptadine and propranolol are the most commonly used medications.

The diagnosis of the epilepsy equivalent syndrome is made far more frequently than the disorder actually occurs. Since both migraine and epilepsy are common, it is not uncommon for a patient to have both epilepsy and migraine headaches. The diagnosis of the epilepsy equivalent syndrome includes nausea, vomiting and altered consciousness. A history of coexisting generalized or focal seizures supports the diagnosis as does a definitely epileptiform electroencephalograph (EEG). A positive family history for epilepsy is frequently present. These spells respond to anticonvulsants. True

epilepsy must be differentiated from migraine with an abnormal EEG.

In conclusion, Dr. Rothner pointed out that headaches may be a sign of depression. Manifestations of depression in childhood and adolescence include mood change, withdrawal, poor school performance, sleep disturbance, aggressive behavior, selfdepreciation, lack of energy, somatic complaints, school phobia, and weight loss.

The postconcussion syndrome consists of headache in association with insomnia, irritability, restlessness, personality change, lassitude, memory problems, school failure and dizziness. A psychologic problem should be suspected when the headaches have persisted longer than several months and clinical examination and laboratory studies are negative.

William G. Speed, III, M.D., F.A.C.P., Associate Professor of Medicine, Johns Hopkins Medical School; Director, Speed Headache Associates, Baltimore, Maryland, spoke on the subject of HEAD INJURY AND HEADACHE. Almost anyone who injures his head will have pain or tenderness at the site of impact for hours or several days and then becomes symptom free. However, about 30% to 50% of such patients will have headache persisting for more than two months, and are called chronic post-traumatic headache.

Dr. Speed continued that lightheadedness, memory impairment, reduced attention span, inability to concentrate, anxiety, depression and frustration are probably the most common group of symptomatology. These symptoms usually develop within twenty-four to forty-eight hours following the trauma, although at times there may be a more delayed onset. These complaints may persist for months or years.

He stated that it appears that damage to nerve fibers is prominent in head injury and there is little doubt that it occurs frequently in cases of mild as well as severe injury.

Dr. Speed reported that muscle contraction is probably the most frequent cause of chronic post-traumatic headache. It is clinically indistinguishable from the chronic muscle contraction headache that is unrelated to trauma. In regard to vasodilatation, pulsating, pounding, throbbing headaches

are commonly seen in some post-traumatic headaches and are produced by vasodilatation. Although many of these headaches are nonmigrainous vascular headaches, it is apparent that the migraine process can be triggered by head injury.

Dr. Speed further stated that there is combined muscle contraction and vasodilatation. Muscle contraction and vasodilatation may occur simultaneously and the term post-traumatic mixed type headache is used to describe this entity.

In conclusion, Dr. Speed commented that a supportive and well structured therapeutic program including rehabilitation, pharmacotherapy, behavioral and psychological management represent the most appropriate therapeutic modalities.

James D. Dexter, M.D., Professor and Chairman, Department of Neurology, University of Missouri, Columbia, Missouri, lectured on MISCELLANEOUS HEADACHE. Dr. Dexter listed *Caffeine Withdrawal Headache* as one of the most common headaches seen. It has the characteristic of being a dull, often throbbing headache, and may be associated with mild nausea as well as complaints of stiffness and myalgias. It is not uncommon to see the consumption of caffeine containing beverages to exceed 16 cups of coffee or an equivalent of 4 liters of cola drink per day. This headache is sufficiently common that it is imperative that a history of coffee, tea, chocolate and cola consumption is taken in every patient who presents with headache.

Alcohol Withdrawal Headache was the second subject covered by Dr. Dexter. This headache not uncommonly presents in a patient who is a problem drinker and who is deeply involved with the denial of the problem. This headache is usually not a daily headache. However, it is characterized by being a morning or a.m. headache occurring three to five times per week.

Dr. Dexter discussed *Exertional Headaches*. The exertional headaches are a group of headache syndromes which typically have a very short onset to peak intensity time that are associated with some physical activity. Among those more frequently seen are the benign orgasmic headache, laugh headache, straining headache and in the recent years, the jogger's headache. While these may occur in isolation they are most com-

monly associated with patients who have inherited susceptibility to migraine.

Dr. Dexter then reported on *ACUTE WEATHER CHANGE HEADACHE* which has had much reader interest. The headaches associated with acute weather changes are variable in populations depending upon the geographic meteorology of the region. These headaches are much more common in the eastern two-thirds of the United States but are also seen very frequently in the areas of central Europe. They are associated with those regions with meteorological characteristics of extremes in both day to day weather and in terms of extremes in seasons. These headaches most commonly occur with the arrival of severe low pressure fronts. However, they may precede the arrival of meteorological changes by as much as 24 hours. These are most common during seasons of rapid weather change such as late spring and fall. The therapy is best accomplished with symptomatic medications which can be taken in anticipation of acute weather changes which can be monitored daily by the patient with review of the reports from the National Weather Service.

Dr. Dexter elaborated on the various food headaches as follows: *NITRATE/NITRITE (HOTDOG) HEADACHE* - while there has been long controversy of the role of food sensitivities in the etiology of headache syndromes there are some compounds contained in many foods that are well known to be major precipitators of pain in the headache patient. Among these precipitating agents are the nitrates which are most common and are contained in many preserved and prepared foods. The nitrate headache syndrome is usually an acute attack after ingestion of a particular food such as sausages, pizza or luncheon meats. However, the headache may be a subacute or chronic headache if the patient is being chronically exposed to these substances.

CHINESE RESTAURANT SYNDROME - this syndrome was described in the mid-sixties and is characterized by a generalized headache often associated with neck and shoulder pain, GI complaints, profuse perspiration, extreme thirst and a physiological depression. The offending agent is monosodium glutamate which is measured in the tons of consumption used as a flavor enhancer.

cing agent in many foods and certainly is not limited to the oriental cuisine.

ICE CREAM HEADACHE - severe head pains can frequently follow from the cold stimulation of the palate, pharynx and esophagus and is most commonly seen during the ingestion of ice cream or cold liquids. These headaches are usually very transient and appear during the cold stimulation.

Seymour Diamond, M.D., Adjunct Clinical Associate, Professor of Pharmacology, The Chicago Medical School; Director, Diamond Headache Clinic, Chicago, Illinois, discussed **BIOFEEDBACK AND HEADACHE**. Biofeedback uses instrumentation to teach a person to bring previously unused or involuntary bodily functions under voluntary control. Norbert Weiner, the mathematician, coined the word feedback and defined it as a method of controlling the system by reinserting into it the results of our past performance.

Dr. Diamond stated that the psychological basis for the effectiveness of biofeedback can be demonstrated by the difference between traditional Pavlovian classical conditioning and instrumental or operant conditioning. Biofeedback, in principle, is consistent with instrumental learning. This can be traced to Ivan Pavlov, the Russian scientist, and his classical conditioning theory.

Pavlovian classical conditioning begins with an unconditioned stimulus. The unconditioned stimulus is paired with a conditioned stimulus. Eventually, the conditioned stimulus will produce what was formerly an unconditioned response. From this emerged the theory of operant conditioning, forming the basis of the biofeedback technique.

A conditioned stimulus is provided along with an opportunity to respond in various ways. The desired response is then reinforced or rewarded. After several reinforcements, the stimulus serves as a signal for performing the learned response.

Biofeedback borrows from past psychological experimentation with the most ancient being the Hindu practice of yoga. Yoga teaches mental discipline over bodily functions to achieve tranquility with the universe. The discipline chants a series of mantras to help achieve inner discipline, with the master acting merely as a teacher. In Germany, Johannes Schultz developed a mind-body training system called autogenic training.

In Schultz's system, the patient directed himself, repeating a series of phrases to help him relax. The physician again acts solely as a teacher; thus the technique falls into the realm of self-regulation. Similarly, Edmond Jacobson devised a system of training known as progressive relaxation.

Dr. Diamond continued that these techniques form the background for the work of Dr. Joseph Kamiya, in which he taught subjects to control their brain waves. With electronic circuitry a tone was produced whenever a subject produced an alpha brain wave; as a result, most subjects learned to produce alpha waves at will. Dr. Neal Miller and his associates have demonstrated that many autonomic responses can be induced in animals by operant conditioning. After administering curare and maintaining artificial breathing in the animals, to rule out the possibility that autonomic responses were controlled by skeletal muscles under voluntary control, animals were taught to increase or decrease blood pressure and heart rate, produce localized blood flow to an ear, and vary urinary secretions or gastric and intestinal contractions. When the animals showed the desired responses, they were rewarded with electrical stimulations to the pleasure centers in the hypothalamus. There has also been success in controlling blood pressure temporarily in humans with biofeedback techniques.

In discussing the history of biofeedback, Dr. Diamond noted that the use of biofeedback techniques in the treatment of migraine headache problems was first suggested by Dr. Elmer Green of the Menninger Clinic. A subject being monitored for relaxation therapy aborted her migraine headache and observed an accompanying increase in hand temperature. This led to further research at Menninger Clinic in which Sargent, Green and Walters experimented with autogenic feedback training. As an aid in training patients to raise hand temperature, the autogenic phases of Johannes Schultz were used, since in previous reports Schultz had shown that some subjects were able to alleviate migraine attacks while practicing autogenic training exercises. The combination of thermal feedback with autogenic training involved simultaneous management of mental and somatic functions. "Passive concentration" was used to induce specific

physiological changes, such as hand warmth, by focusing on visual, auditory, and somatic imagery.

Each training session consisted of the practice of two groups of autogenic phrases; the first group aimed at achieving passive concentration and relaxation of the entire body, and the second group focused on achieving warm hands, followed by the visualization of images while using a temperature trainer. This was accompanied by daily practice and accurate record keeping at home. They found that temperature changes in the hands is directly related to blood flow in the areas as measured by a plethysmograph, and an increase in skin temperature in the hands is used as an index of voluntary control of the sympathetic section of the autonomic nervous system. Subjects were seen weekly until they showed a consistent positive response.

The training phase was later limited to one month, as it was found that most subjects were able to acquire the techniques rapidly. Follow-up sessions were held every one to three months, with the follow-up period lasting at least a year.

At the Diamond Headache Clinic a combination of hand-warming and EMG feedback techniques is used, since many patients suffer from more than one type of headache. This use of both techniques helps to achieve a greater reduction of both vascular and muscle contraction headaches. Since stress can provoke migraine headaches, EMG feedback training plus thermal feedback can benefit these patients. In the initial training sessions an explanation of biofeedback is given to the patient and the goals of therapy are discussed. The importance of home practice is also stressed. Sessions are held in quiet, dimly lit rooms, with patients sitting in comfortable, reclining chairs.

In conclusion, Dr. Diamond expressed his views that the key to successful biofeedback training is motivation on the part of the patient. Biofeedback is not the treatment of choice for all headache patients. It is indicated in patients who have been successfully treated with medication and would like to discontinue pharmacological therapy, patients who may need an adjunct to their medications, and those patients who are not

able to use medications, i.e. pregnant women.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
National Institutes of Health
Bethesda, Maryland 20205
Room 804
Federal Building
December 17, 1984

Dear Colleague:

The World Federation of Neurology Research Group on Neuroepidemiology is planning a very active series of courses and scientific sessions during 1985. These are briefly outlined as follows:

A Workshop/Course on the Epidemiology of Neurological and Psychiatric Disorders will be held at the University of Ibadan, Ibadan, Nigeria, during March 25-29, 1985. The sessions will focus on the application of epidemiologic techniques in developing countries and the design of specific research protocols. For further information, please contact Dr. B. O. Osuntokun, Professor of Neurology, University of Ibadan, Ibadan, Nigeria.

The first Pan American Congress of Neuroepidemiology will be held in Bogota, Colombia, during April 24-28, 1985. Sessions will consist of courses on the principles and clinical applications of neuroepidemiology and the presentation of research studies. The official languages of the Congress are Spanish and English. Individuals are welcome to submit 200-word abstracts of proposed presentations. For further information, please contact Dr. Jaime Gomez, First Pan American Congress of Neuroepidemiology, P.O. Box 90303, Bogota 8, COLOMBIA (South America). A brochure describing the meeting is enclosed.

A scientific session will be held in Dallas, Texas (U.S.A.) in conjunction with the annual meeting of the American Academy of Neurology. The Research Group on Neuroepidemiology will meet on Friday, May 3, 1985. Those wishing to submit abstracts for possible presentation should do so on the enclosed form.

Neuroepidemiology has been selected as one of the four main themes of the forthcoming World Congress of Neurology in Hamburg, Federal Republic of Germany.

As part of this Congress there will be a neuroepidemiology course on Wednesday, September 4, 1985, and a full day (Thursday, September 5, 1985) will be devoted to state-of-the-art lectures describing current research accomplishments in this field. There are also opportunities for free communications. The Congress Organizers should have sent brochures concerning these activities to you in a separate mailing. For further information, please contact: Congress Manager's Office, XIII World Congress of Neurology, Letzter Hasenpfad 61, D-6000 Frankfurt 70, Federal Republic of Germany.

I hope that many of you will be able to participate in these sessions. Best wishes for the Holiday Season.

Sincerely yours,

Bruce S. Schoenberg, M.D., Dr. P.H.
Chairman, Research Group on
Neuroepidemiology

World Federation of Neurology

September 9-13, 1985 - Little Rock, Arkansas

Fourth International Conference on Neurotoxicology of Selected Chemicals: Neurotoxicology in the Fetus and Child.

The theme of the 1984 Neurotoxicology Conference is concerned with chemotherapeutic agents, over-the-counter drugs, malnutrition, environmental factors, and immunizations. A distinguished group of international experts will address clinical and basic science issues relating to the developing nervous system. Contact: Dr. Joan M. Cranmer, Conference Chairman, Department of Pediatrics-#512B, University of Arkansas for Medical Sciences, Little Rock, Arkansas 72205 (501) 661-5997 or 661-5958.

June 12-13, 1985 - Little Rock, Arkansas
Symposium on the Histopathology and Immunology of the Hematopoietic System of the Mouse and Rat.

Contact: Dr. Charles H. Frith, Director of Pathology, Intox Laboratories, #1 Intox Drive, P.O. Box 250, Redfield, Arkansas 72132. (501) 397-5207.

Association for Research in Nervous and Mental Disease, Inc.

Mt. Sinai School of Medicine, 1 Gustave Levy Place, Room 21-74, New York, New York 10029, (212) 348-8133

The Association for Research in Nervous and Mental Disease will hold its annual meeting on November 30 and December 1, 1984 at the Hotel Roosevelt in New York City. The topic of this year's meeting will be Neuropeptides: Implications for Neurologic and Psychiatric Diseases. Recent developments in this very active field will be comprehensively reviewed.

The Program Committee for this year's program consists of President: Dr. Joseph Martin, Vice Presidents: Dr. Jack Barchas and Commissioners: Robert Katzman, Richard Wyatt, Donald Price, Ann Graybiel, Floyd Bloom, Stanley Watson, and Martin Rosser. This Committee has selected a number of leading investigators in this field to review some of the contributions that are currently being made in neuropeptides and their application to basic and clinical investigations. The program will include principles of neuropeptide processing (Edwin Herbert), neuroanatomy of relevant peptide systems in the basal ganglia (Ann Graybiel) cerebral cortex (Edward Jones) and spinal cord (Tom Jessell), and studies of electrophysiologic effects (Alan North). Potential applications of neuropeptide research to behavior and psychiatric disorders will be discussed by Eric Kandel, Stan Watson, Jack Barchas and Philip Berger, abnormalities of neuropeptides in neurological disorders will be discussed by Martin Rosser, Donald Price, Robert Katzman and Joseph Martin.

Further information relative to this meeting can be obtained from the Secretary-Treasurer of the ARNMD, Bernard Cohen, M.D. at Mt. Sinai School of Medicine, 1 Gustave Levy Place, Room 21-74, New York, NY 10029, or by calling (212) 348-8133.

ANNOUNCEMENT RESEARCH FELLOWSHIP PROGRAM

The National Neurofibromatosis Foundation has recently instituted a Research Fellowship Program.

The fellowships will provide salary support of up to \$ 25,000 per year for up to two years.

The deadline for filing applications for awards to be activated during the 1985-86 academic year is May 1, 1985. Selection of

successful candidates will be made by the Foundation's Medical Advisory Board.

Please alert any members of your department who may be interested in these fellowships.

For applications or further information, please contact:

The National Neurofibromatosis Foundation
70 West 40 th Street, 4th floor
New York, NY 10018

Yours very truly,
Felice Yahr
Executive Director

THE PAVLOVIAN SOCIETY CALL FOR PAPERS

**26TH ANNUAL MEETINGS
BALTIMORE, MARYLAND
SEPTEMBER 11-14, 1985**

The 1985 meetings of The Pavlovian Society will be hosted by the Department of Psychiatry and Behavioral Sciences at The Johns Hopkins University School of Medicine, and will be held at the nearby Sheraton-Johns Hopkins Inn in Baltimore, September 11-14. Everyone is encouraged to participate. We are planning at least two symposia, a keynote lecture by an invited scientist, paper sessions organized around particular topics, a cocktail party, and a banquet. In a slight departure from our usual practice of not requiring abstracts, I am asking interested speakers to include a short, 100 word abstract for program planning purposes by May 1, 1985. A final, polished abstract should be brought to the meeting for later publication in The Pavlovian Journal of Biological Science. Also, if you would like to organize a symposium, please send a title, list of those participating, and the central theme.

As many of you may have read in national magazines, Baltimore truly has been a renaissance city in recent years. A short distance from the Medical School is the harbor area, which includes the National Aquarium, Harborplace (a complex of shops and restaurants), boats for hire, and an entertainment/movie complex. Also renowned in Baltimore are the crab dinners!

GENERAL INFORMATION

Continuing Education Credit will be available for physicians and psychologists.

Registration to the conference can be

made in advance by sending \$ 30.00 by July 1, 1985. Add \$ 15.00 if you would like to attend the banquet. Registration cards for both the conference and for the hotel reservations are enclosed.

Send conference cards, abstracts with complete names and affiliations of all authors if you would like to present a paper, and information about audio-visual equipment needed for your presentation to:

Jaylan S. Turkkan, Ph.D.

The Johns Hopkins University School of
Medicine

601 Traylor Bldg., 720 Rutland Avenue
Baltimore, Maryland 21205
(301) 955-3135

September 16-20, 1984
Spoleto (Perugia), Italy
International Symposium on

Development and Plasticity of the Mammalian Spinal Cord First Announcement

Major advances in our understanding of the motor capacity remaining after spinal transection and in the regenerative capacity of spinal systems have reopened the question of functional reconnection of the severed mammalian spinal cord, although this goal may still be in the distant future. Many aspects of spinal cord structure and function still require a greater understanding, however. For example, the mature spinal cord displays less capacity for autonomous motor function than it does in the newborn animal and spinal locomotion in the primate has yet to be demonstrated. Similarly, the amount of plasticity exhibited by the adult spinal cord is much less than in the neonatal cord after damage.

The concept of the organizers is to hold a relatively small, intensive and focused conference of about 20-25 presentations, but to enlarge the scope of the conference through additional poster sessions. In order to achieve the desired focus, a number of important areas of spinal cord research have been omitted, for example, normal anatomy and physiology, supraspinal control and spinal cord research in nonmammals. These have been dealt with at other meetings.

The purpose of this conference is to bring together investigators whose research is focused on the development and plasticity of

the mammalian spinal cord in order to make a sort of progress report and to examine the current status of a number of important areas in spinal cord research.

Sponsors

National Science Foundation
Spinal Cord Injury Association
Associazione per il Progresso Medico Sociale
delle Lesioni Spinali (APPLES)

Scientific Committee

A. Björklund (Lund, Sweden)
M. Devor (Jerusalem, Israel)
S. Grillner (Stockholm, Sweden)
D. Stelzner (Syracuse, USA)
P. Wall (London, U.K.)

Organizing Committee

M. E. Goldberger (Philadelphia, USA)
A. Gorio (Abano Terme, Italy)
M. Murray (Philadelphia, USA)

Enquiries

Dr. Alfredo Gorio
Fidia Research Laboratories
P. O. Box 110
35031 Abano Terme, Italy
Telephone: (049) 810444

Scientific Programme

The symposium will be divided into five major sessions:

1. Development and developmental plasticity; anatomical and functional aspects of postnatal development as a framework for examining compensatory responses of the spinal cord to damage occurring neonatally.
2. Axonal sprouting and alterations in specific transmitter systems in response to deafferentation and sensory deprivation of the spinal cord.
3. Physiological correlates of plasticity: response of spinal neurons to deafferentation, sensory deprivation and conditioning.
4. Regenerative capacity of the spinal cord during development and in the mature animal.
5. Capacity of the mammalian spinal cord for independent motor function (after complete transection) development and recovery of motor function: effects of pharmacological agents and of age.

Speakers

A. Aguayo (Montreal, Canada)
A. Björklund (Lund, Sweden)
B. Bregman (Baltimore, U.S.A.)
R. E. Burke (Bethesda, U.S.A.)
W. DeGroat (Pittsburgh, U.S.A.)
M. Devor (Jerusalem, Israel)
R.G. Durkovic (Syracuse, U.S.A.)
D.G. Ferrington (Syracuse, U.S.A.)
M. Fitzgerald (London, U.K.)
H. Forssberg (Stockholm, Sweden)
M. Goldberger (Philadelphia, U.S.A.)
A. Gorio (Abano Terme, Italy)
S. Grillner (Stockholm, Sweden)
G.F. Martin (Columbus, U.S.A.)
L. Mendell (Stonybrook, U.S.A.)
M. Murray (Philadelphia, U.S.A.)
P. Reier (Baltimore, U.S.A.)
S. Rossignol (Montreal, Canada)
M. J. Rowe (Sydney, Australia)
K. Saito (Tokyo, Japan)
T. Sears (London, U.K.)
J. Smith (Los Angeles, U.S.A.)
D.J. Stelzner (Syracuse, U.S.A.)
A. Tessler (Philadelphia, U.S.A.)
D. Viala (Dijon, France)
P.D. Wall (London, U.K.)

Second Announcement

XIII IFMP - International Congress of Psychotherapy

Opatija, Yugoslavia, October 6 - 12, 1985

The 13th International Congress of Psychotherapy will be held in Opatija, Yugoslavia, from 6th to 12th October, 1985.

The main subject of the Congress will be:

PSYCHOTHERAPY IN HEALTH PROTECTION BY THE YEAR 2000.

We are glad to inform you that by now we have received a great number of registrations for participation at the Congress as well as a lot of papers. Enclosed, please, find a list of thematic sessions which will be held during the Congress. The Congress activities will be organized through these symposia and Plenary Sessions.

We invite you to take active part in the Congress and to send us the title of your contribution till August 25, 1984 and the summary till November 15, 1984. The summary should be sent on one type-written page with double spacing. At the upper left corner of the page, please, indicate your institution and its address and at the lower

right corner your name and profession. It is important that we receive your registration and the summary till these dates so that we might plan the Congress activities in the best possible way and to print the abstracts in time.

The intention of this Congress is also to offer the possibility of intraprofessional meetings and discussions and for that purpose sections for different professional groups will be organized, such as those of nurses, psychologists, social workers, etc. There will also be held a special students' section as well as the programme for the users of health protection and their family members.

Please, inform also your colleagues about this event and invite them to take part. **FURTHER INFORMATION WILL BE SENT ONLY TO THOSE WHO WRITE US TILL THE ABOVE STATED DATE.**

Registration fee for participants is US\$ 120, for accompanying persons US\$ 50, for users and their family members US\$ 20, if paid before January 3, 1985. After January 3, 1985 the fee is US\$ 150.

The fee is payable to Savez za zastitu dusevnog zdravlja SRH (for 13th Congress) at the account no 25730-421-3252833, Zagreb Bank, Savska 66, Zagreb, or by cheque payable to "Savez za zastitu dusevnog zdravlja SRH" (for 13th Congress), Vinogradska 29, 41000 Zagreb.

Simultaneous translation will be partly available in the English language, in the language of the host country and in one more language, what will be decided upon the number of participants speaking different languages.

For all information, please, write to Prof. Vladimir Hudolin or Dr. Branko Lang, University Department for Neurology, Psychiatry, Alcoholology and Other Dependencies, "Dr. M. Stojanovic" University Hospital, Vinogradska 29, 41000 Zagreb, Yugoslavia. Phone nb. (041) 574-666 - extension 145 or (041) 575 - 045.

Doc. dr. Branko Lang
Secretary General of the
Organizing Committee
Prof. dr. Vladimir Hudolin
President of the Organizing
Committee

September 23 - October 4, 1985
Cannizzaro, Catania (Grand Hotel Baia Verde)
International School

Biomembrane and receptor mechanisms Programme Sponsored by

University of Ancona
University of Catania
Consiglio Nazionale delle Ricerche

Scientific and organizing committee

E. Bertoli (Ancona)
A. Cambria (Catania)
D. Chapman (London)
U. Scapagnini (Catania)
G. Toffano (Abano Terme)

Course Directors

E. Bertoli (Ancona)
D. Chapman (London)

Scientific secretariat

E. Bertoli
Institute of Biochemistry, Medical School
University of Ancona
Via Monte d'Ago
60100 ANCONA
Phone (071) 894306
Tx UNIV ANI 216838

Objective

The aim of this course is to convey the major principles and concepts central to an understanding of the structure and function of membranes and membrane bound receptors. These, principles and concepts are drawn from physics, chemistry and biology and are intended at creating an interdisciplinary approach to the topic of cell membrane organization and function.

The course is a series of lectures ranging from a description of structure and biophysical characterization of membranes to more detailed macromolecular interactions as described for lipids, proteins and carbohydrates. Furthermore, topics on the dynamics of ligand binding to receptor sites will be discussed in relationship to the macromolecular architecture of the cell surface.

The goal of this international school is to document the exciting developments in the area of membrane and receptor function and to make them accessible to the intro-

ductory student. An extremely important task for this school is to encourage an active exchange of ideas and discussion on the major facts and theories on the subject of membrane structure and function as well as to promote a continuity in a friendly atmosphere.

Lectures

E.A. Barnard

Imperial College of Science
and Technology

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Institute of Biochemistry,
Medical School

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F. Daemen

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Department of Biochemistry

Geert Grooteplein in noord 21

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Institut de Biologie physico-chimique

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Dept. of PNS and SC

Fidia Research Laboratories

35031 Abano Terme, Padova (Italy)

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Department of Health & Human
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Institute and Botanical Garden

University of Bologna

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Department of Biological Chemistry

Institute of Life Sciences

Jerusalem 91904 (Israel)

A. Lucy

Royal Free Hospital School of
Medicine

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Institute of Biological Chemistry

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Dept. of Pharmacobiology

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P. Pinto Da Silva

Department of Health & Human
Services,

Public Health Service

National Institute of Health

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Rijksuniversiteit Utrecht

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Universität München

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M. Shinitzky

Department of Membrane Research

Weizman Institute

Rehovot (Israel)

M.J.A. Tanner

Department of Biochemistry

University of Bristol, Medical School

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 Dept. of Medicine and Surgery
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 G. Toffano
 Laboratories of Neurobiology
 Fidia Research Laboratories
 35031 Abano Terme, Padova (Italy)
 U. Zimmerman
 Lehrstuhl für Biotechnologie der
 Universität Würzburg
 Röntgenring 11
 8700 Würzburg (FRG)
 H. Wiegandt
 Physiol. Chem. Institut
 I-Philips-Universität
 D- 3550 Marburg / L
 Lahnerge (FRG)

Topics

BIOMEMBRANES: STRUCTURES AND
 MOLECULAR ORGANIZATION
 MEMBRANE ASYMMETRY
 LIPID-PROTEINS INTERACTIONS
 CELL SURFACE RECEPTORS: MOBILI-
 TY AND TOPOGRAPHY
 PROTEIN & RECEPTOR DIFFUSION
 MEMBRANE FLUIDITY & RECEPTOR
 MODULATION
 MEMBRANE FUSION
 ION TRANSPORT MECHANISMS
 RECEPTOR AND ION CHANNEL
 GANGLIOSIDE & RECEPTOR FUNC-
 TION
 PHOTORECEPTORS: ORGANIZATION
 AND FUNCTION
 HORMONAL MEMBRANE RECEPTORS
 NEUROTRANSMITTER RECEPTORS
 BIOCHEMICAL MECHANISMS OF SIG-
 NAL TRANSDUCTION
 DYNAMICS OF CYCLASE-RECEPTOR
 INTERACTION
 RECEPTOR AND PHARMACOLOGICAL
 ACTION

General Information

Place and Date

The Course will be held at the Grand Ho-
 tel Baia Verde, a sea shore Hotel in Ca-
 tania, Sicily.
 There are excellent facilities for lectures,
 leisure, recreation and excursions to histo-
 rical attractions.

Scientific Secretariat

All enquiries should be addressed to:
 E. Bertoli
 Institute of Biochemistry
 Medical School
 University of Ancona
 Via Monte d'Ago
 60100 ANCONA
 Phone (071) 894306, Telex UNIV ANI
 216838

Requirements

Engaged in research of working interest in
 biochemistry and biophysics of membranes
 and receptors.

Registration

The number of participants will be limited
 to 90 persons.

The participants will be selected by the
 Scientific Committee on the basis of their
 experience or interest in the field.

Only those persons who apply and are se-
 lected will be able to participate in the
 school.

Persons wishing to apply should complete
 the application form attached and submit
 it to the scientific secretariat.

**Deadline for submission of application:
 May 31, 1985.**

The Scientific Committee will inform the
 applicants of the result of their application
 in June 1985.

Participants are expected to arrive at Cata-
 nia by Sunday september 22, 1985 and re-
 main for the full duration of the Course
 (September 22 - October 4).

The total fee including full board, lodging
 for the duration of the course based on
 double room accomodation, course material,
 and participation in all scientific and so-
 cial activities, will be US\$ 520.

The deposit of US\$ 80 will be paid by chè-
 que made out to: **Hotel Baia Verde - CT**,
 with the registration form (after acceptance
 of the application form by the Scientific
 Committee) and sent to:

Prof. E. Bertoli
 Institute of Biochemistry
 Medical School
 University of Ancona
 Via Monte d'Ago - 60100 Ancona (Italy).
 The balance of the fee will be due and co-

lected at the arrival of the participants at the site of the meeting.

Posters

Poster sessions and discussions will be included in the programme. Participants wishing to present a poster should include the poster abstract (using the specific enclosed forms) with their registration form.

Attendance certificate

A certificate will be given at the end of the end of the Course only to those who have attended throughout the duration of the school.

Abstracts

Abstracts will be distributed to the participants on arrival.

Proceedings

The proceedings of the International course will be published in "Fidia Research Series".

ANNUAL MEMBERSHIP MEETING

Medical Panel Presented

TSA's annual membership meeting hosted by the Greater DC chapter was held on November 17 at the National Institutes of Health in Bethesda.

Judy Wertheim, President of TSA since 1981, passed the gavel to Eleanor Curry, Executive Vice President, who accepted on behalf of newly-elected President Sue Levi. Anne Abramson, sister-in-law of the late Dr. Sheldon Novick (TSA's Medical Chairman for ten years), officiated at the installation ceremony.

Other business included the adoption of By-laws and a treasurer's report. The business portion of the meeting was followed by a medical panel program.

Dr. Kenneth Rickler, a practicing neurologist affiliated with George Washington University, member of the Board of Directors and medical advisor to the Greater Washington Chapter, and also member of TSA's National Medical Committee, introduced the distinguished panel of guests: Katherine Bick, Ph.D., Assistant Director, NINCDS/NIH; Thomas N. Chase, M.D., PET Studies Section, NINCDS/NIH; and Martha Denkla, M.D., Director, Behavioral Disorders Program, NINCDS/NIH. Each

panelist spoke about the Federal Government's support of Tourette research projects.

MEDICAL PANEL

Dr. Bick reported that NINCDS has received a handsome increase in funding (18.2 %) during 1985. Despite this much needed increase, NINCDS will be able to fund only one-third of approved research grants. Many worthwhile projects will not get funded because there has been an upsurge of grant applications submitted to NINCDS reflecting a new interest in the neurosciences by researchers.

A major national commitment to neuroscience research is needed, Dr. Bick feels. More clinical investigators need to be trained. NINCDS has awarded a series of grants, called Senator Jacob Javits Awards, to provide support to exceptionally talented neuroscience investigators. Still Dr. Bick feels that the nation's commitment to neuroscience needs to be greater.

Dr. Thomas Chase, who is also a member of TSA's Medical Advisory Board, commended the TSA for its efforts to award research grants to young investigators. He described research efforts on most neurological disorders in the following manner: 1) Analyzing the symptoms of the disorder in order to hypothesize where the major defect may be; 2) Localizing the area of the brain where the problem is occurring; 3) Identifying the neurotransmitters involved, and determining the nature of the imbalance; 4) Developing drugs which will correct the imbalance.

Dr. Chase has been working with the PET scan (Positron Emission Tomography), which is a new technology capable of mapping chemical activity in the brain. His studies on Tourette Syndrome have tentatively indicated an abnormality in the basal ganglia (striatum) and over-activity in a connection between the basal ganglia and the cortex. Patients with vocal tics showed an abnormality in the area of the cerebral cortex when vocal tics occurred. Dr. Chase continues to seek TS patients who are willing to participate in PET-scan research.

Dr. Martha Denkla described four extramural research projects which are presently funded by NINCDS: Since 1980 a genetic/epidemiological study has been conducted at Yale University. Geneticists at Yale are

trying to determine clinical heterogeneity and are focusing on obsessive-compulsive aspects of TS. Sixty percent of people with TS have been identified with concurrent Attention Deficit Disorder (ADD). Yale's study of twins with TS, which was partially funded by a TSA grant, showed that 50 % of twins TS showed exacerbated symptoms when treated with stimulants, but out of 6 pair of discordant twins where only one had been treated with stimulants, the untreated twin eventually developed tics anyway. The implication of this finding would indicate that people with TS who have been treated with stimulants may have developed TS with or without stimulant medication.

Another research project at Yale involves an attempt to induce tics and vocalizations in cats, which may hopefully lead to an animal model for TS.

Johns Hopkins Hospital is conducting a TS research project which seeks to identify neuroreceptor binding sites for dopamine and opiate receptors. In addition, Drs. Arthur and Elaine Shapiro at Mount Sinai Medical School have received a grant to compare the effects of Haldol and Pimozide. Attentional, motoric and cognitive variables will be explored.

Dr. Rickler complimented the TSA Newsletters for informing the TSA membership about ongoing research projects. As a clinician he remarked that basic research and clinical research benefit from each others findings, but more feedback is needed between clinicians and the research community. Dr. Rickler feels that individual clinicians have the benefit of long-term observations of people with TS. He feels that problems related to coping with TS need to be explored further.

Questions and answers followed the panel presentation. Dr. Chase felt that Nuclear Magnetic Resonance (NMR) is a new technology which is not yet capable of tracking neurochemicals, but may be of importance to TS research in the future.

Dr. Rickler remarked on long-term use of Haldol which demands vigilance for symptoms of Tardive Dyskinesia, even though the incidence of TD in Tourette is still very low. He noted that people with TS should not use medication unless it is needed when

TS becomes a major interference in one's life.

Dr. Chase remarked that the scarcity of post-mortum TS brain tissue is a shame, and availability of such tissue would lead to major advances in the understanding of TS. Dr. Bick remarked that it is important to encourage scientists to look for animal models of TS.

Panelists also noted that much more needs to be learned about the role of hormones, immunology, prenatal factors and a variety of unexplored areas which may relate to TS. Encouraging researchers to study TS is not an easy job, but Dr. Denckla offered her assistance to any scientists wishing to apply for an NINCDS grant.

This Newsletter is published
by the

**TOURETTE SYNDROME
ASSOCIATION, INC.**

41-02 Bell Boulevard
Bayside, New York 11361
(718) 224-2999

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William Shatner

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Vol. XII, No 1

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Membership: \$25.00,

includes Newsletter

**Newly Elected
National Board
of Directors**

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(Staggered terms so newly instated rotation process may begin. This process does not preclude re-election to the National Board)

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* Mike Bachenheim, NY

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* New to Board

Letters to the Editor

As a teacher at the Summit School in Nyack, New York for nine years, I have had the opportunity to teach several students with Tourette's Syndrome. I have an anecdote to relate which may be helpful to both parents and teachers in coping with the problems people with TS encounter.

Two students in one of my classes — Bob, who has TS and John who does not, were having trouble getting along with each other. Bob's rather exuberant symptoms were annoying to John, who is both short tempered and quick to tease and bully those around him. John began to give Bob a very hard time, teasing him and threatening to do him bodily harm if Bob didn't "cut it out." Since the entire class had already been informed of Bob's condition and were generally aware of its nature, my initial response to John's behavior was an authoritative command to stop teasing. This reduced, but did not stop, John's behavior.

Meanwhile, Bob's motor and verbal tics continued at their previous prodigious rate. Furthermore, a new "tic" developed. In his concern over avoiding conflict with John, Bob became quite fixated on John's presen-

ce in the room. This concern manifested itself in a frequent and quite audible repetition of John's name. John reacted by becoming increasingly hostile.

At this point I asked John to stay after class and explained to him that Bob was repeating John's name just because he was trying so hard to avoid John's wrath. "The thing that Bob least wants to do," I told John, "becomes the thing that he cannot keep himself from doing. The only way that you can stop Bob from repeating your name is to stop bothering him yourself so that you are no longer his main concern in class."

Fortunately, John took my advice. In a short time John's name disappeared as one of Bob's tics, and more order returned to the classroom. As tensions in the room decreased, Bob became more at ease and his other tics also reduced in intensity, thus enabling John to better concentrate on his work.

The point for both parents and professionals to absorb from this story is that the tics of Tourette's Syndrome often represent an inability to repress or "inhibit" specific behaviors which are of particular concern to the person with TS, and are often the very behaviors that the person least wishes to perform. Furthermore, intervention which reduces the stress of concern over that particular behavior may well extinguish the behavior as a part of the person's repertoire of tics.

Victor Gruener

PARIS MEETING TO MARK TOURETTE CENTENNIAL

An historic two-way meeting scheduled for May 2 and 3, 1985 has been planned by the French Neurological Society to mark the one hundredth anniversary of Gilles de la Tourette's description of the Syndrome which bears this French physician's name.

The Tourette Association is sponsoring the participation of our Medical Advisory Board and Medical Committee Chairmen, Drs. Arnold J. Friedhoff and Ruth D. Bruun. In addition, Mr. and Mrs. H.B. Pearl will represent the Association and present a report on our activities throughout the U.S.A.

A special TSA Permanent Research Fund grant in honor of Gilles de la Tourette (to

be awarded to a worthy French scientist) will be announced at the meeting in honor of Gilles de la Tourette.

The scientific meeting will be held at the historic Charcot Amphitheater of the Salpetriere Hospital in Paris. Gilles de la Tourette, a student of Dr. Charcot, accomplished his most important work while associated with this world famous institution.

TSA members who plan to travel to Europe in the spring of 1985 are welcome to attend.

National Committee for Research

At its November 8 annual meeting in Washington the National Committee for Research in Neurological & Communicative Disorders (NCR) celebrated its 5th anniversary as an incorporated not-for-profit coalition now comprised of some 57 voluntary health organizations and professional societies. Mr. H.B. Pearl, TSA's representative and a member of NCR's Executive Board, was the recipient of a 'Recognition Award' for unusual services rendered to the Committee.

Dr. Murray Goldstein, Director for the National Institute for Communicative Diseases & Stroke (NINCDS), reported that the "state-of-the-art" technologies found in current generation Computerized Axial Tomography (CAT) scanning equipment and in the newest of the Nuclear Magnetic Resonance (NMR) brain imaging equipment have given rise to an expectation of far greater possibilities for understanding the basic etiology of a number of disorders, including Tourette Syndrome, than had heretofore been felt possible. Dr. Goldstein also congratulated NCR on being instrumental in achieving for NINCDS, in fiscal year '85, a budget allocation of approximately \$ 397 million which is the largest ever received by NINCDS. This 1985 budget allocation represents the largest proportionate increase in funding of all of the Institutes (other than the National Institute for Aging) operated by the National Institutes of Health. However, Dr. Goldstein also noted that in order for NINCDS to achieve a funding target of 50 % of approved grants the Agency would need at least an additional \$100 million of funding in FY '86.

NCR members were also concerned with a grassroots movement by "animal rights"

activists to halt the experimental use of animals in the study of disease. Researchers explained that the animal rights movement threatens future research advances because scientists would be prohibited from using animals to study the effectiveness of drugs, or to examine how certain substances are responsible for causing a disease to occur, etc. Neurological scientists pointed out that advances in the understanding of many neurological disorders have been slow to occur due to the absence of an animal model for specific disorders.

At the present time the National Institute of Health is supporting a multi-year project which is attempting to create an animal model of Tourette Syndrome. The overzealous "animal rights" movement threatens to halt this and other scientific advances because animal rights activists are more vocal than that sector of our population which supports and values animal experimentation simply because it is preferable to human experimentation. People with TS should let their Congressional leaders know how they feel about this subject.

MAJOR DONATIONS *

We are grateful to the following individuals, foundations, and corporations for their significant contributions in support of TSA's programs of medical and general education, and family and professional services:

Dr. William E. Boggiano
Peter Boleski
Allison and Louis Brandt
Recia H. and I. William Cohen
The Gateposts Foundation
Estelle Gelman
John E. Lovenheim
McNeil Pharmaceutical Corp.
Diane & Darryl Mallah
Barbara and Hyman Mellen
Eleanor and Herbert B. Pearl
Howard and Judy Schatz
White Charity Committee
The Thomas S. Wootton High School
(in honor of the Meringoff Family)

(* - representing \$1,000 or more)

Media Update

TSA public service announcements featuring William Shatner have been airing on radio and TV stations throughout this

country since late June, 1984. The National office has received more than 1,600 phone calls and letters requesting further information about Tourette Syndrome as a result of these "spots".

We know that our public awareness efforts account for nearly 90 % of newly diagnosed people, and we are grateful to the TV and radio stations who have helped identify people with TS by airing the TSA public service announcements.

TSA is also very grateful to Ann Landers who featured a letter about TS in one of her columns in November, and to "Readers Digest" for printing an orphan drug article in their December issue. Over 3,000 inquiries were generated from these sources. From this response we were able to identify a large number of persons who had been diagnosed but heretofore had not been aware of the help they could receive through TSA.

PIMOZIDE DISTRIBUTED

All hurdles related to pimozide's (Orap) approval for marketing in the United States were finally crossed during October 1984, and on November 1, McNeil Pharmaceuticals began distribution of this drug which will be used solely for the treatment of Tourette Syndrome.

Since pimozide will not be a fast selling drug and might take a few days for local druggists to order it from wholesalers, the TSA and McNeil Pharmaceuticals have taken steps to assure that pimozide will be obtainable without undue delay by those who need it:

- The TSA Pharmacy Service, address Iowa, has in stock a large quantity of pimozide which will be sold to TSA members at slightly above cost.
- Revco Drug Stores, a large retail chain in the west and midwest, is stocking pimozide at central warehouses. Local Revco Drug Stores will be able to fill a prescription for pimozide within 24 hours.
- Several major hospitals and research institutions, particularly those with TS clinics, will stock pimozide in their hospital pharmacy.
- Any pharmacy having difficulty obtaining pimozide can contact McNeil Pharmaceuticals in Spring House, Pennsylvania directly.

As a service to our readers, an article by Dr. Ruth Bruun (TSA's Medical Committee Chairman) appears in this issue of the TSA Newsletter describing medical management with pimozide. TS families may want to give this information to their physician.

The TSA is indebted to McNeil Pharmaceuticals for their careful and considerate management of distribution plans for pimozide. Not wanting people who need the drug to experience undue delays obtaining it, yet understanding that not every pharmacy will want to stock this drug, McNeil has carefully distributed sufficient supplies to major TS research and treatment centers so that most patients can fill their prescription at hospital pharmacies in urban areas where they go for treatment.

PLEASE REMEMBER TSA IN YOUR WILL

Persons who are supporters of the TSA may wish to consider extending their support beyond their lifetime by remembering TSA in their Will.

Whether your legacy is large or small, it can help the ongoing programs of the Association. To make a bequest of cash or other property to our organization, your Will (or supplemental codicil, if you do not wish to write a new Will), should state:

"I give and bequeath to the Tourette Syndrome Association, Inc., a not-for-profit corporation, organized under the laws of the State of New York, and having its principal office at 41-02 Bell Blvd., Bayside, N.Y. 11361, the sum of \$—— (or —— per cent of the rest, residue, and remainder of my estate) to be used for general purposes."

Remembering TSA in your Will is a very important and personal way of continuing to give help to people with Tourette Syndrome and their families.

ALL TSA MEMBERS ARE ELIGIBLE FOR PHARMACEUTICAL PLAN

Remember, TSA dues paying family members are eligible to have all their prescriptions filled by the TSA pharmacy. If

your medication is not listed in the brochure, mail your prescription or ask for a price quote.

HOW DO I ORDER PRESCRIPTIONS?

1. Send an original prescription written by your Doctor to TSA Pharmacy.
2. A copy of a prescription or a bottle label from another Pharmacy can be filled only when the Doctor is phoned for permission. Include your Doctor's name, address and phone number if this is necessary.
3. Print your name and address on each new prescription. Use the first name of the family member for whom the prescription was written.
4. If you want to use the less expensive generic medicine, request it.
5. Ask your doctor to indicate the number of refills he authorizes. Refillable prescriptions are kept on file, and you can have them filled again simply by listing the serial number from the bottle label or the invoice.
6. Mail prescriptions to: TSA PHARMACY SERVICE, 200 Main Street, Madrid, Iowa 50156.

HOW DO I PAY FOR MY ORDER?

- a. To charge your costs to VISA or MASTERCARD, list your account number and expiration date.
- b. You can send payment with your order include the 75 cents handling charge, or wait for the invoice and then send payment promptly.

MEDICAL UPDATE

QUESTION: I am an active member of a TSA chapter which has group counseling "rap sessions" every week. I would like my 10-year-old son to participate in the rap sessions, but I'm afraid that he'll imitate other children's tics if he's exposed to symptoms which are different than those he has now. What should I do?

ANSWER: It is true that some people with TS may compulsively imitate other people. However, our experiences with rap sessions, and indeed programs throughout the country which have a relatively large number of people with TS (i.e. summer camps, private schools, etc.) indicates that the compulsion to imitate is only temporary and usually disappears with repeated exposures. That is, a person with TS may report that he has imitated another person's tics for 2 or 3 days after they first met. With subse-

quent meetings the compulsion to imitate diminishes, and finally disappears. This compulsive characteristic does not usually present a problem in families where multiple members have TS and live together.

Only some people with TS experience this type of compulsion, and it is wrong to assume that your son will have this tendency unless you see evidence that he normally imitates other people's movements or adopts another person's accent or inflection. Even if this is true for your son, tics are not "catchy" in a permanent sense, so you should weigh the risks against the benefits of attending rap sessions. Will your son benefit from meeting other children who have had similar experiences, and felt the same deep emotions because they have Tourette Syndrome? Or will he benefit from never meeting other people with TS, continuing to feel different from the rest of society?

Incidentally, TSA has not heard from people with TS who have not gone back to a rap session because he/she felt that the compulsion to imitate outweighed the benefit of being with others who understand the involuntary nature of tics and compulsions. Many rap session participants have probably experienced the pain of this symptom themselves, and are happy to find an environment where it is finally understood and accepted.

TREATMENT OF TOURETTE SYNDROME WITH PIMOZIDE (ORAP)

by Ruth Bruun, M.D.,
Chairman, Medical Committee

Pimozide (Orap) has recently been approved by the FDA for treatment of Tourette's syndrome in the United States. Since clinical trials have indicated that this medication is an effective alternative to haloperidol for treatment of TS, its availability has been eagerly awaited in this country. It should be made clear, however, that pimozide is not necessarily a better drug than those already in use in the United States, only an alternative which may prove better for certain patients. Until there has been considerably more experience with pimozide it should not be utilized as a first choice medication in the treatment of TS. The guidelines issued by McNeil Pharmaceuticals state that: "Orap (pimozide) is

indicated for the suppression of motor and phonic tics in patients with Tourette's Disorder who have failed to respond satisfactorily to standard treatment." Furthermore, it is recommended only for those cases of TS in which symptoms severely compromise daily life functions.

Since pimozide has been found to prolong the QT interval of the electrocardiogram it is contraindicated in patients with congenital long QT syndrome, with a history of cardiac arrhythmias, or those taking other drugs which prolong the QT interval of the EKG (eg. phenothiazines, tricyclic antidepressants and antiarrhythmic agents). Because of the possibility of QT interval prolongations, it is recommended that an EKG be done before administration of the drug and periodically thereafter during the dose finding part of treatment. Should the QT interval be found to exceed 0.47 seconds (children) or 0.52 seconds (adults) or to be more than 25 % above the patient's original baseline, this should be considered a contraindication to any increase of dosage.

One further contraindication to be noted is the concomitant use of drugs which may, themselves, be causing motor and/or phonic tics (eg. methylphenidate, pemoline and amphetamines). Such patients should be withdrawn from stimulant medication first to determine whether it, rather than TS, is responsible for the tics.

Having determined that a patient is indeed a candidate for treatment with pimozide, treatment should be instituted with a minimal dose and raised slowly so as to balance clinical benefits against the development of side effects. With younger children I would recommend a starting dose no higher than 0.5 mg. per day. Adults may be started on 2 mg. per day. Unfortunately the tablets come only in 2 mg. strength and so must be cut into quarters to halves to administer low doses. After 5 to 7 days the dose may be increased in units compatible with the starting dose. If side effects appear early in treatment the dose should be maintained longer at a low level. As a general rule, the slower the dose is increased the less likely a patient is to develop side effects. The maximum recommended dose is 20 mg. per day (or 0.3 mg./kg./day, whichever is lower).

Some physicians feel that anticholinergic medication should be given routinely during early stages of treatment in order to avoid extrapyramidal side effects, particularly acute dystonic reactions which may occur in about 10 % of patients. Others disagree on the prophylactic use of anticholinergics, but prefer to wait for side effects to be manifested. In any case a substantial percentage of patients on pimozide will require anticholinergic medication to control side effects at some point during their treatment.

Since clinical experience with pimozide for treatment of TS has been limited, the more uncommon adverse side effects may still be unreported. The treating physician should consider that any of the adverse reactions associated with neuroleptics may occur including tardive dyskinesia (irreversible). The major limitation of haloperidol in the treatment of TS has been the development of sedation, lethargy, depression, dysphorias and cognitive dulling. These side effects, though they may also occur with pimozide, have been reported to be less frequent and less severe than with haloperidol. This may be because pimozide has more specific dopamine blocking properties and less norepinephrine blocking effect than haloperidol.

Side effects most commonly encountered in clinical trials are: sedation, drowsiness, akathisia, akinesia, dry mouth, constipation, muscular cramps, visual disturbances and impotence. All of these as well as others listed in the McNeil Pharmaceutical package insert for Orap (pimozide) are reversible on discontinuance of the drug or lowering of dosage with the exception of tardive dyskinesia. Since tardive dyskinesia may rather easily be confused with the movements of TS and thus go unrecognized in its early stages, it should be a particular concern. In any case, periodic attempts should be made during treatment to lower the dose of pimozide. Since there may be a transient withdrawal reaction which may appear to be an increase of tics when the medication is lowered, the patient should be given at least two weeks at a lowered dose before the physician can be certain that a tic increase is due to the underlying disease rather than the withdrawal phenomenon.

As with haloperidol a gradual withdrawal is recommended.

Since pimozide is not to be used as a first choice drug it is reasonable to assume that many patients who are suitable for treatment with this medication may already be on haloperidol, clonidine or other medication. It is, of course, better to discontinue any other medication first and to allow a time for complete drug clearance to occur before starting pimozide. However, if a patient has a great deal of trouble in discontinuing haloperidol (because of withdrawal emergent reactions or severe symptomatology) pimozide can gradually be substituted for haloperidol. The dosage equivalent of haloperidol to pimozide is 1 to 2.5 mg. Since both haloperidol and pimozide have long half-lives (at least 4 days), the patient should be monitored carefully during the period when both drugs are present in his system.

SUMMER CAMP FOR YOUNGSTERS WITH TS

Nineteen youngsters from the states of Kansas, Missouri, Texas, Tennessee, Florida, New York and Oklahoma attended the second annual summer camp in Oklahoma this past summer.

In addition to camp activities that included swimming, canoeing, archery, riflery, arts and crafts, fishing, horseback riding, etc., one period was set aside for learning more about Tourette Syndrome, a questions and answer and discussion session.

Both boys and girls attended, those who had completed grades two through eight.

Dates of the camp next summer are June 23 through June 30. Camp brochures are available from the Oklahoma Chapter, Tourette Syndrome Association, P.O. Box 761, Bartlesville, OK 74005.

Make plans early. Many civic groups look forward to helping finance camping and travel costs to send youngsters to summer camp.

NINCDS Invites Applications for Brain-Imaging Research Centers

The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) is seeking grant applications for Brain-Imaging Research Centers to improve understanding of central nervous system function and dysfunction.

Proposed centers should use combinations of imaging technologies to develop and refine information about the living brain under dynamic conditions. Of particular interest are applications emphasizing magnetic resonance imaging and its interrelationship with other methods for measuring biochemical events and anatomical changes within the brain.

Additional details about this research need were published in the November 9, 1984, issue of the *NIH Guide for Grants and Contracts*.

Applications must be received by February 15, 1985. Scientists wishing further information may contact: Dr. George N. Eaves, Stroke and Trauma Program, NINCDS, Federal Building, Room 8A13, Bethesda, Md. 20205; telephone: (301) 496-4226.

NINCDS Makes Neuroscience Awards in Honor of Senator Javits

The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) has chosen 24 grant applicants for special neuroscience awards named for former Senator Jacob Javits. The group joins 61 other scientists who have received Javits awards.

The Javits Neuroscience Investigatorships provide individual scientists with up to 7 years of grant support for basic or clinical research in the neurological and communicative sciences.

The new Javits awardees and their project titles are:

— Robert Barchi, University of Pennsylvania, Philadelphia, Pa., "Studies of Purified Sodium Channels from Sarcolemma".

— Linda Bartoshuk, John B. Pierce Foundation, New Haven, Conn., "Taste Psychophysics".

— Albert Berger, University of Washington, Seattle, Wash., "Respiratory System Integration by the Brain Stem".

— William Cain, John B. Pierce Foundation, New Haven, Conn., "Clinical Olfactory Psychophysics".

— William Catterall, University of Washington, Seattle, Wash., "Voltage-Sensitive Sodium Channels in Brain".

— George De Vries, Virginia Commonwealth University, Richmond, Va., "Molecular Basis of Axolemmal-Glial Interaction".

— Paul De Weer, Washington University, St. Louis, Mo., "Modes of Operation of the Sodium Pump".

— Bertil Hille, University of Washington, Seattle, Wash., "Molecular Properties of Ionic Permeability in Nerve".

— Stephen Kitai, University of Tennessee, Memphis, Tenn., "Experimental Studies of Sensory Pathways".

— Lawrence Kruger, University of California, Los Angeles, Calif., "Cutaneous Morphological Correlates of Pain".

— Renee Margolis, Downstate Medical Center, State University of New York, Brooklyn, N.Y., "Studies on Nervous Tissue Glycoconjugates".

— Anthony Marmarou, Virginia Commonwealth University, Richmond, Va., "Biomechanics of Brain Edema and Intracranial Pressure".

— Dennis McFadden, University of Texas, Austin, Tex., "Auditory Adaptation for Suprathreshold Stimuli".

— Charles Molnar, Washington University, St. Louis, Mo., "Cochlear Mechanics and Neural Encoding".

— William Norton, Yeshiva University, Bronx, N.Y., "The Chemistry of Cells and Cell Portions from the CNS".

— John O'Brien, University of California at San Diego, La Jolla, Calif., "Molecular Basis of Cerebral Degeneration".

— George Ojemann, University of Washington, Seattle, Wash., "Electrocorticographic Changes with Higher Function".

— Karl Pfenninger, Columbia University, New York, N.Y., "Molecular Control of CNS Growth and Regeneration".

— Guillermo Pilar, University of Connecticut, Storrs, Conn., "Ganglionic Synaptic Transmission".

— Michael Raftery, California Institute of Technology, Pasadena, Calif., "Studies of the Nicotinic Acetylcholine Receptor".

— Murray Sachs, The Johns Hopkins University, Baltimore, Md., "Stimulus Encoding in the Auditory System".

— William Schlaepfer, University of Pennsylvania, Philadelphia, Pa., "Neurofilaments: Degradation Turnover and Role in Disease".

— F. Blair Simmons, Stanford University, Stanford, Calif., "Development of a Cochlear Prosthesis".

— Ludwig Sternberger, University of Rochester, Rochester, N.Y., "Monoclonal Antibody Probes for Neurofilament Processing".

The Javits awardees were recommended by the National Advisory Neurological and Communicative Disorders and Stroke Council for the strategic scientific importance of their work and the scientific merit of their specific research proposals. The Council selected the outstanding investigators from the pool of competing applications during the last four grant cycles. Additional Javits investigators will be named at Council meetings in January and May 1985.

Former NINCDS Director Receives Award for Hensing Book

Dr. Donald B. Tower, a former director of the National Institute of Neurological and Communicative Disorders and Stroke, has received the Award of Distinction History Prize from Justus-Liebig University at Giessen for his book, *Hensing, 1719*.

The award is presented for "outstanding works on the history of the University of Giessen, Federal Republic of Germany, or teaching and knowledge about it".

Dr. Tower's book chronicles the beginnings of modern neurochemistry. It examines the life and career of Johann Thomas Hensing (1683-1726) who, while at the University of Giessen, carried out the first chemical investigation of the brain.

The award was presented at the University's academic festival on November 30. It is one of five official prizes that the University can bestow annually.

• Book Reviews

CEREBRO VASCULAR DISORDER

TOOLE JAMES F.

Third Edition 436 pp. - 1984

RAVEN PRESS

This book is considered of fundamental importance for the study and treatment of cerebrovascular diseases.

There is a very interesting preface in which the author comments the Meeting of Yalta held in February 1945, between Franklin Delano Roosevelt, Winston Churchill and Joseph Stalin.

The decisions taken at this meeting have created adverse commentaries, and the three personalities that have participated in it had advanced cerebro vascular diseases.

This is an up-to-date edition reflecting all the advances acquired in the diagnosis and care of the patient suffering from cerebrovascular diseases. In this edition new chapters on noninvasive techniques, cardiovascular causes of strokes, fibromuscular dysplasia, ophthalmic and behavioral aspects of strokes, cerebrovascular causes of headaches and central nervous system effects of microcirculatory diseases, are included. A complete description of new technologies and different kinds of treatment are described and profusely illustrated.

The author emphasizes the extraordinary progress achieved during the last thirty years in the profilaxis and prevention of strokes.

In the first chapters of this book, the clinical implications of the anatomy of brain arteries and the physiology of the cerebral circulation are studied. A detailed information is given to the reader about the evaluation of the patient with a possible neurological disturbance, elaboration of his clinical history, neurological and neurovascular examination and the use of noninvasive screening tests. The computed tomography, digital subtraction angiography, positron emission tomography, regional cerebral blood flow and nuclear magnetic resonance are studied.

This book is of great importance for those physicians in charge of patients suffering from cerebral vascular disturbances. In each chapter the right and useful answer

is found; they are updated and include the latest advances in pathophysiology, diagnosis and medical and surgical managements.

All major cerebral syndromes, transient ischemic attacks, syndromes of the carotid artery, and its branches, syndromes of the vertebral - basilar artery and its branches, asymptomatic cervical bruits and their managements, cardiac cases or cerebral ischemia, cerebral embolism, atherosclerosis, brain infarction, ophthalmologic aspects of cerebrovascular diseases, general principle of managements and rehabilitation, behavioral abnormalities and intellectual decline caused by cerebrovascular disorders, hypertension, lacunar infarction and hypertensive encephalopathies are studied.

Each chapter is preceded by a significative quotation of very appropriate clinical concepts, uttered by great physicians in bygone epochs, when there were not the present day techniques for studying the patient with this kind of ailment.

There is a profusion of significative illustrations many of them accompanied by schemes that facilitate its understanding.

This is a very useful book for all the physicians interested in this important subject, expounded by a world renowned author.

Prof. Dr. Víctor Soriano

ADVANCES IN NEUROLOGY

Volume 38 - THE DEMENTIAS - Editors
Richard Mayeux, Wilma G. Rosen - 272
pages - Raven Press New York - 1983

It is interesting to remark the growing importance assigned to the subject of dementia in the last years, being this an ailment of chronic evolution that causes sadness in relatives and friends of the patient because of the serious derangements of their personality. Recent advances in Neurosciences have stimulated the investigators to study in detail the organic changes originated by this process and to try to avoid the dementia, or to treat it if this has already occurred.

Different kinds of dementia are studied by means of neurochemistry, genetics, neuroradiology, electrophysiology, concerning neuropsychological aspects and in the problems related with the family and the social environment of the demented.

The study of the dementia is a multidis-

ciplinary one and it is expounded in a clear and exhaustive way in the different chapters of this book.

There are studies about the new clinical methods for measuring intellectual performances regarding diagnostic methods used to differentiate dementia from nondementing states and to the observations of qualitative differences in the various stages of the disease.

Advances in medicine for morphologic, neurochemical, and electrophysiological imaging methods for studying brain structures are employed.

We will refer to the titles of the different chapters of this book to give a clear picture of the interesting contents of this publication.

1. - Differentiating Dementia from Nondementing Condition. 2. - Biochemical Changing in Normal Aging in Human Brain. 3. - Clinical Neurophysiology of Aging and Dementia. 4. - Clinical and Neuropsychological Assessment of Alzheimer Disease. 5. - Neuropsychological Investigation of Memory, Visuoconstructional, Visuo-perceptual and Language Abilities in Senile Dementia of the Alzheimer Type. 6. An Up-to-date on the Neurochemistry of Alzheimer Disease. 7. - Experimental Pharmacology of Alzheimer Disease. 8. - Computed Tomography in Aging and Senile Dementia of the Alzheimer Type. 9. - Positron Emission Tomography in Dementia. 10. - Dementia and Cerebrovascular Disease. 11. Recent Data and Hypotheses on Creutzfeldt-Jakob Disease. 12. - Treatable Dementias. 13. - Subcortical Dementia: A Clinical Approach.

It is evident that psychiatrists, neurologists, and neuropsychologists will be greatly rewarded by reading this book with such a valuable data on dementia.

Prof. Dr. Víctor Soriano

NEUROPSYCHOLOGY OF HUMAN

EMOTION. - Editors Kenneth M. Heilman Paul Satz-The Guilford Press - 237 pages 1983

This is a book dealing with the study of a subject that has caused great interest in the scientific circles dedicated to neuropsychological investigation of emotion and affective disorders.

In this book there are concepts inherent

to the dominance of the right hemisphere of the brain in the expression and reception of emotion in the human being and also in animals, written in a clear and explicit way. The research findings are up to date.

The first chapters deal with the materialization of emotions, referring to the neuropsychological investigations of normal individuals, of persons suffering from damage on the right hemisphere and experiments performed in animals. Afterwards the emotional repercussion on different neurological and psychological illnesses on those patients suffering from lesions on the right hemisphere are studied.

The consequences of basal ganglia disorders and lesions of the limbic frontal cortex and emotional complications of epilepsy are investigated.

The emotional implications of psychosurgical procedure of prefrontal leucotomy used in treating schizophrenia has been studied.

It has been established that a neuropsychological approach constitutes a very valuable procedure to psychopathological studies and brings external criterium to the clinical syndromes in psychiatry.

The neuropsychological parameters are very sensitive detectors of disturbed cerebral activities and show in an objective way the laterality and localization of the functional perturbances that may or may not be accompanied of structural cerebral changes. Contents of the book:

Chapter 1. Right Hemispheric involvement in the perception and expression of emotion in normal humans - M.P. Bryden and R. G. Ley

Chapter 2. Affective Disorders Associated with Hemispheric Diseases - Kenneth M. Heilman, Robert T. Watson and Dawn Bowers

Chapter 3. Animal Studies of Laterality - Víctor H. Denenberg.

Chapter 4. Emotional Disturbances Associated with Focal Lesions of the Limbic Frontal Lobe - Antonio R. Damasio and G. W. Van Hoesen

Chapter 5. Emotional Concomitants of Psychosurgery - Donald T. Stuss and Frank Benson

Chapter 6. Emotional changes Associated with Basal Ganglia Disorders - Richard Mayeux

Chapter 7. Personality and emotional complications of Epilepsy - Paul B. Pritchard, Chapter 8. Neuropsychological Studies in Patients with Psychiatric Disorders - Pierre Flor - Henry

This volume is certainly of great value for those scientists interested in deciphering the intricacies of emotion in neuropsychology, psychiatry, neurology, clinical psychology, speech pathology, and neurosurgery.

Prof. Dr. Víctor Soriano

NUTRITION AND THE BRAIN VOLUME 6

PHYSIOLOGICAL AND BEHAVIORAL EFFECTS OF FOOD CONSTITUENTS.

**EDITED BY RICHARD J. WURTMAN and
JUDITH J. WURTMAN - 1983**

281 pages RAVEN PRESS NEW YORK

Problems concerning Nutrition and the Brain are studied in Physiological Behavioral Effects of food constituents. On this subject are treated the various special topics that establish a connection between nutrients and the Brain.

The brain needs in order to function substances that it cannot make by itself. In the study of brain nutrition must be considered different metabolic and Physiological processes involved in the absorption and profit of the nutrients by the brain.

The nutrients reach the brain's cells by the blood stream and are transported through the blood brain barrier by specific mechanism that probably are white capillaries or adjacent membranes.

The access of the nutrients to the blood is a consequence of the food consumption its digestion and absorption by the gut. Besides there exists a synthesis of products within the liver and other organs.

It is very important to call the attention about those substances that must be incorporated to the body with foods, because this is unable to elaborate them by itself.

We will mention for example that compounds useful for the brain such as glucose and choline reach the blood from the foods and from hepatic synthesis, and adenine is secreted by the liver into the blood stream.

The Nutrients of the brain are substrates or cofactors for its enzymes and constituents of its macromolecules or as precursors for its secretions such as the neurotransmitters.

In this volume are studied the effects and pharmacologic disposition of caffeine that is one of the most widely consumed pharmacologically active substances. It occurs naturally in several plant components including the coffee bean, tea leaf, kola nut, cacao seed, and ilex leaf.

It deals with the regulation by the U.S., Food and Drug administration of food constituents that might affect brain function and behavior. A number that exhibit neurotoxic potential have been associated either directly or indirectly with the food supply.

The tests currently available for assessing effects of foods on behavior; specially in children are surveyed. Certain methodological considerations on the conducting of behavioral and cognitive nutritional research and surveys a wide range of behavioral and cognitive measures, available for research use are described.

Control of food selection. More than 40 years ago it was noted that the ability of animals and humans to make dietary selections which are conducive to normal growth and reproduction has not received much attention in modern nutritional studies.

There has recently been a sharp increase in the publication of experimental reports on food selection. Are Protein and Carbohydrate intakes regulated? Mechanisms controlling macronutrient intake. Drugs can produce dramatic effects on the intake of specific nutrients.

Effects of particular dietary aminoacids such as tyrosine, tryptophan, and threonine on brain neurotransmission. Serotonin and the catecholamines dopamine and norepinephrine function as neurotransmitter at certain synapses within the mammalian central nervous system. These compounds are synthesized from the amino acids tryptophan and tyrosine, respectively.

This volume will be of interest to neuroscientists, neurologists, psychiatrists and psychologists physiologists and pharmacologists and people working in nutrition and metabolism.

Prof. Dr. Víctor Soriano