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The Value to the Clinical Neurologist of Electromyography in the 1990s*

E. Stålberg[†]

There has been a continued and rapid progress in neuroscience during the last decade. Imaging techniques, biochemistry, genetics and immunology have offered new possibilities to diagnose and treat nerve and muscle disorders. At the same time the cost of diagnostic procedures and medical care has increased tremendously. Everyone in the medical field participating in this evolution has to adapt to changing conditions, to a great extent determined by cost benefit considerations. The title of this presentation reflects a question raised both within the speciality of clinical neurophysiology and from those referring patients for neurophysiological evaluation. The role of neurophysiology in general or of EMG specifically will certainly depend on general development in neuroscience and on clinical neurophysiologists themselves.

The development in clinical neurophysiology hitherto has been dependent on factors such as technological progress (amplifiers, electrodes and analysis equipment), the development of new recording methods and the general broadened knowledge in neuroscience. With this background new questions may be formulated and tackled with new methodological approaches. This type of dynamic interaction will continue.

What then is clinical neurophysiology today? In Sweden it has been an autonomous speciality since the late 1950s. It is established at each

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university and only the specialists in these institutions are performing EMG, EEG, evoked potentials and neuro-monitoring. Training for the speciality includes 4 years in clinical neurophysiology and 6 months in neurology. In some other European countries a similar system applies. More commonly however, the clinical neurophysiology laboratory is part of the neurology department. In the USA the EMG laboratory is often linked to neurology or physical medicine and rehabilitation. The separation from patient care has the advantage of allowing a high degree of specialisation and specific research in the field. It may have the disadvantage that the electromyographer loses clinical feedback. In many places this has been at least partially compensated for by frequent rounds with referring clinicians.

The position of clinical neurophysiology

The clinical neurophysiological examination is a neurological consultation, not just a laboratory test. It does not only verify or exclude a clinical suspicion but may also help to obtain a more precise definition of site, type and degree of lesion and reveal abnormalities that are clinically uncertain, silent or unsuspected.

In general, the neurophysiological methods describe and quantify functions and pathophysiological changes in the central and peripheral nervous system. They certainly reflect, but do not measure directly, biochemical or morphologic aspects of the central of peripheral nervous systems. This difference from other methods and measurements should be made clear. Adequate techniques should be applied for each specific question to be investigated.

Various categories of morphological and physiological changes are seen in the motor unit in most nerve–muscle disorders. They are either acute and often functional in nature or are slowly developing with morphological correlates. These changes may provide help in the assessment of a diagnosis or in testing the short-term effect of drugs and the latter may also be used to monitor natural changes in a disease or its response to therapeutic measures. The morphological changes may be related to the severity of the disease or to reparative processes. Therefore, some EMG parameters are inversely correlated to the clinical picture, e.g. a high degree of reinnervation may produce a good compensation for a functional deficit which then may be difficult to detect. Sometimes the neurophysiological parameters are poorly related to symptom-producing features, e.g. nerve conduction velocity in Guillain-Barré syndrome or

motor unit potential (MUP) parameters in amyotrophic lateral sclerosis (ALS). These parameters may still be used to establish the diagnosis of a disease, but not to monitor the functional status as expressed by the clinical signs. It should be noted that clinical monitoring is difficult to perform accurately and reliably, which is a reason for developing additional methods. Also, if they are quantitative, many clinical scales are nonlinear. This leads to an understated problem. Clinical data may for example suggest an exponential time course, although a linear progression is more correct and may be seen with other measurement techniques. This may lead to a poor correlation between clinical and laboratory data. Under certain circumstances, the EMG findings may reflect the prognosis, but more research with long-term studies are necessary in this regard.

Neurophysiological methods are useful:

(i) for the diagnosis and quantitative assessment of nerve and muscle disorders, to various degrees of detail depending on diagnosis;
(ii) to diagnose dysfunction of the central and peripheral sensory systems;
(iii) to diagnose autonomic dysfunction;
(iv) to monitor dynamic changes in function of the central or peripheral nervous system, either acutely or over longer time periods, or sometimes to assess prognosis; and
(v) to quantitate aspects of motor control.

One way to facilitate the assessment of the place of clinical neurophysiology in the near future is to give examples of today's use of EMG methods, and to review some aspects of the present status of computerized EMG analysis.

Neurophysiology in the evaluation of nerve-muscle disorders

Neuropathies

Nerve conduction studies Motor and sensory nerve conduction studies are conventionally used to diagnose various kinds of peripheral nerve diseases. These studies include conduction velocity, response–amplitude area, duration, shape, distal latency, amplitude change at different stimulation points and F-wave analysis.

Demyelinating neuropathy is characterized by slow sensory and motor

conduction velocities and relatively well preserved motor and sensory amplitudes. The EMG shows only minor signs of neurogenic involvement since denervation/reinnervation is not a feature of this condition.

In *axonal neuropathy*, conduction velocity may be preserved or only slightly reduced if there is pronounced axonal loss. The M-response amplitude and the sensory nerve action potential amplitude are reduced in relation to the number of degenerated axons. The EMG confirms the diagnosis by revealing signs of denervation and reinnervation.

In cases of *Guillain-Barré syndrome* the typical multifocal nerve conduction block is detected as a progressively diminishing M-response amplitude with more proximal points of stimulation. F-responses, which are the recurrent motor responses after peripheral nerve stimulation, occur with prolonged latencies in all situations with slow nerve conduction velocities, but can also show prolongation in focal proximal lesions while nerve conduction velocity is normal in distal segments, e.g. in the early stages of the Guillain-Barré syndrome.

Nerve conduction studies are very useful in the examination of *nerve entrapment*. The focal lesion may cause axonal degeneration distal to the entrapment site. The amplitude of the sensory or motor response recorded distally is reduced when stimulation is performed both distal and proximal to the lesion. In other types of entrapment focal demyelination may occur. A distal stimulation gives a normal response but proximal stimulation gives rise to a prolonged response with a prolonged latency corresponding to a focal slowing of conduction velocity. In cases of *neurapraxia* (conduction block) the distal response is normal but the proximal stimulation may not generate any response at all. If a patient with a carpal tunnel syndrome has low amplitude motor and sensory responses to stimulation at the wrist but normal responses to stimulation distal to the carpal tunnel, this indicates mainly neurapraxia with a good prognosis. A patient with a clinically complete facial palsy of 5 days duration may show a completely normal facial muscle response upon nerve stimulation at the stylomastoid foramen compared to the healthy side, indicating neurapraxia with a good prognosis. A low amplitude response indicates axonal loss due to degeneration and usually indicates slow recovery.

Nerve conduction studies are fast to carry out and inexpensive and do not cause the patient any significant discomfort.

Sensory evoked potentials In a patients with sensory symptoms in whom sensory nerve studies yield normal results, the central sensory pathways may be studied by means of evoked potentials. This is now a

standard technique[1] and will not be described further. In cases of central demyelination in the sensory pathways, the scalp recorded response is delayed.

Cortical stimulation By means of electrical, or the more recently introduced magnetic cortical stimulation, impulse conduction along the entire motor tract can be studied (for review, see Kimura[2]). A stimulus is applied to the scalp and is followed by contraction in muscles of the contralateral side. If a slight voluntary contraction is maintained in a muscle during the stimulation this causes a central facilitation and therefore a stronger contraction is obtained in this muscle. Amplitude and latency values are measured from recordings obtained with surface electrodes. A prolonged motor latency indicates a slow impulse conduction in central structures, provided the relevant peripheral nerve conduction velocity is already proven normal. Low amplitudes indicate conduction block or loss of upper motor neurons, provided peripheral nerve stimulation yields a normal muscle response amplitude. A slowing is seen (e.g. in MS) and low amplitudes in spinal cord lesions and motor neuron disease.

Myasthenia gravis

Diagnosis A decrementing amplitude of the evoked muscle response to low frequency repetitive stimulation (Figure 1) is one of the neurophysiological criteria for myasthenia gravis (MG).[3] This is caused by the unmasking of the normal decrease in amplitude of successive end-plate potentials during repetitive stimulation, and becoming apparent in motor end-plates with reduced safety margins. The test also includes a short period (10 to 20 sec) of maximal muscle activation, achieved voluntarily or by means of high frequency stimulation.[4] In pathological conditions, the first single stimulus given within 10 sec after activity may give a higher M-response amplitude than initially and the decrement may be less than before, an appearance called post-activation facilitation. This is due to a transiently increased release of acetylcholine. Depending on the severity of the disease and the length of time for activation, a more pronounced defect than that obtained before activation may be seen after a few minutes, called post-activation exhaustion. The initial M-response amplitude after rest reflects the number of end-plates that may respond to at least one nerve impulse and is therefore related to the severity of the disease. The M-response amplitude directly after activation is a measure of the number of end-plates that can be activated with facilitation, i.e.

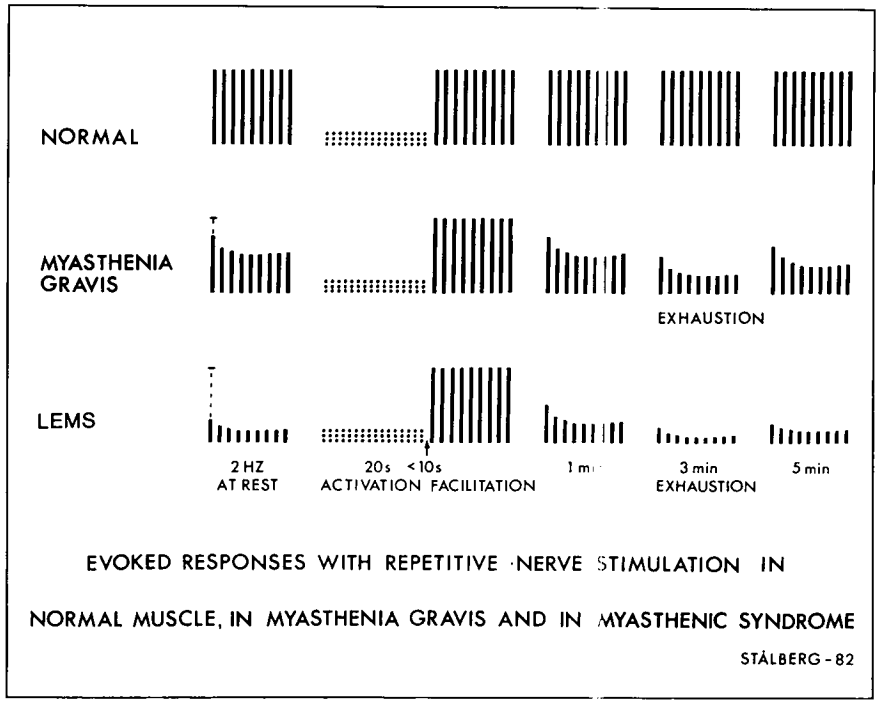

Figure 1. Schematic presentation of findings at repetitive nerve stimulation. (This is an example of a routine test that may need modifications in certain cases). A train of 10 stimuli at 3Hz is given. 20 seconds of maximal voluntary activation is immediately (within 10 seconds) followed by a new stimulus train with the muscle at rest. New trains are given every minute for about 5 minutes.

that are accessible to treatment, and is therefore related to the possibilities for benefit from anticholinesterases. A continuing low amplitude after facilitation indicates loss of functional motor end-plates, e.g. due to destruction of motor end-plates.

Single fibre EMG (SFEMG) is a technique developed to study transmission in individual motor end-plates.[5] It is applied when repetitive nerve stimulation is negative. This technique is able to reveal subclinical neuromuscular defects and is therefore more sensitive than repetitive nerve stimulation.

In a study of patients with clinically diagnosed MG, SFEMG[6] showed the following: in ocular MG, 85% and 59% of the patients were abnormal in the frontalis and extensor digitorum communis (EDC) muscle, respectively; in mild generalized disease, 96% were abnormal; in moderate or severe generalized disease 100% were abnormal; and in patients with

clinical remission 62% showed SFEMG abnormalities in the EDC muscle. The SFEMG abnormalities follow the clinical status, with improvement after anticholinesterase therapy, or cortisone or plasmapheresis.[7] The abnormal jitter increases with increase in temperature and decreases after cholinesterase inhibitors.

Monitoring If a decrementing response is present upon repetitive nerve stimulation, this technique is easier to apply than SFEMG for monitoring changes over time. Both correlate well with clinical status. It should be noted that different muscles are involved to different degrees and that the clinician's judgement should not always be guided by neurophysiological test results from nonvital or otherwise functionally less significant muscles.

Lambert Eaton myasthenic syndrome

Diagnosis In cases of this rare syndrome, myasthenia gravis has often been suspected initially and its diagnosis has been the referring question. The neurophysiological picture is usually but not always typical and is different from that of MG. A pronounced post-activation facilitation from a low initial M-response amplitude is the classical finding (Figure 1), reflecting the increase in release of ACh after a short period of maximal activity.[6] Exceptionally, the typical abnormalities are seen only in a few muscles while the findings in other muscles may resemble those in MG. SFEMG often shows pronounced changes.

Monitoring The M-response amplitude reflects neuromuscular status better than clinical testing since only a few impulses are necessary for the test, so avoiding facilitation and fatiguing. The test is standardized and does not depend on the degree of patient cooperation. The M-response amplitude at rest increases in parallel to the effect of therapy.[8] The difference between M-response amplitude at rest and after facilitation reflects the number of presynaptically blocked end-plates. In a therapeutical sense, this difference may be used as a prognostic sign.

Repetitive nerve stimulation and SFEMG are relatively simple tests; they cause moderate discomfort to the patient, and are reliable, fast and inexpensive. The risk of misinterpreting false-positive findings, e.g. in reinnervation giving both decrement and abnormal jitter, is avoided by studying additional EMG-parameters. A relatively firm opinion about the patient' s neuromuscular transmission can be obtained and reported within one hour of examination.

Table 1. Principal EMG and SFEMG changes in denervation and reinnervation.[8]

	Routine EMG	Single Fibre EMG
Denervation		
	fibrilation potentials, positive waves, complex repetitive discharges	fibrilation potentials, complex repetitive discharges
Reinnervation		
Very early	small MUPs with satellites	increasing FD, jitter and blocking
Ongoing	polyphasic MUPs, (very) long duration, satellites	increasing FD, increased jitter
Late stage	long duration, high amplitude	increased FD, normalizing jitter

Table 2. Principal EMG changes in different stages of muscular dystrophy.[8]

Stage	EMG MUPs	Possible Cause
Subclinical	high amplitude	compensatory hypertrophy
Early	polyphasic	diameter variation
Later	polyphasic, short duration low amplitude	scattered loss of muscle fibre, regeneration
End-stage	variable	fibrosis, regeneration

Denervation-reinnervation

Electrophysiologically, the reinnervation process can be monitored by means of many parameters.[9,10] The process is characterized by initial signs of denervation. With reinnervation, motor units become denser and will contain an increasing number of fibres, shown as increased fibre density (FD) and long duration of motor unit potentials (MUP). During ongoing reinnervation, jitter is increased, seen both as increased jitter in SFEMG and as unstable MUPs in conventional EMG (Table 1). Later, transmission becomes more stable.

SFEMG, characterized as a selective recording from a small area of the muscle, is used to study the local organization of muscle fibres in the motor unit (fibre density) and the transmission in the peripheral parts of the nerve tree (jitter). These parameters change in an orderly way with maturation of reinnervating structures.

Conventional EMG, recording from a relatively large portion of the motor unit, can be used to study degree of denervation, motor unit changes related to reinnervation (Table 2) and the number of remaining motor units that may be activated.

The total number of fibres in the motor unit can be studied with so called Macro EM. This is a non-selective technique in which the recording is performed from the cannula of a modified SFEMG electrode. The signal obtained is related to the number and size of fibres in the entire motor unit. After severe denervation, the reinnervating motor units may contain as many as 10 to 20 times the normal number of muscle fibres.

Radiculopathies

Electromyography is a useful method to establish the presence of a root lesion causing axonal degeneration. Denervation in paraspinal muscles differentiate root lesion from more peripherally located nerve lesions. Because of innervation from overlapping segments, the EMG in the paraspinal muscles usually can not be used to determine the level of a root lesion. This is made possible by performing an EMG on the limb muscles. Additional studies such as reflex studies (H-reflex from the flexor carpi ulnaris for C7, H-reflex from the soleus for the S1 root) or needle stimulation of spinal roots are sometimes performed for further clarification of root disorders.

Motor neurone disease (amyotrophic lateral sclerosis)

Diagnosis EMG is a useful and sensitive method in the diagnosis of this disease. It shows signs of denervation in many areas, representing the area of supply of different roots and nerves. Other conditions giving the same EMG picture such as axonal neuropathies should be excluded electrophysiologically. In addition to diagnostic aspects, EMG may add information about the dynamics of the disease processes since its parameters reflect the cycle of denervation-reinnervation-denervation.[4,11] In cases in whom there is very fast progression, allowing little time for each axon sprout and new motor end-plate to mature, the FD is moderately increased, the jitter is increased and the degree of blocking is high. The motor unit potentials are very unstable. In more slowly progressive cases, the FD may be very high, but jitter and blocking are less abnormal. The motor unit potentials are generally more stable and of higher amplitude than in cases with fast progression. In this way, general information is obtained about the rate of the denervation-reinnervation process.

Monitoring The dynamic changes in the motor unit have also been followed in longitudinal studies by means of various EMG methods. An

initially effective compensatory reinnervation gives rise to large motor units. Later, the maximal capacity for reinnervation is reached, deterioration occurs and the muscle force decreases. Whether this is due to loss of the largest motor units or peripheral deterioration of the large reinnervated motor units has not been established.

These dynamic changes may be followed by various EMG methods, but these methods are relatively cumbersome both for the patient and doctor. The M-response amplitude obtained from a few distal and proximal muscles is an easy and relatively accurate way to monitor changes over time.

Myopathy

The EMG shows typical changes in cases of myopathy (Table 2). The classical EMG abnormalities have been interpreted as signs of loss of muscle fibres but other changes also take place in the motor unit in myopathies. SFEMG recordings indicate that the local concentration of muscle fibres in a given motor unit, the so-called fibre density, is increased. At the same time the total size of the motor unit, investigated with Macro EMG, is unchanged or small.[12] These findings indicate that regenerative processes are also present. This picture changes with time and is related to the dynamic changes in the motor unit.[10]

In the early stages of myopathy there are increased signal amplitudes in some types of EMG recordings (Macro EMG). This may be due to compensatory fibre hypertrophy and subsequent splitting of inherently weak muscle fibres, or to hypertrophy after overuse of non-involved muscle groups. In later stages, findings compatible with desynchronisation of the electrical activity (polyphasic and complex MUPs) may reflect fibre diameter variation, a typical biopsy finding.

With progression, many EMG parameters indicate more profound changes in motor unit topography, such as loss of fibres in certain areas of the motor unit (scanning EMG) and local regenerative processes with splitting, innervation of sequestered muscle fibres or regenerating muscle fibres.[12] In scanning EMG,[13] in which an electrode, e.g. a concentric needle one, is pulled through the muscle in small steps (50μm), an electrical cross-section of the motor unit is obtained. In myopathies this technique has revealed silent areas indicating focal loss of fibres in the motor unit.

These MUP changes are certainly valuable in assessing motor unit abnormalities compatible with myopathy. They vary in degree and ex-

pression between patients and with the underlying cause. For a given patient, changes in MUP parameters may be used to monitor changes over time. The EMG changes alone do not differentiate between different types of muscular dystrophy. On the other hand, some myopathies such as various types of myotonia and myositis, have relatively distinct and differentiating EMG appearances. In myotonia congenita the myotonic discharges are abundant and the MUP parameters are normal, whereas in myotonic dystrophy, myotonic discharges are present but the MUP parameters are abnormal. In polymyositis the MUPs are polyphasic and of short duration, indicative of myopathy. In addition, fibrillation potentials are more abundant than in other myopathies.

Recording methods and computer-aided analysis

Development of clinical neurophysiology is dependent on development of recording methods and analysis procedures, mainly based on computer methods. These methodological aspects will be presented with some emphasis on their practical use (for review of computer methods, see Stålberg and Stålberg[14]). The computer may be an integrated part of the EMG equipment or consist of an externally connected computer, e.g. a personal computer. The following functions are provided;

(i) enhanced signal processing;
(ii) quality control of recordings and analysis results;
(iii) comparison to reference values;
(iv) database storage; and
(v) reports produced as graphs and numeric tables.

Motor nerve conduction studies

Recordings are performed according to standard methods. The computer automatically measures latency, amplitude, area and F-response latencies. It calculates conduction velocity and relates the results to reference values. As a quality control, amplitude and area decay between distal and proximal stimulations are measured. If there is a significant decay, or if the decay in amplitude and area differ considerably, the signals are checked for recording artefacts. In addition to conventional cursor setting for the shortest latency, the computer also measures latency to another point of the M response. If a significant difference occurs for

different latency values, the computer requests a check of the recording quality or of the analysis.

Motor velocity spectrum

Different methods for the assessment of the motor velocity spectrum have been developed. Examples of such methods are direct axonal stimulation, the collision technique,[15,16] and F-wave dispersion. For different reasons these methods have not reached wide routine use.

Sensory nerve conduction velocity

Standard methods are used for recording, usually with surface electrodes. Latency, duration and amplitude of the sensory action potential are measured automatically. Conduction velocity is calculated and the results are compared with reference values.

Spectrum of conduction velocities in sensory or mixed nerves

Similarly to the situation for motor velocity studies, estimation of the velocity spectrum for sensory or mixed nerves is not widely used. A conduction spectrum may be obtained either on the basis of shape changes in the recorded nerve action potential elicited from 2 stimulus sites using one recording site, or from one stimulus site using 2 recording sites.[17] Another way is to record the nerve signal with near nerve electrodes using averaging techniques to also detect low amplitude responses from slowly conducting axons.[18] This method needs facilities for averaging, but not a computer.

The advantages of automatic nerve conduction measurements include the following:

(i) measurements are performed in a standardized way;
(ii) parameters that cannot be measured manually are available (e.g. area under the signal);
(iii) time saving due to easier handling of data and faster calculations;
(iv) direct comparison with reference values;
(v) results can be retrieved for comparison next time the patient is investigated;

(vi) direct printout of results is possible; and
(vii) results can be stored directly into a database for collection of new reference values.

Motor unit counting

The technique of motor unit counting was introduced by McComas *et. al.*[19] The muscle response is recorded with surface electrodes during slowly increasing nerve stimulation. The stepwise incrementing amplitude of the response is considered to reflect the addition of new motor units during stimulation. These steps in relation to a maximal response can be used to estimate the size and total number of individual motor units in the muscle studied. Theoretical and practical aspects of the method have been discussed over the years. Technical improvements and added experience have refined the technique and proven its usefulness.[20] The size of individual motor units can also be obtained by voluntary activation with so-called spike-triggered averaging using surface recordings[21] or by Macro EMG.[22] These techniques for motor unit counting are implemented on a personal computer.

Surface EMG

Surface EMG recordings have been used in studies of movement disorders, in ergonomic studies and in fatigue studies. Changes in the frequency spectrum during prolonged activity have been used to quantify myoelectric fatigue.[23] Furthermore, a progressively developing discrepancy between electrical output and force generation is taken as a sign of muscle fibre fatigue due to electromechanical uncoupling. These and similar tests have a potential interest in fatigue studies in a routine laboratory. Improved signal analysis may even give us methods to differentiate pathological conditions from the normal and from each other, but the diagnostic yield in the field of neuromuscular disorders is still uncertain.

Decrement of motor response on repetitive nerve stimulation

Muscle responses obtained with repetitive nerve stimulation, used for neuromuscular testing, are analysed by a computer. Amplitudes and

areas of signals obtained during various procedures are measured and compared.

Decrement studies using double pulse stimulation

Another way to test neuromuscular transmission is by means of double pulse stimulation using different interstimulus intervals to study the dynamics of neuromuscular transmission.[3] Double stimuli are delivered by the computer with a frequency of 0.5Hz, with interstimulus intervals randomly varying between 20 and 500ms. The relative difference in response amplitude (and area) between the conditioning (first) and test (second) response is calculated and plotted against interstimulus intervals.

The advantage of computerized decrement measurements include the following:

(i) accurate amplitude measurements are obtained;
(ii) the area parameter is included;
(iii) the method is fast;
(iv) a summary of results is available during the investigation, which is particularly valuable when long-term tests are made (monitoring effect of activity, injection of drugs); and
(v) quality control of recordings and results is available.

EMG with concentric or monopolar needle electrodes

No single technique can be used to quantitate all features of the EMG record and therefore a variety of methods is necessary, analysing individual MUPs as well as their summated activity during increasing and full effort, the so-called interference pattern.

The motor unit potential (MUP)

Background Over the years there has developed a much better understanding of the relationship between the motor unit potentials and the signal generator, the muscle fibre and motor unit. This has led to modifications of existing techniques and to the development of new parameters. It has been demonstrated that duration and area parameters

are related to the number of muscle fibres within a few millimeters of the electrode tip. The amplitude and shape depends mainly on fibres within 0.5mm, normally only a few fibres.[24] The duration of the MUP reflects the number of muscle fibres in a motor unit within about 2.5mm of the electrode tip. Complex and polyphasic potentials indicate temporal dispersion of action potentials, e.g. due to fibre diameter variations, more than to loss of muscle fibres. Thus the classic MUP parameters, viz. amplitude, duration and complexity reflect different aspects of the motor unit morphology and therefore need separate quantitation. The stability of the motor unit potential, reflecting jitter among the composite muscle fibres, is a useful parameter to assess neuromuscular transmission not only in myasthenia gravis but also in conditions where there is reinnervation. It will help differentiate between ongoing denervation-reinnervation and a stationary situation after previous denervation.

Computerized analysis of the MUP is under development. The following are examples of the present status of the method.

Extraction techniques Before the MUP can be analysed, it must be extracted from a trace containing many different motor unit potentials.

Averaging One of the most commonly used technique is to extract MUPs by averaging. The process is triggered by the selected MUP. Disturbing activity from other motor units can be cancelled and one motor unit extracted.

Template Consecutive MUPs are compared to one automatically selected MUP called the template.[25] When 8 potentials of sufficient similarity have been obtained they are averaged. This averaged MUP is then analysed according to criteria described below. By using a continuous data collection, any signal can be used as template for comparison with successive signals. In this way many acceptable MUPs may be obtained in one run.

Decomposition The interference pattern obtained during moderate and strong voluntary activity can be studied by decomposing the signal. Some methods use a combination of pattern recognition and statistical analysis methods.[26,27] All these methods require powerful computation. At least one of them[27] is now tested for routine use in an integrated EMG system.

Analysis of MUPs Independent of the technique for extraction of a single motor unit, the same parameters are commonly used for its

quantitation.[28] They are assumed to reflect different aspects of the motor unit. The following MUP parameters are commonly analysed:

Amplitude is measured peak to peak from minimum to maximum.
Area is calculated by integrating the rectified MUP over the duration.
Duration A number of algorithms have been suggested to define the duration from the start of the initial slow components to the end of the slow wave component (see review[28]).
Spike duration The time between the first and last turn.
Number of phases The number of baseline crossings plus one, within the MUP defined by its duration. The amplitude must then exceed the baseline by 10μV to be counted.
Number of turns The number of peaks that differ from the preceding turn and succeeding peak by at least 50μV.
Number of satellite potentials Spike components occurring after the end of the slow wave component in the MUP.

Other MUP parameters Parameters describing firing characteristics (mean frequency, variability, on-set frequency) are used in some laboratories. These parameters are not included in automatic routines for MUP analysis.

Another feature that may discriminate abnormality is the shape variation of the MUP. This parameter reflects the internal jitter of the components generating the MUP. It is increased in cases of recent reinnervation and in myasthenia gravis. By changing the high pass filter settings to 500–1000Hz the spike components of the MUP can be extracted from the low frequency parts.[29] This is a helpful technique to visualize shape variability. Attempts are made to quantify this parameter by computer. We have implemented different algorithms to express the variability in order to find the optimal method for routine use.

The advantages of computerized MUP parameters include:

(i) it is much faster than manual measurements;
(ii) the measurements are standardized;
(iii) more parameters can be measured than by manual techniques; and
(iv) direct comparison with reference values is possible.

Interference pattern

Different methods have been developed to analyse the interference pattern in such a way that biologically relevant or clinically useful data

are obtained. Frequency analysis, period analysis, power spectrum, RMS values, integration etc., have been used. Willison[30] introduced the concept of analysing turns and amplitude of the signal at a given force. We have modified the method and developed the following analysis[31] based on the relationship between turns and amplitude obtained at various force levels without measuring the force. The averages of turns and amplitudes for each recording epoch are measured and plotted on an X-Y axis. At each electrode position 2 to 3 recordings are obtained, using different degree of activity, after which the electrode is repositioned. Twenty such epochs (250–1000msec duration) are collected with a short muscular rest between each.

Normal values have been collected. EMG recordings of myopathic muscles occur in the high turns and low amplitude region, while recordings of neurogenic lesions show low turns and high amplitudes (Figure 2).

Single fibre electromyography

Methodological aspects This technique has been established as a routine procedure in many centres.[5] Technology has helped to promote the method, since facilities for jitter analysis are provided in all modern EMG equipment. Stimulated SFEMG has recently become interesting since it offers new possibilities to study motor unit microphysiology.[32] A teflon-coated monopolar electrode inserted into the muscle is used as the cathode (Figures 3, 4). A surface electrode is the anode. A weak stimulus gives rise to muscle contractions and an SFEMG electrode is inserted into the twitching part to record SFEMG action potentials. If an intramuscular nerve is stimulated, there is a stimulus-response jitter of more than 5μsec. In this way neuromuscular transmission may be studied under well standardized conditions to investigate the degree and type of activity. In MG some motor end-plates show more dysfunction upon increased stimulation rates up to 15Hz, while others already show improvement at low frequencies, which is the typical pattern in all motor end-plates in Lambert Eaton Myasthenic Syndrome. If the jitter is less than 5μsec the muscle fibre is directly stimulated and various membrane parameters can then be studied. Repetitive direct stimulation of muscle membrane in myotonia congenita has shown, among other things, a decrementing amplitude of the response upon repetitive stimulation,[33] a phenomenon not seen in the normal muscle fibre. This may contribute to the weakness after activity in this disorder, reflecting an underlying ionic defect. The denervated muscle fibres show hyperexcitability in various ways, giving rise to spontaneous activity (fibrillation potentials), retriggering of activity

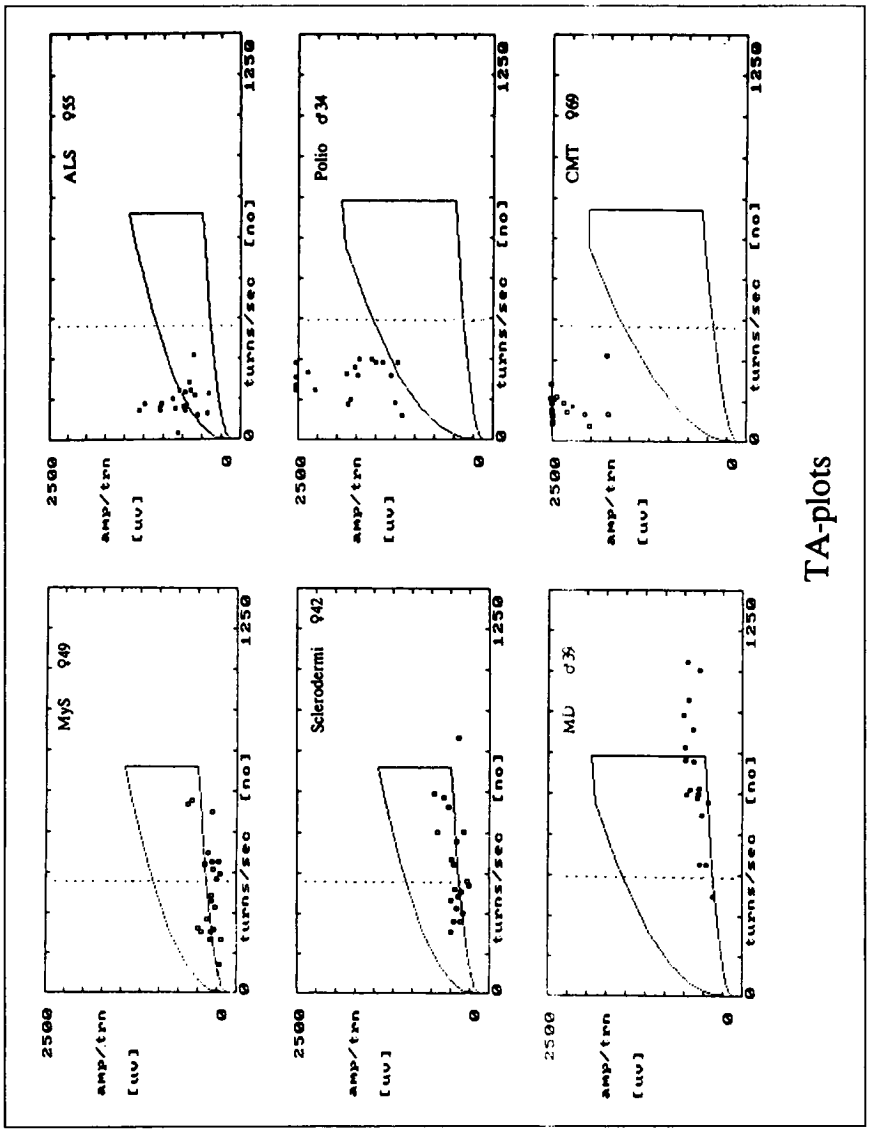

Figure 2.
Example of T/A analysis of the interference pattern. Turns/sec and mean amplitude/turn are plotted on an X-Y axis. In myopthy (left), results from 20 recordings (each analysing an epoch of 400msec) from each muscle show high number of turns and low amplitudes. Neurogenic conditions (right), show low number of turns and high amplitudes.

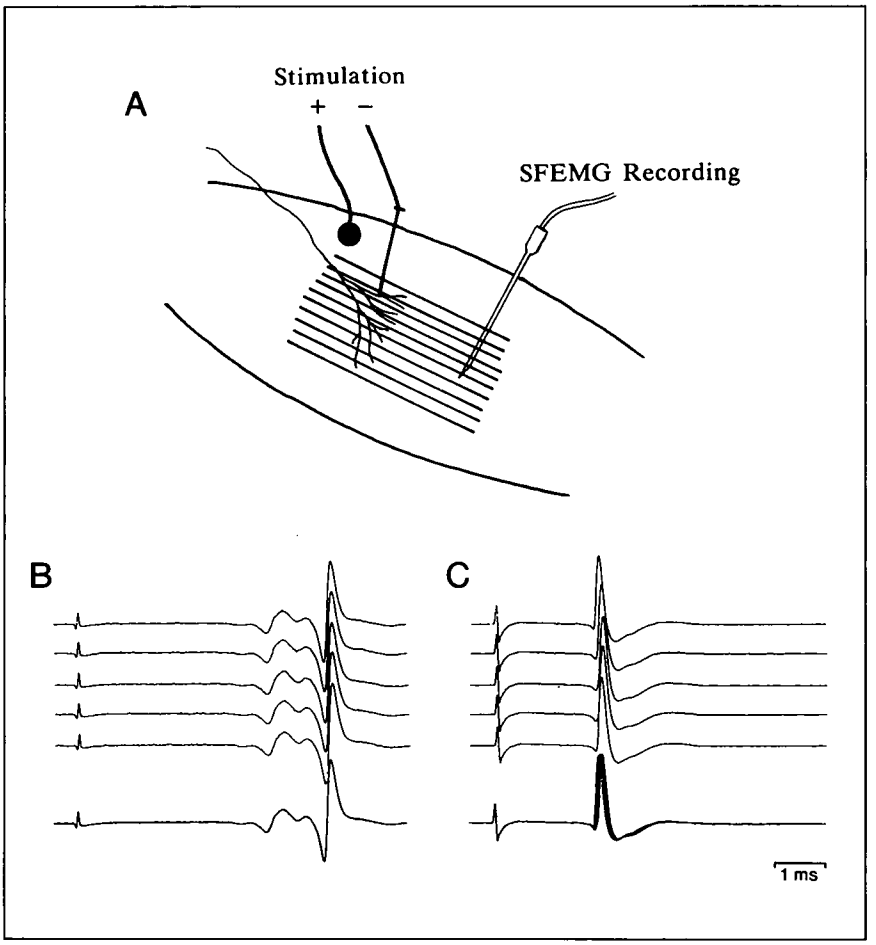

Figure 3. Intramuscular stimulation and SFEMG. A: stimulation and recording electrodes. The muscle fibre is activated directly or via its intramuscular nerve branch. B: Five recordings showing a jitter of less than 5μsec, indicating direct muscle fibre stimulation. C: Five recordings with a jitter of more than 5μsec indicating axonal stimulation.

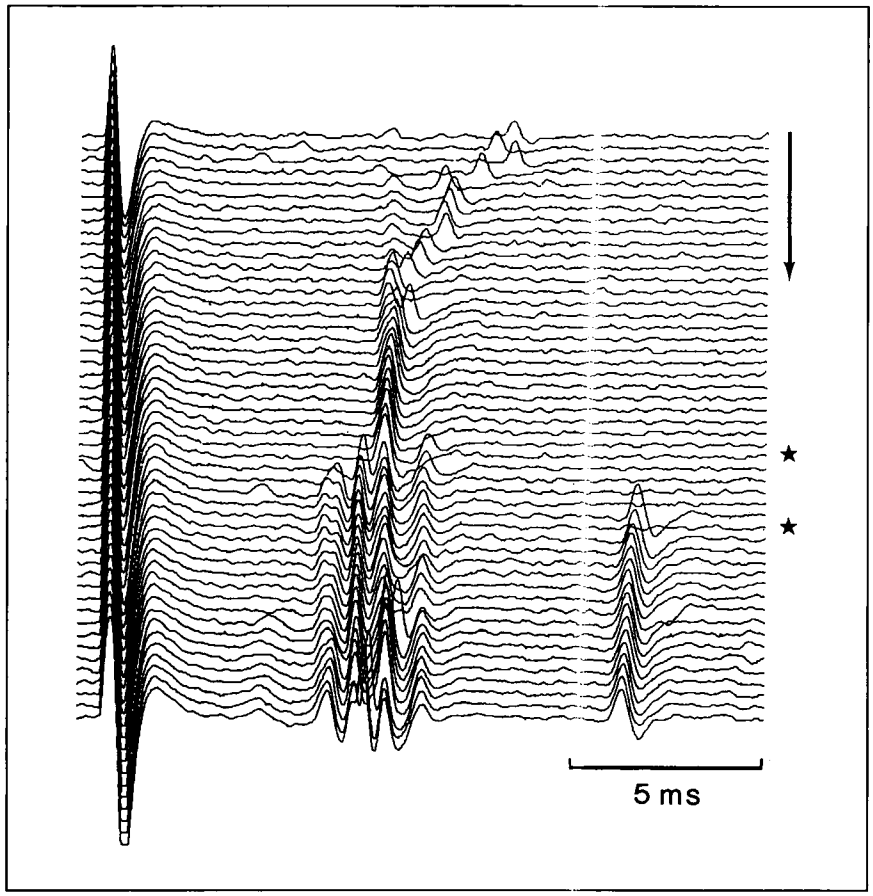

Figure 4. Effect of increasing stimulation strength (downwards in the Figure) during axonal stimulation and SFEMG recording. New components are successively recruited, initially with higher jitter and longer latency than during suprathreshold strength for that nerve branch. A certain stimulation strength (*) may be suprathreshold for one nerve branch/muscle fibre but liminal for another, just recruited.[10]

from one site along the muscle fibre (double responses to one stimulus) and ephatic transmission between fibres (locked fibrillation potentials, complex repetitive discharges). No patient cooperation is necessary for stimulated SFEMG.

Analysis Modern EMG equipment has inbuilt jittermeters. An external personal computer can also be used for the purpose when equipped

with a small electronic device. Jitter parameters are measured and displayed. Erroneous values are cancelled according to the following quality control procedures:

(i) interpotential intervals exceeding ±4 SD from the mean of 100 to 200 data sets are automatically cancelled by the computer before final analysis;
(ii) in equipment with amplitude window triggering, the amplitude of the triggering potential may be confined to narrow limits, thus preventing other signals being included in analysis;
(iii) with systems other than the personal computer system described, pattern recognition algorithms may be implemented to assure that the shape of accepted signals is constant within given limits;[34] and
(iv) in systems storing all signals, visual shape control may be performed and obviously erroneous signals cancelled.

Scanning EMG

A method developed to study the electrophysiological cross-section of the motor unit to obtain a better understanding of its topography is called scanning EMG.[13]

Recording technique Two electrodes are used: a single fibre electrode for triggering, and a concentric EMG electrode (or sometimes other electrodes) for recording (Figure 5). The concentric electrode is automatically pulled through the motor unit, to give a map of the cross-sectional activity. This method is not used as a routine but helps to understand the routine EMG and is a useful research tool.

Report generation

It is important, and therefore of increasing interest, to produce adequate reports of a neurophysiological examination. In our department, data from the conduction studies are presented in tables, usually not sent to the referring doctor, and as a graphical plot showing different parameters in relation to reference values (Figure 6). The EMG report is based on the input of measurements of individual MUP parameters. An expert system gives suggestions for interpretation and produces a coloured plot, the muscle man (Figure 7).

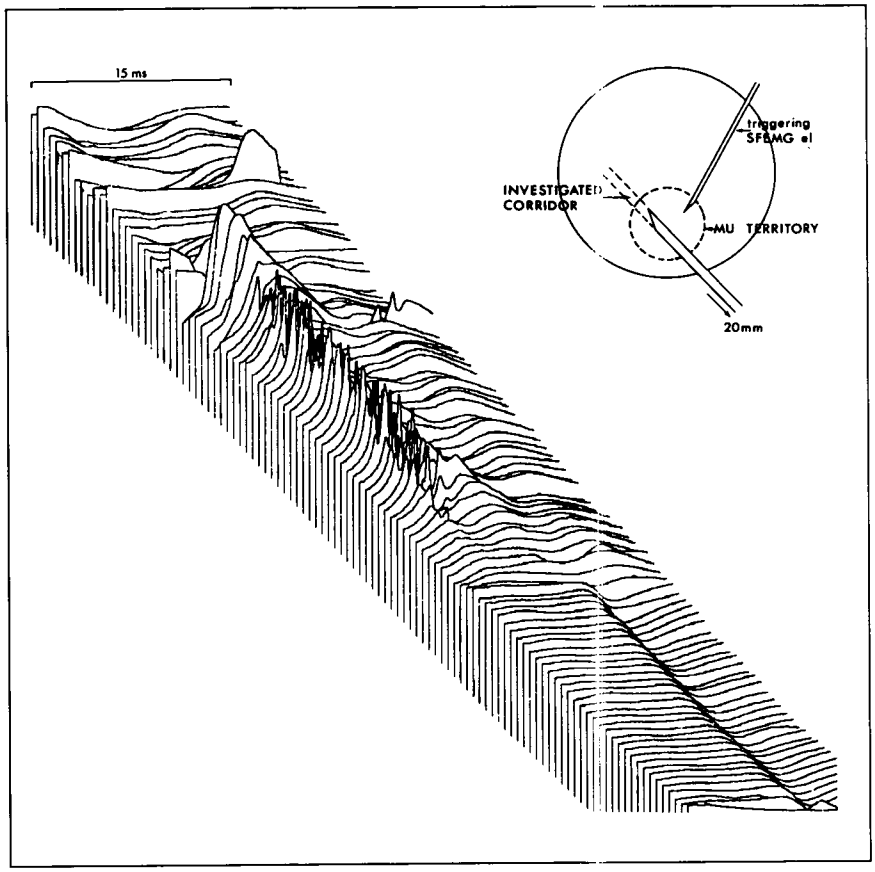

Figure 5. Principle for scanning EMG. An SFEMG electrode is used to trigger the oscilloscope sweep and to initiate a step motor pulling an EMG electrode, e.g. a concentric needle electrode. Each step is 50μm. When the concentric electrode records activity from the triggering motor unit, action potentials occur time-locked on the oscilloscope screen. The temporal and spatial distribution of activity within the recording corridor can be analysed.[13]

General impact of computers in the EMG lab

Computer analysis is of great importance to improve the value of clinical EMG. To make use of all advantages offered by computer-aided analysis, the techniques should be used with care. The computer may fail or make errors and therefore the user must have sufficient knowledge of the principles of the analysis procedures. The user should be able to

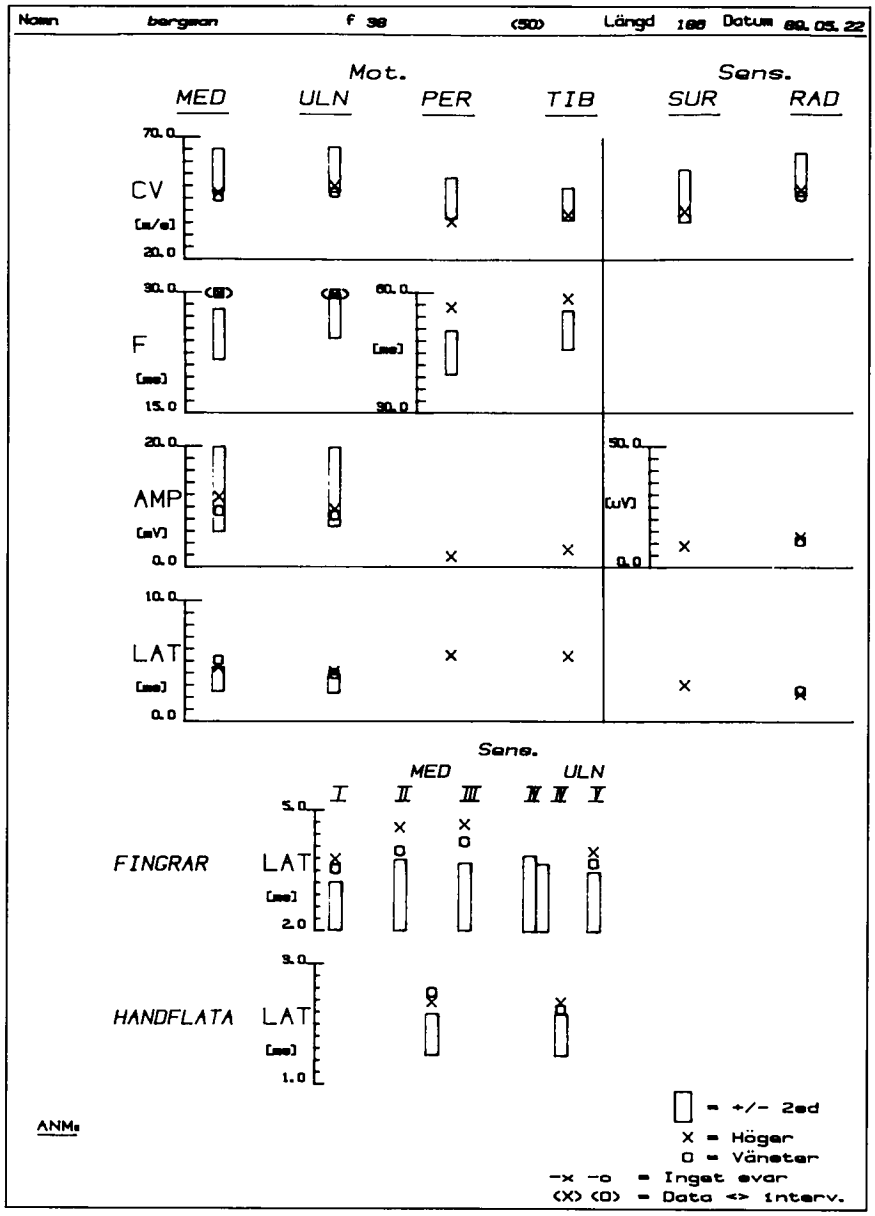

Figure 6. Automatically produced graphic report of a nerve conduction study. Reference value (±2SD) for patient's age and height are indicated as boxes. Results from right (x) and left (o) side are presented. The results indicate polyneuropathy.

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ref 85D
EMG: 891130

Muscles	Innervation	Spont act	Fib	Ampl	Dur	Poly	Stability	IP	Interpretation
Frontalis Sin	facialis	No(ex.fib)	0	N	N	N	N	N	N
Pectoralis major Sin	C5(c6) pec.lat	No(ex.fib)	9	++	++	+	instable	Red. ---	Pron subac Neur
Triceps brachii Sin	C7(c6,c8) rad	No(ex.fib)	7	+	+	+	N	Red. -	Sl subacute Neu
Triceps brachii Dx	C7(c6,c8) rad	No(ex.fib)	9	+	++	+	instable	Red. ---	Pron subac Neur
Quadriceps rectus fem Dx	L2(l3) fem	No(ex.fib)	9	+	++	+	instable	Red. ---	Pron subac Neur
Tibialis anterior Sin	L5(l4) per prof	No(ex.fib)	10	?	?	?	?	No act.	Complete denerv
Tibialis anterior Dx	L5(l4) per prof	No(ex.fib)	10	+	++	+	instable	Red. --	Mod subac Neur

SUMMARY:

Neurography: see enclosed figure - normal findings

EMG: see enclosed figure - pronounced neurogenic changes in many segments.

CONCLUSION:
Findings compatible with motor neuron disease

Erik Stalberg

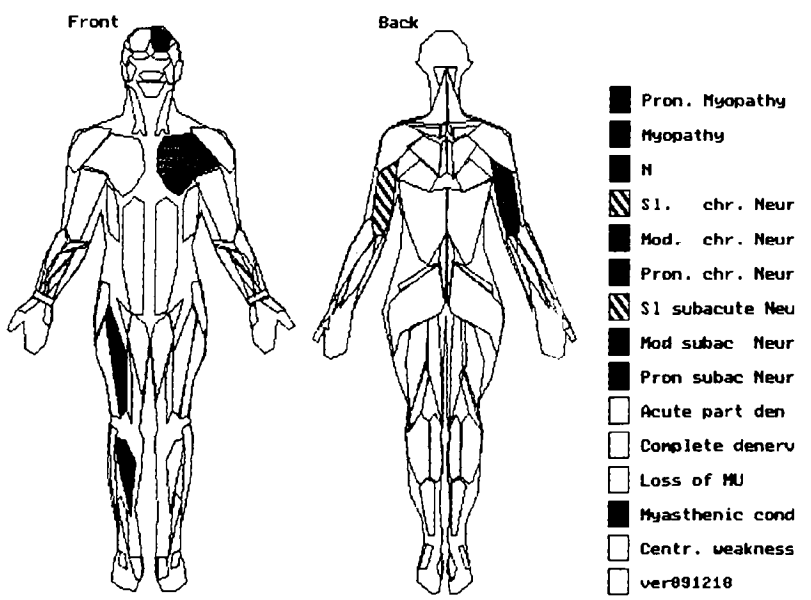

Figure 7. Automatically produced EMG report. EMG findings (obtained by computer-guided interpretation in an expert system) are given in a table and as a 'muscle man' where the results are in colour or (here) pattern-coded in relation to type of finding for each muscle. This gives a quick overview of the extent of examination and principal results. A free text gives the final conclusion.

override the computer, being its master and not its slave. The following general comments about computerized EMG can be made.

Quantitative aspects Economy of time is crucial for both the doctor and the patient. With the computer, many tests are performed faster and several important parameters which were not earlier measured are added to the routine analysis. This provides extra information without expending extra time. Since most doctors do not have extensive experience with computers, handling of a system (starting, running, moving between programs) must be guided by clear instructions. The reliability of computer-aided EMG analysis is of paramount importance in a busy EMG lab. Errors and partial failure or even breakdown reduce the usefulness and popularity of the computer system.

Qualitative aspects Accuracy and persistence are higher when measurements are performed by the computer than when manual methods are used and therefore the quality of the studies is improved. The electromyographer must however retain the skill to perform the tests manually, according to the traditional methods, to be able to supervise the computer analysis and to continue the investigations in case of computer failure.

Effect on knowledge and skill Does the introduction of computer-aided techniques decrease the level of common knowledge in neurophysiology and detrain the doctor and assistant? This has not been the general experience. On the contrary, the introduction of computers in neurophysiology has necessitated better methods to analyse the signals and their relationship to their biological generators. This is particularly true in laboratories working with development of their own analysis programs or systems. Therefore, in general terms, the introduction of automated methods has triggered much work in clinical neurophysiology, signal analysis, simulation and comparative studies of function and structure.

Development of expert systems Within the field of medicine, the area of EMG has been chosen as a test bench for the development of expert systems since numerical data are available, general rules to classify findings are defined and final interpretation is sufficiently complex to offer a challenge to artificial intelligence systems.[35–39]

We have developed a small personal computer based expert system

intended to give guidance in interpretation, to produce standardized and practical reports of EMG findings and to be used in teaching. The results from MUP analysis are inserted manually or automatically into the system, from which a suggested interpretation of the appearance for each muscle is presented. When the study is completed, the results from all muscles are presented in a table and in a colour-coded form on a 'muscle man', giving a direct impression of which muscles have been studied and the principal results. Added comments given as free text complete the report (Figure 7).

Summary

Increased knowledge in neurosciences and development of morphological and biochemical methods will continue to demand a greater sophistication of neurophysiological methods in relation to both recording and analysis. Today there are a number of EMG methods and parameters that have been proven useful in the laboratories where they have been developed. Wider use of these methods will improve the general quality of EMG studies, promote further understanding of pathological conditions and therefore be of value for the speciality of electromyography. Furthermore, even rather small computers are extremely helpful in improving analysis methods. The consistency, accuracy and possibilities of extracting new information offered by computer-aided analysis of neurophysiological signals will hopefully increase our understanding of muscle–nerve physiology and pathophysiology and improve the diagnostic yield of the methods used in the neurophysiology laboratory. Often the neurophysiological evaluation is inexpensive and can be carried out quickly and adds new facts to the picture.

In summary, clinical neurophysiology continues to develop a number of sophisticated methods for better understanding of pathophysiological mechanisms. EMG describes the functional status of the central and peripheral nervous systems and is complementary to other techniques for evaluation of the patient with neurological disorders.

Acknowledgment

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The Evolution of J. Hughlings Jackson's Thought on Epilepsy

*M.J. Eadie**

Every senior medical student is likely to be familiar with the entity of Jacksonian motor epilepsy, while every neurologist must surely be aware that our modern understanding of epilepsy stems largely from John Hughlings Jackson's insights more than a century ago. Some may have been touched by the tragic irony that, after 11 years of childless marriage, Jackson was to see his wife die of cortical thrombophlebitis which caused the very pattern of unilateral motor epileptic seizures whose implications Jackson had already made plain to his generation, and which were later to bear his name. But fewer may have had the interest and the patience to make their way through Jackson's voluminous and somewhat repetitive writings on epilepsy, writings which seem at first sight to reflect a pattern of thinking which, according to one apocryphal source, was like the 'love of God which passeth understanding'. Yet if the effort is made, and one puts aside modern ideas and tries to approach the subject from a standpoint akin to what Jackson's probably was, Jackson's text is not particularly difficult to follow. One then begins to understand why Jackson's later writings on epilepsy in a sense embody a partial retreat from the radical brilliance of his earlier insights, complicated by the creation of a schema of brain functioning which to the modern mind proves of quite unnecessary and rather intimidating complexity.

To begin to understand Jackson's writings, one needs to know a little

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about his life and times, and something of the medical profession's understanding of epilepsy in the days when Jackson was beginning his great work.

John Hughlings Jackson (1835–1911)

Several accounts of Jackson's life are available, e.g.[1,2] He was born in Yorkshire, formally educated only to the age of 15 years and then apprenticed to a general practitioner in York. In 1853 he entered the York medical school and in 1856 took the Licenciate of the Society of Apothecaries of London and the Membership of the Royal College of Surgeons of England. He returned to York to work in the City Dispensary where he came under the influence of Thomas Laycock, later Professor of Clinical Medicine at Edinburgh. Laycock's hypothesis that the cerebral cortex functioned as the highest level reflex centre in the nervous system had lasting consequences for Jackson's thought. In 1860 Jackson took the external MD of St Andrew's University. By this time he was living in London with Jonathon Hutchinson, who became his life-long friend. There the two at first earned their livings by medical journalism. Jackson's interests moved increasingly towards the nervous system and in 1862 he was elected Assistant Physician to the National Hospital at Queen Square, with which institution he maintained a connection to the end of his life. In 1865 he also joined the staff of the London Hospital. In this same year he married his cousin Elizabeth Dade Jackson. After her death 11 years later he became an increasingly lonely, indeed solitary and in some ways eccentric, figure. His friend Hutchinson wrote on 4 January 1886:[3]

> Dr. Jackson and I had a pleasant walk in the Park and Zoo yesterday morning: we did not look at anything in the latter, but simply talked. He seemed to have pleasure in going back to old times, and talked much about his wife, whom he still very bitterly regrets. All would be well with him if she were only living.

By the end of his life the greatness of Jackson's achievements and the gentle inoffensiveness of his ways were generally acknowledged and admired by his peers, and he had become something of a living legend. By sheer power of intellect he had reasoned his way from the correlation of clinical and pathological data to the insight that the human cerebral cortex was not simply the organ of the mind but that in it there was localized representation of at least motor and sensory function. Moreover, he had come to this realisation several years before such localiza-

tion was demonstrated experimentally in animals by Hitzig and Fritsch in Berlin, and by David Ferrier in Britain. When he died, Jonathon Hutchison[1] wrote that his old friend was: 'the nearest to a genius that it is my privilege to have known!'

Epileptogenesis around 1860

At the time when Jackson commenced his study of the epilepsies, it was generally believed that the motor element of a convulsive seizure was determined at medullary level,[4,5] with the loss of consciousness in the seizure being due to cerebral hemisphere ischaemia produced by cerebral arterial spasm evoked by the medullary events. As Jackson, looking back, wrote in 1866[6] (p. 348*):

> When I first began the investigation of nervous diseases I supposed, as most other physicians then did, and as perhaps most still do, the seat of epilepsy to be the medulla oblongata!

Jackson's thought on epilepsy

From Jackson's writings it is possible to see three overlapping periods in the development of his understanding of the genesis of epilepsy. The first period, the 1860s, which saw Jackson writing of a variety of clinical manifestations of epilepsy, culminated in 1870 with the publication of his great interpretative lecture 'A study of convulsions' (pp. 8–35) in which the majority of his revolutionary concepts were first brought together and enunciated, though not always in their fully developed forms. Over the following decade or rather longer he further explored ramifications of these concepts, filled them out and fitted certain additional clinical manifestations of epilepsy into his framework of ideas. From 1880 on, he began to make increasing efforts to reconcile his ideas with the prevailing notions about epilepsy while at the same time he interpreted various types of seizures in relation to the hierarchies of neural functioning which he was working out. Jackson's 1870 paper can be seen as the great landmark statement which began the transformation of man's understanding of epilepsy. From the perspective of the 1870 paper it could be argued that Jackson's subsequent writings on epilepsy represent little more than the refinement of a system of ideas he had already developed by the time

* All page numbers relating to Jackson's work refer to Taylor's (1931) edition of Jackson's Selected Writings[6].

he was 35 years of age. Before taking this line of argument further, it is important to recognize that Jackson's whole approach was reflected in his 1873 interpretation of clinical phenomena such as epilepsy, or hemiplegia, or chorea, as being the results of 'experiments made by disease on the brain of man' (p. 37). For a long time his interest was more in how the human brain functioned than in epilepsy *per se*. Thus, also in 1873, he could write (pp. 78–79):

> It is a small matter to me whether a case of convulsions or other paroxysmal nervous seizures is to be called epileptic or not. What I labour to find out is the *part* of the brain of the functions of which the convulsion is the brutal and sudden development.

In his attitude and interests Jackson was not so much an epileptologist as a theoretical neural physiologist.

Major concepts in Jackson's 1870 paper

Jackson began his 1870 paper (pp. 8–35) with the radical proposition:

> A convulsion is but a symptom, and implies only that there is an occasional, an excessive and a disorderly discharge of nerve tissue on muscles. This discharge occurs in all degrees; it occurs with all sorts of conditions of ill health, at all ages, and under innumerable circumstances.

He explained that the great majority of chronic convulsions fell into two classes, viz. (i) bilaterally simultaneous seizures with either no warning or with a very general one, e.g. an epigastric sensation, or an indescribable feeling in the head—this variety being so-called 'genuine' or 'idiopathic' epilepsy, and (ii) unilateral motor (epileptiform) seizures. In a footnote (p. 8—Jackson was much given to footnotes) he indicated that the two classes of convulsion differed only in degree, not in kind:

> In both there are occasional, excessive and disorderly expenditures of force on muscles, the discharges depending on instability of nervous tissue.

The difference in degree was:

> Not merely in degree of more or less spasm—more or less instability of nervous tissue—but also in degree of evolution of the nervous processes which are unstable.

Jackson had earlier given indication (in 1866) of how wide ranging was his conception of epilepsy (p. 4):

> Thus epilepsy would not, in this sense, convey the idea of convulsions, but of temporary disorders of functions of many kinds, sensory as well as motor and mental as well as physical.

After this glimpse of his conception of the range of phenomena embraced by the term 'epilepsy', Jackson indicated that he would confine himself to unilateral motor seizures in the 1870 paper. He drew parallels between such seizures and hemiplegia, discussed the march of the visible motor events of the episode in relation to the postulated spread of the seizure discharge in the brain and interpreted post-seizure hemiparesis (which he recognized as having previously been studied by Robert Bentley Todd) as being due to local neural exhaustion. He located the site of his postulated abnormal neural discharges as being in the cerebral cortex (earlier for a short time he had thought the striatum to be their site) and he adduced clinicopathological correlation data to support his interpretation. He equated convulsions beginning unilaterally with the presence of a local brain lesion which might be either 'coarse' (e.g. embolism, tuberculoma, tumor, gumma) or else too minor to be readily detected. At that time he believed there were no visible lesions in the brain in 'genuine' epilepsy. He discussed impairment of consciousness as a later manifestation in attacks of convulsions beginning unilaterally, but offered no explicit view as to its mechanism. Fits without insensibility he called 'partial' fits, a term he had used even earlier (in 1868—p. 7). He perceived that epilepsy was not merely a matter of having a persistent unstable lesion in the brain. Something also had to bring the instability of the lesion to the stage where it produced a clinical seizure.

Thus Jackson had opted for a wide concept of epilepsy, had perceived that the disorder arose from discharging lesions in the cerebral cortex and had deduced that its clinical expressions were determined by the site of the discharge origin and the extent of the discharge spread. Most of his main subsequent themes concerning epilepsy were already present in the 1870 paper, though he later went into the question of epileptic insanity, discussed seizure auras, looked carefully at the timing of the onset of altered consciousness in seizures and greatly developed the concept of levels of evolution of neural function to which he had alluded in the 1870 paper, but only in a footnote (p. 8).

Subsequent development of some of the 1870 concepts

'Epilepsy'

Between 1870 and 1875 Jackson's published papers suggest that his concept of 'epilepsy' was becoming even broader. In 1873 he wrote (p. 99):

> First—Epilepsy is not one particular grouping of symptoms occurring occasionally; it is a name for any sort of nervous symptom or group of symptoms occurring occasionally from local discharge. Whether the discharge puts muscles in movement or not—that is, whether there be a convulsion or not—matters nothing for the definition. A paroxysm of 'subjective' sensation of smell is an epilepsy as much as is a paroxysm of convulsion; each is the result of sudden local discharge of grey matter.
>
> Secondly—It does not matter for the definition whether there be Loss of Consciousness or not; loss of consciousness is a fundamental thing in most of the accepted definitions. If there be no loss of consciousness, there is, according to most physicians, not epilepsy, and the term 'epileptiform' is used. But even when using the term 'epilepsy' in the ordinary sense of the word the separation into cases where there is and where there is not Loss of Consciousness has no *physiological* warrant.

Jackson took this line of thought further and speculated that epilepsy represented the effects of occasional cerebral discharges, chorea the result of interrupted continuous discharges and tetanus the consequence of uninterrupted continuous discharges (pp. 100–101).

> But, as stated, numerous and very different nervous symptoms may be epileptic in my definition of the term. And as any part of the grey matter of the cerebrum may become unstable, there will be all varieties of epilepsy, according to the exact position—according to the extent of the grey matter altered—and there will be all degrees according to the degree of instability.

By 1875 Jackson had begun to back away from the radical implications of his definition of 'epilepsy'. He began to speak rather of two classifications of epilepsy, (i) a practical one which corresponded to the one generally accepted by his contemporaries and (ii) a scientific one, which was Jackson's own. He also began to adopt the generally accepted definition of epilepsy in his papers, while still retaining his scientific definition to allow him to discuss his interpretation of cerebral functioning. Thus, when discussing epileptic discharges in sensory centres he could speak of: '... some cases of migraine, which in my nomenclature are epilepsies' (p. 139).

He was still writing of the 'numerous epilepsies' in 1879 (p. 277), but then based his discussion on the empirical classification (p. 279) which divided cases of epilepsy into those with (i) epilepsy proper, and (ii) epileptiform seizures. As the years passed Jackson seemed to place less weight on his scientific classification. Thus by 1890, again in one of his almost inevitable footnotes (p. 416), he confessed:

> I formerly used the term 'epilepsy' generically for all excessive discharges of the cortex and their consequences. ... So that under the term 'epilepsy' used generically there were epilepsy proper, epileptiform seizures, and migraine (the last mentioned being then spoken of as a sensory epilepsy), and, indeed, any paroxysmal symptoms attributable to sudden excessive discharges of any part of the cortex. I now use the term 'epilepsy' for that neurosis which is often called 'genuine' or 'ordinary' epilepsy, and for that only.

By this time Jackson was also writing of 3 rather than of 2 main types of epileptic seizure, but this particular matter is more easily discussed in relation to Jackson's ideas about hierarchies of brain functions and brain evolution.

Jackson's changing definition of 'epilepsy' over the years adds to the difficulty in interpreting his writings. In his defence, it must be said that Jackson's primary concern was consistently focussed on how epilepsy threw light on brain function rather than on epilepsy as a phenomenon in its own right. It is likely that Jackson continued to give his intellectual allegiance to the great conception implicit in his 'scientific' definition of epilepsy, but increasingly moved away from giving public expression to it to allow his views to be more easily accepted by his contemporaries.

Mode of seizure onset

Jackson's concept of epileptogenesis had, by 1873, led him to the realization that (p. 68):

> There is nothing more important than to note where a convulsion begins, for the inference is, that the first motor symptom is the sign of the beginning of the central discharge.

Or, in more general terms (p. 90):

> The mode of onset is the most important matter in the anatomical investigation of any case of epilepsy.

This axiom is still of the utmost importance in clinical practice.

Behaviour of the 'discharging lesion'

Although Jackson never made it explicit in his writings, it seems very probable that he thought of the epileptic discharge as something rather explosive and akin to electricity in its nature. In yet another footnote (p. 391), this time to one of his later papers (1886), he explained that some of his contemporaries agreed that they could understand the idea of an ulcer 'discharging', but not of nerve cells doing so. By 'discharging lesions' he meant:

> a vast exaltation of the function (hyper-physiological alterations) of cells of small parts of the cortex caused by an abnormal nutritive (pathological) process involving an increased but an inferior kind of nutrition.

Whether this explanation would have clarified the matter seems open to doubt.

As he continued to think about the behaviour of his 'discharging lesion' Jackson speculated (1873—p. 101) that the discharge would spread, as it were, laterally to other centres at the same hierarchial level of brain functioning, but would also 'explode' into healthy lower centres. He used this insight to explain various epileptic phenomena, as will be discussed later. However, he also realised that, in practice, there were relatively few patterns of epileptic seizure, and not the 'innumerable varieties' that would be expected to occur if every point in the cortex could discharge, and the discharges from each point could spread to different extents in different episodes. Therefore he (1876) was forced to the view (p. 156) that: '... parts of the nervous system are more liable to *become diseased* than others are;', a truth that has become more evident with the years.

Altered consciousness in epilepsy

In Jackson's time loss of consciousness was held to be the *sine qua non* of 'genuine' epilepsy. Jackson, in his 1870 paper, pointed out that seizures beginning unilaterally, i.e. epileptiform seizures, could go on to loss of consciousness in the same episode. Hence the presence or absence of loss of consciousness was not sufficient to distinguish between 'genuine' epilepsy and epileptiform seizures. The key to the distinction was the timing of the altered consciousness. In 1875 (p. 121) he first made the

cardinal point that consciousness was altered very early in the paroxysms of 'genuine' epilepsy, but was altered later, or not at all, in the course of individual epileptiform seizures. The need to explain this difference in the timing of the onset of altered consciousness in the two main forms of seizure disorder admitted by the empirical classification encouraged Jackson further into developing his concept of levels of neural functioning.

The presence of brain pathology in epilepsy

Jackson's 'scientific' classification of epilepsy, to which he gave open intellectual allegiance for many years, was centred round the insight that all seizures arose from malfunctioning areas of cerebral cortex related to detectable or occult local lesions. Because of this belief he could give little emphasis to the distinction customarily made between 'genuine' epilepsy, where there was believed to be no detectable pathology, and epileptiform seizures where there might be detectable lesions. He believed that consciousness was altered immediately at or soon after the outset of the seizures in 'genuine epilepsy', and took this as the essential criterion for diagnosis of this entity. As a consequence of this, he included in the rubric of 'genuine epilepsy' seizures which began with various forms of psychic alteration, episodes which we would now regard as partial seizures which became secondarily generalized. He therefore was relatively untroubled when, late in his career (in 1898) he came across an instance of 'genuine' epilepsy beginning with an 'intellectual aura' or 'dreamy state' and which at autopsy had a structural lesion in the left uncinate gyrus (pp. 458–463). The presence of this pathology did not disturb his interpretations. His conception of epilepsy allowed him to expect that such pathology would finally be found in cases of 'genuine' epilepsy.

Levels of neural functioning

Early in his adult life Jackson came under the influence of Herbert Spencer's philosophy and, when he began to study the function of the brain, found Spencer's notions of 'evolution' and 'dissolution', together with a concept of hierarchial levels of brain functioning, useful tools to interpret the phenomena of neurological disease. There is only a minimal reference to such ideas in Jackson's 1870 paper. By 1873 he equated the

'highest processes' of the brain with 'the substrata of consciousness' (p. 46) and in this year tentatively suggested that the timing of the altered consciousness during a seizure was related to the level of brain function in which the seizure arose. Around the time when Jackson began his ambivalent retreat from his radical concept of epilepsy (1875–76), he gave an explicit indication of his interpretation of the relation between consciousness and the levels of neural functioning (p. 146):

> The distinction scientifically is that consciousness is lost at the onset of the paroxysm, or almost at the very first, when the discharge *begins in the very highest nervous centres*, these centres being the substrata of consciousness. Consciousness is lost late when the discharge beings in a subordinate centre—in some part of Hitzig and Ferrier's region for example. In epileptic discharges of these centres consciousness may not be lost at all; all depends on the momentum of the discharge, and therefore on how far it spreads.

Thus he could equate discharges beginning in his highest centres with epilepsy proper, and discharges beginning in the lower or subordinate centres with epileptiform seizures. In 1879 he speculated (p. 282) that when a discharge began and remained within the highest centres, there was altered consciousness only—'petit mal'. When such a discharge spread to the subordinate motor centres there was a 'grand mal' seizure. He located his highest centres in front of, and behind, the sensory-motor cortical areas of the cerebral hemispheres.

By 1886 Jackson was writing (p. 348) of 3, not 2, levels of evolution of central nervous system function, comprising (i) the lowest level—corresponding to the spinal cord and brain stem (ii) the middle level—the sensory and motor regions of the cerebral cortex, and (iii) the highest levels (frontal, prefrontal and occipital lobes). Corresponding to these 3 levels there were now 3, not 2, types of epileptic fit. He had here introduced a new category of lowest level fits in addition to epilepsy proper and epileptiform seizures. The lowest level fits included 'inward fits' or respiratory convulsions (laryngismus stridulus), spasmodic asthma and rigors. In 1902 he published details of a case exhibiting his lowest level fits, in which the first seizure manifestations had appeared in the chest muscles (p. 474). Possibly his intention in this paper was to provide clinical verification of the existence of his category of lowest level seizure.

Thus, over a period of two decades, Jackson's thought had gone through almost a full circle. He had first moved the location of the seat of epilepsy from the medulla to the cerebral cortex, and then had finally come to acknowledge that a medullary origin was possible for some seizures.

Jackson's thought in the light of today's knowledge

Within his purview of epilepsy Jackson included entities such as migraine and asthma which would now be considered of an entirely different nature. The 'lowest level' seizures of his latter years also would not now be regarded as epileptic in their nature, leaving only two categories of epilepsy, viz. epilepsy proper and epileptiform seizures. The latter Jackson sometimes referred to as 'partial' seizures, raising the question of how well Jackson's classification of epilepsies correlates with the International League Against Epilepsy's[7] division of seizures into partial and generalized ones. This question becomes even more pertinent when it is remembered that, for Jackson, epilepsy proper comprised both 'grand mal' and 'petit mal'. The answer seems to be that Jackson's 'epilepsy proper' would include not only what is embraced by today's generalized epilepsies, but also would take in all varieties of today's partial seizures if there was any possibility that consciousness might be altered, however slightly, at or near the outset of the seizure. Within the category of epilepsy proper Jackson's 'petit mal' would have included many instances of complex partial seizures as well as true absences and his 'grand mal' would have taken in some partial seizures which became secondarily generalized in addition to primarily generalized seizures. His 'epileptiform seizures' would be merely one subvariety of today's simple partial seizures.

Jackson's main achievement in relation to epilepsy lies in his interpretation of the process of epileptogenesis and in his location of the site of origin of epileptic discharges as being within the cerebral hemispheres. If he had written nothing after his 1870 paper he would still have bequeathed to subsequent generations the intellectual tools to study and understand epilepsy. However, a single paper, published in an obscure journal (as it was), might easily have gone unnoticed. It seems likely that it was in part the sheer volume of Jackson's writings over more than three decades, with the repeated statement and working out of his fertile insights, that brought his ideas to notice. Jackson knew the risks of error that he ran when he struggled to give public expression to the unorthodox concepts stemming from his intellectual explorations. In 1873 he wrote (p. 78):

> I have not simply repeated accepted doctrines with slight variations and new illustrations. Working on a novel method, I run continual risk of making novel blunders. But in thinking for one's self there are certain kinds of blunders which almost must be made.

Jackson had the courage to make his blunders as he struggled to build a new conceptual edifice. He continued on, despite the prolonged devastation of his life brought about by his wife's death, and his long years of subsequent self-imposed isolation, circumstances which may have undermined his resolve to explore his early radical vision of epilepsy to its limits. Parts of the intellectual edifice he constructed may not have withstood the progress of experimental knowledge. However, the great insights which formed its foundations have provided a legacy of extraordinary richness and versatility for his successors.

Summary

By 1870, and within 5 or 6 years of his beginning to analyse the clinical phenomena of epilepsy and to correlate them with autopsy data, the 35-year-old John Hughlings Jackson had come to a view of the nature of epilepsy that was radically different from that of his contemporaries. He recognized that epileptic seizures arose in the cerebral cortex, and not in the medulla oblongata, as was then thought, and he saw that there was no fundamental difference between so-called 'genuine' epilepsy and epileptiform seizures. His great lecture, 'A study of convulsions', published in 1870, contains the essence of nearly all our modern ideas concerning the nature of epilepsy.

While Jackson spent the next 30 years of his life in further interpretation of the phenomena of epilepsy, as he did this he began to back away from many of the more radical implications of his earlier brilliant insights. He seems to have done this to make his views more palatable to his contemporaries, but this also encouraged him to interpret varieties of epilepsy in relation to a conceptual scheme of 2, and later 3, hierarchal levels of nervous system functioning. The result is that today's reader of Jackson's later papers can be left rather bewildered and it is only by reading the whole corpus of his work that his enormous conceptual contribution to present-day epileptology can be appreciated.

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Thirteen Years Longitudinal Study of Computed Tomography, Visual Electrophysiology and Neuropsychological Changes in Huntington's Chorea Patients and 50% at-risk Asymptomatic Subjects

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Huntington's chorea is estimated to occur in 4 to 7 per 100 000 persons.[1] The disease is an extra-pyramidal idiopathic degenerative disorder of the central nervous system. The characteristic clinical features consist of chorea, dementia and a history of familial occurrence. The disease is inherited as an autosomal dominant trait with complete penetrance, affecting half the offspring of an affected individual.[2] It affects males and females equally, with an average age of onset between 35 and 40 years and an average course to death of 14 years.

In 1983 Gusella *et al.*[3] found the first genetic marker for Huntington's chorea. Since then, numerous scientific reports have advanced the genetic mapping of the disorder to the point where work has shown the gene for Huntington's chorea to be located at the tip of the short arm of chromosome 4, with all the known markers proximal to it and very little DNA

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between it and the end of the chromosome.[4] It remains, however, to identify the gene.

The outcome of these advances is to have made predictive testing for the disease a reality. Centres in the United States, Canada and Britain provide presymptomatic testing for the gene, allowing modification of individual risk upward to 95% or downward to 5%. This is not to say that predictive testing for Huntington's chorea sits comfortably amid the present-day techniques of the geneticist. Predictive testing is still under evaluation with little known about the long-term outcome of such testing.[5]

Reported here is the outcome of a 13-year longitudinal study of 68 persons, 45 of whom were at risk for Huntington's chorea. Five of the at-risk group have developed the disease since the beginning of the study, affording a rare opportunity to document, in detail, the clinical course of the disorder.

Preliminary results of the radiology and electrophysiology were published in 1979[6] and of the neuropsychology in 1981.[7]

Methodology

Neuropsychology and psychiatry

Classification and testing Data collection and patient classification for the entire project was coordinated by one of us (SZ) and earlier by M/s S. Priest, who periodically reviewed patient records and arranged for routine follow-up. This occurred in conjunction with neuropsychological and psychiatric examinations and involved: (i) establishing the family pedigree for Huntington's chorea; (ii) psychiatric interview (RME); (iii) neuro-psychological examination (SZ); (iv) neurological examination; and (v) patient classification (at risk *v* affected).

Family pedigree Inclusion into the study rested with verified establishment of a family history of Huntington's chorea. To this end, psychiatric and social work histories were essential in securing birth and death records, hospital and nursing home records and, when available, post mortem and coronial records. No case was included in this series unless it could be established without doubt that there was a positive family history of Huntington's chorea.

Psychiatric interview Patients in this study were seen regularly for psychiatric as well as social work interview. This provided the major psychosocial contact and support for the many participants in this study.

It was through this interview that all results from the various examinations (neuropsychological, electrophysiological, neurological and neuroradiological) were coordinated and any decision was made regarding change of diagnostic status.

Neuropsychological examination All patients were administered a routine neuropsychological examination consisting of:

Wechsler adult intelligence scale
Block design learning test
Modified word learning test
Symbol digit modalities test
Halstead Reitan battery

These tests were selected for their documented reliability and validity in assessing higher cognitive and intellectual functions as well as lower level sensorimotor functions in patients with known or suspected brain dysfunction.[8] Patients were seen individually for examinations which took approximately 3 hours. At-risk individuals were given the full battery of neuropsychological tests while modification in assessment was often needed for affected individuals owing to their mental state and condition. As the goal of this longitudinal study was to document the natural history of the emergence of the disorder this latter fact was not seen to be a major design problem.

All data were recorded on standardized forms, verified and key punched as part of the computer record kept on each patient assessment.

Neurological examination At approximately 2-yearly intervals patients were given a routine neurological examination. This entailed a full cranial nerve examination, a mental status examination and, as well, an assessment of motor coordination, sensation and gait. An overall score (abnormal, equivocal, normal) was assigned following the neurological assessment.

Patient Classification Following each examination cycle, the neuroradiological, electro-physiological, neuropsychological and neurological results were collated by two of us (RME and SZ) and the patient's diagnostic classification was reviewed.

Initially, a 3-level classification for subjects in this study was used: (i) affected; (ii) early affected; and (iii) at-risk asymptomatic.

Clinicians working with Huntington's chorea will appreciate the difficulty in making a definitive diagnosis and the gravity of moving a patient from an at-risk status to one of affected. For this reason the decision to finally classify a subject as affected rested with the psychiatrist, who reviewed the diagnostic data and examined the patient. In all cases, the decision to classify a subject as affected was based upon positive findings in one or more of the assessments and *the presence of an emerging disorder of movement and deterioration in mental functioning*. Where changes could be documented but a pattern of movement disorder with deterioration in mental functioning was not clear-cut, the patient was classified in the early affected category to await a further assessment cycle. In some cases, the time between moving from the early affected category to the affected category was shorter than the inter-assessment cycle (approximately 2 years) and a full examination cycle was undertaken at this time.

CT methodology

Between March 1976 and July 1977, examinations were carried out on an EMI Mark I water box scanner using 13mm tomographic cuts, without intravenous contrast.

From August 1977 to October 1985, studies were made on an EMI CT 1010 scanner using 9mm tomographic cuts. From October 1985 to July 1989, the Siemens DRH CT unit using 8mm cuts was used.

All examinations were made using cuts parallel to the anatomical base line. Concurrently, with each machine change, normal control studies were undertaken and, as well, a small number of persons were scanned on the preceding machine and on the new machine on the same day in the case of the change over from the EMI CT 1010 to the Siemens DRH CT unit, but within 4 weeks in the case of the change over from the EMI Mark I water box scanner to the EMI CT 1010. This check established that scoring for atrophy was comparable and also that the measured density of white and gray matter was the same using the different CT machines.[9] All CT studies were carried out not less than one year apart and usually at intervals in excess of 18 months.

The studies carried out on the at-risk, clinically healthy group conformed to the NH & MRC guidelines for the irradiation of healthy volunteers and all gave informed consent. The request for the programme to be made came in the first place from the Huntington's Disease Association of Western Australia.

Basis of CT scoring A scale of 0 (normal) to a maximum of 4 (grossly abnormal) was established and this was used to assess the caudate nucleus, general convexity, cerebellar vermis and cerebellar hemispheres for atrophy. The scores were considered against the findings from the normal control data.[9]

When a subject was studied serially, prior knowledge of the previous score and the clinical category was not available to the recorder.

Visual electrophysiology methodology

Quantitative electro-oculographic studies of eye movements used were as previously reported.[10] Jump and pursuit eye movements were measured for most individuals and the majority of these also had visual evoked potentials recorded.

Method of electro-oculography During the first part of the test, a continual recording of bilateral eye position was made by a PDP-11 computer as the patient moved his eyes between 2 horizontal fixation points 35° apart. The electro-oculographic data were displayed on a graphics terminal, together with a record of instantaneous velocity for each eye. This test was used to calibrate the system for the individual patient's corneoretinal potential. No quantitative analysis was undertaken but the calibration procedure provided an important indication of a patient's ability to perform refixation eye movements in a coordinated fashion. In a normal subject, such refixations are usually achieved with only one saccadic movement. Results from 2 at-risk subjects are shown in Figure 1. These have been scored as normal (top) and abnormal (bottom).

The second part of the test measured the subject's ability to execute a sudden 15° jump movement to follow a moving target. Three parameters were calculated for each jump movement and averaged at the end of the test; they were: (i) the latency, or the delay between the start of movement of the target spot and the attainment of maximum velocity of movement of the patient's eyes; (ii) the peak velocity of the eye jump; and (iii) the accuracy of the resulting jump, i.e. the relationship between the final position of the target and the position of the eyes after the first saccade.

The pursuit electro-oculography test required that the subject track a target spot moving at constant velocity. A number of velocities were used ranging from 10° per sec to 70° per sec, selected at random by the computer.

Method of visual evoked response This was carried out with a black and white chequerboard pattern stimulator subtending 6° at the patient's eyes. The pattern was reversed pseudo-randomly approximately every 1.7 seconds and a study consisted of 125 pattern reversals. Data were collected on-line to a PDP-11 computer and analysed retrospectively. Parameters studied were the general shape of the response, the latency and amplitude of the principal component and the root mean square voltage of the overall response.

Visual evoked responses from two at-risk subjects are shown in Figure 2. One (top) was scored normal and the other (bottom) was scored as grossly abnormal.

Scoring methodology for visual electrophysiology Scoring was carried out by 2 or 3 individuals working entirely independently. Scores were later averaged and are referred to as 'mean scores' throughout this paper. Scores were allocated by each scorer for each test separately as follows: normal results = 0; marginal = 1; clearly abnormal = 2; and grossly abnormal = 3.

Results

Overall results

Twenty-three patients were classified as clinically affected, comprising 10 males and 13 females with a mean age of 43.7 years and a standard deviation (SD) of 12 years. The age range was 20 to 70 years. Forty-five persons were classified in the at-risk group at the first visit; these persons comprised 29 males and 16 females with a mean age of 32 years (SD 12 years). Their age range was 14 to 70 years.

Of the 45 at-risk subjects, 5 later became symptomatic. One of these subjects subsequently died and a post mortem examination confirmed the diagnosis of HC. The age range of the 5 at the first visit was 31 to 43 years. It is noted that a sixth person, a 31-year-old male, may, on examination of the records, have had early features of HC at his first visit. This subject has nevertheless been retained in the at-risk group for the data analysis. Of the 5 persons who changed classification, 3 had an abnormal caudate nucleus at the first CT and 4 during the study had abnormal visual electrophysiology whilst symptom-free, 3 being abnormal at the first visit. One of the 5 persons had abnormal neuropsychological tests at the first visit and the other 4 were still normal at the time they were classified as affected, when a tremor was evident.

The age range of 5 other individuals who may later become symp-

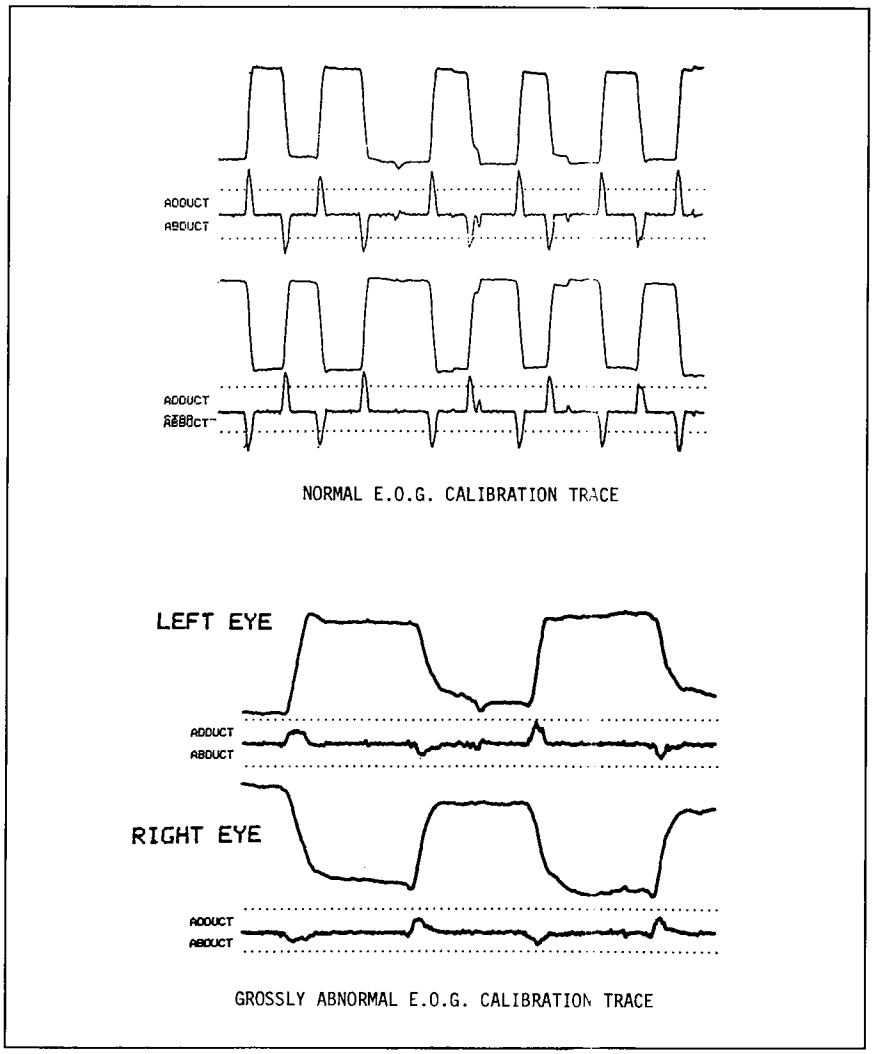


Figure 1. Electro-oculography calibration of at-risk subjects. Normal trace—above. Grossly abnormal trace—below

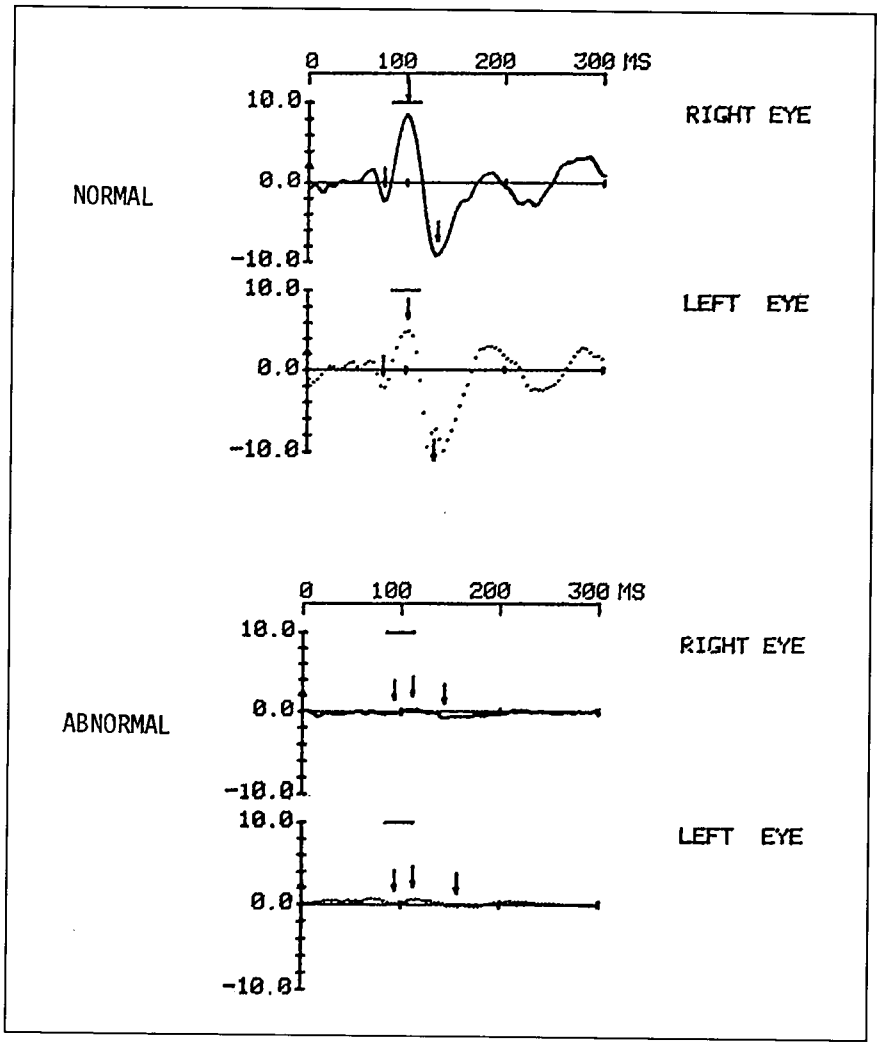


Figure 2. Visual evoked responses in at-risk subjects. Normal trace—above. Grossly abnormal—below.

tomatic as judged by abnormal CT results varies from 15 to 46 years with a mean of 34 years (Nos 30, 31, 36, 52 and 53).

The age range of 19 individuals who may later become symptomatic as judged by marginally abnormal visual electrophysiology is 15 to 67 years, with a mean of 31.8 years (SD 13.9 years) (Nos 30, 33, 36, 37, 43, 45, 46, 47, 49, 50, 52, 53, 56, 57, 63, 66, 84, 87 and 93).

Of these 19, 4 also had an abnormal CT study (Nos 30, 36, 52 and 53). No. 52 is the 31-year-old male referred to above, whose classification is problematical because it is not quite clear whether he should have been classified affected or at risk from the outset. In any event, there are certainly 3 persons who may well develop HC in the future.

One of the 45 at-risk group had a neuropsychological profile resembling the HC affected group prior to symptoms appearing but the other 4 who changed their classification were considered to have had a normal study.

Results of neuropsychological examination

Twenty-two patients affected with HC and 45 subjects at risk were followed longitudinally (one patient with HC was not examined). Previous work[11] has shown a close relationship between the onset of symptomatic HC and early sensory-perceptual changes in HC.

Classification of the at-risk subjects was carried out through the application of multivariate discriminant function analysis of each at-risk subject's neuropsychological test results using the following 8 neuropsychological tests: Face-hand test of double simultaneous sensory stimulation, double simultaneous auditory stimulation test, visual sensory imperception test, finger localization test, fingertip number writing, speech sounds perception, Seashore rhythm test and category test. These are described more fully elsewhere.[11] It is important to note that classification was, in effect, done via statistical rather than clinical judgement.

Of the 45 subjects at risk, as already stated 5 were ultimately diagnosed as suffering from HC. The diagnosis of HC was made through independent psychiatric evaluation (RME) without recourse to the neuropsychological findings. The diagnosis rested upon the emergence of symptomatic HC as noted previously.

Discriminant function evaluation of the 8 neuropsychological tests on the 22 HC patients and 45 at-risk subjects proceeded, utilizing a direct solution based on all 8 tests. This yielded discriminant classification coefficients used to predict group membership. The success rate for correct

classification was 89%. Of the mis-classifications, 4 were at-risk subjects subsequently diagnosed as having the disease. In other works, 4 of the 5 patients later found to have the disease were classified on neuropsychological tests to be at risk and one of the 5 had test results similar to the HC group. From the neuropsychological tests, none of the other 40 at-risk subjects was identified as likely to develop HC.

CT results

Affected group Twenty-two patients were studied, with 8 of these making a second visit, one 3 visits, and one 4 visits. One other patient had the structure of the caudate nucleus decided by post-mortem examination, not by CT.

Of the 22 patients studied, it was found that at the first visit, 5 had a normal caudate nucleus, 4 had very early atrophy (grade 1), 4 had moderate atrophy (grade 2), 8 had advanced atrophy (grade 3) and one had very severe caudate nucleus atrophy (grade 4)—see Table 1. Figure 3 shows how a 20-year-old male subject moved from grade 2 to grade 4 in just over 5 years.

All but one of the 22 patients had varying degrees of generalized cortical atrophy which was excessive for the patient's age—see Table 2.

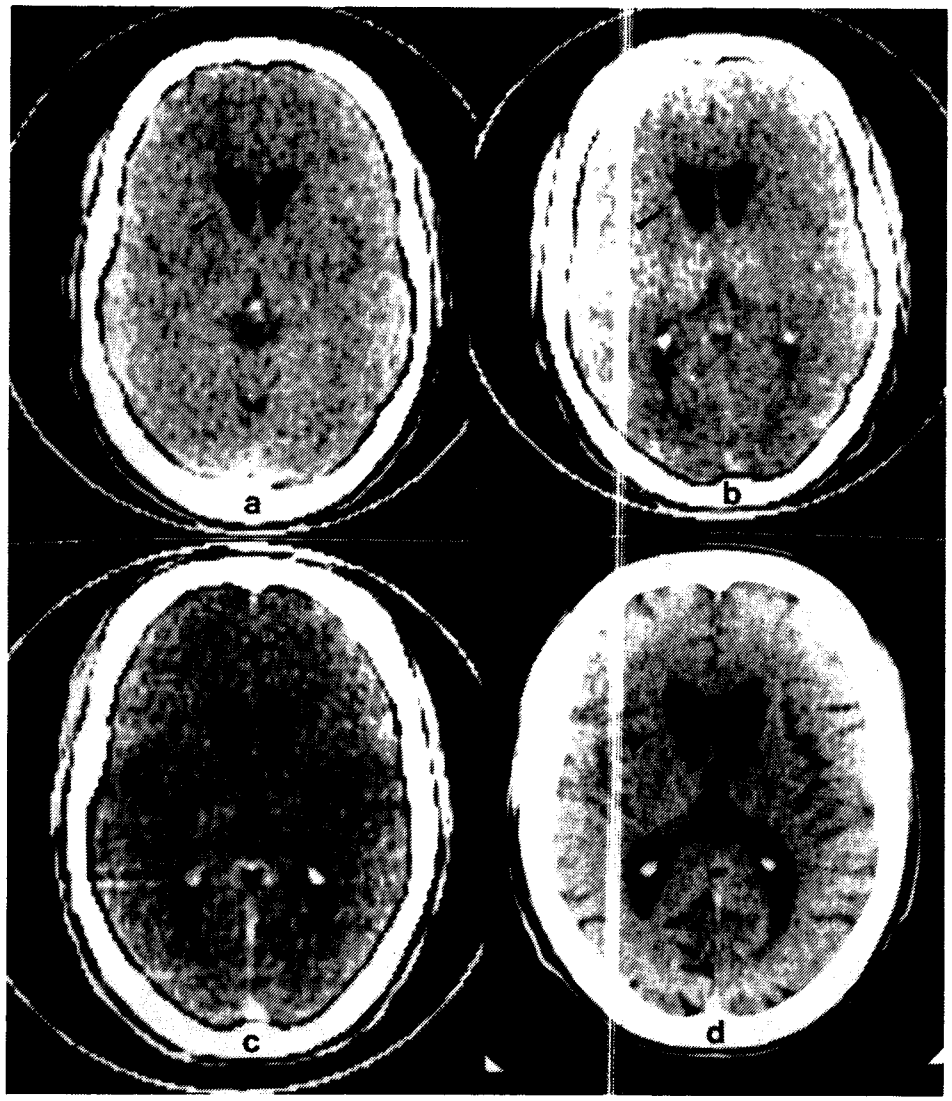
At-risk subjects Forty-five subjects were studied, with 13 attending for only one visit, 9 for 2 visits, 13 for 3 visits, 4 for 4 and 6 for 5 visits.

Thirty-seven of the 45 had a normal caudate nucleus at the first visit. None of these changed to a different grade during the period of the study. However, 7 had a grade 1 atrophy of the caudate and of these only one subsequently moved to a grade 2. The one subject with a grade 2 caudate moved to a grade 3 within 18 months—see Table 3.

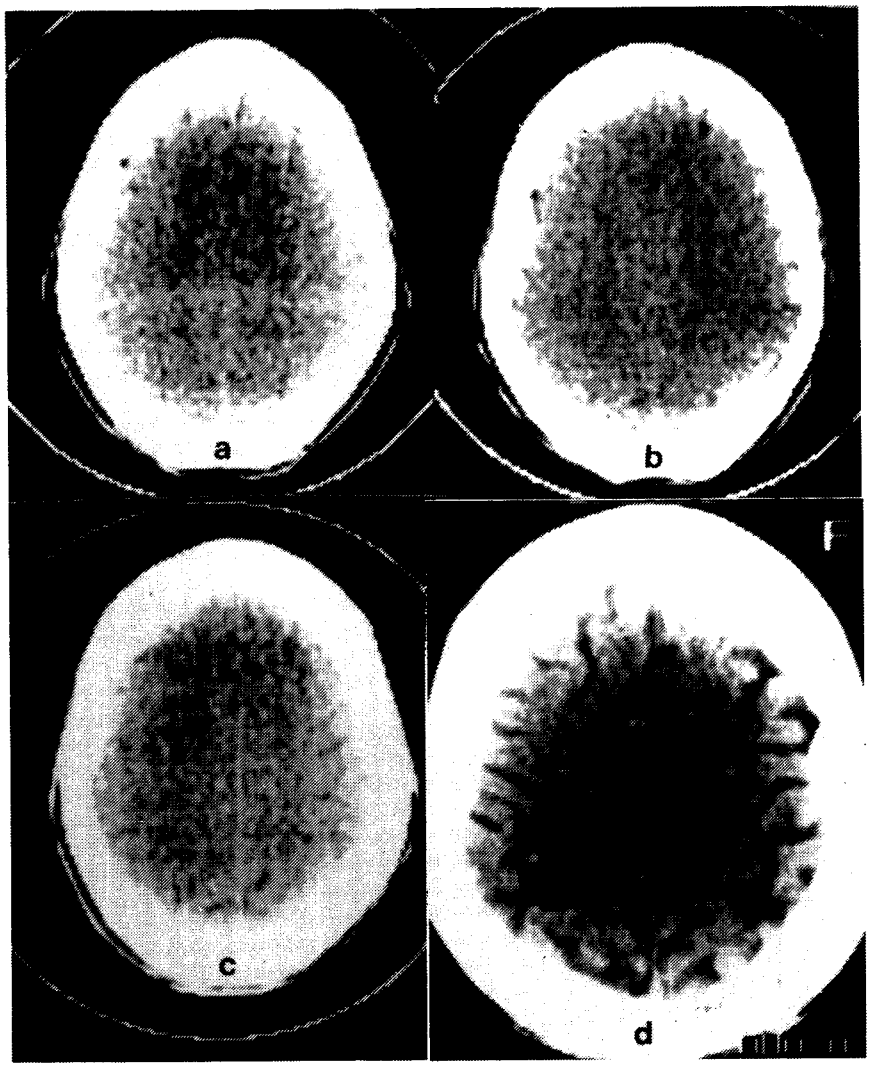
Fifteen of the 45 subjects had no generalized cortical atrophy. Six moved to another grade during the study, 2 reaching a grade 3 but none a grade 4—see Table 4. Fifteen started as a grade 1 cortical atrophy; 9 of these deteriorated to a higher grade, 5 reaching a grade 3 and one a grade 4. Of the 10 subjects starting as a grade 2 cortical atrophy, 3 reached a grade 3 and one a grade 4. There were 5 subjects with a grade 3 cortical atrophy who did not progress to higher grades. None presented with a grade 4 cortical atrophy.

Of the 5 subjects who changed their clinical category during the course of the study to affected, only 3 had an abnormal caudate nucleus on CT on the first visit.

Figure 3A and 3B. Serial CT examinations of an affected male, 20 years of age at the first visit. a = 8/7/81; b = 30/12/82; c = 30/4/85; d = 18/11/86.



3A—Cut at the level of the caudate nucleus, the arrow indicating ballooning of the lateral wall of the lateral ventricle due to progressive atrophy of the caudate nucleus. a = grade 2; b = grade 3; c = grade 3; d = grade 4 caudate atrophy.



3B—Cut at the level of the convexity sulci which show a marked increase in width over 5½ years. a = grade 1; b = grade 3; c = grade 3; d = grade 4 cortical atrophy.

Table 1. Affected subject—Caudate atrophy.

	CT Score		
1st visit	2nd visit	3rd visit	4th visit
Score 0 $n = 5$ (Nos 10, 12, 21, 95, 97)			
	Score 2 (No. 10)	Nil	Nil
	Score 3 (No. 12)	Nil	Nil
Score 1 $n = 4$ (Nos 22, 28, 26, 81)	Score 1 (No. 81)	Nil	Nil
Score 2 $n = 4$ (Nos 5, 25, 27, 73)	Score 2 $n = 1$ (No. 5)		
	Score 3 $n = 1$ (No. 27)	Score 3 $n = 1$ (No. 27)	
			Score 4 $n = 1$ (No. 27)
Score 3 $n = 8$ (Nos 1, 2, 6, 9, 14, 15, 23, 24)	Score 3 $n = 4$ (Nos 1, 6, 14, 15)	Nil	Nil
Score 4 $n = 1$ (No. 4)	Not retested.		

However, there were another 5 subjects who did have caudate atrophy on the first visit, with a mean of 12 years since their first visit, who might at some future date change clinical category, including the one who may have had symptoms at the first visit (No. 52).

Visual electrophysiology results

Affected group Of the 23 subjects in the affected group 18 had saccadic eye movements, 17 had pursuit eye movements and 14 had visual evoked responses studied. Some subjects were unable to perform some of the individual studies, particularly eye movements. The results are summarized in Table 5.

In general patients who were clinically affected were not scheduled

Table 2. Affected subjects—Generalized cortical atrophy.

	CT Score		
1st visit	2nd visit	3rd visit	4th visit
Score 0 $n = 1$ (No. 10)	Score 2 $n = 1$ (No. 10)		
Score 1 $n = 3$ (Nos 21, 27, 73)	Score 3 $n = 1$ (No. 27)	Score 3 $n = 1$ (No. 27)	Score 4 $n = 1$ (No. 27)
Score 2 $n = 2$ (Nos 5, 95)	Score 2 $n = 1$ (No. 5)		
Score 3 $n = 8$ (Nos 2, 12, 15, 22, 23, 25, 26, 81)	Score 3 $n = 3$ (Nos 12, 15, 81)		
Score 4 $n = 8$ (Nos 1, 4, 6, 9, 14, 24, 28, 97)	Score 4 $n = 3$ (Nos 1, 6, 14)		

for repeat studies. The results in the 3 cases where repeat studies were performed are presented in Table 6.

At-risk subjects The number of subjects studied for each individual test and the average 'mean score' for the first visit of members of the at-risk group are given in Table 7.

It is noted that the average value for each of the tests corresponds to a normal result, i.e. score less than 1.5, but the ranges given indicate that some of the subjects yielded abnormal results at the first visit. Fifteen individuals had mean scores >1.5 for 1 or more of the 3 tests at first presentation. Of these 15, 3 later changed classification from at risk to clinically affected. A profile of the serial testing of at-risk patients is given in Table 8.

Table 3. At-risk subjects—caudate atrophy.

CT Scores				
1st visit	2nd visit	3rd visit	4th visit	5th visit
Score 0 $n = 37$	Score 0 $n = 24$	Score 0 $n = 15$	Score 0 $n = 6$	Score 0 $n = 2$
i.e. none with Score 0 progressed to any other Score				
Score 1 $n = 7$ (Nos. 30, 31, 36, 39, 52, 53, 91)	Score 1 $n = 5$ (Nos. 30, 31, 36, 39, 52)	Score 1 $n = 4$ (Nos. 30, 36, 39, 52)	Score 1 $n = 2$ (Nos. 36, 39)	Score 1 $n = 2$ (Nos. 36, 39)
			Score 2 $n = 1$ (No. 52)	Score 2 $n = 1$ (No. 52)
Score 2 $n = 1$ (No. 38)	Score 2 $n = 1$ (No. 38)			
		Score 3 $n = 1$ (No. 38)		

There were no persons with a Score 3 or Score 4 caudate nucleus atrophy on the first visit.

Changed classification During the course of the study 5 subjects moved from the at-risk category into the clinically affected category. The temporal changes observed in scores for the electrophysiological tests for these 5 individuals is shown graphically in Figure 4.

Discussion

The investigation has shown that CT and electrophysiology are useful tests in the diagnosis of Huntington's chorea. It was found that 24 of 45 at-risk subjects had abnormal visual electrophysiology prior to onset of symptoms and 5 of these have already become symptomatic. Eight of the 45 at risk had an abnormal caudate on the CT scan and 3 of these and possibly a fourth (No. 52) have already developed symptoms.

Of the 19 subjects who may still become symptomatic, as judged by visual electrophysiology, 3 also have an abnormal caudate nucleus on CT scan (Nos 30, 36 and 53). Although it is possible that at-risk subjects showing abnormal visual electrophysiology may prove to be false positives because the tests are not specific for Huntington's chorea, the 3 persons with an abnormal caudate nucleus on CT, as well as positive findings on electrophysiology, must be regarded as very likely to develop

Table 4. At-risk subjects—generalised cortical atrophy.

CT Scores				
1st visit	2nd visit	3rd visit	4th visit	5th visit
Score 0 *n* = 15 (Nos 34, 36, 44, 46, 48, 49, 50, 53, 54, 58, 65, 69, 84, 85, 88)	Score 0 *n* = 7 (Nos 44, 46, 48, 49, 50, 69, 85)	Score 0 *n* = 3 (Nos 44, 48, 49)	Score 0 *n* = 1 (No. 48)	Score 0 *n* = 1 (No. 48)
	Score 1 *n* = 3 (Nos 34, 36, 54)	Score 1 *n* = 2 (Nos 46, 54)	Score 1 *n* = 1 (No. 46)	
	Score 2 *n* = 2 (Nos 58, 65)	Score 2 *n* = 3 (Nos 36, 58, 65)	Score 2 *n* = 1 (No. 54)	
		Score 3 *n* = 1 (No. 34)	Score 3 *n* = 2 (Nos 34, 36)	Score 3 *n* = 1 (No. 36)
Score 1 *n* = 15 (Nos 7, 30, 31, 33, 37, 38, 43, 45, 47, 52, 56, 57, 66, 77, 89)	Score 1 *n* = 10 (Nos 7, 31, 33, 37, 39, 45, 47, 52, 56, 43)	Score 1 *n* = 4 (Nos 37, 43, 39, 52)		
	Score 2 *n* = 2 (Nos 30, 66)	Score 2 *n* = 2 (Nos 7, 33)	Score 2 *n* = 2 (Nos 43, 52)	
	Score 3 *n* = 1 (No. 61)	Score 3 *n* = 2 (Nos 45, 57)	Score 3 *n* = 2 (Nos 7, 39)	Score 3 *n* = 2 (Nos 39, 52)
		Score 4 *n* = 1 (No. 56)		
Score 2 *n* = 10 (Nos 51, 59, 61, 63, 64, 38, 70, 76, 93, 72)	Score 2 *n* = 3 (Nos 63, 72, 76)	Score 2 *n* = 1 (No. 63)		
	Score 3 *n* = 2 (Nos 59, 64)	Score 3 *n* = 2 (Nos 64, 76)	Score 3 *n* = 1 (No. 63)	Score 3 *n* = 1 (No. 63)
	Score 4 *n* = 1 (No. 38)	Score 4 *n* = 1 (No. 38)		
Score 3 *n* = 5 (Nos 79, 87, 90, 91, 94)	Score 3 *n* = 2 (Nos 79, 87)	Score 3 *n* = 1 (No. 87)		

There were no at-risk subjects with a grade 4 cortical atrophy at the first visit.

Table 5. Summary of visual electrophysiology results—affected subjects.

	'Mean score'		
	VER	Saccadic eye movement	Pursuit eye movement
n	14	18	17
mean	2.0	2.1	2.4
SD	1.1	1.1	0.8
range	0.0 to 3.0	0.7 to 3.0	0.5 to 3.0

mean score = mean of scores assigned by 2 or 3 individual assessors working independently.
n = number of subjects.
mean = average value of 'mean score'.
SD = standard deviation of 'mean score'.

Table 6. Repeat visual electrophysiology studies on affected subjects. Mean scores for initial and subsequent studies are given for each individual test.

Age at first visit (years)	Time between visits (months)	'Mean score'		
		VER	Saccadic	Pursuit
39	18	1.3 3.0	0.0 3.0	Not tested 3.0
69	15	3.0 2.7	1.7 2.3	2.3 2.7
20	17	1.0 2.0	2.3 1.5	1.3 1.0

Table 7. Summary of visual electrophysiology results of first visit—at-risk subjects.

	'Mean score'		
	VER	Saccadic eye movement	Pursuit eye movement
n	37	42	40
mean	0.6	1.1	0.8
SD	0.9	0.8	0.7
range	0.0–3.0	0.0–3.0	0.0–3.0

mean score = mean of scores assigned by 2 or 3 individual assessors working independently.
n = number of subjects.
mean = average value of 'mean score'.
SD = standard deviation of 'mean score'.

Table 8. Profile of serial visits for visual electrophysiology of at-risk subjects.

No. of visits	0	1	2	3	4	5
No. of subjects	2*	13	10	12	4	4

*These two subjects did not have any electrophysiology tests.

the illness. However, some or all of the other 16 may become symptomatic at a later date. It has been found that, although the CT is specific for Huntington's chorea, the changes generally appear later in the illness than the changes in electrophysiology.

It is important to note that the diagnostic tests are recording only the state of affairs at the particular point in time at which they are carried out. One subject changed classification within 6 weeks of the tests, but another did not do so for a further 11 years, with the last CT study being carried out 5 years previously. However, if the subject who changed classification only 6 weeks after testing had presented a few years earlier, a very much longer time interval between the onset of an abnormal caudate nucleus and the appearance of symptoms may have been observed—see Table 9.

The remaining 40 at-risk subjects may never become symptomatic, although the inheritance pattern suggests that approximately half will. To the present, the mean time interval since the first visit is approximately 10 years, with a range of 2 to12 years.

In one of the 5 subjects who became symptomatic, neuropsychological examination revealed the presence of early sensory perceptual changes well in advance of the emergence of the movement disorder. However, 4 did not have abnormal neuropsychology and none of the remaining 40 persons has neuropsychological features indicative of Huntington's chorea.

In the clinically affected group, all cases had a positive CT scan and electrophysiology, so these tests are reliable or sensitive, but in the case of electrophysiology not specific for HC.

From Table 9, it can be seen that no CT study was carried out after 1984 in subject No. 7. If one had been, even at the time of the electrophysiology in 1988, it is quite possible that the result would have been abnormal prior to the onset of tremor. However, subject No. 64 did have CT at the time electrophysiology was abnormal and the CT was normal.

It may perhaps be inferred from this that the electrophysiology is the more sensitive investigation but subjects No. 38 and 39 each showed an abnormal CT scan 3½ years and 1½ years respectively prior to abnormal

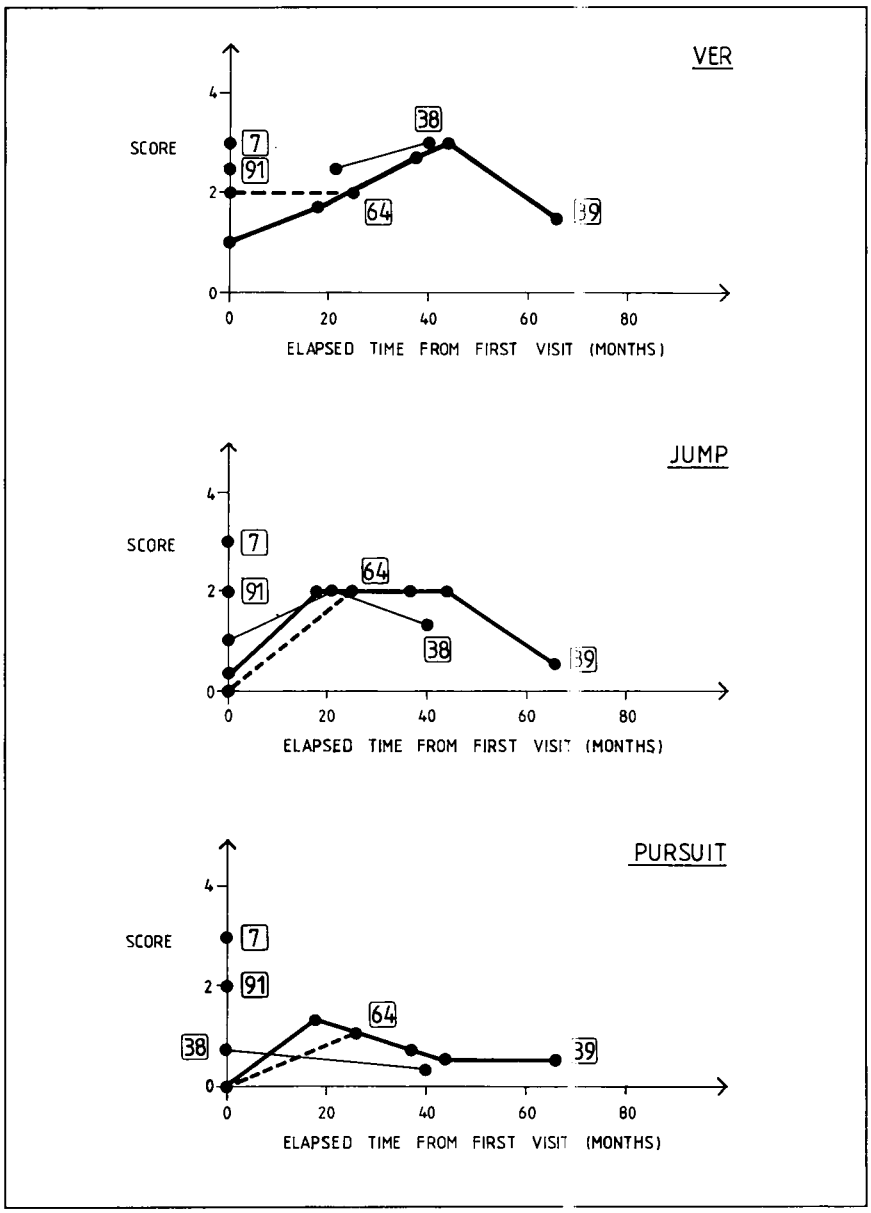


Figure 4. Changing scores in the visual electrophysiology for the 5 at-risk subjects who became clinically affected during the study.

Table 9. At-risk subjects who changed classification. Date of abnormal CT and electrophysiology related to date of onset of clinical symptoms and signs.

Subject No.	Abnormal CT scan	Abnormal visual electrophysiology	Date onset tremor	Time from first visit to symptoms
38	24.5.78	2.9.81	6.2.80	21 months
39	6.9.78	12.3.80	12.3.80	18 months
64	still normal 12.5.82	12.5.82	3.11.82	6 months
91	28.5.86	28.5.86	15.7.86	6 weeks
7	still normal 11.12.84	7.6.88	18.7.89	11 years

electrophysiology. Hence definite conclusions cannot be drawn as to one test being better than the other in detecting early changes.

In the 19 subjects with an abnormal electrophysiology result, the mean time between first visit and the present (1990) is 7.5 years, with a range of 4 to 12 years.

Generalized cortical atrophy excessive for the patient's age was observed in the at-risk group. It may be that this is a more sensitive indicator that a subject is going to develop HC than is caudate atrophy, but unfortunately it is not specific for HC. Rapidly progressing cortical atrophy would lead to suspicion that the subject was at high risk for development of HC, in the absence of any other factors such as a history of excessive alcohol ingestion, chronic bronchitis or hypertension.

It would thus seem that, in the 45 at-risk subjects studied longitudinally in this investigation, visual electrophysiology has been the most sensitive indicator for the early detection of HC, followed by the CT scan and then neuropsychology and, lastly, by clinical examination.

Summary

The aim of the study was to determine whether CT, visual electrophysiology and neuropsychological changes could assist with the detection of pre-clinical Huntington's chorea (HC). It was also hoped that the examination protocol would be of use in patients with early symptoms or signs of disease but with no family history of HC.

Twenty-three patients with HC and 45 subjects at 50% risk, were studied serially. Each visit normally entailed a CT study without intravenous contrast, visual evoked response and eye movements studies, as

well as a comprehensive psychiatric, neurological and neuropsychological assessment.

Over the 13 years of the study 5 persons, initially symptom free on clinical grounds, developed HC. Of these, 3 had had early atrophy of the caudate nucleus on the first visit and 4 had shown abnormalities in the visual electrophysiology before becoming symptomatic.

It is concluded that CT, visual electrophysiology and neuropsychological assessment may assist in the pre-clinical diagnosis of the at-risk HC subject and in the management of the early clinical case.

Acknowledgements

We would like to thank the Huntington's Disease Association of Western Australia for encouraging us to undertake this longitudinal study and also to thank Ms S. Priest for undertaking the original neuropsychological assessments between 1976 and 1981. Ms T. Liebeck, social worker, contributed to the coordination of the tests and made available her notes to the classification of the subjects. Drs A. Fisher, P. Thompson, W. Knezevic and A. Nencki examined the affected and at-risk subjects for evidence of physical signs of HC over the 13-year period. Dr G. Thickbroom, Mrs S. Kay and Ms T. McLaren provided invaluable technical assistance with the electrophysiological tests.

Finally, thanks go to the Board of Management of Sir Charles Gairdner Hospital for permitting the radiology and electrophysiology studies on a gratis basis.

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Mitomycin C Induces a Delayed and Prolonged Demyelination and Conduction Block due to Schwann Cell Destruction

K. Westland, J.D. Pollard* and A.J. Sumner†*

Schwann cell disorders have been proposed as the basis for inherited and acquired peripheral nerve demyelinating diseases. Experimental manipulations used to produce Schwann cell injury in adult animals have been limited by the coexistence of early myelin and axonal damage.

In this study we describe the sequential morphological and the electro-physiological features of a demyelinating neuropathy which results from the intraneural injection of the alkylating agent, mitomycin C. This compound produced conduction block and segmental demyelination while sparing axons, by causing delayed Schwann cell necrosis.

Methods

Intraneural injections

Mature Wistar rats of 350 to 400g weight were anaesthetized (2% halothane/O_2) and, under an operating microscope, each sciatic nerve was exposed by surgical incision between the sciatic notch and popliteal fossa. Intraneural injections of 12μL of mitomycin C in physiological saline were slowly made into the endoneurium of the

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posterior tibial branch of the sciatic nerve with a hand-held microsyringe fitted with a 30 gauge needle. The other sciatic nerve of each rat was similarly treated but received a saline injection only.

To determine the dose-response relationship, mitomycin C was injected into 6 pairs of rats at concentrations of either 3.12, 6.25, 12.5, 25, 50, or 100μg/mL in saline.

For detailed serial studies, a further set of rats was injected with that dose which produced the largest but still incomplete conduction block (25μg/mL), 25 animals being used for histology and 10 for the electrophysiological studies.

Electrophysiological techniques

Evoked response amplitudes and nerve conduction velocities were measured in both hind legs of all rats by stimulating proximal and distal to the injection sites and recording the compound muscle action potentials from the dorsal surface of the hind foot as has been described elsewhere.[1] During measurements, the leg temperature, as measured by an intramuscular thermocouple, was maintained at 37.0 $\pm$ 0.2°C with a heat lamp. Recordings were made during the entire course of the mitomycin C reponse (97 days) or up to the time of the animals' sacrifice for morphological studies.

The degree of conduction block was measured in terms of the reduction in the ratio of evoked muscle potential amplitudes produced by proximal stimulation (V_{hip}) compared to distal stimulation (V_{ankle}).[2]

Histological techniques

Twenty-five rats were used for this segment of the study. These were sacrificed with an overdose of intraperitoneal sodium pentobarbitone at 5, 8, 10, 12, 13, 16, 18, 20, 22, 23, 25, 30, 45 and 60 days after mitomycin C injection. Sciatic nerves were fixed in situ with 3.6% glutaraldehyde in 0.1 M phosphate buffer and were excised, dissected into 4 portions and fixed further in glutaraldehyde solution, followed by 2% osmium tetroxide. Specimens were dehydrated in graded concentrations of ethanol and propylene oxide, and embedded in epoxy resin. Transverse and longitudinal sections were examined which were taken at the site of injection, and at intervals of 1 and 2cm above and below the site of injection. Semi-thin sections, 1μm in thickness, were stained with methylene blue and examined by light microscopy. Ultrathin sections were mounted on copper mesh grids, double stained with lead and uranyl acetate and examined with a Philips 101 electron microscope.

Results

Electrophysiology

Dose–response study The 2 lowest concentrations of mitomycin C produced no significant electrophysiological abnormality. At concentra-

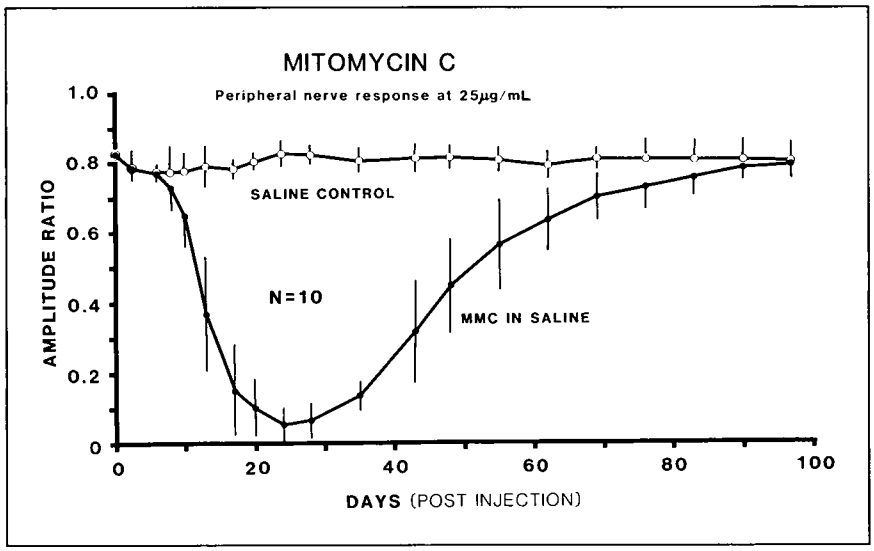

Figure 1. Serial responses of muscle action potential ratios following stimulation at sciatic notch compared to stimulation at the ankle. Lower trace, mitomycin C in appropriate vehicle; upper trace, vehicle only.

tions of 12.5μg/mL and above, a conduction block appeared after a delay of from 4 to 10 days. When mitomycin C was injected at a concentration of 50 or 100μg/mL, a decline in the proximal response began at day 4 and progressed until complete conduction block was apparent by day 11. The distal response began to fall at day 12, and continued to do so until day 41, reaching 10% of its initial value, a sign of extensive axonal degeneration. In the 2 animals given 25μg/mL, conduction block began at 6 days and was complete by 24 days. Unlike the response at higher doses, this occurred with no delayed drop in the distal amplitude for up to 61 days post-injection. Thereafter a progressive return of the proximal response was seen. This dosage was therefore chosen for the further detailed electrophysiological and histological studies which form the main body of this paper.

Detailed serial study Ten rats injected with the 25μg/mL dose were studied by serial electrophysiological measurement. Conduction block occurred in all animals after a delay of 6 days and reached a maximum at 24 days (Figure 1). The mean ± SD V_{hip}/V_{ankle} amplitude ratio fell from a pre-injection value of 0.83 ± 0.02 to 0.06 ± 0.06 by day 24. Thereafter, nerve conduction gradually increased, stabilizing at a near control level

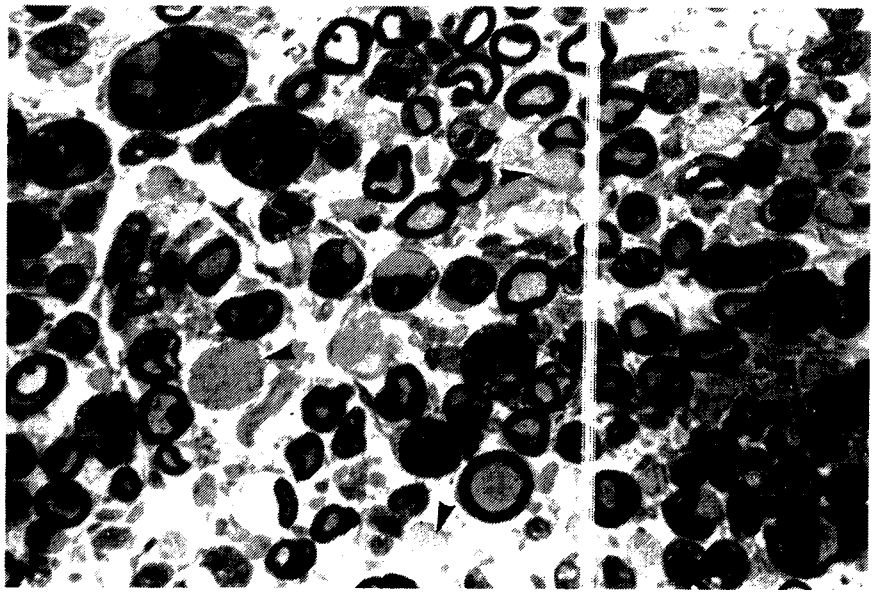

Figure 2. Mitomycin C at 22 days. An optical micrograph of a transverse section through the injection site. Many fibres are demyelinated and are devoid of any Schwann cell cytoplasm. Arrow heads point to several such axons.

after 97 days. Initally, the amplitude ratio of the control nerves followed the same time course as the experimental nerves up to day 6, but thereafter remained at a relatively stable level well above that of the experimental nerves.

Histology

Light microscopy The sites of the mitomycin C injections could be identified by the presence of focal areas of needle track artifacts but these were not different from those seen with the injection of saline into the other nerve at the same time. The first abnormality was apparent at 8 days, near the beginning of the conduction block; several Schwann cells showed swollen cytoplasm which appeared more basophilic than that of the surrounding Schwann cells. At 10 days, early paranodal demyelination was present. At 13 days the degree of demyelination was more extensive. In addition to paranodal demyelination, loss of myelin occurred along internodal segments. This process was more extensive with successive time intervals up to 25 days. By this time extensive demyelina-

tion was present (up to 75% of fibres in the transverse section at the site of injection). Schwann cells containing myelin debris surrounded demyelinated axons at 13 days. These cells were less apparent at 25 days when about 25% of axons in a given section appeared to be without Schwann cells, and foamy macrophages were more prominent in periaxonal positions.

Promyelinated and thinly remyelinated fibres, signs of early remyelination, were not seen in the region of injection until 35 days. In regions distal to the lesion, i.e. 1.5cm distal in the posterior tibial nerve, evidence of remyelination was seen as early as 20 days. Only occasional fibres in distal regions showed axonal degeneration.

Electron microscopy The earliest change seen, at 8 days, corresponding to the first observed drop in conduction, was a hyperplastic change present in about 25% of the Schwann cells examined. The cytoplasm of these cells appeared swollen. Polyribosomes, smooth-walled vesicles, mitochondria and Golgi apparatus were very prominent (Figure 3). At 10 days this change persisted in some cells, but in others the cytoplasm had become oedematous and in some, degenerative (as is illustated, though at later times, in Figures 4 and 5). Later, a prominent phenomenon was the accumulation of membranous whorls around sequestered cytoplasm. These whorls where occasionally continuous with the external mesaxon, but were invariably associated with oedematous or degenerative changes in the Schwann cells (Figures 4, 5a). In association with these degenerative changes in Schwann cells the early changes of demyelination were seen, viz. splitting of the intraperiod line and major dense lines resulting in prominent intramyelinic oedema and subsequent vesticular degeneration. These changes were noted at their early stage at both external myelin lamellae and adaxonally (Figure 5a). In longitudinal sections at this stage, nodal retraction of myelin was seen with simplification and atrophy of the nodal Schwann cell cytoplasm (Figure 6).

Changes within myelin membranes were apparent early, adjoining the nodal terminal loops of Schwann cell cytoplasm and at the Schmidt-Lanterman incisures. From studies of the longitudinal sections (Figure 6) and from serial transverse sections (Figure 4), it could be seen that other regions of the myelin and even Schwann cell cytoplasm along the internodal region might, at the early stage, be of normal appearance. Later, at 12, 15 and 20 days, a progressive vescicular disruption of myelin was seen throughout the entire internode, and the myelin was removed by macrophages which were present in abundance by the twelfth day.

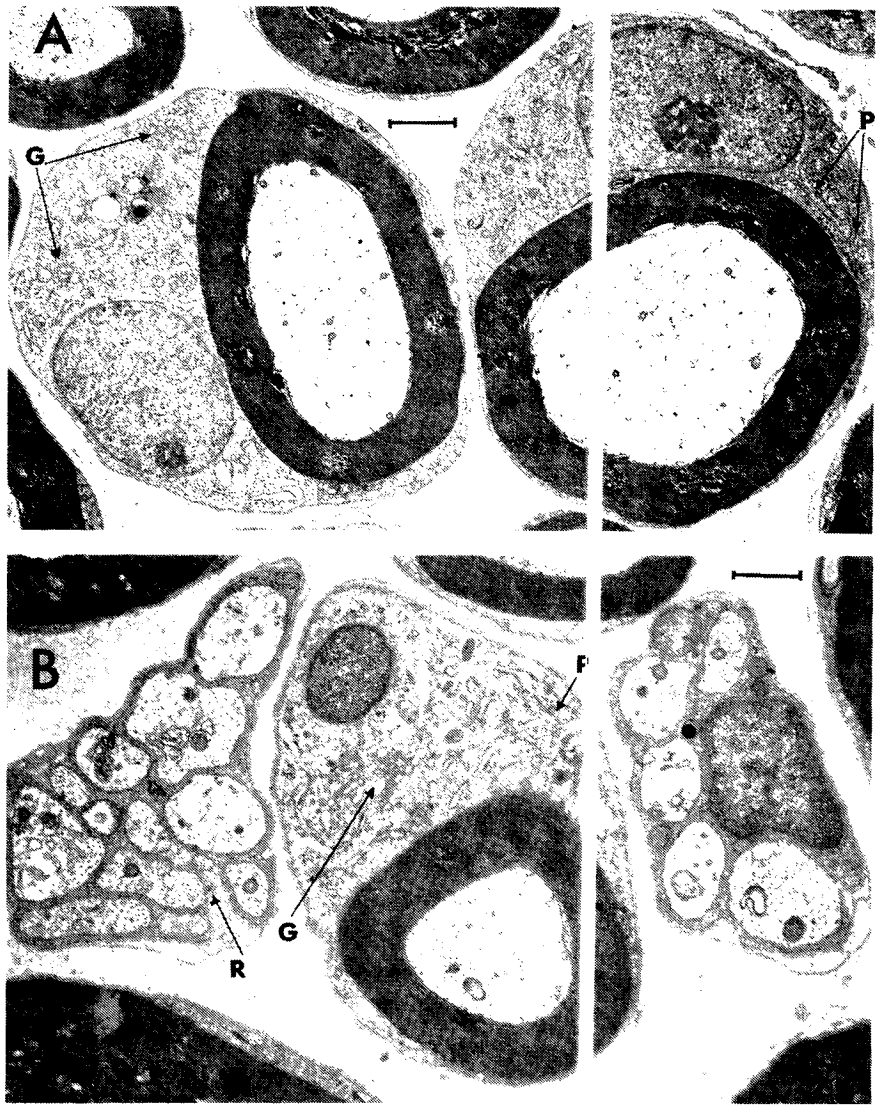

Figure 3. Mitomycin C at 8 days. Reactive changes within Schwann cell cytoplasm. Golgi apparatus (G) and polyribosomes (P) are prominent. There is minor retraction (R) of Schwann cell cytoplasm from around unmyelinated fibres.
(A) scale bar = 2μm (B) scale bar = 1μm

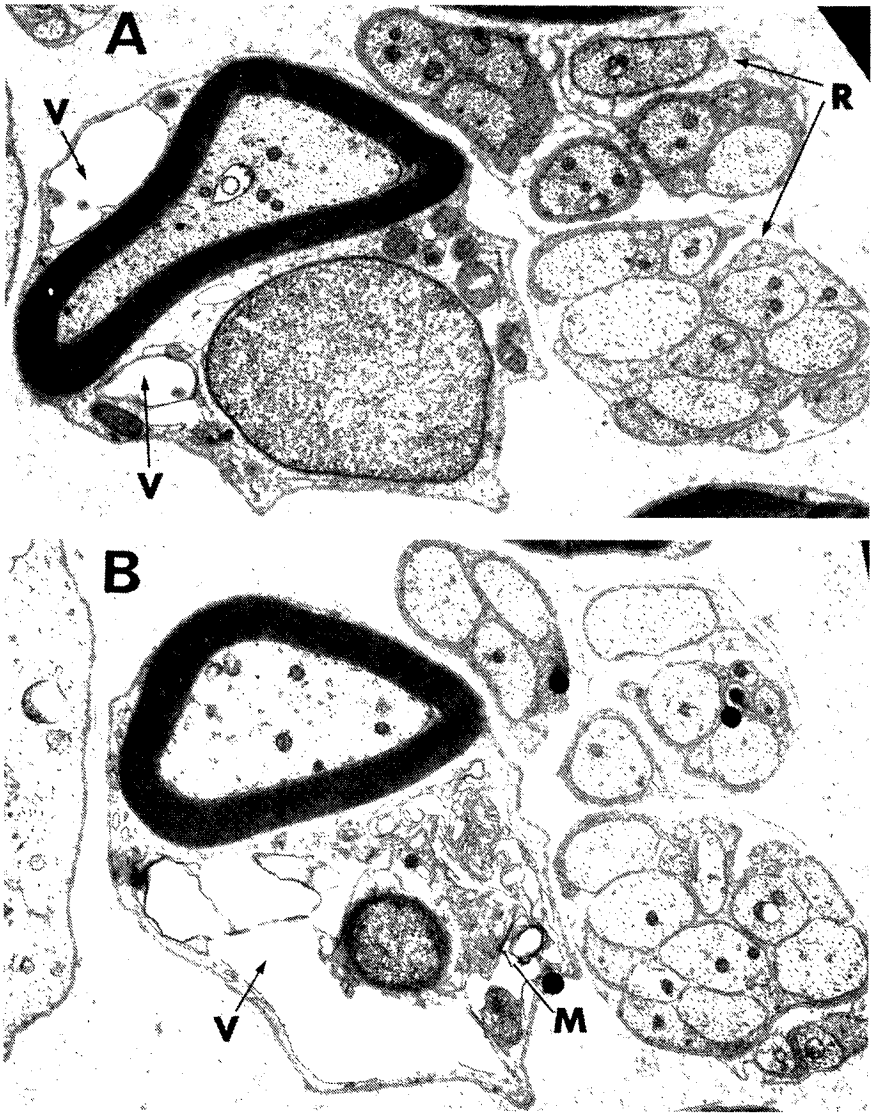

Figure 4. Mitomycin C at 12 days. Transverse section of the same myelinated fibre at 3 different levels.
(A) Two vesicles (V) within Schwann cell cytoplasm which otherwise is of normal appearance and supports normal myelin and axon. There is some retraction (R) of Schwann cell from around unmyelinated fibres.
(B) Vesicles (v) at this level are more prominent and membranous whorls (M) form from shrinking Schwann cell cytoplasm.

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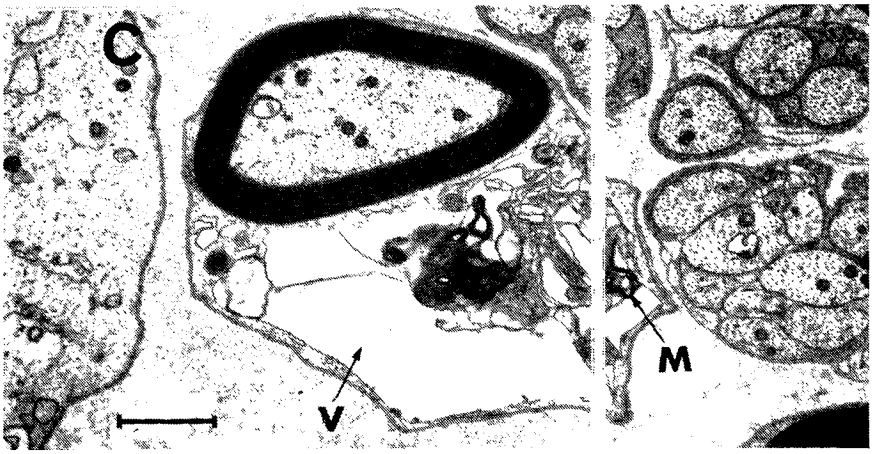

Figure 4. (continued)
(C) Prominent membranous whorls (M) associated with degenerate cytoplasm. The myelin and axon are apparently intact.
Scale bar = 1μm

A characteristic finding from 12 days onward was the presence of axons within the Schwann cell basal lamina, frequently convoluted, with no surrounding Schwann cytoplasm at all (as in Figure 7). Eventually these axons were often naked over considerable distances, i.e. more than one complete internodal region. This change was very prominent at 25 to 35 days, at which stage no reduplication of Schwann cells had occurred. Supernumerary Schwann cells were not seen throughout this entire period.

Schwann cells associated with unmyelinated axons were relatively unaffected but some retraction of Schwann cell cytoplasm from around C fibres was seen (Figures 4 and 5). Reduplication of Schwann cells and signs of remyelination were first evident at regions distant from the injection site bordering on zones of surviving Schwann cells, such zones being found closer to the injection site after approximately 40 days.

Discussion

The first use of mitomycin C in studies of peripheral nervous system demyelination was reported by Hall and Gregson[3] who, in a series of papers, examined the effects of the agent on nerve demyelinated by lysophosphatidyl choline (LPC). These workers noted the prolonged inhibition of division of Schwann cell affected by mitomycin, so that axons demyelinated by LPC remained demyelinated for at least one month after

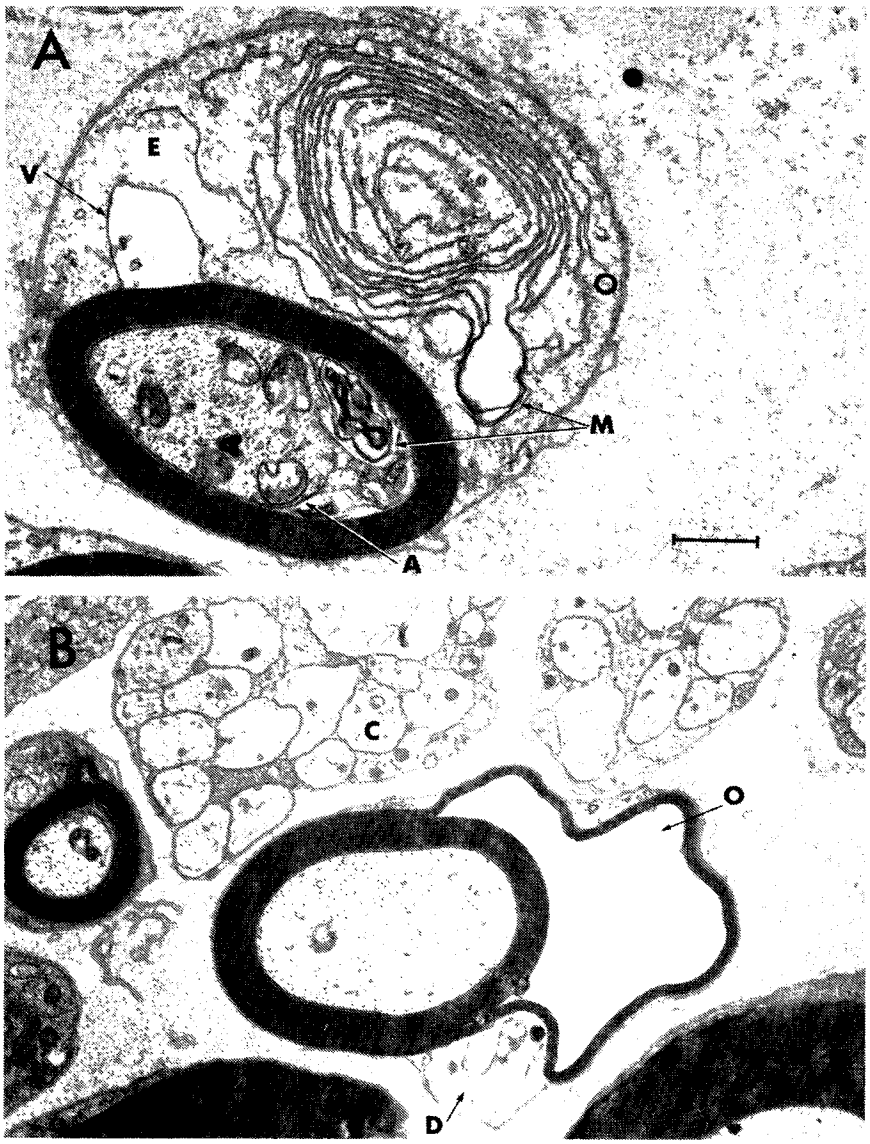

Figure 5. Mitomycin C at 15 days
(A) Membranous whorls (M) have formed within oedematous (O) degenerating Schwann cell cytoplasm, both external to the myelin layers and adaxonally. The axolemma (A) is intact. The beginning of myelin breakdown is seen as a vesicle (V) is formed by separation of the outer myelin lamella.
(B) Associated with degenerate Schwann cell cytoplasm, the intramyelinic oedema (O) has accumulated around an intact axon. Retraction of Schwann cell cytoplasm from around unmyelinated axons (C) has left many without Schwann cell ensheathment.
Scale bar = 1μm

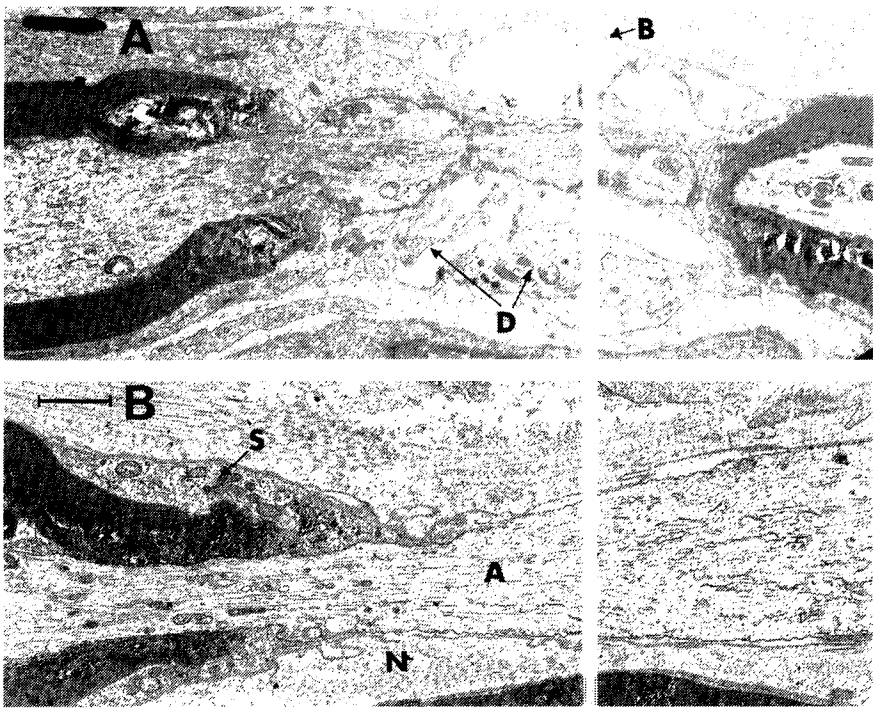

Figure 6. Mitomycin C
(A) 15 days. At the node of Ranvier, Schwann cell cytoplasm has retracted, shrunken from the basal lamina (B), and is clearly degenerate (D). The normally complicated system of villiform cytoplasmic projections is lost.
(B) 22 days. The Schwann cell (S) and associated myelin to the left of the node (N) are intact. The adjoining internodal segment has lost its Schwann cell and myelin.
Scale bar = 1μm

LPC injection. They did not, however, record the finding that mitomycin alone could produce a profound demyelination.

The demyelination in the present study, illustrated by electrophysiological and histological techniques, occurred as a consequence of Schwann cell damage. This was illustrated morphologically by:

(i) degenerative changes in Schwann cells prior to myelin breakdown;
(ii) early myelin breakdown seen only in association with degenerative Schwann cells; and
(iii) indubitable widespread Schwann cell death which resulted in long lengths of axons without any Schwann cell ensheathment, persisting over prolonged periods.

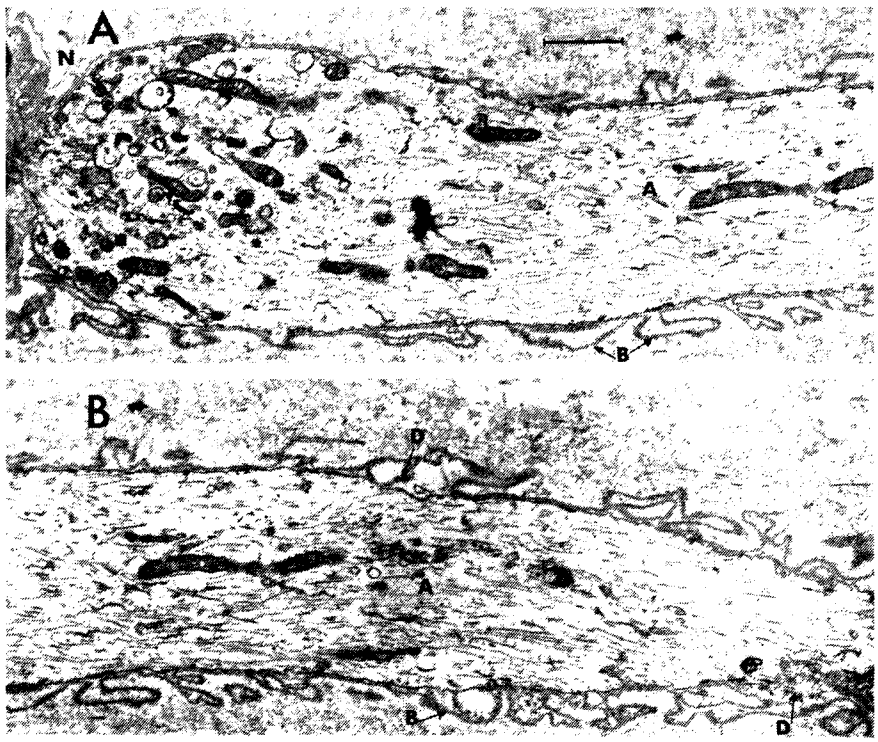

Figure 7. Mitomycin C at 22 days. (A) and (B) are 2 contiguous segments of the same axon (A), which lies within a folded Schwann cell basement membrane (B). Fragments of degenerate Schwann cell cytoplasm (D) can be seen within the basal lamina. Beyond the node (N) there is Schwann cell cytoplasm associated with the adjacent internode.
Scale bar = 2μm

The correlation between physiological and morphological findings was very close in this study. A drop in the response due to proximal stimulation was characteristically seen by 8 days after injection and it was at this time that reactive changes in Schwann cell cytoplasm were first noted. By 10 days post injection, with the conduction block less than one-quarter of that value finally attained, observable abnormalities in myelin were first detected. Thus, Schwann cell cytoplasmic abnormalities are associated with the onset of axonal conduction block, and these in turn herald observable myelin abnormalities. During maximum conduction block, demyelinated axons were prevalent in the body of the lesion. With the onset of remyelination and Schwann cell duplication at the edges of the lesion, nerve conduction began a recovery phase 24 days

after injection, with histological recovery and el ctrophysiological recovery highly correlated thereafter.

The delayed onset of peripheral nerve den yelination, so late after exposure to mitomycin C injection (6 days), is not yet explained. The action of mitomycin C in this setting is unlikely t) depend upon its effect as a mitotic inhibitor as Schwann cell division is not a prominent feature in normal peripheral nerve[4] and the introducti n into the nerve of an innocuous solution with a volume even as great a 50μl does not stimulate profound Schwann cell division.[5] Subsequent s udies of chemical substances related to mitomycin C have delineate a small group of compounds which produce similar results when inje ed intraneurally. These include mithramycin, doxorubicin, and actinomy in D. These compounds all share the property of affecting DNA-directe RNA synthesis.[6]

Various reports have ascribed peripheral ne vous system demyelination to primary Schwann cell damage. The so rces of damage include diphtheria toxin,[7] lead,[8] tellurium[9] and irradia on.[10] In each of these, except irradiation, proliferative and regenerat ve changes in Schwann cells occurred simultaneously with degenerativ changes so that frank necrosis of Schwann cells was not a dominant eature. Masurovsky and Bunge[11] noted that only in their report of the eff cts of irradiation *in vitro* was total degeneration of the myelin-related S hwann cell seen. Thus, irradiation *in vitro* and the present in-vivo stud are unique in that not only is Schwann cell death prominent, but rege eration of Schwann cells is inhibited over prolonged periods so that areas of axons quite devoid of Schwann cell ensheathment are obtained. This i triguing situation should allow further studies basic to an understandin of the relationship between Schwann cells and axons.

Hall and Gregson[12] noted in their study tha unmyelinated fibres and their Schwann cell ensheathment were relatively unaffected. Their finding was confirmed in the study here described. The mplication of the finding is that Schwann cells may be vulnerable by virtue of the metabolic processes associated with myelin maintenance and production. In this regard it is interesting that our findings of mem ranous whorls in degenerative Schwann cell cytoplasm are virtually ider tical to those reported by Breheny and Lampert[13] in tellurium neuropathy n rats. Tellurium is toxic to Schwann cells (when give orally) only durin the weanling stage, i.e. at a stage of active myelin production. The lifferential sensitivity of Schwann cells in this study is in contrast to he effects of irradiation reported by Masurovsky *et al.*[10] where the Schw nn cells of unmyelinated fibres were more radiosensitive than the myelin ating Schwann cells.

Clearly intraneural injection provides a m ans of probing Schwann

cell metabolic processes with any number of antimetabolites or other agents. Such studies should provide further information on myelin maintenance and production as well as on axon-Schwann cell relationships.

Summary

The intraneural injection of 25μg/ml of mitomycin C produced a prolonged conduction block of delayed onset within the injected nerve. No change in electrophysiological parameters was seen for 6 days after injection, but thereafter a marked drop in the compound muscle action potential (CMAP) amplitude from stimulation proximal to the site of injection occurred, with recovery not being complete until day 97. CMAP amplitude from stimulation distal to the injection site remained unchanged. The reason for this prolonged period of conduction block was apparent from histological examination of the nerve. Light and electron microscope studies demonstrated Schwann cell death, clearly evident at day 8 and followed by subsequent macrophage removal of myelin and Schwann cell debris. Remyelination was not seen until day 40. Hence for periods of about 30 days naked axons persisted through the area of injection. Schwann cells associated with unmyelinated fibres were relatively unaffected, suggesting that myelinating Schwann cells were vulnerable to this agent by virtue of the metabolic processes associated with their myelin maintenance and renewal.

These findings indicate that mitomycin C injected intraneurally provides an excellent model to study the effects of Schwann cell disease.

Acknowledgements

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Pleuropulmonary Fibrosis due to Bromocriptine Treatment for Parkinson's Disease

D.H. Todman, W.A. Oliver† and R.L Edwards‡*

Bromocriptine is an ergot derivative which has been used in the mangement of Parkinson's disease since 1974. It is a dopamine agonist, usually administered in combination therapy with levodopa. Many of the side effects of bromocriptine are dose related and may be managed by appropriate dosage adjustments. There have been occasional reports of pleuropulmonary fibrosis as a complication of bromocriptine treatment[1–4]. Although this is an uncommon reaction, it represents potentially the most serious adverse effect of the drug. This report describes 2 patients who developed pleuropulmonary changes while taking bromocriptine.

Case Reports

Case 1

A 58-year-old man first developed symptoms of Parkinson's disease in 1984. Bilateral hand tremor was the main feature, and initial treatment was with biperiden.

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In 1987, treatment with levopdopa-benserazide was substituted because of progression of the disease, with limb rigidity. Bromocriptine was added with dosage increments up to a total dose of 30mg per day, with a good therapeutic response.

In 1988, 12 months after commencing bromocriptine the patient presented with the gradual onset of exertional dyspnoea and chest heaviness. There was an occasional cough but no sputum or wheeze. Although there was mild dysphagia for dry food, there were no features to suggest aspiration pneumonia. The chest examination revealed showers of coarse crackles in both lung bases, while the chest X-ray showed a bilateral pulmonary infiltrate with pleural plaques. A barium swallow was normal, with no evidence of aspiration.

Bromocriptine therapy was ceased. The dyspnoea improved and the pulmonary crackles resolved in one week. Improvement was evident on X-ray at one month.

Case 2

A 79-year-old man was first diagnosed as having Parkinson's disease in 1979. The main symptoms were limb tremor and rigidity. He was treated with anticholinergic medications until 1986 when levodopa–benserazide treatment was commenced. Bromocriptine in a dose of 15mg per day was added in 1987, because of fluctuations in response to levodopa. In 1988, 5 months after commencing bromocriptine intake, the patient presented with progressive dyspnoea and a dry cough. Chest examination disclosed coarse crackles at both lung bases while a chest X-ray showed a bilateral pulmonary infiltrate with pleural thickening.

The chest symptoms were initially attributed to pneumonia, but there was no response to courses of antibiotics. Bronchoscopy showed clear air passages and a transbronchial lung biopsy was performed. The histology revealed mild interstitial fibrosis. Bromocriptine therapy was then ceased and prompt improvement occurred over approximately 3 weeks.

Discussion

This report describes 2 patients with Parkinson's disease treated with bromocriptine who developed progressive dyspnoea and radiological evidence of pulmonary fibrosis. Histological confirmation was available from a lung biopsy in Case 2. In each case bromocriptine was administered in combination with levodopa-benserazide. There is strong evidence in both cases that bromocriptine was the cause. Investigations did not disclose any other cause for the disorder and clinical and radiological improvement followed promptly on cessation of bromocriptine intake. Both patients have since been maintained on levodopa–benserazide therapy alone and have been free of pulmonary symptoms over a 2-year follow-up period. The chest X-ray in these cases showed a pleural reaction

in addition to pulmonary changes. This consisted of scattered pleural plaques in Case 1, and basal pleural thickening in Case 2. Progress chest X-rays showed resolution of these changes following withdrawal of bromocriptine.

There have been occasional literature reports of pleuropulmonary fibrosis due to bromocriptine since 1981.[1–4] It is an infrequently observed adverse effect, and a causal relationship has been questioned.[5] There has also been a single report of retroperitoneal fibrosis as a complication of bromocriptine treatment.[6]

In all reported cases, this advese effect has been reversible on cessation of bromocriptine intake. However, serious morbidity may result if this side effect is not recognized early.

The frequency of this reaction is uncertain. The only survey published was by Rinne,[7] who found 7 affected patients out of 123 receiving long-term treatment with bromocriptine. These patients were taking bromocriptine in doses of 20 to 90mg per day. Other reports have suggested that the reaction is more likely to occur on higher doses. However, Case 2 demonstrates that the reaction may be evident with doses as low as 15mg per day.

The mechanism of this effect is unknown. Bromocriptine is an ergot derivative with a similarity in molecular structure to methysergide[8]. In the case of methysergide, retroperitoneal and pleural fibrosis may be mediated by the systemic release of serotonin. Fibrotic complications also occur in the carcinoid syndrome, in which there are high levels of circulating serotonin. Bromocriptine has an effect at serotonergic synapses with a weak agonist action,[9] and this may be relevant in relation to pulmonary fibrosis associated with the drug.

There appears to be a case for the monitoring of pulmonary symptoms in patients receiving long-term bromocriptine treatment. The possibility of drug-related pulmonary fibrosis should be considered whenever such patients present with pulmonary problems.

Summary

Pleuroplumonary fibrosis is an uncommon but potentially serious adverse effect of bromocriptine used in the treatment of Parkinson's disease. Two cases of this reaction, which occurred 12 months and 5 months respectively after commencing therapy are here reported. In both instances prompt clinical and radiological improvement occurred when bromocriptine intake was ceased.

Fibrotic reactions to bromocriptine may be mediated by a serotonergic mechanism. Periodic monitoring of pulmonary symptoms is warranted in patients receiving bromocriptine treatment for Parkinson's disease.

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Commencement of a Paediatric EEG-video Telemetry Service

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This report concerns the establishment of a EEG-video telemetry service within the Department of Child Neurology at Prince of Wales Children's Hospital, Sydney. The following account covers the first 18 months of operation, until the end of March 1990.

Telemetry has been in widespread use in adult neurology for some time. Reports in journals began appearing in the late 1970s, giving the results of telemetry in large numbers of adults. Its use in paediatrics has taken a little longer to become widespread.

In what follows we discuss some of the problems more peculiar to paediatrics, and the characteristics of the population referred for telemetry.

Methods

Our practice is to record 24 channels of EEG, along with a video of the patient using a closed-circuit video camera. The system used is the 24-channel La Mont Video-Telemetry Unit, from Medical Systems International. Scalp electrodes only are used, secured to the scalp with collodion gel. The EEG leads are then connected to the pre-amplifier, which is either mounted on the head or in a special pocket on the T-shirt worn by the patient. The leads, the child's head and, if head mounted, the pre-amplifier, are firmly wrapped in bandages. This prevents little fingers prying leads loose and also cuts down on movement artifact.

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Many children intensely dislike sitting still and having the electrodes applied. The use of a hairdryer has halved the electrode application time. Another particular dislike of the children is the solvent used to remove the electrodes. The addition of vanilla has vastly cut down the tears and struggles after the recording.

Parents are used as observers, which has both advantages and disadvantages. The parents are usually in the best position to recognize the events for which the child is being monitored. However, in an article reviewing intensive neurodiagnostic monitoring, Gumnit[2] recommended the constant presence of specially trained technologists, saying that, without this, important data may be missed. At the moment our service cannot support this level of staffing. We find that the parents do a good job, especially if informed of their responsibilies. This includes staying up all night for day-night studies, and keeping the child entertained. To this end, we ask the parents to bring along the child's favourite activities and toys. The parents mark the time of any event, both on the video with an event marker and also on paper as a backup. The video and the paper printout of the EEG are then analysed for this event, and the inter-ictal EEG is also looked at. The telemetry unit we use has the facility of printing out the EEG in a variety of montages, and we select the montage to suit our purpose.

Results and discussion

Over the first 18 months of the service, telemetry was performed on 82 patients, 42 males and 40 females. Their ages ranged from 2 months to 16 years, with a median age of 6 years. This indicates a slight bias towards younger patients. The length of the studies varied. Forty-two were day-time studies only. The shortest of these was 3 hours in duration but the children usually remained monitored for 6 to 8 hours. Thirty-seven studies were both day and night studies, usually lasting 24 hours although several were for longer periods. Three studies were night-time studies only.

Reasons for referral

The reasons for referral, or indications for telemetry, are the same in both adults and children, although there are differences in emphasis. These differences reflect the different epileptic syndromes, associated neurological conditions and treatment strategies in the two age groups.[3]

The commonest indication, in 76% of patients, was to decide whether an event was ictal or not. The problems obscuring diagnosis in children are varied. The parent's description may be confusing or inaccurate. The younger child, and especially the infant, can indulge in activities that look decidedly strange, such as repetitive movements or staring. The younger child cannot describe how he or she is feeling at such times, and testing for consciousness can be difficult. The standard EEG represents only 30

minutes of random activity, and it is usually interictal. The paediatric age group is particularly prone to show normal or nonspecific EEG findings that can be misinterpreted as supporting a diagnosis of epilepsy. As with all age groups, the determination that a child does not have epilepsy is as important as a positive diagnosis of epilepsy.[2]

A second indication, which applied in 4 children, was to localize the seizure onset in the EEG. This is becoming more important, as imaging techniques become more precise and surgical expertise more readily available. Of course, to make the final decision regarding surgical treatment of epilepsy, it may be necessary to record a number of seizures using depth eletrodes.[4] However, surface recordings are part of the early work-up.

Two children underwent telemetry to ascertain the exact frequency of seizures. This is especially helpful for nocturnal or clinically inapparent events.

One child had telemetry purely to classify her seizures, although a further 8 children needed to have both seizure classification and frequency determined, and another 2 required classification plus EEG localization of seizure onset.

Of the remaining 3 children, 2 were thought to be having pseudoseizures in addition to their recognized epilepsy, and a third had strong clinical and EEG evidence of absence epilepsy, but no response to treatment.

Referral symptom

We asked for a parental description of the event for which the patient was referred, and used that together with the referring doctor's comments to classify the referral symptom.

Thirty-five patients underwent telemetry because of unusual motor activity of episodic nature. Nine patients had isolated episodes of staring, although a further 13 had a stare plus accompanying unusual motor activity, and 5 had a stare accompanied by a change in behaviour. Six children had episodes of altered behaviour, seemingly unexplained by their surroundings. Two children had telemetry because of distressing visceral sensations, 2 because of episodic depression of level of consciousness, and 4 because of apnoea.

Other events that were referred included a fall off in school performance and previous seizures, although no clinically apparent seizures were occurring. Another had weird laughter for no apparent reason; there were episodes of screaming with food intake.

Events noted

Of the 82 patients who underwent telemetry, events were noted in 66. This is a positive finding rate of 80%. Of the 66 positive studies, 23 events (35%) were ictal.

Seizure classification

The seizures were classified according to the International League Against Epilepsy (ILAE) revised classification of epileptic seizures. Five children had complex partial seizures, 4 generalized tonic seizures, 4 generalized myoclonic seizures, 2 generalized absence seizures, 2 generalized atypical absence seizures, and 1 had generalized atonic seizures. A further 4 children had different combinations. Two had a combination of absence, atonic and myoclonic seizures; 1 had absence and pseudoseizures and 1 had myoclonic seizures and strange behaviours. One child had gelastic seizures.

Other events

The remaining 43 patients, who had non-ictal events recorded, involved a wide array of diagnoses. A few children had strange habit tics, and others merely the normal jerks of sleep. Pertussis was diagnosed in a 14-year-old girl who woke her parents at night with choking. There was a pallid syncopal attack, complete with anoxic jerks of the limbs. Extrapyramidal movements were recorded in a preterm neonate. Some of the children referred because of staring were simply ignoring their mother. A case of night-time bruxism was diagnosed and also a case of Munchausen syndrome was recognized by proxy. There was a case of shudders, as described by Holmes and Russman.[5] Finally, several of the abrupt changes in mood proved to be purely bad behaviour.

Overall assessment

Telemetry was judged to have influenced management of the patient in 76% of cases. From the experience of the first 18 months of using the procedure, we have established 3 criteria for performing telemetry on

children. The first is that the event in question does not fall into a readily recognizable diagnostic category. The second is that the child has at least 1 event per day, 7 days out of 7. The third is that the child has a willing parent able to accompany him or her throughout the procedure, althougth this last criterion may change in the future if additional staffing becomes available.

Summary

The diagonosis of epilepsy is sometimes difficult in childhood. The events witnessed in children may be atypical and the interictal electroencephalogram (EEG) may be normal or contain non-specific abnormalities. The problems may be overcome by recording events on video-EEG telemetry. Over the first 18 months of this service, 82 patients were monitored—42 males and 40 females. Forty-two were daytime studies, 37 day and night, and 3 night only. Surface electrodes only were used.

The system used was the 24-channel la Mont Video-telemetry unit from Medical Systems International. Parents served as observers. Events and a sample of interictal data were analysed.

The commonest reason for referral was to determine whether an event was ictal. Other reasons included seizure frequency, classification or localization of onset. Presenting events were unusual motor activity, staring, change of behaviour, distressing visceral sensations, combinations of the above and miscellaneous phenomena. Events occurred during the recording in 66 of 82 subjects. Of these, 23 were judged to be ictal. These were complex partial seizures, absence seizures, myoclonic jerks, generalized tonic seizures, gelastic seizures and mixed seizure disorders. The non-ictal events were commonly habit tics or normal sleep phenomena, although pertussis, pallid syncopal attacks and extrapyramidal movements occurred. In 76% of cases the management of the child's condition was influenced by the telemetric study.

Acknowledgement

Louise Healy, Clinical Nurse Consultant in the Department of Neurophysiology at the Royal Prince Alfred Hospital, Sydney, is thanked for the expert advice and suggestion about modifying the procedures used to make them more suitable for children.

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P_{300} Event-related Potentials in *de novo* Parkinson's Disease

J.S. Graham, C. Yiannikas,* E. Gordon,† S. Coyle† and J.G.L. Morris**

Idiopathic Parkinson's disease (PD) was originally described by James Parkinson in 1817 as a motor system disorder, 'the senses and intellect being uninjured'. Recent studies, reporting subtle cognitive deficits in many non-demented PD patients as well as moderate to severe dementia in a sizeable proportion of PD patients (review: Growdon and Gorkin[1]) challenge this definition. Perceptual motor impairments (difficulties discriminating stimuli and selecting, initiating and executing a response) are amongst the most frequently reported cognitive deficits in PD.

Long latency event-related potentials (ERPs), which index the nature and timing of a cognitive response to a stimulus,[2] are one approach to assessing cognitive dysfunction in PD. In particular the P_{300} component of the EPR, thought to be associated with stimulus evaluation and stimulus categorization,[3] may reflect abnormalities in perceptual motor performance.

Long latency ERPs have been recorded previously in PD patients but all subjects studied to date have been medicated. Anti-PD medication may itself affect cognition so there is a need to assess ERPs in *de novo* patients. In addition, the paradigm used in most previous studies (silent

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count of target stimuli) allows the average ERP to include responses to incorrectly identified targets. A button-press response overcomes this problem.

In this study we recorded the P_{300} using a standard auditory oddball paradigm with a button-press response in a group of *de novo* PD patients.

Methods

Subjects

Fifteen *de novo* PD patients (12 male, 3 female; aged 37 to 77 years, median 59 years) were recruited over a 6-month period. All had stage I to stage III disease[4] and had been diagnosed for 2½ years or less. Patients had no clinical or laboratory indication of any other significant medical disorder and no patients were taking neuroleptics. Patients were compared to 100 control subjects (44 male, 56 female; aged 17 to 92 years) recruited from the community and from workers at a large general hospital.

Stimulus

ERPs were elicited using an auditory oddball paradigm. Subjects were presented with binaural tones (80dB SPL for each ear, 50msec duration, 5msec rise-fall time) through headphones at a rate of 0.8Hz. Of the tones, 90% were background (1kHz) and 10% were target tones (2kHz). Approximately 300 tones were presented in random sequence, with the constraint that no 2 target tones were presented sequentially. After confirming that subjects could differentiate clearly between the targets and background tones, subjects were instructed to ignore the background tones and press 2 reaction time buttons 'as quickly as possible' in response to the target tones (simple reaction time task). Subjects used the middle finger of each hand and the faster time was recorded as the reaction time for each trial.

Recording

ERPs were recorded using Ag/AgCl electrodes at Fz, Cz and Pz referenced to linked earlobes (impedance less than 3kohms). Responses were recorded at 50 000x gain (bandpass: 0.05 to 100Hz) and sampled at 1000 points per second for 100msec prestimulus and 700msec postsimulus. Responses were computer averaged on-line and digitally filtered using a non-recursive 30Hz low-pass filter.

The EOG was recorded between electrodes placed 1cm above and below the outer canthus of the right and left eyes, respectively. Trials in which the EOG potential exceeded 75% of the input voltage range (±5V) were autorejected. In each

recording session 2 consecutive averages of the first 15 artefact-free trails were obtained to ensure reproducibility. These were later collapsed to produce an average of 30 responses to target tones.

Analysis

The latency of the P_{300} component was determined by computer as the most positive point between 250 and 650msec. Visual inspection of the data confirmed that the latencies were similar across sites and that EOG and other artefact had been appropriately autorejected. The amplitude of the P_{300} was measured from the prestimulus baseline (average voltage of 100msec prior to the stimulus onset) to peak. The P_{300} latency and amplitude of individual patients were tested against age normograms (mean ±2.5SD) constructed from the data of the control subjects. The P_{300} latency and amplitude of the PD group were compared with those of a group of 60 controls aged 37 to 77 years (median 61 years) using a Mann-Whitney U test.

Results

ERPs were recorded in 15 PD patients. One record was excluded due to eye movement artefact; the data for the remaining 14 patients were analysed.

A P_{300} was absent in 2 patients (P7 and P14 of Figure 2). In all other patients the amplitude of the P_{300} was within normal limits (mean ±2.5SD) at all sites (Fz, Cz, Pz) (Figure 1A). The P_{300} latency was prolonged in 2 patients, at all sites in one patient and at Pz in the other (Figure 1B). There was no difference in the P_{300} amplitude or latency of the Parkinsonian group compared with the age-matched control group at any site (Table 1).

We compared the 14 PD patients with 14 randomly selected controls, age-matched to within 2 years of their Parknsonian counterparts. Patients were grouped according to their age at disease onset (<60 years and ≥60 years) and their respective controls were grouped as under of over 60 year of age. The grand average ERP waveform for each group was calculated (Figure 2). The P_{300} component at Pz was dispersed or absent in 7PD patients, 5 of whom were under the age of 60 years. By contrast, the P_{300} component was dispersed in only 1 control under the age of 60 years. This was reflected in the averaged waveforms. The averaged P_{300} component for the young PD group was dispersed compared with that of the young controls. The averaged P_{300} component for the older patients and the older controls (≥60) were comparable.

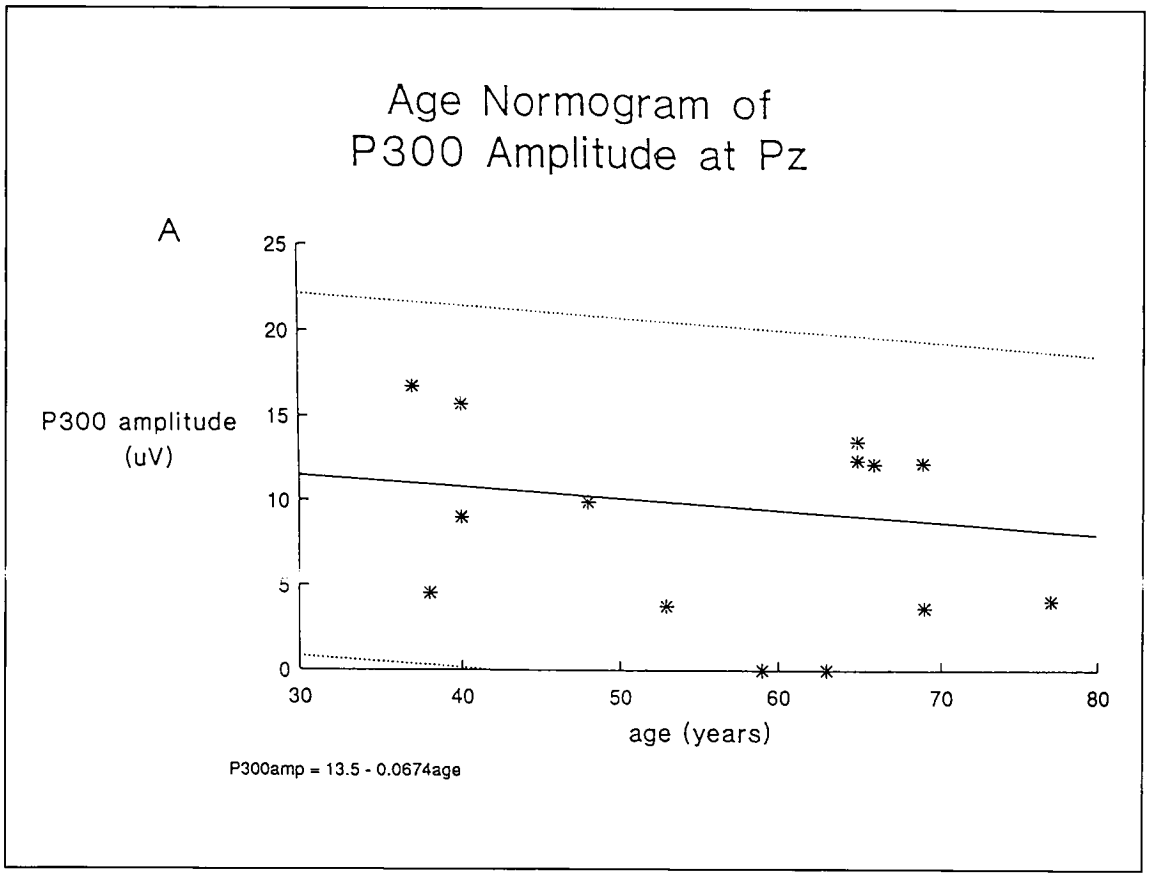
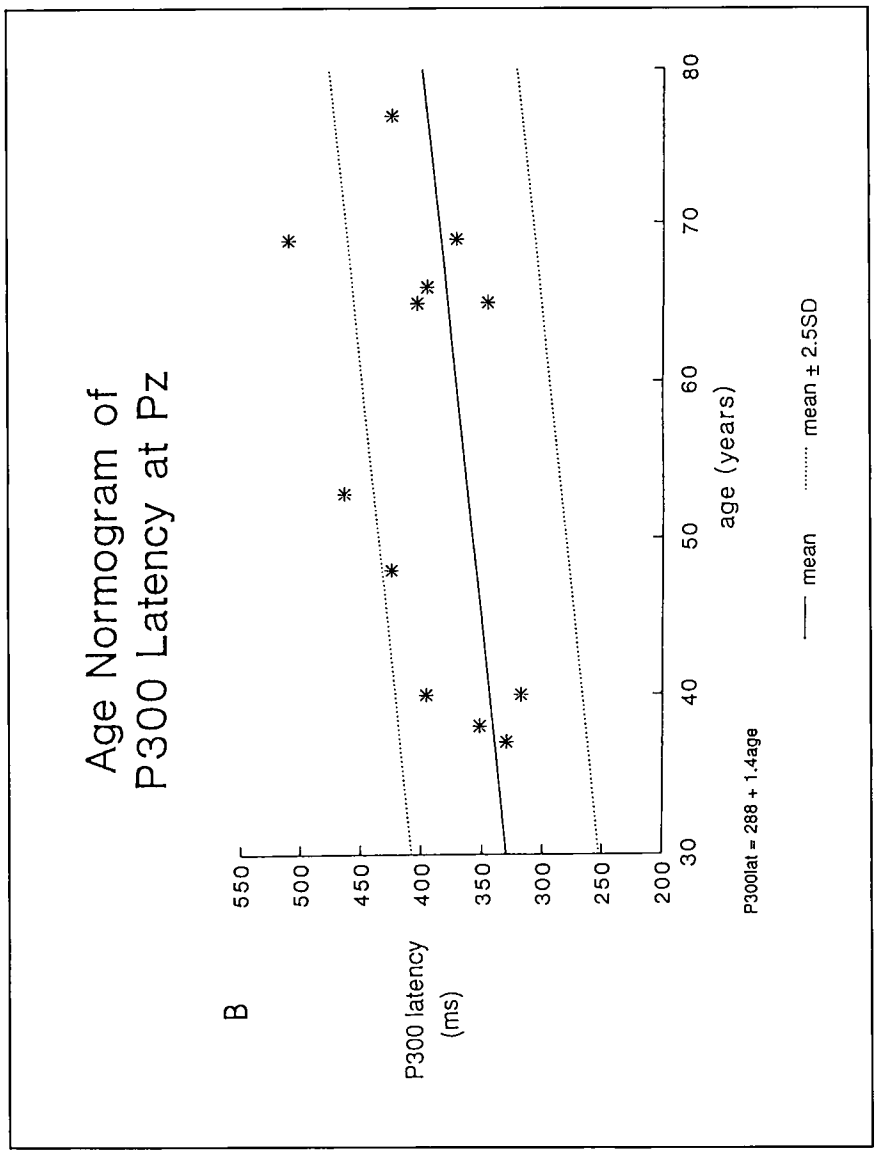


Figure 1.
Regression lines and 98.8% (±2.5SD) confidence limits for P_{300} amplitude (A) and latency (B) vs age, constructed from 100 control subjects. The amplitude and latency of P_{300} in individual PD patients is shown (*). The P_{300} was absent in 2 patients; in all others the amplitude of the P_{300} was within normal limits. In 2 patients the latency of the P_{300} was prolonged.


Age Normogram of
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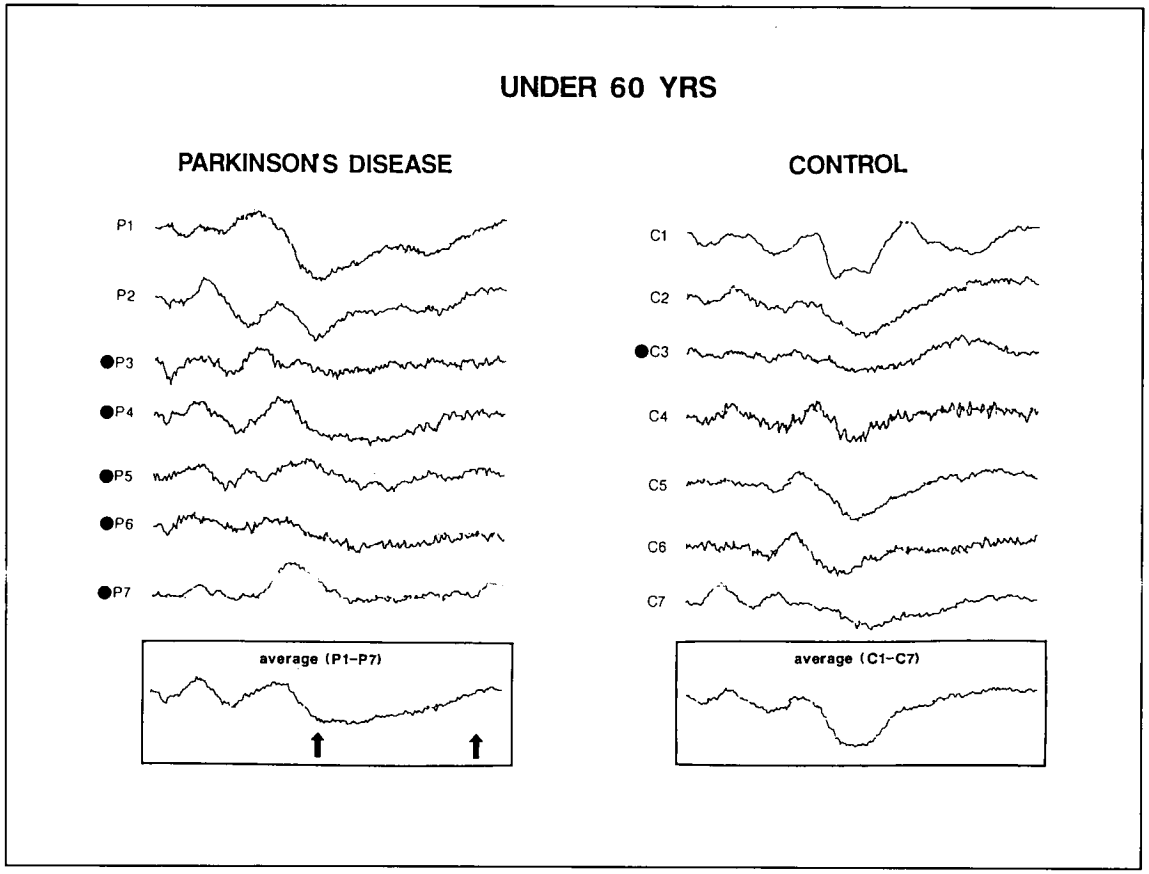

Figure 2.
P_{300} at Pz in early (<60 years) and late (≥60 years) onset PD patients (P1–P7, P8–P14) compared with age-matched control groups (C1–C7, C8–C14). The grand average for each group is shown below the waveforms for the individual subjects. The P_{300} was dispersed in 5 of the 7 early onset PD patients and in only 1 of the younger control group. The averaged P_{300} waveform of the older onset PD groups was comparable to that of the older control group.

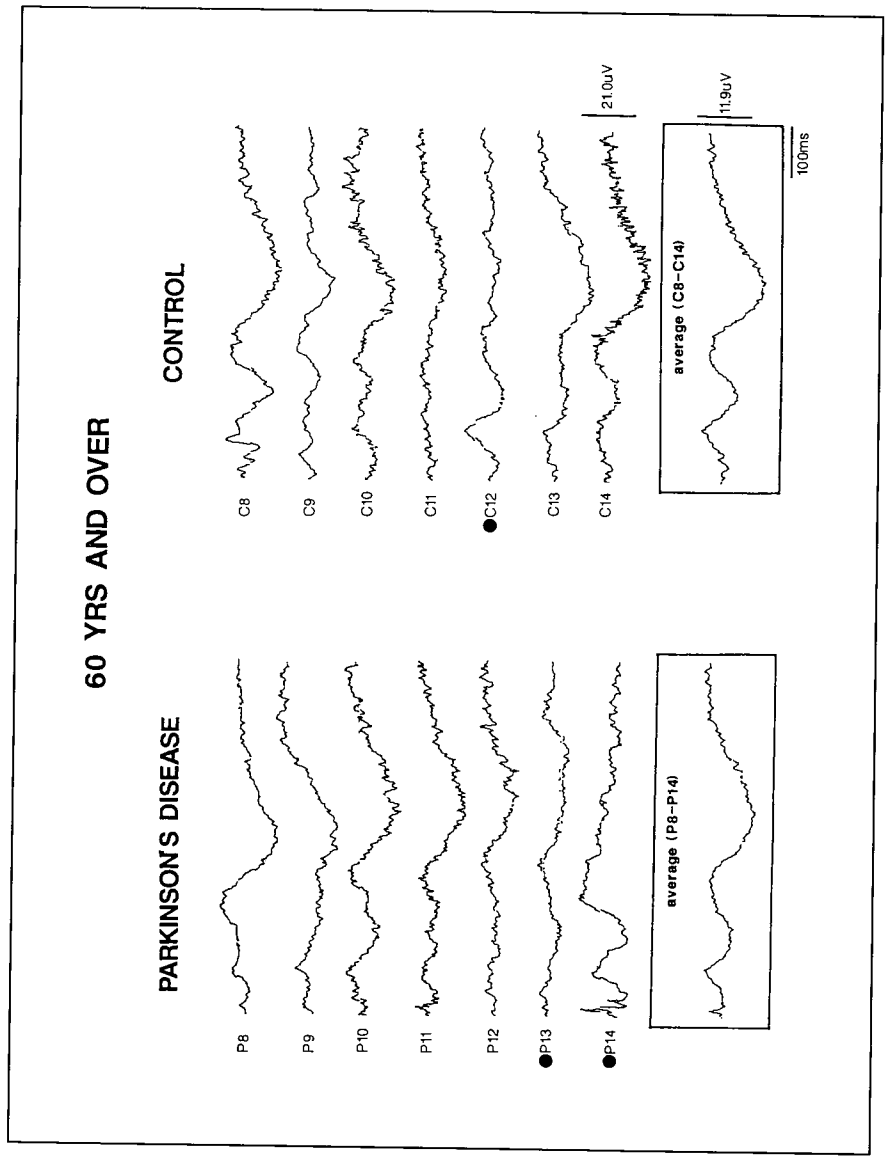
60 YRS AND OVER
PARKINSON'S DISEASE
CONTROL
P8
P9
P10
P11
P12
P13
P14
C8
C9
C10
C11
C12
C13
C14
average (P8–P14)
average (C8–C14)
21.0uV
11.9uV
100ms

Table 1. Comparison of 14 PD patients (aged 37 to 77 years, median age 59 years) with 60 control subjects (aged 37 to 77 years, median age 61 years) using the Mann Whitney U test. There was no group difference between the PD and control groups in the amplitude or latency of P_{300} at any site (Fz, Cz, Pz).

	Pakinson's Disease Median value	Control Median value	Significance of Mann-Whitney statistic
Age	59.00	61.00	0.6788
P_{300} amplitude			
Fz	5.585	6.895	0.1930
Cz	7.360	7.580	0.6488
Pz	9.450	9.590	0.5704
P_{300} latency			
Fz	368.5	355.0	0.3816
Cz	375.0	358.0	0.4005
Pz	396.0	364.0	0.1122

Discussion

The incidences of P_{300} amplitude and latency abnormalities in individual PD patients were low and there were no group differences in the amplitude or latency of the P_{300} in the PD and control groups. These findings suggest that the amplitude and latency of P_{300} elicited using the paradigm of this study are not sensitive indices for differentiating PD patients from controls. It may be that a silent count of targets (used by others) or a simple reaction time task does not place a sufficient load on the specific cognitive deficits in PD.

It is known that the execution of simultaneous or sequential motor actions requiring decision making and motor planning is impaired in PD. Therefore future investigations will include an assessment of other long-latency ERP components, in particular the N_{200}, which is thought to be associated with response selection and execution. Reaction time (RT) and the relationship between N_{200}, P_{300} and PT and PD will also be examined. A choice reaction time task will be incorporated in the auditory oddball paradigm; such a task should place a greater load on the specific cognitive deficits in PD and may, therefore, be more sensitive in differentiating PD from control subjects.

The P_{300} was broad and dispersed in a large proportion of the early onset PD patients and, as a result, the averaged P_{300} waveform in this group was markedly dispersed relative to that of the young control group. The averaged P_{300} waveform of the late onset PD group was comparable to that of the older control group. Our findings are consistent with neuropsychological data.[5] Although more significant cognitive impairment

is found in the later onset group, selected cognitive tests show greater differences between the early onset PD group and their age-matched controls than between the late PD onset group and their controls.

The precise relationship of the P_{300} to specific congnitive processes is still unclear. However, the observation that P_{300} morphology is differentially affected in the early onset PD group may be support for the suggestion of distinct subgroups in PD. Another explanation for our findings may be that because the variability in the P_{300} increases in all subjects with age, group differences in the older population are less marked than those in the younger population.

The apparent difference in the P_{300} between the early and late onset PD groups will be further investigated in a larger patient group using ERPs and neurophysiological assessment.

Summary

Recent studies indicate subtle cognitive deficits in many non-demented Parkinson's disease (PD) patients. Long-latency event-related potentials (LL-ERPs) index the nature and timing of a cognitive response to a stimulus and have been used to assess cognitive function in PD. Studies to date have only assessed patients receiving long-term anti-PD therapy, which may itself affect information processing.

In this study we recorded the P_{300} using a standard auditory oddball paradigm with a button-press response in a group of *de novo* patients. A P_{300} was absent in 2 patients and prolonged in 2 patients but there was no difference in the latency or amplitude of the P_{300} in the Parkinsonian group compared with the age-matched control group. The averaged P_{300} of the young PD group was dispersed compared with that of the young controls.

Our findings suggest that the amplitude and latency of P_{300} elicited using the paradigm of this study are not sensitive indices for differentiating PD patients from controls. A paradigm which places a greater load on the specific cognitive deficits of PD will be investigated. The dispersion of the P_{300} component in the young PD group may be support for the suggestion of distinct subgroups in PD.

Our findings suggest that the latency and amplitude of LL-ERP components elicited by our paradigm were not sensitive indices for distingusihing PD patients from controls. The significance of the prolonged P3-RT measure is not clear.

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Revised EEG Coma Scale in Diffuse Acute Head Injuries in Adults

*V.M. Synek**

Trauma is the most frequent cause of death before the age of 18 years and is the fifth leading cause of death in adults, while craniocerebral trauma accounts for nearly half the deaths related to injury. Among fatal disorders of the central nervous system, head injuries are second only to cerebrovascular disease.[1] Severe head injury and its consequences provide great problems for the medical profession and society as a whole.[2] Head injuries are frequently complicated by loss of consciousness for a variable length of time. It is difficult to assess such head injured patients as sedative and muscle paralysing drugs are routinely used in the management of those admitted to intensive care units. Radiological investigations often fail to give specific guidance in this situation and the EEG remains a very helpful ancillary investigation.[3,4]

Since the introduction of the EEG into clinical medicine,[5] many grading scales for the EEG assessment of the patient in coma have been described. The most important advance was provided by Hockaday *et al.*[6] who divided the EEG in anoxic coma into 5 major categories. Adjustments to this scale were later made.[7–10] These scales divide EEG in coma into the following categories: grade I: near normal record; grade II: theta activity dominant; grade III: delta activity dominant; grade IV: burst suppression pattern; grade V: isoelectric EEG.

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Over the years many other important EEG patterns occurring in coma have been described and it has become desirable that these should be incorporated into the existing 5-grade scale. Such a revised scale has been recently published.[11,12] This revised scale is based on the presence of dominant frequencies, their persistence and amplitude, the presence of other activities including their distribution and, most importantly, their reactivity. This scale includes patterns such as 'alpha coma',[13] 'spindle coma',[14] 'theta pattern coma'[15,16] and some other important types of EEG appearance. The scale divides the EEG features into 5 grades and 10 subdivisions, 4 being benign as regards survival, 4 of uncertain significance and 7 malignant.

It is realized that repeated investigation of EEG activity in the unconscious head injured patient is desirable but important questions regarding the possibility of survival are justifiably raised during the first days after admission. Because of this, the reliability of the suggested scale in predicting survival was tested in 90 adults with head injuries requiring admission to the Department of Critical Care Medicine at Auckland Hospital. The predictive value of EEGs performed within 36 hours after the injury was measured retrospectively without knowledge of the clinical data or outcome.

The degree of neurological deficit after discharge from the hospital was correlated with the EEG pattern obtained within 36 hours of the injury, although the adjusted scale was primarily focused on the prediction of survival. Only patients with evidence of diffuse cerebral trauma were studied, while patients with focal lesions and somatic complications were excluded as the suggested scale applies only to diffuse encephalopathies.

Patients

During 1986 and 1987, 142 patients were admitted to the Department of Critical Care Medicine at Auckland Hospital with a diagnosis of acute head injury. Of these, 52 were excluded as they had focal injuries or other problems (subdural haematoma, bilateral subdural haematoma, extradural haematomas, massive intracerebral haemorrhage, multiple trauma, multisystem failure) or were children under the age of 16 years. Only patients showing evidence of acute diffuse post-traumatic encephalopathy were included in the study. In the group of 90 patients remaining after the above exclusions there were 44 females and 46 males. The age

range was 16 to 79 years (median age 37.6 years). Injuries were due to motor vehicle accidents in 64, to falls in 16 and to assaults in 10 patients.

Plain skull X-rays were performed in all and showed vault fractures in 6 and basal fractures in 11. Computerized tomography (CT) of the brain was performed in all soon after admission, with normal findings in 35 patients. The remaining 55 showed various abnormalities (oedema, multiple contusions, subarachnoid haemorrhage). The score on the Glasgow Coma Scale (GCS) introduced by Teasdale and Jennet[17] was assessed on admission in all cases. This scale takes into account the best reaction for eye opening and the type of response to verbal and motor stimuli. The best outcome is seen in patients with scores on this scale approaching the possible highest value of 15 points, while a score of 3 is the lowest one consistent with survival. Six patients having epileptic seizures before their EEG investigations were treated with phenytoin (4) and diazepam (2). Twenty patients died. Autopsies were performed by a forensic pathologist and the cerebral findings assessed by a neuropathologist.

Neurophysiological investigations

EEGs were recorded using platinum alloy subcutaneous needle electrodes placed according to the 10–20 International System; the time base was 0.3sec., recording speed 30mm/sec., filters 0.5 to 70Hz. Recordings were made 24 to 36 hours after the injury and muscle paralysing drugs and opiates (scopolamine) were used when needed. Seventy-five patients required assisted respiration. EEGs were recorded once in 12 patients, twice in 49 and thrice in 29. All records were assessed without access to the clinical data. Only the age, the sex of the patients and the drugs used were known at the time of EEG assessment. The EEG patterns were assigned according to the published revised grading scales where detailed descriptions of grades and subgrades, with appropriate illustrations, were provided.[11,12]

The following are regarded as benign from the point of view of survival:

> Grade 1—near-normal record with preserved reactivity to external stimulation; Grade 2—reactive with rhythmic theta activity dominant attenuated by external stimulation; frontal rhythmic delta activity in Grade 3,[18] usually reactive, and 'spindle coma',[14] where the sleep pattern of stage 2 sleep usually occurs in the form of rhythmic 12 to 14Hz spindles, with other transients of that sleep stage, usually reactive to external stimulation.

The following EEG patterns are regarded as 'Uncertain for survival':

Grade 2 abnormality with mixed theta and delta activity which does not react to external stimulation; Grade 3 abnormality with dominant delta activity, which may or may not be reactive to external stimulation: 'alpha pattern coma'[13] of reactive type[19] and the presence of epileptiform discharges on a base of Grade 3 abnormality with diffuse delta activity.

The following patterns are regarded as malignant from a survival point of view:

Low amplitude delta activity in Grade 3 abnormality, with brief intervals of isoelectricity (1sec), non-reactive to stimulation; Grade 4 abnormality with 'burst suppression pattern' with prolonged intervals of isoelectricity and bursts of activities within the alpha, theta and delta frequency ranges; epileptiform activity with Grade 4 abnormality; alpha pattern coma, non-reactive with activity within the alpha frequency range either widely distributed or more prominent anteriorly;[19] 'theta pattern coma', with clusters of 5Hz activity maximal anteriorly, often superimposed on low amplitude delta, typically non-reactive; low output EEG in Grade 4 abnormality, typically non-reactive and Grade 5 abnormality, when the EEG becomes isoelectric.

The effect of sedation and/or hypothermia must be excluded and principles out-lined in the American EEG Guidelines[20] must be applied. As was pointed out by Bennet *et al.* in 1976,[21] a few patients may survive an isoelectric EEG, but suffering a total loss of sapient life and remaining in a vegetative state. The revised EEG scale is summarized in Table 1.

Results

The details of data, EEG findings and outcomes in the group of 90 patients are given in Table 2. There was no correlation between the patients' ages and the abnormality grades, the most severe abnormalities being recorded even in relatively young patients.

There was a very significant relationship between EEG grades and the GCS scores, when the latter were divided into scores of 6 points or less and 7 points or more ($\chi^2 = 70.2$, $P < 0.001$). This indicates a strong association between malignant EEG paterns and low GCS score, while benign EEG patterns are associated with a higher GCS score. Likewise, there was a significant relationship between EEG grades and CT appearances categorised into normal and abnormal ($\chi^2 = 30.6$, $P < 0.001$). Again, the relationship was most apparent between malignant EEGs and abnormal CT scans, and between benign EEGs and normal CT scans.

Table 1. Revised EEG grading scale in traumatic and post-anoxic encephalopathies.

Frequency of Incidence	Benign	Uncertain	Malignant—if Persistent
Frequent	Grade 1 Grade 2, Reactive	*Grade 2 Non-reactive* Grade 3, Diffuse Delta, (Reactive/ Non-reactive)	*Low Amplitude Delta, Grade 3* 'Burst Suppression Pattern' Grade 4 Epileptiform Discharges in Grade 4 Low Output EEG—Grade 4 Isoelectric EEG—Grade 5
Rare	'Spindle Pattern Coma' in Grade 3 *Frontal Rhythmic Delta Grade 3 (Reactive/ Non-Reactive)*	*'Alpha Coma Reactive'* *'Epileptiform Discharges in Grade 3'*	*'Alpha Pattern Coma' Non-Reactive* *'Theta Pattern Coma'*

Revised concepts are indicated by italics.

EEGs of uncertain prognostic significance were not clearly associated with either GCS scores or CT scan findings. 'Benign' patterns occurred in 30% (27 patients), 'uncertain' in 50% (45 patients) and 'malignant' in 20% (18 patients).

Recovery was seen in 56.7% (51 patients), residual disability in 21.1% (19 patients) while 22.2% (20 patients) died. Autopsy and microscopy of brain structures showed evidence of diffuse axonal injury in all 20 patients, contusions and oedema in 18, tentorial herniation in 6 and extensive subarachnoid haemorrhage in 3. Of 19 patients who remained disabled, 6 had quadriparesis, 8 dementia, 2 a Parkinsonian syndrome and 3 were in a vegetative state with total dependence for nutrition and hygiene. The patients who did not recover sapient life originally presented low amplitude delta non-reactive types of grade 3 abnormality.

EEG patterns which were described as 'benign' correlated with a very good prognosis and all such patients were discharged within 14 days. Of these patterns 'spindle coma' occurred in 11.1%, a reactive type of grade 2 abnormality in 16.7% and a frontal rhythmic delta grade 3 abnormality in 2.2%.

Patterns regarded as 'uncertain' for survival occurred in 50% of subjects. Of this group, a grade 3 abnormality of reactive type was most

Table 2. Comparison of EEG findings within 36 hours after injury with clinical details and outcome.

Grade	Subdivision	Patients	Median Age	GCS on Arrival		CT		Outcome		
				Mean	Range	N	A	Recovered	Disabled	Died
2	Reactive	15	31	8	5–12	10	5	14	1	—
	Non-reactive	5	40	4	3–5	1	4	—	3	2
3	Reactive	28	29	8.5	3–13	12	16	24	3	1
	Non-Reactive	12	19	6.5	3–12	6	12	1	9	2
	'Frontal delta'	2	13	6.5	5–8	2	—	2	—	—
	'Spindle coma'	10	17	7.8	6–12	9	1	10	—	—
	Low delta	5	27	3.6	3–8	—	5	—	3	2
4	Burst suppression	1	24	4		—	1	—	—	1
	Alpha coma (non-reactive)	3	29	5	4–6	—	3	—	—	3
	Theta coma	1	56	4		—	1	—	—	1
	Low output EEG	1	19	3		—	1	—	—	1
5	Isoelectric EEG	7	32	4	3–6	—	7	—	—	7
						Total =		51	19	20

* Abbreviations: GCS = Glasgow Coma Scale; CT = Computerized tomogram of the brain; N = Normal; A = Abnormal.

common, occurring in 31.1% of patients: of these only 3 were left disabled while 1 died, the other 24 recovering. Grade 2 and grade 3 abnormalities of non-reactive type had a far worse prognosis, with 12 patients remaining disabled and 4 dying. The state of EEG reactivity in grade 2 and 3 abnormalities was more important for prediction than was the quality of background activity. All patients with grade 4 or 5 abnormalities died. Subdivisions were predictively more accurate regarding outcome than the original 5 major grades. Repeated recordings showed signs of improvement in those who survived while in those left disabled there was little change. In patients who died there was a progressive EEG deterioration towards an isoelectric pattern. Illustrations of 'spindle coma' and 'non-reactive alpha pattern coma' are shown in Figures 1 and 2.

Discussion

Several important questions are raised by the results of this study. The definitions of individual grades and subdivisions of EEG change in post-traumatic and anoxic encephalopathies[11] allowed for easy allocation of abnormalities without knowledge of clinical data or outcome. It is acknowledged, however, that unexpected or transitional patterns may be found to occur in a larger series than the 90 patients studied. It was a major purpose of the published classification to enable a similar prognostic assessment to be reached by other neurophysiologists dealing with the assesment of EEGs in diffuse encephalopathies associated with coma.[12] It is notable that most of the suggested 15 grades and subdivisions occurred in the study. This research was intentionally used in patients admitted with acute head injuries during a relatively limited time period of 2 years during which treatment strategies did not change to any extent. Such alterations in treatment policy may have been present in previously published studies covering long periods of time.[22,23]

The predictive accuracy of the present study was influenced by several factors. Firstly, 'benign' patterns occured relatively frequently (30%). The reactive type of grade 2 abnormality, as well as the rhythmic frontal delta activity with a grade 3 abnormality, are both well recognized as carrying a benign prognosis in coma.[8,12,18] This was so in this study, when all 16 such patients recovered and only one was left disabled. Another benign pattern was 'spindle pattern coma' which, since its first description,[14] has been shown in several studies to predict a benign

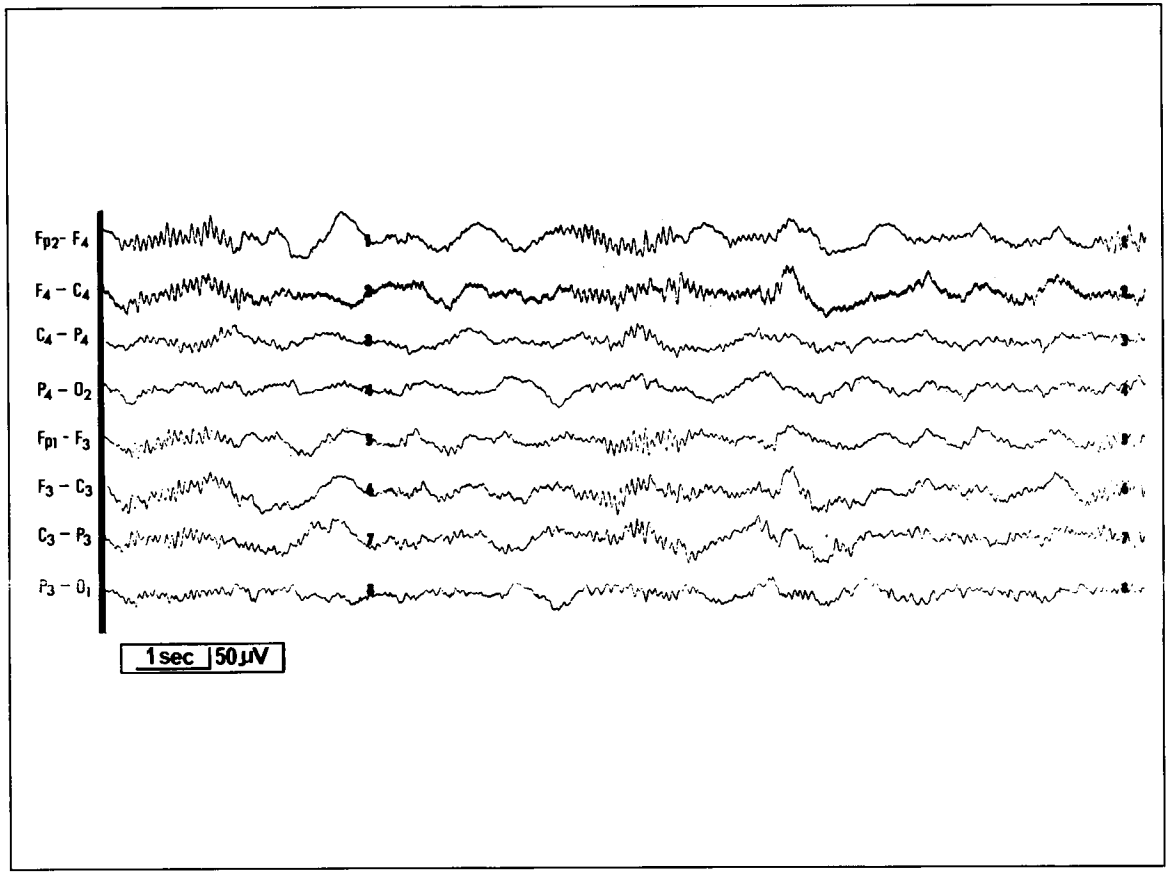

Figure 1.
'Spindle coma'. The patient was a female aged 18, who suffered a head injury after a car accident. The recording was made 24 hours after the trauma and the patient was unconscious and not sedated. The EEG shows prominent spindle 12Hz, maximal anteriorly, on a background of irreguar delta activity. CT scan of the brain was normal and the patient recovered within 11 days.

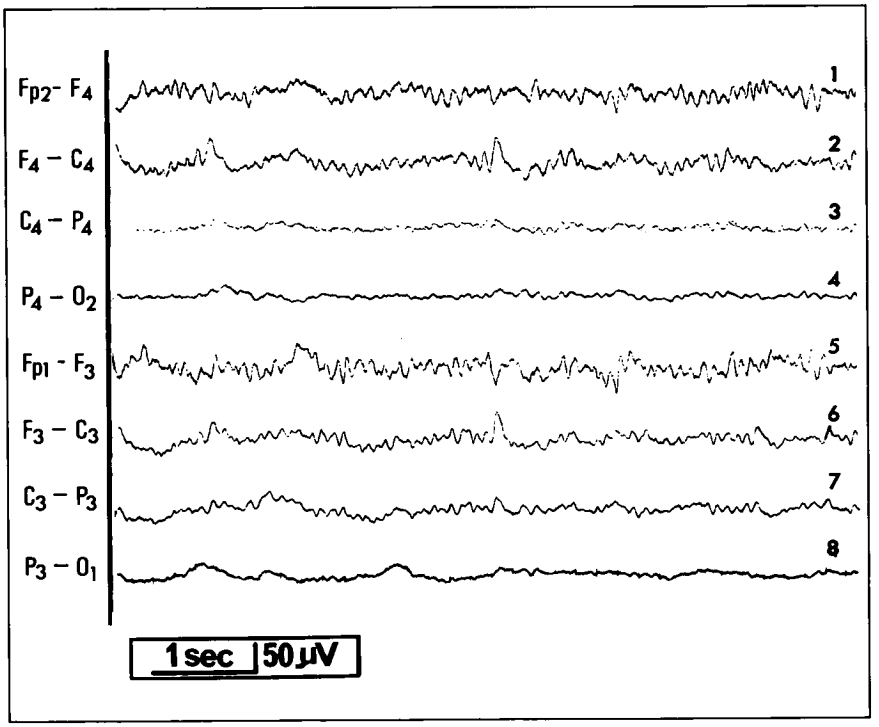

Figure 2. 'Non-reactive alpha pattern coma' . The patient was a male aged 25 years, who suffered a fall from a second floor causing multiple skull fractures. He was deeply unconscious until his demise 4 days after the trauma. A post mortem showed multiple brain contusions, and tentorial herniation. The EEG performed 30 hours after trauma showed prominent activity within the alpha range (10Hz), maximal anteriorly, in the presence of irregular delta activity of the same amplitude. There was no reaction to external stimulation.

outcome.[3,24,25] This pattern occurred in 11.1% of the patients, and all recovered.

The frequent occurrence of EEG patterns of uncertain significance, in 50% of the series, causes concern. This is, and probably will remain, an intrinsic characteristic causing difficulty in assessing prognosis in patients with head trauma requiring admission to intensive care departments. Several important features were noted. A non-reactive grade 2 abnormality proved unfavourable, as none with this appearance recovered, 3 patients remaining disabled and 2 dying. In a grade 3 abnormality with diffuse delta activity there was a clear distinction between the outcome for those with reactive and with non-reactive patterns; 93% of

patients with reactive grade 3 abnormality recovered, while in the non-reactive group only one made a good recovery and the rest died or were left disabled. It is thus very probable that reactivity of the EEG pattern is far more important for prognosis than the quality of the background activity, both in grade 2 and grade 3 abnormalities. In comparison with other studies, there was a surprising absence of epileptiform activities, but 6 patients were treated for early epileptic seizures before the EEG was performed.

Nearly all patterns designated as 'malignant for survival' occurred in those who died. It has been previously suggested that when generalized 'burst suppression pattern' occurs in post-traumatic coma an anoxic cerebral insult has been superimposed.[26] Such an assumption is supported by the findings of Graham *et al.*[27] who showed there was ischaemic damage in 91% of patients who died of non-missile head injuries. Changes were most frequently in the hippocampus and basal ganglia and less frequent in the cerebral cortex and cerebellum. Failure of cerebral perfusion, resulting from variations of intracranial pressure and distortion of vessels with brain shifts and tentorial herniation, were the main causes of ischaemic damage occurring soon after the injury.

There was a significant relationship between the Glasgow Coma Scale results and the EEG abnormality grades. There was also a clear relationship between the CT scan findings soon after the injury and the EEG findings. All patients who died showed evidence of diffuse anoxal injury, sometimes complicated by oedema, contusions and subarachnoid haemorrhage, at autopsy. There were no specific pathological patterns correlating with individual EEG abnormality grades or subdivisions. The high rate of diffuse axonal injury in those studied pathologically underlines the importance of this type of injury, which is thought to be closely associated with the final outcome in head trauma.

Even if it was not originally intended that the adjusted EEG coma scale would be related to the degree of neurological recovery, it was of interest that those who remained disabled originally presented EEG patterns regarded as uncertain for survival, with the exception of one patient who at the beginning had a 'benign' pattern.

If previously published definitions of grades[3,6,7,8] had been used to evaluate the EEG data, then 30% of patterns would not have been allocated a grade. This applies in particular to 'alpha and theta coma patterns' and 'low amplitude delta in grade 3 abnormality'. This greater ability to allocate grades accounts for the increased sensitivity of the revised grading system and heightens the prognostic accuracy if it is used.

In repeat EEGs, there was evidence of improvement in those who survived and of deterioration in those who died, as also observed by Silverman.[8] It is suggested that repeat EEG recordings should be made in patients, as indicated clinically. However the results of this study show that significant information about the effect of acute head injury on cerebral function can be obtained early after the injury.

Summary

The validity of a recently published EEG grading scale applied to patients with acute head injuries has been investigated. This scale is based on 15 individual grades and subdivisions and 3 major groups: 4 patterns are benign regarding survival, 4 are of uncertain significance and 7 patterns are prognostically malignant. The evaluation was performed in 90 adult patients with acute head injuries in whom EEGs obtained during the 36 hours after the injury were evaluated retrospectively without knowing the clinical details or the outcome. By employing previously reported definitions it was possible to allocate EEG abnormalities in all cases. The assumption was made that at the time of the EEG investigation the impact of the head injury on cerebral function was already established. All patients displaying 'benign' patterns survived. 'Uncertain' patterns were the most common ones and in patients with these the reactivity of EEG activity was more important for prognosis than the quality of the background activity. All but 3 of the patients with a 'malignant' pattern died, and the survivors remained in a vegetative state. There was a correlation between the EEG findings and the Glasgow Coma Scale score on admission and also with the results of computerized tomography of the brain. In those patients who died there was no significant relationship between EEG signs and autopsy findings. Repeated EEGs are always desirable with severe head injuries but the results of this study suggest that useful prognostic information can be obtained from an EEG recorded within 36 hours after the head trauma.

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Magnetoencephalography and Late Component ERPs

E. Gordon, C. Rennie† and L. Collins†*

The prospect of obtaining improved spatial localization of neuronal generators in 3 dimensions, with millisecond temporal resolution, has motivated considerable effort to investigate the brain's magnetic fields by magnetoencephalography (MEG), utilized alone or in combination with the electroencephalogram (EEG) and event-related potentials (ERPs).

Early ERPs reflect the integrity of sensory pathways in the brain, whereas late component ERPs are thought to reflect electrical activity of neuronal networks underlying cognitive processing. Late component ERPs such as the CNV, N_{100}, P_{300}, N_{400} and P_{620} reflect aspects of the cerebral mechanisms underlying preparation for movement, attention, information processing, language and recognition memory respectively.

Delineating the underlying sources of late component ERPs is an essential step in determining their ultimate clinical utility. There are, however, fundamental limitations in extracting the 3-dimensional distribution of electrically active brain sites from electrical potentials recorded at the scalp. The scalp EEG/ERP is only indirectly related to neuronal generators, since it arises from the extracellular volume currents that flow throughout the brain and its coverings. The poor conductivity of the skull and inhomogeneous impedance of the brain attenuate and smear the spatial pattern of the EEG, so it is difficult to locate its underlying source.

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Table 1. Comparison of electrical currents and magnetic fields in the brain.

EEG	MEG
Electrical Current	Magnetic field
Confined within head	Extend outside
Radial source	Tangetial source
Potential difference	Absolute
Extracellular	Intracellular
Volume conducted	Fall off $1/r^3$
Smeared by skull	Transparent
Poor localization	Accurate

The theoretical advantage of the MEG, on the other hand, is that the magnetic fields of the brain are not distorted by the medium through which they pass, since biological tissue is essentially transparent to magnetic fields. In addition, the magnetic field measurement is absolute (there is no MEG counterpart to the EEG reference electrode). The unambiguous circular geometry of the magnetic fields measured outside the head provides the means to calculate accurately the origin (depth, location, magnitude) of its source within the brain.

In a homogenous spherical head, a simple dipolar current generator would produce a simple magnetic field which enters and leaves the head symmetrically at 2 extremes. The underlying source would lie midway between the extremes, its direction would be perpendicular to this line, its magnitude would be reflected in the width of the extremes and its depth related to the distance between the extremes. One strength of the MEG approach is that it is not sensitive to radial sources, with the result that sources (with some tangential component) give rise to less complex and more easily interpreted waveforms than those recorded electrically. Nevertheless, electrical recordings provide the missing information from MEG measures, namely those concerning radial sources, although it is in practice difficult to make use of this information in isolation. The combination of electrical and magnetic measures provides the most effective means to utilize their complementary information.

Measurement of magnetic fields

Magnetic field strength is expressed in teslas (T). Brain fields are measured in units of femotesla ($1 fT = 10^{-15} T$) and are typically in the 50 to 1000 fT range. The earth's field is approximately one billion times larger than the brain's magnetic field. MEG became feasible only with the

development of sensitive super-conducting quantum interference devices (SQUIDS) and gradiometers (systems of detector coils that cancel or discriminate against distant noise sources). The SQUID and its gradiometer must be refrigerated to temperatures near absolute zero in a cryogenic dewar.

Applications of MEG

MEG systems have evolved swiftly from cumbersome single-channel systems to 37 channel array research systems that are currently being assessed in a number of centres. Current research applications include: (i) epilepsy—non-invasive localization of seizure foci and spread patterns; (ii) examination of migraine—slow biphasic wave followed by a general reduction (spreading depression) of activity lasting approximately 10 minutes; (iii) source localization of brain dysfunction in head trauma and stroke, senile dementia and visual defects of neurological origin; and (iv) early and late component ERPs.

The P_{300} late component ERP

The P_{300} has been the most studied of the late component ERPs and serves as an instructive example with which to begin to assess the practical problems and relative merits of MEG and EEG to determine non-invasively the underlying source of the potential. The P_{300} occurs approximately 300msec post-stimulus in response to unexpected task-relevant stimuli. Its amplitude is thought to reflect factors such as decision certainty, and its latency to reflect the speed of discriminating task-relevant from task-irrelevant stimuli.

Intracerebral recordings of the P_{300} in patients with intractible epilepsy have shown polarity reversal in the hippocampus[1–4] and thalamus.[5,6] However, Valesco *et al.*[7] failed to confirm P_{300} reversal in the thalamus and postulated volume conduction from the hippocampus as one possible explanation for this finding in other studies. In addition to these possible subcortical generators of the P_{300}, Wood and McCarthy[8] reported P_{300} activity in intracerebral recordings from the frontal lobe. Given the limited spatial sampling of intracerebral recordings and the likely complexity of the P_{300}, additional generators may also be possible. On the balance of current evidence the most likely combination of generators appears to be from the hippocampus and the frontal lobe. Attempts

thus far at employing MEG recordings to determine the source of P_{300} have been unconvincing, primarily due to the poor spatial sampling of the instrumentation employed.

Using a single channel MEG system (acquiring the data from one site at a time over the head) Richer *et al.*[9] studied 3 normal subjects and concluded that the generator of the P_{300} elicited by auditory target stimuli was located in the temporal cortex. In our Cognitive Neuroscience Unit, we have investigated 2 subjects and similarly have found, using a single channel biogradiometer, that the P_{300} was localized to the auditory cortex. In the visual modality Okada *et al.*[10] studied 3 subjects, using a single-channel MEG, and concluded that the generator of the P_{300} was within the hippocampus.

The only MEG P_{300} study using a multichannel system has been undertaken by Lewine *et al.*[11] Using a 7-channel MEG in 4 subjects 'preliminary data suggest a deep mid-temporal source for auditory magnetic P_3, although the exact location and orientation of the source was variable from subject-to-subject' .

Whether late component ERPs are examined with one, 7 or contemporary 37 recording channel MEG systems, there is one overriding concern. The problem is that factors such as arousal, attention, habituation, performance and particularly fatigue, will not be equivalent between the 4 (for 37 channels) to 80 (for single channels) data collection runs. Hence these independent variables may disproportionately confound the measurement of the P_{300} across the multiple trials currently needed to acquire sufficient data for source localization. This mitigates against localization of the P_{300} with any sense of confidence, using a small number of recording channels. Location of the source underlying late ERP components such as the P_{300} must await acquisition of the MEG data on a full head (100 plus channels) imaging system—where multichannel recording of all time-locked information is simultaneously sampled from the brain in a single run. Projected completion times for such MEG imaging systems, according to 3 groups at the World Biomagnetism Conference in November 1989, is between 1 and 2 years. The reality test thereafter will be how well such MEG systems, coupled with EEG/ERP measurement, will be able to discriminate between what are likely to be overlapping cortical and subcortical sources.

Localization of single and multiple sources

The method that is conventionally employed to localize a single source dipole is the equivalent current dipole method (ECD). This in-

Table 2. Possible means of analysis of difference sources.

	Type I	Type II	Type III	Type IV
Example	Localized and stationary (Somatosensory ERPs)	Localized and non-stationary (Epileptic spike)	Distributed and stationary (Alpha)	Distributed and non-stationary (Information processing)
Analysis	ECD	Simulated annealing	Minimum norm estimates	Temporal sequencing

Source types I–IV according to Nunez.[12]

volves optimizing the 5 parameters characterizing the tangential current dipole (orientation angle, 2 lateral position coordinates, depth, and strength) until the computed and measured fields agree sufficiently. This procedure can be extended to account for multiple dipole sources. However, the computational requirements escalate rapidly as the complexity of the problem increases (Table 2).

In theory, localization of late component ERPs such as the P_{300} does seem feasible if we consider the limited facts at hand (2 sources) and from theoretical models of these sources—for example (Figure 1) such as that undertaken by Grognard and Seagar[13] at the CSIRO Division of Radiophysics. A theoretically feasible strategy can be proposed to localize such multiple sources, using a combination of MEG and EEG analysis.

The first step required is a realistic mathematical description of head shape.[14] The second step concerns the mathematical methods necessary to determine what electrical and magnetic field measurements can be expected for a given head shape and source or sources (the forward solution) and then produce the optimal source localization from an iteration of the forward solution matched to the measured data. These first 2 steps may suffice for many cases. The third step involves making full use of the temporal information from both EEG and MEG as proposed by Scherg[15] for multiple overlapping components. This method separates out the multiple components, essentially by principal component analysis.

There is a great deal of unsubstantiated theory concerning the P_{300} and other late component ERPs and it seems appropriate that some emphasis be shifted to examine their underlying sources.

Conclusions

MEG and EEG are the only tools we currently have to examine electrical brain function with millisecond resolution in healthy humans. These tools seem to be coming together to enable us to identify both

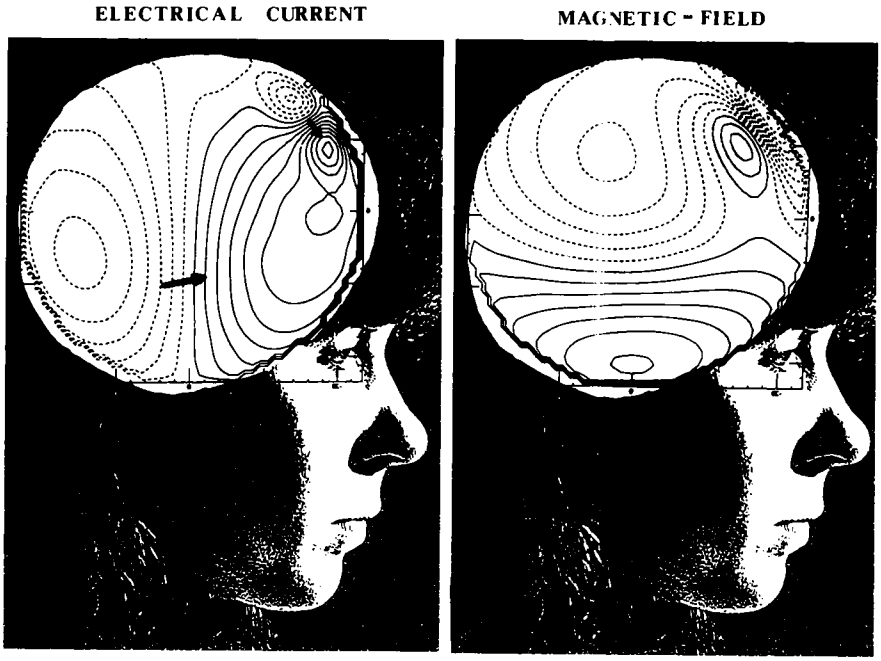

Figure 1. Multiple sources of P_{300}—modelled data, undertaken by Grognard and Seagar[13] of electrical current (left) and magnetic fields (right) showing overlapping surface distribution from 2 generators of the P_{300} component. One generator is in the frontal lobe and one is in the hippocampus.

superficial and deep sources. From the cognitive viewpoint this approach is becoming pressing, since we can see large signals at late latencies from subcortical sources. However the relevance or actual functions of the signals has not been unambiguously determined. Much of the evidence concerning the function of subcortical sources has been derived from primate research and patients with intractable epilepsy or specific brain lesions, each of which has serious limitations in terms of inferring specific higher order information processing.

Summary

The recent emergence of magnetoencephalography is a development that is already yielding results. Its intrinsic sensitivity to the actual source activity, rather than to volume currents, means that its particular value lies in source localization. As well as having proven value in research

relating to early evoked responses and epilepsy, biomagnetic measurements have been applied to later components. For example, results for the auditory P_{300} potential indicate the source to lie either in the temporal cortex or the hippocampus. More definite conclusions await further development of the instrumentation. Also, there is much scope for more sophisticated analysis of the magnetic fields, of the electric potentials, or ideally of both together. This is likely to elucidate the largely unknown functional circuitry corresponding to the late components of the response.

Acknowledgements

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Physical Disability After Stroke in the Perth Community Stroke Study

*C. Anderson, K. Jamrozik and E. Stewart-Wynne**

Epidemiological information on the residual disability of stroke survivors is of fundamental importance in planning health and related services. The proportion of survivors with significant disability following a stroke varies from study to study depending on differences in patient samples, timing of assessments and variation in measurement instruments. The few community-based studies available suggest that, 6 months after a stroke, 25% to 53% of survivors are dependent in one or more activities of daily living (ADL) and 3% to 9% are totally dependent in self-care. However, this picture may be distorted if pre-stroke disability is not considered, particularly because the elderly have the greatest risk of both stroke and other causes of impairment and disability.

The aim of the study here reported was to measure the frequency and severity of dependence in self-care among the first 100 consecutive survivors of acute stroke from a community register of strokes in a defined population.

Materials and methods

The Perth Community Stroke Study is a prospective community-based epidemiological study of acute stroke in a representative segment of the city of Perth, Western

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Table 1. The Barthel ADL index—total scores ran from 0 to 20.

Bowels
0 = incontinent (or needs to be given enemata)
1 = occasional accident
2 = continent

Bladder
1 = incontinent, or catheterized and unable to manage
1 = occasional accident
2 = continent

Grooming
0 = needs help with personal care
1 = independent face/hair/teeth/shaving

Transfer
0 = unable—no sitting balance
1 = major help (two people), can sit
2 = minor help (one person, verbal/physical)
3 = independent

Dressing
0 = dependent
1 = needs help, but can do half unaided
2 = independent (including button, zips, laces, etc)

Toilet use
0 = dependent
1 = needs some help
2 = independent (on and off, dressing, wiping)

Feeding
0 = unable
1 = needs help cutting, spreading butter, etc.
2 = independent

Mobility
0 = immobile
1 = wheelchair dependent
2 = walks with help of one person
3 = independent (but may use any aid, e.g. stick)

Stairs
0 = unable
1 = needs help (verbal/physical/aid)
2 = independent (up and down)

Bathing
0 = dependent
1 = independent (or in shower)

Australia (1986 census population 134 690). 'Stroke' is a clinical diagnosis based on the WHO definition. Every effort has been made to obtain pathological documentation of the stroke subtype by CT and/or MRI imaging or necropsy.

Functional ability has been measured using the Barthel Activities of Daily Living (ADL) Index (see Table 1), a simple weighted scale that is quick to administer, well-validated, reliable and a sensitive measure of mobility and ADL. Each patient's ADL was assessed at 4 months after the index event and was compared with the patient's pre-stroke pattern estimated using the best available information from the patient or carer. The current pattern of activities, rather than his or her potential ability, was recorded and patients were not asked to demonstrate their ability on each item.

Patients were arbitrarily divided into 5 groups based on their ADL score: 0–4 for 'very severely disabled'; 5–9 for 'severely'; 10–14 for 'moderately'; 15–19 for 'mildly' disabled, with 20 indicating independent living but not necessarily normal living. The assessment of physical disability formed part of a broader assessment of social acitivities, behaviour and emotions.

Results

Of the first 150 patients registered with stroke events (new and recurrent), 48 had died before review at 4 months, 1 refused to cooperate

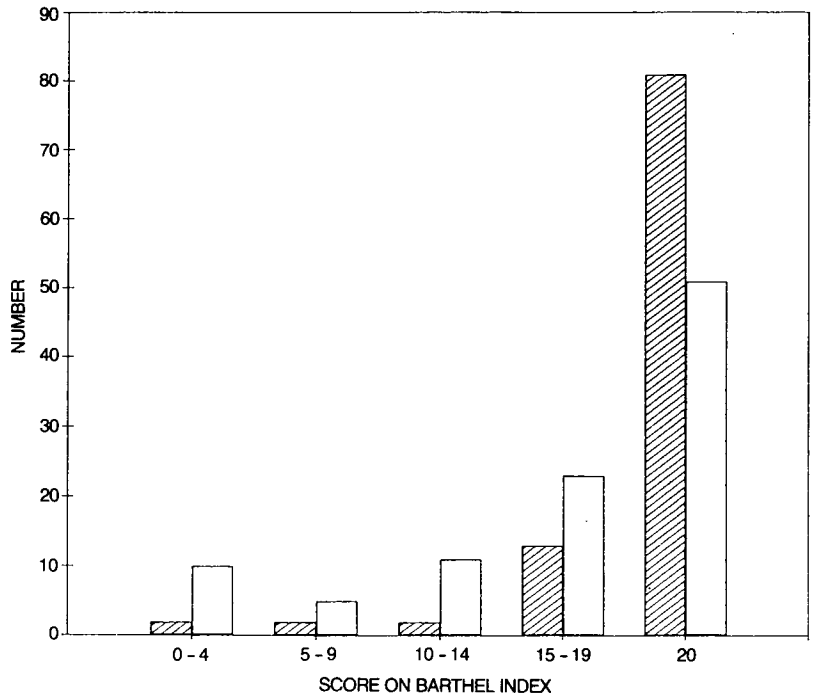

Figure 1. Perth Community Stroke Study. Disability pre-stroke and at 4 months (100 survivors of stroke). Hatched columns = pre-stroke; open columns = 4 months post-stroke.

and 1 was unavailable for assessment. The remaining 100 patients had a mean age of 73 years (range 43 to 95 years); 56 were men.

Before the stroke in question the ratio of functionally independent to dependent patients was 81:19. After the stroke the ratio was 57:49. A total of 61 patients had full recovery to their pre-morbid level of function while 39 had a worsened disability status (Figure 1).

Conclusions

At least 50% of surviving stroke patients had complete functional independence 4 months after their acute episode.

Of 49 patients who were disabled at 4 months after their index event, 19 had also been disabled at the time of onset of their stroke. Thus, the crude case-fatality at 4 months was 33% and the cumulative incidence of new disability was 20% for all cases and was 30% among survivors of the episode.

The prospects for recovery of mobility and activities of daily living among patients who survive an acute stroke appear good. However, it should be appreciated that minor disability and handicap are more likely to be reflected in altered social functioning and psychiatric morbidity than in reduced capacity for activities of daily living.

Perth Community Stroke Study: Design and Preliminary Results

*C. Anderson, E. Stewart-Wynne, K. Jamrozik, P. Burvill and T. Chakera**

The epidemiological study of stroke is complicated by 2 important facts:

(i) Unlike ischaemic heart disease, a sizeable proportion of patients who suffer a stroke are never admitted to hospital. Therefore, hospital-based stroke registers provide a misleading reflection of the burden of disease borne by the community as a whole.

(ii) Stroke is not a single pathological entity. Further understanding of the relative importance of risk factors for stroke and thus preventative measures, as well as development of effective treatments, can come only from the study of pathologically homogeneous groups.

Aims of the study

The Perth Community Stroke Study commenced on 20 February 1989. It uses a community-based register of acute cerebrovascular disease events in a representative segment of the population of Perth, Western

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Australia. The study follows methods employed in a pilot study conducted over a 10-month period in 1986.[1] When completed, it will span 3 years including 2 years' registration and 12 months' follow-up of patients.

There are 4 main aims to the study, viz:

(i) to determine the incidence of stroke and its pathological subtypes in a defined population;
(ii) to determine the relationship between the subtypes of stroke and defined risk factors;
(iii) to measure the outcome of stroke in terms of survival, disability, medical care and use of services; and
(iv) to determine the incidence and aetiology of psychiatric disturbance following stroke.

Methods

The study is being conducted in a segment of Perth geographically defined by the Swan River to the south and east and a major road to the west. This road is also the nominal boundary between the drawing areas for Royal Perth Hospital in the city centre and Sir Charles Gairdner Hospital to the west. The area covers 8 complete postal code districts and part of a ninth. According to the 1986 census the population of the area was 134 690, its members being slightly older and less likely to have moved over the previous 10 years but otherwise representative of the population of the remainder of Perth.

All patients who experience a stroke or transient ischaemic attack are registered with the study. An age and sex matched control sample with persons drawn at random from the electoral roll and whose residence is also in the study area, is being collected concurrently.

Standard definitions are used for stroke and TIA events. Multiple sources of case ascertainment are used including: general practitioners; physicians and institutional medical staff; hospital admission forms and casualty registers are checked regularly; the coroner's offices and death certificates are checked regularly, and, following publicity surrounding the study 2 patients were self referred and one patient was notified from the control sample to date.

All patients are seen as soon as possible after their event and assessment includes a clinical history and examination, with determination of the risk factor profile, disability status before stroke and social factor profile. Every effort is made to document the stroke pathology by CT scan, MRI or necropsy. Following baseline assessment survivors are followed up at 4 and 12 months from their index event. In the first year of the study, assessment at 4 months will also include a formal semi-structured psychiatric interview. Data about the presence and severity of a wide range of psychiatric symptoms are used to derive a clinical diagnosis using standard psychiatric classification. Subsequent follow-up assessment of psychiatric morbidity will use a screening instrument currently being validated within the study.

Table 1. All stroke events February–December 1989.

Pathological sub-type	Number	%
Cerebral infarction		
a. Thrombotic	121	45
b. Embolic	32	12
c. Lacunar	27	10
d. Boundary zone	7	3
Primary intracerebral haemorrhage	27	10
Subarachnoid haemorrhage	10	4
Undetermined	42	16
Total	266	100

Table 2. Incidence rates for first stroke (per 100 000 person-years—all ages), February–December 1989.

	Males		Females	
	1986	1989	1986	1989
Crude rate	166.6	180.9	108.1	163.0
Age-standardized rate*	120.2	130.9	55.9	78.1

* Standardized to the 'World' population using the direct method

Preiminary results: February–December 1989

In the first 10 months of the study a total of 370 events was registered, accounting for 312 cerebrovascular events. There were 193 first-ever in a life-time strokes, 73 recurrent strokes and 46 TIAs.

Figures for the pathological sub-types of stroke for all events are presented in Table 1. A pathological diagnosis has been obtained in 84% of events. Large-vessel 'thrombotic' cerebral infarction was the most common, accounted for 45% of stroke events. Primary intracerebral haemorrhage and subarachnoid haemorrhage accounted for 10% and 4% of events respectively.

Crude and age-standardized (standardized to the 'World' population using the direct method) incidence rates for first stroke per 100 000 person-years and all ages are presented in Table 2. Rates for males and females are presented separately and compared with those obtained in 1986. The overall rate has increased. The crude rate for males of 180.9 is within the originally determined confidence intervals, but there has been a marked increase in the rate for females (to 163.0). These changes may reflect random fluctuations in the community but probably relate to improved case-ascertainment in the current study.

Table 3. Incidence of first-ever stroke—comparison of population-based registers (annual age-standardized rates per 1000 persons aged 55 years and over).

Site of study	Period studied	Rate
Rochester, Minnesota[2]	1980–84	5.11
Auckland[3]	1981	5.03
Oxfordshire[4]	1981–86	5.94
Soderhamn, Sweden[5]	1984	8.46
Trasimeno, Italy[6]	1987	5.31
Perth	1989	5.50

Finally, the annual standardized incidence rate per 1000 persons (males and females combined, aged 55 years and over) is presented in Table 3 and the rate is also compared with those obtained from other major population stroke studies conducted over the last decade. The striking finding is that with the exception of Soderhamn, Sweden (rate 8.46), all the rates are very similar (rates from 5.03 for Auckland, to 5.94 for Oxfordshire, UK). This relative uniformity is very different from ischaemic heart disease mortality and presumably incidence, which varies widely between these countries.

Summary

The first aim of the study, to see every case of stroke and TIA which has occurred in a representative population, unbiased by hospital admission and with high pathological documentation, is being achieved. To date, the incidence rates for stroke in Perth are strikingly similar to those in other major population-based studies in the Western world. Further data on risk factors are likely to contribute greatly to our understanding of the aetiology of stroke. The data on stroke outcome should be of international significance.

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Subdivision of Articles: Manuscript should be prepared and paginated in the following manner.

1) Title page
2) Text pages
   - Introduction
   - Methods
   - Results
   - Discussion
3) Summary
4) Acknowledgements
5) List of references
6) Tables
7) Figures and captions
8) Footnotes

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Chapter in a book

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Drug names: Generic names should always be used, but if not available, brand names which take an initial capital can be used. In original articles, the maker of the study drug must be given.

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