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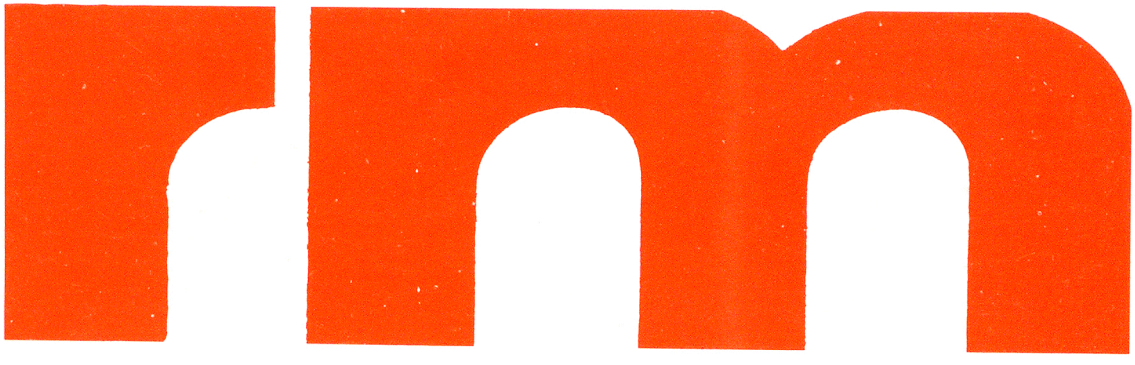

ROYAL MEDICAL SOCIETY 1974

RES MEDICA

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CONTENTS

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EDITORIAL

This issue of Res Medica is largely concerned with the subject of epilepsy, a chronic and often crippling condition, against which even the forces of modern medicine and surgery can only offer a feeble opposition.

One man in Edinburgh who was concerned about the plight of the epileptic was Professor Norman Dott. A great pioneer in the field of surgical neurology, his interests extended outside the operating theatre to the problems of his patients and their fellow sufferers in the community. He campaigned actively for them as leader of the Epilepsy Society in Edinburgh.

We were greatly saddened to hear of his death during the preparation of this issue, he will be sadly missed.

We would like to thank our contributors, and Dr. G.W. Ashcroft, Miss H. Harkins, and Mrs. P. Strong for their assistance in producing this issue.

EPILEPSY

HORACE R. TOWNSEND

Epilepsy is an unusual disease. For most of the time the sufferer does not suffer at all except from apprehension, the expectation that he or she may have a fit.

The epileptic fit

The treatment of epileptic fits is a quite different subject from the treatment of epilepsy. Most epileptic fits require no active treatment whatever and provided that the patient is safe-guarded from obvious hazards – falling into water and drowning or being run over by passing vehicles – then recovery will occur naturally and the patient can resume a normal life until next time. Occasionally there are complications, such as if a patient should vomit during an attack and from this point of view the treatment of the epileptic fit is not different from the management of unconscious patients in general.

Status epilepticus

Very rarely, when the condition of epilepsy is severe, fits follow one another so frequently that there is no perceptible gap in between, and the patient is said to be in 'status epilepticus'. Such a condition is an acute medical emergency and is extremely difficult to treat. Management usually involves anaesthetising the patient, paralysing the muscles with curare and thereafter maintaining the respiration by mechanical means. The condition of Status Epilepticus, however, is almost always precipitated by some severe cerebral insult – a head injury, poisoning or the presence of an intracerebral clot – and treatment to be effective must be directed at removing the cause.

The diagnosis of Epilepsy

As I have said, however, the actual fit and its treatment or management is not the problem. The patient comes to his Doctor because he is apprehensive about attacks in the future. The diagnosis of epilepsy involves an estimate of the probable frequency, nature and intensity of future fits, which implies some idea of the causal factors. One hundred years ago Hughlings Jackson wrote "...we do not make a diagnosis worth calling one, if when we are called to a person who has had a severe convulsion and of whose case we have had no history we turn out to be right in having said 'It is a case of epilepsy ....".

Treatment of epilepsy may be aimed either at removing or reducing the cause of the attacks or may simply involve trying to modify that re-action of the brain which manifests itself as epileptic fits.

Theories of Epilepsy

Almost any brain injury, whether caused by violence, with contusion or actual piercing or tearing of the structure of the brain, or caused by inflammation, or bleeding within the brain, or by infarction due to shutting off of the blood supply to a region of the brain, or by the presence of a

congenital malformation or new growth, all may irritate the brain substance and cause the occurrence of epileptic fits. Jackson hypothesised that epilepsy was accompanied by a "discharge" in the grey matter of the brain "convulsions and other paroxysms are owing to (1) sudden (2) excessive and (3) temporary nervous discharges" and "it is the function of nervous tissue in health to 'store up' force and to expend it in an orderly manner at the provocation of special excitations. The discharge in disease differs from the expenditure of nerve force in health, in quantity and in that it is provoked by a more general excitation". When Hans Berger in 1929 published the results of his recordings of electrical potentials from the surface of the brain, and scalp, it became possible to demonstrate this discharge in the form of an electrical disturbance in living and conscious patients. Since then Jackson's insight has been amply confirmed and electroencephalography has proved to be a most valuable tool for the study of epileptic phenomena. The work of Penfield and Jasper in Montreal, Canada, showed the relationship of the spike discharge to cortical scars and traced from the reports of conscious patients the subjective phenomena accompanying these discharges. Not only did their work emphasise that epilepsy is frequently triggered from a focus of brain which is functioning abnormally, but not dead, around the edges of the scar but they also showed that these scars could be excised surgically and that if the resulting wound was carefully made to avoid leaving ischaemic regions of cortex then it would heal with minimal irritation of surrounding brain and the patients were commonly free, or almost free, from epileptic manifestations thereafter.

The Borderland of Epilepsy

The older neurologists, such as Gowers, had not only realised that muscular jerkings were a form of epilepsy but also has speculated upon many unusual phenomena involving short-term disturbance of consciousness or behaviour which had some of the characteristics of, or were associated with, epileptic fits. The contribution of electroencephalography has been to elucidate the details of the relationship between disturbances in particular parts of the brain and these overt disturbances of behaviour. The temporal lobe has turned out to be a region particularly associated with memory as well as including receptor areas for the peculiarly evocative senses of smell and hearing. A generalised theory of epilepsy has grown up which seeks always to identify the focus of origin of epileptic attacks. "Jacksonian" attacks have a clear focus of origin in the motor cortex. Similar attacks involving a march of sensation along a limb have a focus in sensory cortex. Attacks involving flashing lights or more or less formed visual hallucinations (these are rare) have foci in occipital cortex. The disturbances of consciousness and behaviour which used to be known as "epileptic equivalents" appear to arise because of focal discharges in the temporal lobe, and almost more surprisingly epileptic discharges may occur in the frontal lobe without and discernible subjective or objective concomitants (just as quite large lesions of this region of the brain may be made without discernible impairment of normal cerebral functioning).

Idiopathic Epilepsy

But what of the ordinary or old-fashioned varieties of epilepsy, the Grand Mal and Petit Mal of the French neurologists! Grand Mal epilepsy characteristically is accompanied by immediate loss of consciousness and a generalised tonic contraction of all muscles of the body simultaneously passing gradually into the clonic phase of jerking which is the fit proper and followed by a more or less prolonged period of unconsciousness and confusion. Sometimes the patient is aware of an impending attack. This awareness, a state of altered sensibility, sometimes a feeling of heightened clarity of vision and all forms of perception which may last for hours or even days, was termed an "aura". By contrast, there is Petit Mal, a disease of children and teenagers, characterised by brief, sometimes almost imperceptible, losses of consciousness usually without and other objective phenomena such as jerking or falling. These are of course classical descriptions. Every fit, like every patient, is an individual. Nevertheless, they have features in common. In general, sudden complete loss of consciousness. The implication in terms of the focal theory of epilepsy is clear, the discharge must be occurring in the sea of consciousness itself, but where can this be?

The Centrencephalon

Since the pineal body fell from favour as the probable seat of the soul there has been a tendency to discount the possibility of one small region of the brain being the seat of consciousness. In the event a rather unlikely structure emerged, the central retricular activating system, dismissed generally in the anatomy books as "a layer of grey matter containing numerous multipolar nerve cells", the central retricular system has been promoted to the *centrencephalon* discharge in which causes instant loss of consciousness and propogates disturbances to all parts of the cortex which may result in the generalised motor phenomena of the Grand Mal fit.

Research

It is a sobering thought that we are scarcely any more advanced in our concepts than were Jackson and his contemporaries. Our knowledge is more detailed, diagnosis of cerebral lesions is more reliable, the techniques of neurosurgery are immeasurably improved, but we still know very little about how to treat Idiopathic Epilepsy. The difficulty lies in the nature of the disease, fits occur at unpredictable intervals. All attempts to produce a reliable test for epilepsy have failed, and hence all measurements of the effects of drugs must be based on statistical techniques. The use of laboratory animals in whom epileptogenic are induced can provide material but computer techniques must be used to make the very large numbers of measurements needed to obtain statistically significant results.

The Patient

With all the statistics, the computers, and the drama of Neurosurgery we must not forget the individual for whom all this work is being carried out. The patient, as I said at the start, suffers not from Fits but from Fear. His own fear that he may suffer a convulsion at a dangerous or socially embarrassing moment. The fears of his parents and his friends, of his employer and of society at large. It is an open question whether the truculence of the "epileptic personality" is a result of any specific organic leison or merely a response to the intolerable pressures of "living with fits". Education can help Society to loose its irrational fears. Psychiatrists and Social Workers can offer support. The Doctor's role is to try and find and treat the cause, but most important of all, to help the patient to plan his life with realism and to live it with confidence.

References

1. Berger H. 1929. Uber das Elektrenkephalogramm des Menschen. Arch. Psychiat. 87:527–570. Ibid. 1931, 94:16–61; 1933, 100:301–320; 1933, 101:452–469; 1934, 102:538–557; 1936, 104:678–689.
2. Selected Writings of John Hughlings Jackson. Basic Books, Inc. N.Y. 1958. Ed. James Taylor.
3. Epilepsy and the Functional Anatomy of the Human Brain by W. Penfield & H. Jasper. Churchill, 1954.

CURRENT TOPICS IN EPILEPSY

IAN TULLOCH

Introduction

Human epilepsies, by definition, are recurrent, self-sustained, paroxysmal disorders of brain function characterised by excessive firing of cerebral neurones. The underlying biochemical and morphological disturbances in the brain which are responsible for epilepsy are not clearly understood except that they appear to be diverse and hence the immediate difficulty in advancing a common mechanism for these disorders. Most probably they are different diseases but the clinical manifestations of these are similar. This view would certainly be compatible with the complex nature of neuronal control mechanisms both at the cellular and organisational level. In this article there will be a stress on possible biochemical disorders both in humans and in experimental epilepsies, the drug treatment of these, and an evaluation of the clinical relevance of experimental animal models.

Many cases of epilepsy are idiopathic, in that no underlying lesion can be found in the brain. This has led to the view that everybody has a threshold for epilepsy and it is this which determines whether or not seizures may develop. Genetic make-up seems to be important in some cases, especially gene-dependent errors of metabolism which are inherited as autosomal recessives, such as phenylketonuria, which results in accumulation of products of phenylalanine, and this is often accompanied by convulsions but the cause-effect mechanism is unknown. Numerically, however, these particular diseases are rare. *Conrad* (1935–38) did a study of twins with idiopathic and symptomatic epilepsy. He studied monozygotic and dizygotic twins and his results showed that 19 out of 22 of the monozygotic twin pairs were concordant with regard to epilepsy, and in 127 dizygotic pairs there was concordance only in approximately 4%. His studies were an attempt at measuring the correlations between a given genetic make-up, and brain electrical activity as measured by the EEG; he concluded that heredity did have a determining role in epilepsy which was idiopathic in nature. Symptomatic epilepsy, i.e. where there is a known lesion, was also included and heredity only played a minor part in this syndrome.

Refsum (1972) proposed a hypothesis of a polygenic influence being important in a predisposition to epilepsy and this interplays with various environmental precipitating factors.

Classes of epilepsy

Epilepsy can be divided into two main groups:

(a) *Focal epilepsy*

In many areas of the brain localised lesions can cause focal epilepsy. Usually the hyperactive neurones are localised in or around the lesion area. Lesions can be caused at birth, after head injury or more obviously by a tumour. These lesioned areas exhibit abnormal firing as shown by the EEG. The temporal lobe is particular susceptible to lesions and much interest has been shown in this type of epilepsy.

(b) *Generalised Epilepsies*

Petit mal and grand mal come under this heading and are characterised by abnormal electrical activity in large areas of brain rather than in a focal area. These are the more serious types of epilepsy since they result in loss of consciousness and severe seizures may occur. Petit mal is a very characteristic type of epilepsy in which there is a sudden complete loss of consciousness lasting for a few seconds followed by a sudden and complete return to normality. Grand mal is only diagnosed when unconsciousness and convulsions are known to have occurred. An important point here is that focal epilepsy can progress to a grand mal seizure, but grand mal seizures frequently occur independently of focal epilepsy.

These epilepsies are the main ones, but there are many others which have different clinical manifestations.

Neurochemistry of Epilepsy

(a) *Problems*

Biochemical research into epilepsy is greatly restricted by the difficulty in obtaining human biopsy and autopsy material. A study of a particular lesioned area from the brain may not reveal much concerning the initial cause of the epilepsy since the tissue that is actually epileptic may only be a small part of the sample or the tissue may be gliosed and neurones may be degenerated. *Pope* has proposed that the actual epileptic area is on the periphery of the lesion and perhaps more emphasis should be placed on studies of this region.

This difficulty in obtaining neural tissue and the need for screening tests for anti-epileptic drugs has necessitated the use of experimental animal models. These models should ideally show similar behavioural and electrical manifestations to the particular type of human epilepsy under investigation. Many experimental models are now in use for different types of epilepsy, and this allows for a detailed biochemical and histological analysis of the brain. A detailed description of all models is not presented but only the most useful ones.

(a) *Animal Models*

(1) *Focal epilepsy*

Included in these are the topical convulsant metals, e.g. cobalt and alumina cream. These agents can be used to produce localised lesions in the brain but degeneration can be quite widespread as has been shown by histological study of the cobalt metal. Cellular destruction occurs at the lesion site and makes biochemical analysis of the tissue difficult and so many studies have investigated the secondary focus. Briefly, this is a focus which is homotopic to the original focus, if cortical in position, and has the advantage that it is an epileptic focus not accompanied by gross cellular destruction.

Drugs are tested for their ability to prevent focal discharge or to prevent seizure propagation and part of the clinical relevance of the model can be evaluated from these studies. Increasingly, more workers are doing biochemical studies on experimental models and trying to relate these to the human situation. For example, the recent work of van Gelder showed that in freshly excised cortical tissue from focal epileptogenic lesions in man there was a fall in glutamic acid, GABA, taurine and a significant rise in glycine in the area of the active focus. These amino acids are thought to have a transmitter function in the CNS and a change in their levels may indicate an imbalance between excitatory and inhibitory mechanisms. In a parallel study by Koyama on cobalt focal epileptogenic lesions in the cat, significant and very similar changes in transmitter levels were observed in the actively discharging focus.

An advantage of an animal model is that the development of epilepsy can be studied and Koyama was able to show that the fall in glutamic acid as measured in the

tissue was paralleled with an increased release of free glutamic acid from the cortical surface and the fall in GABA was a later development. Perhaps the initial release of glutamic acid, a postulated excitatory CNS transmitter, might be responsible for the development of a pool of hyperactive neurones. The fall in GABA, probably an inhibitor transmitter, is probably a result of a decrease in its precursor glutamic acid but it may be an important biochemical change with regard to the chronic nature of the experimental model.

Cation levels, intracellular and extracellular, are very important for neurone stability. The enzyme Na-K ATPase is membrane bound and requires ATP to transport Na^+ and K^+ ions across the neuronal membrane. Another important function of this enzyme is the re-uptake of transmitteres into nerve endings, a mechanism which is very important in the inactivation of transmitter activity on the post-synaptic receptor. Impairment of activity in this enzyme system might result in changes in ionic gradients and in alterations in transmitter release and re-uptake.

Hunt and Craig in a recent study on the cobalt model in rats, investigate cation levels and Na^+-K ATPase activity in brain during the development of epilepsy. Their results were indicative of a change in ion transport since they reported an increase in Ca^+, Na^+, Mg^{++} and a fall in K^+, Na-K ATPase and protein content in the area of the lesion. No significant changes were detected in the secondary focus of epileptogenic activity.

(2) *Generalised Epilepsies*

I. *Grand Mal*

Two models are most commonly used in the evaluation of drugs effective in grand mal:

(i) The Maximal Electroshock Seizure (MES) pattern test.

This is a relatively crude test that involves measurement of the dose of a drug that abolishes the tonic extensor component of the seizure induced by supra-maximal stimulation of the brain in 50% of all animals. Basically it is a measure of the drug's ability to prevent propagation of the epileptic discharge through brain tissue, and it is valuable since all drugs that have anti-grand mal activity in man are effective in the MES test in animals. Drugs that are effective in cases of grand mal were discovered by empirical screening in various animal models, particularly the MES technique and the literature is lacking in detailed information on the mechanisms of drug action.

(ii) A possible action of anti-grand mal drugs is an inhibition of post-tetanic potentiation. Briefly, this is an enhancement of release of transmitter/volley for periods lasting up to several minutes after stimulating a nerve cell at a high frequency. A model frequently used is:
Recording the Mono-synaptic reflex in the spinal cord. After tetanic stimulation at the dorsal root for a minute has ceased, the amplitude of the mono-synaptic reflex increases. This increase can be almost completely blocked by diphenylhydantoin, a drug which is used extensively in chronic treatment of grand mal.

II. *Petit Mal*

The models for petit mal are not so well developed or tested as the grand mal models but a few models are useful. Systemic administration of pentylenetetrazol induces seizures which are decreased by anti-petit mal drugs such as ethosuximide. This model is poorly understood, especially since there are conflicting reports on what the action of pentylenetetrazole is.

These and many other experimental models have been used to study transmitters and energy metabolism in the CNS and a good deal of information is available relating to possible causal mechanisms for epilepsy. Manipulation of central transmitter levels by various methods has implicated all the known central transmitters in experimental epilepsy, but at the clinical trial level, as well as in experimental models, disappointing results have been obtained by attempts to treat epilepsy by altering specific transmitter levels in a known manner. This is perhaps forwarding a rather bleak picture concerning the rational treatment of epilepsy, but a certain degree of success has been obtained.

A notable example is the amino acid, GABA, for which there is good evidence from release, uptake, localisation and iontophoretic studies that it is an inhibitory transmitter in the CNS and at the neuromuscular junction in the crayfish. Glutamic acid is the precursor of GABA and the enzyme responsible for the catalysis is glutamate decarboxylase which requires vitamin B_6 as a co-factor. An important point is that the co-factor is weakly bound and, therefore, the enzyme is very susceptible to a vitamin B_6 deficiency or B_6

anti-metabolites. B_6 deficiency is not responsible for many cases of epilepsy but at least this evidence links a specific transmitter with a known cause of epilepsy, i.e. vitamin B_6 deficiency. This disease is probably due to some genetic abnormality.

Recent work on taurine, a possible neurotransmitter has shown that this amino acid prevents epilepsy in cobalt induced epilepsy in the cat and mouse, and van Gelder found a decrease in taurine levels in human focal epilepsy in the region of the focus. Physiological data indicate that iontophoretically applied taurine depresses activity in Renshaw cells, spinal interneurones and cerebral cortex cells which is strongly indicative of an inhibitory neurotransmitter function. Taurine is being used in clinical trials but no results are available as yet.

Changes in glutamate and GABA could possibly be *due* to a fault in the brain energy metabolism. The GABA shunt pathway provides an alternative route to part of the TCA cycle which is the chief energy generating system in oxidative metabolism. If some form of metabolic uncoupling is possible between the TCA cycle and the GABA shunt this could result in a change of GABA and glutamate levels. Alternatively the TCA cycle may not be properly functioning in cells and this could have the effect as previously mentioned as well as causing an ATP deficiency which may in itself be responsible for epilepsy. Certainly many experiments using metabolic poisons, e.g. cyanide, ouabain, have shown that convulsions are produced by these agents but the exact mechanism responsible for epileptic discharge of a cell is debatable.

An essential requirement for proper brain cell function is the maintenance of ionic gradients across neuronal and glial membranes and hence correct polarisation, e.g. high Na^+ concentration extracellularly and low intracellularly in the normal state. The stress is on ion distribution rather than absolute amounts and research into this is limited because of the difficulty in the measurement of these gradients. Research into transmitter involvement in epilepsy is also complicated by compartmentation of these into metabolic and functional, i.e. neurotransmitter pools.

Clinical Aspects

Although changes in neurotransmitters, energy metabolism and ions have been implicated in experimental and human epilepsy, it is quite disappointing that so few new forms of successful treatment have emerged. Although newer drugs are available, some of the drugs of choice are virtually unchanging and perhaps the major reason for this is that the new drugs are no real improvement on existing, well-tried drugs. Attention has recently centred on the correct plasma concentrations of anti-epileptic drugs and Marselli et al. have drawn attention to the lack of correlation between oral dose of diphenylhydantoin and plasma concentration in human patients. The main reasons for this are the differences between individuals in the rate of metabolism of drugs.

Adverse side effects are a major feature of the use of anti-epileptics since they are not specifically acting on epileptic cells but on normal cells as well. This is probably a major determining factor in the use of a given drug. A study by Gibberd throws light on the importance of clinical supervision over patients in their abilities to follow given dosage instructions. The reason for this may be that the side effects of the drugs are less tolerable than the actual epilepsy and this is clearly evidence for improvement in drug therapy. Correct plasma concentrations of anti-epileptic drugs are very important for them to be effective and also to reduce the side-effects.

Newer drugs are emerging for the treatment of some forms of epilepsy. The drug Diazepam, which is a benzodiazepine tranquilliser, has been found to be very effective in the treatment of status epilepticus in both adults and children and carbamazepine which is closely related to imipramine chemically, is effective in grand mal and temporal lobe epilepsy.

Concluding Remarks

Diphenylhydantoin and phenobarbitone are given on a chronic basis to epileptics and studies using animal models have rarely investigated chronic drug effects. Empiric screening of drugs in a battery of animal models has the disadvantage that it does not necessarily single out drugs that could be effective on a chronic basis. Onset of human epilepsy, especially after head injury, can occur and it would be very helpful if this could be prevented, possibly by administration of an anti-epileptic drug immediately after the injury. 80% of epileptics are treated by drugs and many of these are helped a great deal. However, there is a need to specify the modes of action of the anti-epileptic drugs and to develop drugs which are more specific to the disease.

In order to find out at first hand about this disabling condition, Res Medica went to see Mr James Glover, who for several years has been suffering from petit mal epilepsy. He told us about his condition:

"My first inclination on taking these turns came wth sick tremors in my stomach. They then developed into the tremor followed by a black-out lasting a few minutes. This can happen anywhere, any time. It is like losing my memory. If I am talking I completely change the subject I am discussing. When the turn is over I return to where I was with the original conversation.

This started after a fall from a 20ft scaffold. I was sent to hospital and had an E.E.G. for the top half of my brain: no damage was found. This was twelve years ago. They associated it with my having tubercular meningitis when I was 19 years old. I was put on various drugs over the years without much success. Last year my doctor and I agreed that I should try the Andrew Duncan Clinic in Edinburgh to see if the illness was psychological. When I was having my last talk with the doctor I took one of these turns. The doctor made arrangements for me to have a lower E.E.G. done. This determined that my brain is damaged and an operation could cure me.

My experience with petit mal is one of frustration and annoyance. It has affected my working life. I am an electrical engineer and when I first took these turns was working with the transmission section of S.S.E.B. My work involved heights and high voltage electricity, also driving. I was retired from S.S.E.B. on the grounds that I was a risk.

I am now in charge of maintenance at the Roxburghe Hotel, Edinburgh, and have worked there for three years handling all types of electrical and mechanical maintenance. My work is regarded as very satisfactory.

My home and social life is normal except for my complete impotence on which I blame these turns.

I am chairman of two committees for handicapped children: one is a parents' committee, the other is a rebuilding fund for the first secondary school for these children. I have proved that the latter will work and is worthwhile for the children's education and confidence.

My own little girl is slightly retarded and when I discovered this I blamed myself for her condition. When I found out that my wife was pregnant again I wanted the birth terminated. However, the doctor advised against it, and I thank God as everything has turned out fine.

The effects of this illness cause great embarrassment when in company as I not only do rather stupid things but sometimes can lose control of my bladder, and having to explain the situation to strangers is rather awkward.

I have now been assured by my neurologist that an operation is definitely possible and may be carried out in the very near future. This will be a very happy day for me as it should mean a return to normal life and I can now set my sights higher as these turns have held me back enormously regarding promotion."

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THE TREATMENT OF CHRONIC ATHEROSCLEROTIC OCCLUSION OF THE LOWER LIMBS – A REVIEW OF 30 CASES

DAVID M.A. FRANCIS

Introduction

Atherosclerosis affects large elastic and muscular arteries, the most commonly and severely affected being the aorta. The cerebral, coronary, and renal arteries, and the arteries of the lower limbs are also frequently involved. The principal pathological changes are intimal thickening and fibrous tissue proliferation, which cause narrowing and occlusion. Ischaemia of tissues distal to points of obstruction occurs unless adequate collateral channels have had time to develop. Although atherosclerosis is a generalised disease, three main sites of occlusion in the lower limbs are recognised (Macpherson et al., 1971), the aortic bifurcation (aorto-iliac disease), the superficial femoral artery (femoro-popliteal), and more distant arteries (peripheral).

The purpose of this paper is to review the results of direct arterial surgey to the aorto-iliac vessels in a consecutive series of 30 patients and to correlate them with the indications for surgery and the nature of the lesions as determined by pre-operative arteriography.

Material and Methods

Direct arterial reconstructions were performed on 30 patients in the two year period January 1970 to December 1971. The period of follow-up was 1–2 years. All operations were for chronic atheromatous occlusion of the aorta and iliac arteries. The operations were:

Endarterectomy	(Total = 15)
(a) aortic	(2)
(b) aorto-iliac	(3)
(c) iliac	(10)

Prosthetic by-pass	(Total = 15)
(a) aortic 'Y' graft	(8)
(b) aorto-iliac (unilateral)	(2)
(c) aorto-femoral (unilateral)	(2)
(d) ilio-femoral (unilateral)	(3)

There were 23 males and 7 females. Nine males and 6 females were in the endarterectomy group and 14 males and 1 female in the by-pass group. All the patients were chronic cigarette smokers, 90% smoking 20 or more cigarettes a day.

Age

The age groups of the patients are shown in figure 1. The youngest patient was 42 and the oldest was 65 at the time of operation. Both the range and distribution of ages are similar to those of occlusive vascular disease in general. The age distribution of the endarterectomy and by-pass groups differs slightly, the average ages being 51.6 years and 56.0 years respectively.

Indications for Surgery

In cases of disease of the aorta and aortic bifurcation both lower limbs are threatened, although not necessarily to the same degree, and so symptoms may be expected in both limbs. In 22 patients the indication for operation was intermittent claudication in the buttock, thigh, or calf of one (20) or both (2) lower limbs severe enough to hinder the patient at work or getting to and from his work. The claudication distance was between 50 and 100 yards. Intermittent claudication was the indication for operation in 24 limbs and was a sympton but not the indication for operation in 5 other limbs (Table I). In 7 patients (7 limbs) the indication was rest pain with or without ischaemic lesions. As rest pain usually means that gangrene is imminent, this group is referred to as the "pre-gangrene" group. One patient was referred because of failure of a wound on the foot to heal and recurrent wound infection, and he has been included in this group. Four "pre-gangrene" patients suffered from intermittent claudication in the other limb. In one patient there was frank gangrene in one toe of one foot and intermittent claudication in the other leg.

Thus there were 23 asymptomatic and 37 symptomatic limbs, 29 with intermittent claudication, 7 with symptons or signs of pre-gangrene, and 1 exhibiting frank gangrene.

Associated Disease

The patients were investigated for any associated medical conditions, those of chief interest being hypertension, cardiac disease, and diabetes mellitus.

Hypertension was defined as a recorded diastolic blood pressure consistently greater than 100 mm Hg. It was present in 7 patients, 4 in the endarterectomy group and 3 in the by-pass group. The term "cardiac disease" includes patients with ECG abnormalities or a history of myocardial infarction, and patients with controlled cardiac failure. It was found in 4 patients. Diabetes mellitus was found in only 2 patients and in both the presenting sympton was intermittent claudication.

Patterns of Occlusion

The pattern of arterial occlusions is the principal factor determining (a) the feasibility of surgery and (b) the possible operative procedure. To establish the patterns of occlusion pre-operative arteriography was performed on all patients, by either direct translumbar puncture of the aorta, or retrograde catheterisation of the femoral artery of the asymptomatic limb. The occlusions were classed as either single or multiple (Table II). There were 3 single occlusions involving the aorta and common iliac artery on one side, 8 involving one common iliac artery alone, and 1 involving one external iliac artery. These 12 were treated by endarterectomy. Two single occlusions of the external iliac and common femoral arteries were treated with ilio-femoral by-pass procedures. Multiple occlusions were classified as unilateral or bilateral; these were further divided into "aortic" and "non-aortic" depending on the presence of occlusions in the aorta, iliac and femoral vessels, or the iliac and femoral vessels alone. There were 6 multiple unilateral occlusions, 2 involving the aorta, and 10 multiple bilateral occlusions of which 8 involved the aorta. Thirteen of the 16 multiple occlusions were treated with prosthetic by-passes.

Operative Procedure

The aim of direct arterial surgery is to maintain the artery's essential function of transmitting blood at an adequate rate. The selection of the procedure depended more on the type of occlusion and the state of the vessel wall above and below it than on the actual vessel involved. Each operation was designed for the individual patient. Endarterectomy was the procedure of choice in cases of short, usually single occlusions with good proximal and distal vessel wall (Table II). These conditions were more often found in younger patients (figure 1). Endarterectomy is easier to perform in younger patients, as they usually have a non-calcified and rubbery type of disease which enables a plane of cleavage to be found (Cannon, 1965). Of the 15 endarterectomies only one was done bilaterally and this was for multiple occlusions at the aortic bifurcation. Prosthetic by-pass operations were performed when occlusions were long or multiple. The prostheses used were all of the crimped, woven Terylene variety, these having theadvantage over the knitted grafts of less initial leakage after proximal and distal clamps are released (Rains, 1965). Crimping of the grafts enables them to be bent without the lumen becoming occluded. The synthetic fibres of the prosthesis remain unchanged as the intermediate layer of a vascular tube. A layer of dense fibro-cellular tissue surrounds the prosthesis and penetrates between the fibres to form a "pseudo-intima". This becomes lined on the inner surface by endothelial cells, though probably only in short implants is the lining complete (Macpherson and Muir, 1963). In 8 patients aortic bifurcated 'Y' prostheses were used, the upper anastomosis being to the aorta and the lower limbs being anastomosed to the common iliac (2), the external iliac (2), and the femoral arteries (4).

In 5 by-pass operations local endarterectomy was performed at sites of anastomosis. Sympathectomy was carried out in conjunction with direct operation in 5 patients in whom it was known that there were also distal occlusions, so as to combine an increased head of pressure proximally with maximum dilatation of peripheral vessels.

Results

Patients were reviewed for 1–2 years after operation. There were no deaths in the series within the period of reviews

Clinical assessment was based on five criteria:

(a) exercise tolerance
(b) ankle oscillometry
(c) pulses in the limb
(d) skin temperature of the limb
(e) improvement of symptoms

Ankle oscillometry was done before and after operation in 26 patients and an increase of 0.5 units was accepted as an improvement.

Improvement in four or five of the above indices was taken as evidence of continued patency of the artery or prosthesis and is classified as a 'good' result. If there was symptomatic improvement without definite objective evidence of improvement or only minor amputation was required, then the patient's condition is said to be 'improved'. 'Failure' indicates subsequent major amputation or re-exploration, or where there was neither subjective or objective improvement.

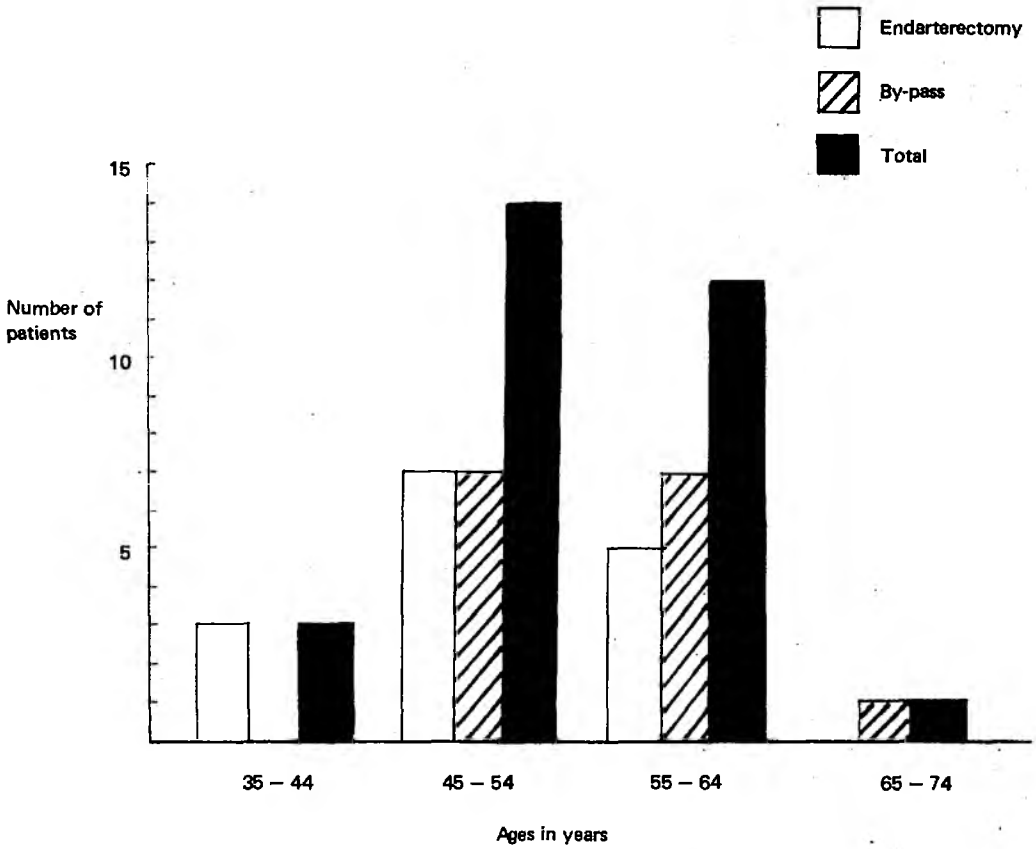

Figure I – Ages of patients submitted to surgery

TABLE I – Indications for Operation

Indication for Operation	*Symptom in Other Limb*	*Endarterectomy*	*By-Pass*
IC	AS	14	6
	IC	–	2
PG	AS	–	3
	IC	1	3
	PG	–	–
FG	AS	–	–
	IC	–	1
	PG	–	–
	FG	–	–

AS = Asymptomatic limb
IC = Intermittent claudication
PG = Pre-gangrene
FG = Frank gangrene

The results at the time of post-operative review are shown in Tables III and IV. Results are expressed in terms of limbs because procedures involving arteries of both lower limbs may produce different results in each limb.

Following endarterectomy there were 13 good results in 16 limbs and 2 were subjectively improved. There was only one failure. After by-pass procedures 17 of 21 showed a good result, 1 was improved, and 3 were failures.

Post-operative complications occurred in 17 patients (Table V). However, most were minor and there was no instance of infection of the prosthesis.

Discussion

Over the 2 year period 30 patients with chronic occlusive vascular disease of the aorto-iliac region were treated by endarterectomy or prosthetic by-pass procedures with no post-operative mortality. In several larger series the mortality rates for similar operations have varied between 0 and 11% (Healey, 1964). The mortality rate is dependent upon many factors, in particular the selection of patients for operation. The importance of careful selection for reconstructive arterial surgery has been emphasised (Macpherson, 1970). Reconstructive vascular surgery has perhaps most to offer to patients whose limbs are in danger, but it is these patients who are most likely to have established coronary disease or generalised conditions causing decreased efficiency of the cardio-vascular system. With the inclusion of such patients mortality and morbidity rates may be expected to rise. In this series 12 patients had associated diseases likely to prejudice the outcome of surgery, but as a group their results were as good as those of patients without these conditions.

In Table VI the pattern of occlusions is correlated with the results of operation. It is evident that where there was only a single occlusion the results of direct arterial surgery were in general good, regardless of the site of occlusion or the method of treatment.

There were 4 failures in the series. All of these were multiple occlusions and 3 were bilateral. In the only unsuccessful endarterectomy the indication was intermittent claudication in one limb due to multiple occlusions in the iliac and femoral arteries. Three months after the original procedure ilio-femoral by-pass was performed and this was entirely successful. This second operation is not included in this series as it was done after the period of review. In 2 of the 3 by-pass failures the indication was intermitten claudication in one limb, and pre-operative arteriography showed multiple bilateral occlusions involving the aorta and both iliac systems and a poor run-off in peripheral vessels. 'Y' graft procedures were, therefore, necessary and in one case bilateral sympathectomy was also done. There was no change in either subjective or objective indices after operation, but there was no subsequent deterioration in either the symptomatic or the asymptomatic limbs. The third by-pass failure was in a hypertensive man who had frank gangrene in one toe and rest pain in the calf on the right side and intermittent claudication on the left. Arteriography revealed multiple bilateral occlusions of arteries below the aortic bifurcation. The left side benefited and had a good result. On the right side the operation did not prevent the spread of gangrene to the mid-calf and a through-knee amputation was performed on the 9th post-operative day. The patient made a good recovery from the second operation and was well and active when last reviewed. The original operation was complicated by reaction to incompatible blood transfusion, acute renal failure and a respiratory tract infection.

In the one improved case the indication for the aorto-femoral by-pass was rest pain in the foot and calf of one side. Subsequent amputation of 4 toes for gangrene was necessary, but there was otherwise complete relief of symptoms. Thus multiplicity of occlusions and a bilateral distribution are two factors which adversely affect the results of direct arterial surgery.

Another factor that may influence the outcome of direct surgery to the aorta and iliac arteries is the presence of occlusions in more peripheral vessels. In 26 of the 37 symptomatic limbs it was possible to assess the run-off in the peripheral vessels by pre-operative arteriography. Eight had a patent superficial femoral artery with good filling of the popliteal artery and all had a good result from direct operation. In 10 limbs the superficial femoral artery was blocked, but the politeal artery filled well from collaterals from a patent profunda. Nine of these had a good result. In 8 cases where there was poor peripheral run-off with minimal or no filling of the popliteal artery from collaterals, indicating occlusion of the profunda, 3 were failures, 1 was improved and 4 had good results. Harris (1968) states that a profunda circulation with a good head of pressure is sufficient to maintain viability of the lower limb. In the good and improved results a profunda circulation sufficient to keep the limb viable was achieved by increasing the head of pressure in the artery by successful reconstruction of the aorta and iliac arteries. In the 3 cases of failure the femoro-popliteal disease was severe enough to warrant treatment on its own merits. These 3 cases

TABLE II – Types of Arterial Occluions and Methods of Treatment

Type of Occlusion	*Site of Occlusion*	*Number of Cases*	
		Endarterectomy	*By-Pass*
Single	Aorto-Iliac	3 (3)*	–
Single	Common Iliac	8 (8)	–
Single	External Iliac	1 (1)	–
Single	External Iliac & Common Femoral	–	2 (2)
Multiple Unilateral	Aortic	–	2 (4)
	Non-Aortic	2 (2)	2 (2)
Multiple Bilateral	Aortic	1 (2)	7 (11)
	Non-Aortic	–	2 (2)
		15 (16)	15 (21)

* The figures in brackets indicate the number of limbs.

TABLE III – Correlation of Pre-operative Symptoms in limbs with the Results of Endarterectomy

Symptom	*Number of Limbs*	*Result*		
		Good	*Improved*	*Failure*
AS	14			
IC	15	12	2	1
PG	1	1	–	–
FG	–	–	–	–

AS = Asymptomatic limb
IC = Intermittent claudication
PG = Pre-gangrene
FG = Frank gangrene

TABLE IV – Correlation of pre-operative Symptoms in limbs with the Results of Prosthetic By-pass Procedures

Symptom	*Number of Limbs*	*Result*		
		Good	*Improved*	*Failure*
AS	9			
IC	14	12	–	2
PG	6	5	1	–
FG	1	–	–	1

AS = Asymptomatic limb
IC = Intermittent claudication
PG = Pre-gangrene
FG = Frank gangrene

TABLE V – Post-operative Complications

Complication	*Number of Cases*
Respiratory Tract Infection	12 a b*
Urinary Tract Infection	3 a
Wound Infection	3 a c
Acute Renal Failure	1 b
C.V.A.	1 c
Incompatible Blood Transfusion	1 b
Jaundice Following Halothane Anaesthetic	1

* a, b, c = occurred in the same patients.

TABLE VI – Types of Arterial Occlusions Correlated with the Results of Operation

Type of Occlusion	*Site of Occlusion*	*Number of Limbs*	*Result*		
			Good	*Improved*	*Failure*
Single	Aorto-Iliac	3	3	–	–
Single	Common Iliac	8	8	–	–
Single	External Iliac	1	–	1	–
Single	External Iliac & Common Femoral	2	2	–	–
Multiple Unilateral	Aortic	4	4	–	–
	Non-Aortic	4	2	1	1
Multiple Bilateral	Aortic	13	11	–	2
	Non-Aortic	2	1	–	1
		37	31	2	4

had multiple bilateral occlusions in the large arteries of the pelvis, and when this type of lesion can be demonstrated it is likely that there are also occlusions in the more peripheral arteries of the lower limbs.

Arteriography can be misleading in the pre-operative assessment of the extent of disease and the choice of procedure. Arterial calcification should be demonstrated by vascular survey before contrast studies are attempted. When X-ray films are taken in one plane only, anterior and posterior atheromatous plaques may not be obvious and lateral view may then be of great help to the surgeon. On routine antero-posterior arteriography films the origin of the profunda artery is frequently not well visualised, and in this situation oblique films are often required.

The importance of demonstrating the whole arterial system of the lower limbs has been emphasised. When attempting to show intra-arterial lesions in the distal parts of the limbs trans-lumbar aortography has the disadvantage that the contrast medium is injected a considerable distance from the vessels being defined. As flow through diseased arteries is slow the medium is frequently dispersed through other channels before it has time to reach the distal vessels. Thus, the nearer the initial bolus of contrast medium is to the area being investigated the more successful the investigation is likely to be. This may be achieved by direct puncture of the common femoral artery on the affected side if the femoral pulse is palpable. The complications of femoral artery puncture for diagnostic procedures have been reported by Bouhoutsos and Morris (1973). They found that atherosclerosis was not an important predisposing factor in the causation of thrombosis following arterial puncture, but that if thrombosis did occur in the atherosclerotic patient he was at great risk of the thrombus propagating distally with subsequent loss of the limb.

Summary

Thirty patients with chronic atherosclerotic occlusion of the lower limbs treated by direct surgery to the aorta and iliac arteries have been reviewed. There was no post-operative mortality. The patency rate was 93.7% for endarterectomy and 86.3% for prosthetic by-pass procedures. Indications and results have been expressed in terms of the number of limbs involved rather than the number of patients as this gives a more accurate analysis of the outcome of surgery. The type and length of the occlusions were the principal factors determining the operative procedure. If the occlusions were short and usually single, then endarterectomy was the operation of choice; if the occlusions were long and multiple, then a prosthetic by-pass procedure was preferred. The important factors affecting the outcome of reconstructive arterial surgery are the selection of patients, the distribution and multiplicity of arterial occlusions, and the state of the vascular tree distal to them and in particular the patency of the profunda femoris.

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References

Bouhoutsos, J., and Morris, T. (1973) "Femoral Artery Complications after Diagnostic Procedures". British Medical Journal, *3*: 396.

Cannon, J.A. (1965) "A Current Technique of Aorto-iliac and Femoro-popliteal Endarterectomy for Obliterative Atherosclerosis." Thomas, Springfield, Illinois.

Clarke, R.J. and Provan, J.L. (1969) "The Surgical Treatment of Aorto-iliac Disease." British Journal of Surgery, *56*: 250.

Harris, J.D., Jepson, R.P., and Miller, J. (1968) "The Management of Aorto-iliac Disease." Australian and New Zealand Journal of Surgery, *38*: 1.

Healey, S.J. (1964) "Reconstructive Operations for Aorto-iliac Obliterative Disease." New England Journal of Medicine, *217*: 1386.

Macpherson, A.I.S., and Muir, A.R. (1963) "Synthetic Fabric Prostheses Implanted 1 to 6 years: Studies by Light and Electron Microscopy." Scottish Medical Journal, *8*: 262.

Macpherson, A.I.S., Hannid, T.K., and Baird, A. (1970) "Occlusive Arterial Disease of the Lower Limbs with Special Reference to the Indications for Direct Arterial Surgery." British Journal of Surgery, *57*:598.

McCormick, J.St.C., and Macpherson, A.I.S. (1971) "Chronic Atherosclerotic Occlusion of the Lower Limbs Treated by Direct Arterial Surgery." Journal of the Royal College of Surgeons of Edinburgh, *16*: 356.

Rains, A.J.H. (1965) "Arterial Surgery." Nursing Times, April 1965, page 13.

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THE AUTHORS

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Dr. Horace Townsend is Consultant in Clinical Neurophysiology at the Western General Hospital.

David Francis is a Houseman in the Royal Infirmary.

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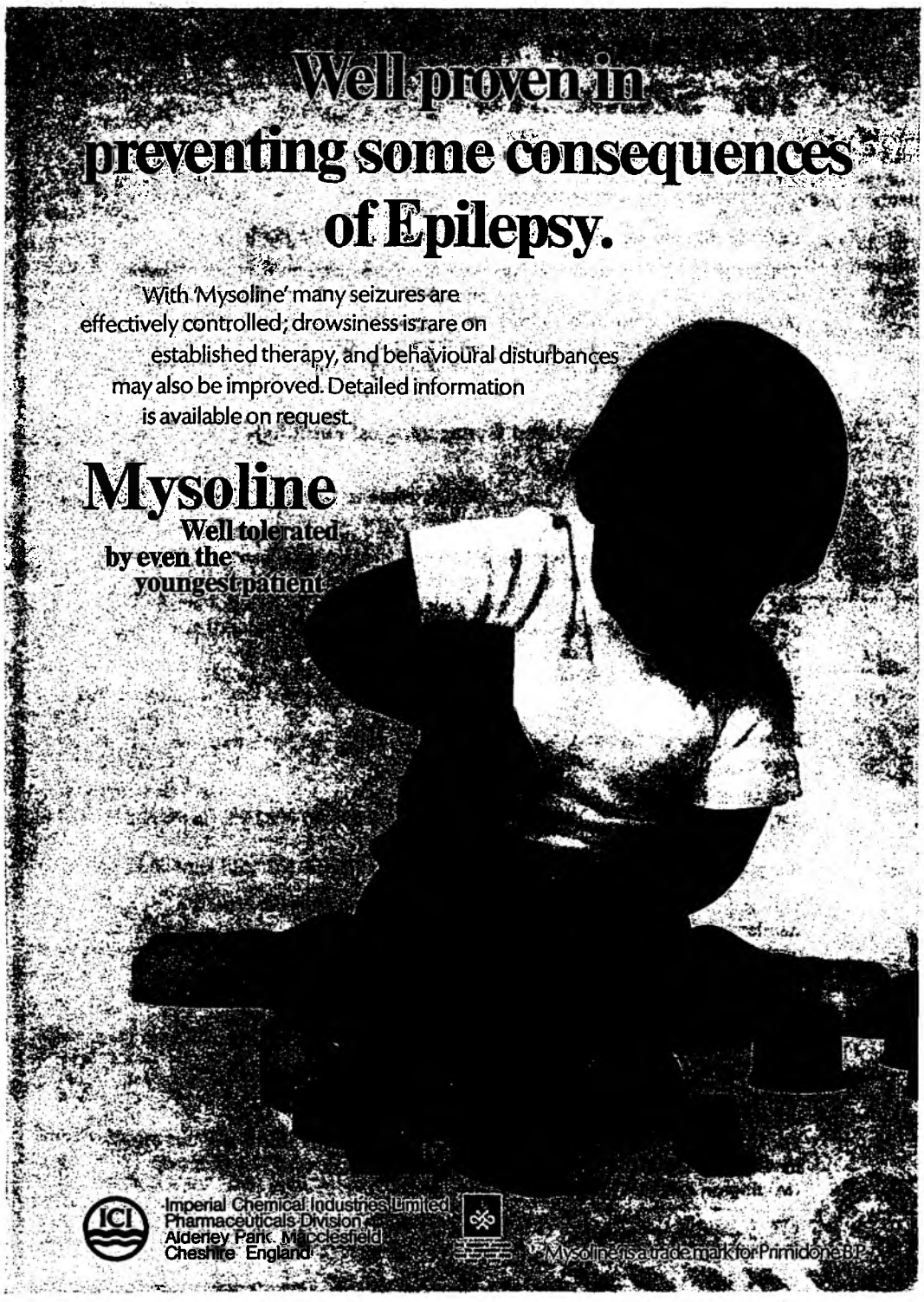
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