*The first Carmichael Memorial Lecture** **Neurophysiology on Man**

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Before the 1939-1945 war and for some years afterwards Dr Carmichael ran a very successful small discussion group called the Neurological Club. Members were widely recruited and there was a contingent from Cambridge which included Rushton, Hodgkin and Huxley. Rushton was my director of studies as an undergraduate at Cambridge, and I suspect it was because he knew Carmichael through the Neurological Club that I came to do research on the Unit. I first met Dr Carmichael in his little room on the first floor here on 9 November 1945, almost exactly 35 years ago. It was one of the best things that ever happened to me. After two brief talks and almost no formalities, I started in the MRC Neurological Research Unit at Queen Square in January 1946. Bates and Dawson were already at work and I learnt from them how to set about experiments. Carmichael kept the lightest of hands on the reins. Each person was given his head and the only perceptible element of direction was that Carmichael would take a lively interest in and generally encourage any new lines of investigation that seemed to him profitable—and a very good nose he had for what would turn out to be profitable. The atmosphere in the Unit reflected the Boss's genial nature and his lively sense of fun, which somehow permeated most of what we did. It was an ideal place to start research, but I am afraid I didn't make the best of my opportunities; indeed I never have. So it is a cause of some wonder that half a lifetime later I find myself, undeservedly honoured and flattered, giving the first lecture in memory of Carmichael, a man who to our deep regret was conspicuously not honoured even as he deserved.

Carmichael's hope always was that concurrent work on healthy human subjects and on patients would be mutually catalytic. I was already familiar with this belief, because Rushton, my teacher at Cambridge, had come much under the influence of

Thomas Lewis, its high priest at University College Hospital, and had caused me to read Lewis's book "Clinical science, illustrated by personal experiences".^{1,2} Although unlike Carmichael and Lewis, I have made almost no headway in the direction of understanding diseased physiology, I thought it might be a fitting commemoration of Dr Carmichael and his aims to devote this lecture to propaganda, mainly from my own personal experiences, on the advantages of working on man.

Carmichael himself had done some very fine work on these lines until the war stopped him. My favourite is the paper on shivering with Richard Jung and Joe Doupe,³ in which they unravelled the parts played by skin sensations of cold and by fall of body core temperature in causing people to shiver. It was shown by cooling the legs of paraplegics in cold water they could not feel, that core temperature had to fall about 1°F before shivering began in the upper half of the body. Conversely blowing ice cold air at stripped healthy subjects, caused them to shiver very soon and so violently that sometimes their core temperature actually rose. Turning off the blower and directing radiant heat onto the subject caused the shivering to stop forthwith, before any significant change in blood temperature could have taken place. Thus two mechanisms that cause shivering were neatly distinguished. As an aside it was noted in a patient with unilateral cerebellar ataxia, that shivering was ataxic, virtually choreiform, on the affected side. I wonder that modern theoreticians of the cerebellum would make of that?

That was the heroic age of clinical research. In a paper on the effects of acetyl choline in man, Carmichael and Francis Fraser⁴ showed that as much as half a gram subcutaneously or intramuscularly was without effect. Intravenously 10-30 milligrammes given rapidly would usually cause the heart to slow for a few seconds. I remember Carmichael telling me of the following experiment, which I later read. "In one patient, aged 51, 30 milligrammes of acetyl choline hydrochloride caused no slowing, but half an hour after 0.85 milligrammes of eserine salicylate" (which prevents the enzymic breakdown of acetyl choline) "the same

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dose of acetyl choline stopped the heart beating for 11.8 seconds and a convulsive attack followed with auricular fibrillation which lasted two hours." There is no comment on this in the paper other than a bald statement in the summary: "The previous injection of eserine intensifies and slightly prolongs the response", but Carmichael (who had been in the trenches in the first war) used to say that those 11.8 seconds were the worst of his life. He was not at all the sort of person whom Shaw had in mind when he wrote: "beware of people who are not afraid of sacrificing themselves, they won't be afraid of sacrificing you either"; and he could condemn those of whom he thought that was true.

I began at Queen Square by looking for a curare-like substance said to be liberated by myasthenic muscles. One patient, after exercising his forearms with the circulation occluded, reported weakness and diplopia so soon after the cuffs were released that I became suspicious and decided to measure circulation time. The method I devised, which I hoped would make Carmichael feel I was an apt pupil, was to take a single breath of 100% CO₂ from a Douglas bag and note the time of the violent inspiration that seized the subject about 5 seconds later. It was shown, by simultaneously compressing both carotids, that this measured circulation time to the medulla via the basilar artery. In practice, a much lower percentage of CO₂ works equally well; and I suspect the method, which is extremely convenient, is perfectly safe; but it never caught on.

To be serious or, at any rate, systematic, I have listed six advantages of human physiology.

The first is the possibility of making a discovery which inherently, or at the time, would be more difficult to make on an animal. The prime example is Harvey clinching the arguments for the circulation of the blood by experiments on the superficial veins of the forearm that a child can perform. These brilliant experiments make the point, which cannot be made too often or too strongly that the best human experiments have a directness and a certainty that equal anything done on animals. Then there is Erb's and Westphal's independent discovery of tendon jerks in 1875, the importance of which one need not emphasise; and Helmholtz's invention of the ophthalmoscope the significance of which one cannot emphasise too much. The ophthalmoscope is only one instance of an instrument made from curiosity, because you cannot cut a man up to find out what goes on inside, which has proved immensely important. Dawson's development of averaging techniques, which are now ubiquitous throughout medicine and physiology, was originally aimed at detecting certain small electrical responses of the brain through the scalp in healthy subjects.

Other famous discoveries could be cited but I prefer to take the opportunity to advertise some phenomena, old and new, whose significance is yet to be fully explored. I start with the little-known Piper rhythm.⁵ This is an oscillation discovered by Hans Piper in 1912 of 30-50 cycles per second, seen in the electrical responses of a human muscle that is contracting as hard as it can; for example in the biceps muscle when hanging from a beam. More or less the whole muscle is involved, all the motor units beating synchronously at the Piper frequency. We know this because the Piper beats are nearly as large as an artificially synchronised action potential caused by stimulating all the fibres with an electric shock.⁶ Figure 1 shows the Piper rhythm, recorded with surface electrodes, the beating motor units seen with a fine twin-wire needle electrode inside the muscle, and an electrically excited synchronous action potential for comparison. It is not known at all why, in a strong contraction, all the motor units get together in this way. One has the feeling that if one could answer that question one would understand significantly more about how a voluntary effort throws a muscle into activity than we understand now. As far as I know a full-blown Piper rhythm has not been recorded from an animal, and one can see why not.

Fig 1 The Piper rhythm during a strong voluntary contraction recorded simultaneously from A, surface electrodes over the abductor of the little finger and B, a bipolar needle electrode in the muscle near the tendon. The discrete bursts of unitary action potentials from the needle match in size and spacing the Piper waves from the surface electrodes. C, maximal action potentials from stimulation of the ulnar nerve at the wrist recorded from the same electrodes at the same gain. Time marks 20 ms and, faintly, 5 ms. (Merton, unpublished records, March 1957.)

Another phenomenon, discovered on man, in which Nature is clearly trying to tell us something, unsuccessfully once again, is the influence of vision on muscular tremor. In a conventional manual tracking task with visual guidance, the tremor of the

hand that does the tracking is often found to have a conspicuous oscillation at a frequency of about 10 c/s. If the tremor is recorded and subjected to a frequency analysis, this oscillation shows up as a peak in the spectrum at that frequency, as in fig 2. In 1955, Sutton⁷ at the Radar Research Establishment made the unexpected and remarkable observation that the peak disappeared if the subject closed his

Fig 2 The visually-determined 10 c/s tremor peak in voluntary contraction. The subject's task was to press with a force of 2.3 kg on a vertical joystick held in his fingers. Runs of 30 s were recorded with, alternately, the subject watching a visual display on an oscilloscope of force exerted, or, under otherwise identical conditions, with the eyes closed. Sixteen runs of each kind were recorded and analysed. The mean error spectra with the eyes open (filled circles) and with the eyes closed (open circles) are plotted. The error bars at selected frequencies represent twice the standard error of the mean. The interrupted line has a slope of 6 db/octave.⁸

eyes, as the figure shows. This very careful work^{8 9} was confirmed and extended by Rashbass, Morton and myself.¹⁰ The significance of this discovery and its extensions is that this particular 10 c/s peak cannot be, as had been supposed, a latent oscillation of a purely neuro-muscular circuit (although such an oscillation at about the same frequency may also occur¹¹). Vision must enter into muscular control at a much earlier stage than usually suspected, and in a quite subconscious way—for no-one is more surprised than the subject when his 10 c/s oscillation is shown to have vanished. This discovery of Sutton's is a fine illustration of human experiment giving an unexpected and unconventional glimpse into the ways of the brain.

An example which reaches much further back than either of these is eye-rolling. If you look at your eye in a mirror and rotate your head about its fore and aft axis by tilting it first towards one shoulder and then the other about once a second, the eye can be seen to roll in the orbit in the opposite sense, so as to tend to stabilise the retinal horizon. Or these eye movements can be perceived after putting a linear after-image on the retina by staring at a fluorescent light tube, and again tilting the head.¹² From looking in the bathroom mirror I had been familiar with these rolling movements since childhood, so I was surprised to find that their existence is discounted by Helmholtz in Section 27 of his great work "Physiological Optics"¹³ (1st edition 1866). It proves, however, that eye-rolling and its function (to stabilise the retinal image) were clearly described in man by no less a person than John Hunter in the eighteenth century under the title "The use of the oblique muscles".¹⁴ Helmholtz's mistake may be responsible for the relative neglect of the phenomenon. Eye-rolling is the most easily demonstrated vestibulo-ocular reflex, partly because fixation reflexes do not compete or interfere with it; nevertheless it still arouses no clinical or physiological interest. It can be recorded by an optical method, with the result shown in fig 3.¹⁵ The subject sits in a side-to-side swing with his eye at the centre of rotation. Eye rolling does not stabilise the retinal horizon completely, but at that frequency of swinging it reduces the amplitude of the oscillation of the eye relative to the external world to about one quarter of what it would be if the eye were fixed in the orbit. The smooth motion of the eye is broken by sharp saccadic rolling movements which, interestingly enough, occur around the time when the swing is moving fastest and the head is upright, not when it is at its greatest inclination. These saccadic movements in roll were described by Hunter but I do not know that they have been mentioned since then until our records

Fig 3 Records of compensatory rolling of the eye. The subject swings from side to side in a swing, with his eye at the centre of rotation. He wears a contact lens carrying a birefringent plate of mica on a stalk. Eye rotation relative to the fixed surroundings is measured using polarised infra-red light. The large smooth sinusoidal trace is the excursion of the swing. The smaller broken trace is from the eye. Disregarding the irregular saccadic movements, the eye moves roughly one quarter of the amplitude of the swing and lags by about 15° . Similar records were obtained in pitch darkness. In the calibration record, taken with the mica plate attached to the swing, the two traces superimpose, showing that the sensitivity of the two records is equal. The calibration scale of degrees is approximate.¹⁵

were made. This may be because you cannot see them on yourself in a mirror; apparently vision is suppressed during a rolling saccade as it is in an ordinary saccade that changes the fixation point; but you can at once see them on someone else who tilts his head from side to side. This is a very simple and convincing experiment that anyone can try and, like Hunter's original observations, it conveys some of the appeal of human physiology.

My final instances of new phenomena coming to light in experiments on man are taken from work done in this hospital with HB Morton and CD Marsden. One is the automatic control of the sensitivity or, as we call it, the "gain" of the stretch reflex.^{16 17} If a muscle is pulled upon, it tends to pull back. This is the stretch reflex, named by Liddell and Sherrington in 1924 from experiments on decerebrate cats.¹⁸ A similar reflex, which may or may not correspond exactly with their reflex, is seen in human subjects. I ought to say that we distinguish the stretch reflex, which in the intact subject is the response of the muscle to bending the appropriate joint, from the impulsive response seen in the tendon jerk. In the human subject the sensitivity or gain of the stretch reflex, the vigour with which the muscle responds, depends on the force the muscle is exerting to start with. The muscle's responses match the heaviness of the task it is engaged in; indeed in some situations they are fairly closely in proportion. When a muscle is properly relaxed there is no stretch reflex to speak of, or only such slight response as contributes normal tone, normal resistance to passive movement—if that is what tone is. The stretch reflex only manifests itself when the muscle makes a contraction, and it becomes brisker the harder the contraction. Nothing of the kind seems

to have emerged from animal experiments; but the idea makes sense and it adds new latitude to the interpretation of deranged muscle tone in disease. Gain control of stretch-reflex-based mechanisms also turns out to be important in offsetting the effects of muscular fatigue; human subjects performing skilled tasks were known to compensate surprisingly well, even for fatigue intensified by arresting the circulation, and this now becomes more intelligible.¹⁹

Finally, recent experiments have uncovered an apparently new class of very sensitive and rapid postural reactions in human subjects who are standing or kneeling, which falls squarely in the category of things which would be more difficult to investigate in animals. It is found that quite small mechanical disturbances applied to the hand while it is carrying out a voluntary task cause responses, detected in the electromyogram, in muscles of the shoulder, of the trunk and as far away as the lower leg.²⁰ It would not be surprising if movement of the upper arm and sway of the trunk should, through the stretch reflex, elicit reflex contractions or relaxations of relevant muscles to maintain posture; but it proves that the responses that occur begin at such short latency (55-100 ms in different muscles) that sway of the body caused by the perturbations to the hand, does not, as recorded, exceed a few micrometers. From this and other evidence it is clear that the afferent limb of these distant postural reflexes is from the active hand and not from the postural muscles themselves;^{21 22} in this way the postural muscles can react so early that they anticipate disturbances of posture and are thus in a position to prevent disturbances rather than to correct them after they occur. This appears to be a novel mechanism. Traub, Rothwell and Marsden have already shown

that it is put out of action in many moderately advanced cases of Parkinson's disease.²³

A second attraction of human work, allied to new discovery, is that things sometimes turn out differently in man from what might be expected from the animal results. An instance of this comes again from the human stretch reflex. In movements of the thumb, mechanisms based on the stretch reflex can be shown to assist automatically in overcoming external obstacles or, conversely, in diminishing contraction if the load against which the muscle is working is suddenly and unexpectedly removed. This is the so-called servo control of muscular contraction (the existence of which, incidentally, was first proposed from consideration of human experiments²⁴). Usually these automatic servo responses are greatly diminished if the thumb is anaesthetised—the thumb itself that is, leaving the muscles that move it unharmed.^{16 25} Figure 4 shows the effect. The left hand side is for the normal unanaesthetised thumb. At the bottom are records of thumb position in various movements. The upper traces show the activity of the relevant muscle in a mode of recording its electrical responses in which the slope of the traces is a measure of the degree of contraction of the muscle. The traces in the middle are for unobstructed movement, showing a steady movement of the thumb and a nearly constant amount of activity in the muscle, as indicated by the constant slope of the upper trace (control). An obstruction is shown by the flattening of the movement trace; in this case the slope of the upper trace increases, showing that the muscle is working harder (halt, H). The other records show movements that are forcibly reversed (stretch), which gives a bigger effect than mere obstruction; or allowed to accelerate by a reduction of load (release), which results in diminished activity and slope. The right hand half of the figure shows that with the thumb anaesthetised, by a ring block with local anaesthetic at its base, all these responses are greatly diminished, although the muscle can contract well enough otherwise. Now in a decerebrate cat Sherrington found that cutting the joint nerves and skinning the limb did not affect his stretch reflex. So the result with the thumb was quite unexpected. Elsewhere in the human body, anaesthesia of the extremities does not interfere with stretch reflexes.²⁵ They behave, that is to say, like those in the cat. The peculiar, but quite definite, result with the thumb may reflect the fact that in primates the thumb is particularly under the control of the cerebral cortex and through the cortex of its own skin afferents. Whatever the explanation, the human experiments have again turned up something new and intriguing.

Figure 4 shows a second way in which the human stretch reflex here behaves unexpectedly. There are

Fig 4 Stretch-reflex-based compensatory responses (servo responses) from the long flexor of the thumb: and the effect on them of anaesthesia of the thumb. The records at the bottom are of angular position of the distal phalanx of the thumb. The records above are integrated electromyogram from surface leads over the long flexor in the forearm. The subject makes repeated flexion movements, once every few seconds, and attempts to keep a constant rate. The load is initially the same in all movements and in some it does not change, giving the records labelled "control" (C). In other movements (randomly chosen) 50 ms after the recording starts, the load is increased sufficiently to arrest the movement (halt, H); or increased by a larger amount so as to reverse the movement and stretch the muscle (stretch, S); or reduced so as to allow the movement to accelerate (release, R). In the normal thumb the mechanical perturbations cause brisk compensatory responses in the electromyogram; but with the thumb anaesthetised (the muscle itself being unaffected) the responses are greatly diminished. Each trace in these records is the average from 16 movements.¹⁶

no responses of spinal latency. Tendon jerks, which give a measure of the time round the reflex arc to the spinal cord and back, have a latency of about 22 ms in the forearm muscle in question. But the responses in the figure do not start for double that time. The time from when the movement is halted, or reversed, or allowed to accelerate, to when the slope of the electrical records changes is about 50 ms. So there is nothing to show that these responses are spinal. Animal experiments always led us to think, perhaps not very critically, that stretch reflexes had a spinal arc, like tendon jerks; but here there is no sign of an active spinal arc at all. Perhaps, we wondered, these responses in the human thumb are not spinal.^{26 27} The idea was not new. Hammond, working on the human biceps at the Royal Radar Establishment, had suggested from similar estimates of latency that the

stretch reflex arc might run through the brain;²⁸ and Charles Phillips at Oxford had speculated about a stretch reflex arc through the motor cortex, from his pioneering studies on the baboon.²⁹

This brings me to a third advantage possessed by human physiologists and one particularly close to Dr Carmichael's heart—the ready ability to turn for assistance to abnormal and pathological material. The transcortical theory of the stretch reflex which we found attractive was open to experimental test. Marsden in particular saw that, if it were true, our type of stretch reflex must disappear if the sensory tracts to the brain were out of action. Figure 5 shows records from a golfer with damage to the right dorsal column at C2. He had no stretch-reflex-based responses in that thumb. The other side gave normal responses. The right side had normal strength and what is more, normal tendon jerks; so the spinal pathway was open. But damage to the long sensory tracts had killed the stretch reflexes, as expected.³⁰ Subsequently it was shown that lesions of the motor cortex or of the pathways beneath it also interfered with the stretch reflex, as they ought.³¹

The converse type of subject was a Cambridge undergraduate, healthy in every way, but clinically without tendon jerks. Figure 6 shows his records, compared with mine under identical conditions.²⁷ The responses based on the stretch reflex are effectively identical; so a sluggish or an inactive spinal

pathway is of no consequence to the stretch reflex, as again would be expected if the responses were not spinal.

All this time we had in mind Dr Carmichael's famous myoclonic case, Langdon, who died in this hospital in 1947.³² Langdon had giant electrical responses in the cortex accompanying the myoclonic jerking of his body, and these giant responses and jerks could also be evoked by peripheral nerve stimulation. It was on him that Dawson recorded the first human evoked responses³³ and was led on to build his averaging machine for recording the much smaller ones in normal subjects.³⁴ For our purposes it was remembered that Langdon's jerks had a latency of about 50 ms in the arms; double the latency of the giant evoked waves in the cortex. So there was the right length of time for a nerve volley to get to the cortex to evoke a giant wave and for one from the cortex to get back to the muscles to cause the jerks, assuming that both volleys travelled at about the same speed. Dawson used the term transcortical reflexes to describe the jerks³⁵ (the first use of the term transcortical reflex that I know) on the assumption that they came from where the giant waves were found. (On the opposite page Macdonald Critchley reports a paraplegic eunuch with lues.) Langdon also jerked if he was touched, and Dr Alan Norton, then a clinical clerk, from many hours of meticulous observation concluded that an essential

Fig 5 The effect of damage to the ascending sensory pathway on stretch-reflex-based responses in the thumb. The methods were the same as for fig 4, but here the displacement records are on the right and the integrated electromyograms on the left. The patient had a sensory loss in the right hand due to a dorsal column lesion at C2. The upper records, from the unaffected left hand, show normal responses in the long thumb flexor; but in the right hand (lower records) they are virtually absent.³⁰

Fig 6 Stretch-reflex-based responses from the long thumb flexor contrasted with finger jerks. *A*, in a subject, otherwise healthy, with clinically absent tendon jerks. *B*, in a normal subject (PAM). The main records, which are very similar in the two subjects, were obtained by the same methods as fig 4. The electrically-recorded finger jerks, which appear as insets, were elicited in the ordinary way by striking against the lightly flexed fingers with a hammer incorporating a microswitch to trigger the sweep. Each record is the average of 32 and they are raw electromyograms (not rectified and integrated as the others). For the inset in *A* the recording gain was 8 times that for the one in *B*. The peak to peak size of the averaged electrical jerk responses was $800 \mu V$ in *B*, but only $73 \mu V$ in *A*, from the subject with clinically absent jerks. So normal stretch reflexes can exist alongside tendon jerks which are less than 10% of normal size. In *A*, the electrically recorded jerk is multiple, with the second component at stretch-reflex latency. The insets are arranged so that the start of the record, when the tap was delivered, is above that point in the main records (50 ms from the beginning) at which the perturbations (halt, stretch, or release) were applied: the timing lines give the time in milliseconds from that point too.²⁷

ingredient of any stimulus that caused a jerk was muscle stretch. Were his jerks, then, enormously exaggerated trans-cortical stretch reflexes? To help us answer this Dr MJ McArdle, at the critical moment in 1972, produced a myoclonic patient, not unlike Langdon in behaviour, who gave a fine myoclonic jerk, spreading up the arm, when her thumb was stretched, at precisely the magic latency of 50 ms, as fig 7 shows.

That is all I am going to say on how patients and exceptional subjects help human physiologists, for I still have three points to make. One is the simple one that in working on the motor system it makes all the difference to be able to get the subject to do exactly what you want. It might be possible to train monkeys to do the sort of experiments we do on human stretch reflexes, but it would be a big job. But in experiments on the Piper rhythm, on voluntary fatigue or on the maximum firing rate of single motor units,³⁶ how would you ever know that the monkey is really trying? Again, in their magnificent experiments on

single human sensory fibres, Hagbarth and Vallbo³⁷ simply manipulate a fine electrode by hand into the median nerve until they get a single unit. The subject has first to keep dead still and then to make little finger movements. Could a monkey ever be trained to oblige? On another topic, could we ever have trained a monkey to make repeated saccadic eye movements of the same size in pitch darkness, to show that they are slower than those of the same amplitude made in the light?³⁸

The fifth point, a very obvious one, is that, in matters of sensation, it's a great help if you can ask the subject what he feels. There are sometimes ways round the difficulty with trained animals, but I wonder how one would arrange matters to do the following key experiment on the function of muscle spindles, the most interesting and numerous of the sense organs in muscle. It was first done by Helmholtz over a century ago ("Physiological Optics" Section 29).¹³ Look steadily at a photographic flash tube. Press the button and you get an after-

Fig 7 The stretch reflex from the long thumb flexor in a case of myoclonus. The records were taken by the same methods as for fig 4. There appear to be no responses to halt or release, but stretch causes a large response at the usual latency of 50 ms. The stretch response was seen to spread to other muscles, causing a myoclonic jerk of the whole arm. (Marsden, Merton and Morton, unpublished records, May 1972.)

image. Now look at a blank surface. Shut one eye and move the other eyeball by jerking at the outer canthus. The after-image does not move. You interpret what you see precisely as if the eye had stood still. Now the muscles that move the eye are full of muscle spindles, which must be excited by the jerks. Since the appearance of the after-image on the retina is as if the eye had stayed still, as if no messages had come from the eye muscles to say that the eye had been moved at all, it follows that muscle spindles do not give conscious information about eye position, at any rate not information which can be used to correct visual impressions. This is one of my favourite experiments. I regard it as a very telling and a very human one, and it has that note of certainty about it which I have urged already as a characteristic of the best human experiments. I first read it as a direct result of Dr Carmichael shrewdly commissioning that a review article we were writing on muscle spindles should discuss the function of those in the eye muscles, then newly rediscovered.³⁹ (The eye-rolling work was another outcome.)

Lastly I come to a propaganda point which has some topicality. You can sometimes do useful experiments on man which you would be unlikely to be allowed to do on animals. When asked whether he was prepared to continue with an experiment on himself which was obviously causing distress,

Professor RHT Edwards at University College Hospital has been heard to reply "yes, it's only pain". This option is not available to us with conscious animals, so we can risk bigger electric shocks and more intense ischaemic pain on ourselves. This is the point for a little debunking (although not of the ischaemic pain experiments). It is clear that, undreamt of in the philosophy of immunologists, human subjects develop antibodies to electricity. The very large electric shocks sometimes used now, although they seem unpleasant to start with, rapidly become a matter of little concern.

Two fields of investigation in which large electric stimuli are needed are direct stimulation of human muscle with DK Hill at the Royal Postgraduate Medical School⁴⁰ (which has been used to study voluntary fatigue⁴¹—another enquiry for which human subjects have proved particularly favourable, if not uniquely suited); and stimulation of the human brain through the scalp.^{42–44} Both are quite new. The latter is easily demonstrated (fig 8). A stimulating electrode is placed over the arm area of the motor cortex. To stimulate, a condenser, charged to 1500 volts, is discharged through the electrode by means of a Morse key. The muscles of the opposite hand give a twitch. The threshold is lower if the muscles make a slight voluntary contraction to start with.

Fig 8 Stimulation of the motor cortex through the scalp. A pair of pad electrodes on a holder is applied so that the electrode that will go positive is over the surface marking of the arm area. To stimulate, a 0.01 μF condenser, charged to about 1500 v, is discharged through the electrodes via a Morse key. The muscles of the opposite hand respond with a brief twitch. (Demonstration at an undergraduate lecture, February 1980. RH Adrian and PA Merton, as subject.)

This experiment would probably not be feasible on an animal. Their skulls are thicker and tend to be covered in muscle; they have fewer monosynaptic corticospinal fibres; and the threshold would anyway be higher if they were not tensing the desired muscles in advance. All these things mean that they would need much bigger shocks, which would probably be regarded as unjustifiably painful. So, at any rate with present techniques, stimulation of the brain from outside is an essentially human pastime.

So much for propaganda for human neurophysiology. I must just put in that nothing I have said is to be taken as in any way meaning that I underestimate the enormous importance of experiments on animals, from primates to protozoa. If I were the Medical Research Council and was given a million pounds to be used to support either work involving animals or work involving human subjects, but not both, I can easily see myself allocating it to those who use animals and who are making such tremendous advances. It is only that I would like to see the balance of achievement redressed. If I were able to put it over properly, I am sure you would find my propaganda powerful, as I really believe it is. Why do more people not do human experiments? At the risk of becoming sententious I will try to make a start at answering that question. I am sure that the main reason is the obvious one: that in an animal experiment you can dictate the experimental conditions—even down to perfusing squid axons and so determining the chemical environment both inside and outside a cell membrane. So it is easier to ask clear-cut and quantitative questions in animal work; (whether it is really easier to ask imaginative questions and get answers to match is another matter). In human work what one can do to the subject is very obviously restricted and the initial hurdle is to think of the kind of questions to ask that will give an answer under the many constraints imposed—to quote Claude Bernard, to have the knack to elicit by experiment “the response that Nature gives to the physiologist who knows how to interrogate her”. A good dose of the works of the masters in the field no doubt helps to promote the required attitude of mind, but is rarely administered in undergraduate physiology courses. What seems to be required is a deliberately acquired cast of thought and a measure of confidence: confidence that there are fine experiments to be done on man, if only one could think of them; and confidence to attempt them; confidence which, I suspect, only comes from experience of working with human subjects and getting a feel for what can be achieved in devising valid and acceptable methods.

The stress on confidence, “one of the most important ingredients in the scientific attack” as he

put it, derives from Adrian.⁴⁵ I will end by demonstrating how failure of confidence and perseverance can hold things up. I have here a device I built in about 1947 to stimulate the brain through the scalp. It consists of an old-fashioned gramophone motor driving contacts which connect a condenser alternately to a battery and then to the subject. We used long trains of stimuli and large plate electrodes on either side of the head. This was unsuccessful because it became too painful before the voltage could be turned up enough to make it effective. I now show that using this original stimulator but with the right sort of electrodes in the right place, and limiting the number of stimuli to a few at high voltage, we could have succeeded all those years ago in stimulating the motor cortex—and given pleasure to Dr Carmichael, who was always ready to incite us to this kind of escapade.

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