WHERE

Leading acupuncture research towards clinical relevance

by Alan Bensoussan

This paper follows the presentation of a seminar on acupuncture research organised by the Register of Traditional Chinese Medicine in London. The turnout was surprising, most especially as research has never been a popular area of study for TCM practitioners. It was, however, clear from the debate that was generated that a number of practitioners have given considerable thought to the issues involved.

Like all healing interventions the question must be asked of acupuncture as to how much of its efforts are 'scientific' and consistently predictable and how much of its success depends upon the skill of its practise (which may include the art of applying TCM theory). One way to begin to answer this is to look at what we know is scientific about acupuncture, and for this it seems necessary to delve into substantial reviews of the research literature.

It is my argument that there is a great deal of well established research demonstrating that acupuncture has a profound effect on a wide range of physiological systems, and yet the existence of this research still needs to be brought to the community's attention. Until now most reports (for example, the National Health and Medical Research Council report in Australia (1989) and the Dutch metaanalyses (ter Reit et al, 1990(A), 1990(B); Kleijnen, 1991) attempt to make fairly final statements about the known clinical benefit of acupuncture by reviewing solely the clinical studies. Clinical studies are only one way of providing evidence for the success of acupuncture; experimental work both with animals and more especially with humans provide different yet equally valid evidence. Often this work is completely ignored in critiques of the scientific validity, and therefore the clinical potential, of acupuncture.

Furthermore, so many of the problems with the clinical research studies in the past have been precisely a consequence of investigators misappropriating acupuncture in their studies and this has been due largely to them being non-practitioners or poorly trained in the field of TCM. The fact that so much of the related research has been performed, and the commentary dominated by poorly trained and insufficiently practised acupuncturists must augur badly not only for the validation of TCM but also by undermining the profession's authority and expertise. (Yet acupuncturists have also at times slipped into making the same mistakes as so many researchers exploring acupuncture, in that they have not read the literature before commenting.) Melzack & Wall's gate control theory had to be revised on a number of occasions because it didn't fit in with (well established) clinical reality (Bensoussan, 1990, p.77.) The popular endorphin theory itself can only be maintained with difficulty in view of the studies that demonstrate long-term benefits (two months to two years follow-up) of acupuncture (Bensoussan, 1993, p.236).

Identifying Research Needs

The difficulty is that many of the theories on the mechanism of the action of acupuncture as far proposed have been incapable of completely addressing the clinical portrait of acupuncture. Yet the research does show unequivocally that physiological changes occur that are distinguishable from stress and placebo, and related to the acupuncture process. There is sufficient data available in this area not to pursue this line of research much further. Hence, when acupuncturists call for more research it is important that the areas of concern or interest are clearly identified.

So what areas of research are needed? When will the health authorities say 'OK, we have enough reliable knowledge about acupuncture - let them practice freely'? It is my impression that this will not come about through the accumulation of scientific knowledge (to some form of acceptable proof - which of course in itself is rather elusive), but through further professionalisation and successful development of ourselves as TCM practitioners. And I firmly believe that this will only occur when we scrutinise more closely our most sacred cow - TCM theory. When we understand better how to apply it; when we evaluate what is of best use to us now and how to contextualise it. This lack of examination of our sacred cow represents the largest current gap in research (most particularly in the West). Few acupuncturists would falter in crediting a fair degree of importance to TCM theory most especially in their practices, and conversely none that I know have not at some time entertained nagging doubts about some significant aspect of theory. What parts of TCM theory are important to us and to what degree? In the United Kingdom the seasons are marked although no real 'late summer' exists. In Australia in the north there is a definite 'late summer' but not as clear a demarcation of seasons. Does this affect the clinical value of Five Phase theory? Whilst this may seem a trite question, it is the application of TCM theory that we need to address.

Unschuld argues that the popularity and level of acceptance of TCM theories and schools of thought varied throughout Chinese medical history in response to shifts in religious behaviour and socio-political ideologies (Unschuld, 1985, pp.8-14). Others developed in a more pragmatic manner as a reflection of environmental (climatic) differences. It should not be surprising then that the broad
movement of traditional Chinese medicine to the West should also be affected by shifts, modifications and selectivity of theory.

That TCM theory is clearly important in practice is demonstrated by a simple survey of clinical studies (Bensoussan, 1993, p.15) or by a theoretical example (Bensoussan, 1991, p2). Clinical studies, however, are often difficult to interpret (due to the variety of variables selected for study) and, therefore, are subject to varying interpretations in terms of their contribution to scientific knowledge. The same study is vulnerable to being interpreted in different ways (and here again possibly reflecting the reader's familiarity with TCM practice and literature).

An analytical review and critique by the author of the clinical and experimental studies in acupuncture reveals:

- Stress analgesia and acupuncture analgesia are different processes. They differ in nature and neurological pathways
- Acupuncture point specificity is important to obtain positive results. There is a difference in outcome between real and sham treatments
- The use of TCM theory is important to obtain positive results. A number of Chinese studies illustrate this, although it is not easily demonstrable in animal studies
- Formula acupuncture may produce results equally as good as individualised treatment in some disorders. Nevertheless, individualisation of treatment is important wherever possible (and this is the challenge to studies – to remain flexible and be able to consider all categories of variables)
- Studies have generally been poorly designed (from a TCM point of view)
- Qi sensation is important in relieving clinical symptoms, but not necessarily in longer term curative effects.

Neurohormones

Whilst the outcomes of a range of clinical and experimental studies implicate a variety of physiological systems, almost all studies on the mechanisms of action focus on pain management. Despite this unilateral direction of investigation, and fortunately because of the diversity of endogenous analgesic mechanisms, this research can still generate further insights into the physiological mechanisms of acupuncture. Hence (interference at) the main pain pathway has been the focus for research on where and how acupuncture works, and as an unfortunate consequence of this neurological thesis, even Melzack and Wall’s gate control theory is still currently proposed as the principle mechanism of action in some contemporary texts.

The following is a summary of neurohormones that research has demonstrated to be involved in acupuncture:

<table>
<thead>
<tr>
<th>Biochemical substances involved in acupuncture</th>
<th>Neuropeptides</th>
<th>Monoamines</th>
<th>Simple amino acids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids</td>
<td>Acetylcholine</td>
<td>Dopamine</td>
<td>Glutamic Acid</td>
</tr>
<tr>
<td>Enkephalins</td>
<td>Noradrenaline</td>
<td>GABA</td>
<td></td>
</tr>
<tr>
<td>Substance P</td>
<td>Substance P</td>
<td>Intracellular secondary enzymes</td>
<td>Cyclic AMP, Cyclic GMP</td>
</tr>
<tr>
<td>Cholecystokinin</td>
<td>Serotonin</td>
<td>Glutamic Acid</td>
<td></td>
</tr>
<tr>
<td>Angiotensin II</td>
<td>Dynorphin A</td>
<td>Glutamic Acid</td>
<td></td>
</tr>
<tr>
<td>Corticotrophin</td>
<td>Dynorphin B</td>
<td>Glutamic Acid</td>
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acupuncture. In the ideal analgesic response, both central serotonin and opiate activity was high, in moderate analgesia only one remained high, and in poor analgesia both exhibited low levels of activity. And for those of you who were deluded enough to believe there was a chance of escaping basic mathematics by turning to acupuncture, here is one of the regression equations that was derived and is broadly reproducible in a number of species:

\[
y = 0.64 x_1 + 0.48 x_2 - 75 \text{ where } y = \text{acupuncture analgesia effect measured as the average percentage increase in pain threshold over the basal level;}
\]

\[
x_1 = \text{central serotonin content expressed as percentage of the normal level;}
\]

\[
x_2 = \text{opiate activity expressed as a percentage of the normal level.}
\]

(\(r = 0.69, n = 27, P < 0.001\))

This is further evidence to show that no single neurohormone solely determines any acupuncture effect.

In overview there are five principal lines of evidence that endorse the distinctive role of 'traditional' acupuncture over stress (or undirected) responses:

1. LESION EXPERIMENTS demonstrate that selectively severing neuroanatomical connections is capable of differentiating between real and sham treatments.

2. PHARMACOLOGICAL MANIPULATIONS have been conclusively employed to highlight the neurohormones involved in real as opposed to placebo or sham treatments.

3. EVOKED NEUROLOGICAL RESPONSES (EEG's and unit potentials) are evidenced to alter differently under real and sham acupuncture. This concurs with the results of the lesion studies.

4. BIOCHEMICAL ASSAYS of animal brain extracts demonstrate acupuncture-induced biochemical changes in specific brain nuclei.

5. CLINICAL CORRELATION of the animal and human studies with the experimental neurophysiological research. Most importantly the first four lines of evidence are basically inconsistent and corrobore with the clinical evidence.

Following these lines of evidence there is no doubt that traditional acupuncture is doing something distinctive. Whilst it is important to maintain that fact in the forefront of our minds, there are problems that the research has not been successful in addressing and it is worthwhile turning to these now.

Evidence For Tradition

INTERESTING AS they are, these five lines of evidence provide insights that are largely a *posteriori*, that is, they provide us with retrospective understanding. Because of its complexity, none of the outcomes of the neurophysiological research are capable of being used in a predictive manner in clinical applications. (Even Han's regression equations are not clinically applicable because not only would there be dubious value in measuring central serotonin and opiate activity in order to predict analgesic response, but more importantly, these regression formulae were calculated retrospectively after specific and uniform acupuncture treatments were performed, and did not take into account potentially different effects from different treatments.) Clearly a new understanding is needed to make sense of this neurophysiological research.

Other problems exist with the neurophysiological research. It has been performed largely (although by no means solely) on animals and the broad extrapolation of these results to humans raises many concerns. A consequence of the dominance of animal studies has also caused there to be restrictions in the testing of TCM theory both by way of limited diagnosis and by way of point selection (as a very limited number of points are usually used on animals, principally for ease of access). Furthermore, electrostimulation has often been the most popular form of regulating the level of stimulation on the subject, yet this too may not be a good representation of traditional practice, most especially in the extrapolation of data from studies where animal subjects are often subjected to higher levels of stimulation than ordinarily tolerable by human patients. This brings us to a final difficulty with this research - that still too often sham treatments have been omitted as a form of comparison to the real treatment. Whilst there are sufficient studies that have demonstrated differences between real and sham effects, the sham comparison should become a principal point of protocol in all acupuncture studies. Sham treatments have been shown to cause responses different to both real and placebo acupuncture effects.

Practical Applications Of Research

IN WHAT WAYS is it possible to make acupuncture research more useful to the profession? The current theories of mechanisms of action provide little excitement principally because they have limited clinical applications, (they are not able to be used in a predictive manner), and they do not necessarily coincide with clinical characteristics. Hence, firstly, if research is to be more useful to the profession it ought to be more predictive in a clinical context. Focusing on testing TCM theory will sharpen our tools and equip us with more defined guidelines to steer clinical engagement and improve clinical reliability.

Secondly, it is important to attempt to integrate the solid neurophysiological research into a better understanding of the clinical characteristics of acupuncture. The most fundamental claims of acupuncture and the traditional protocols of its practice have too often been overlooked.

What is the most important claim of acupuncture? Without a doubt it must be that acupuncture can have a lasting impact on health. Yet none of the neurophysiological research directly indicates that acupuncture treatments are cumulative in their effect. Why should one treatment affect another a few days apart? Yet a number of studies have performed two months to two year follow-ups, and show acupuncture has mobilized a permanent change (Helms, 1987; Wang, 1987; Cheng & Pomerans, 1987; Slawinski et al, 1984; Abenon et al, 1984; Shi & Tan, 1986; Shi et al, 1987; Bullock et al, 1987; Marcus, 1979; Loh et al, 1984).
It is apparent from these studies that some 'build-up' of effect does occur that causes a lasting change away from a pattern of illness. We know from acupuncture practice that performing a series of treatments is usually important, as are the relative proximity of treatments. The question must be asked as to whether acupuncture can treat disorders by altering physiological patterns of behaviour, for example, permanently changing 'set points' of physiological controls. Moreover, it appears quite feasible that acupuncture could be perceived as a form of retraining on a physiological level.

Clinical characteristics of practice such as close repetition of treatments, the need for breaks between courses of treatment, and the development of acupuncture tolerance (Han et al, 1986) as a form of habituation, all mimic learning behaviour. To repeat a sensory experience such as acupuncture is similar to receiving a series of lessons which is capable of generating new (physiological) memory. Most of the neurohormones discussed thus far have been linked with memory and learning. The repetitive firing of these neurons can alter the transmission of impulses at synapses and ultimately generate synaptic change. That acupuncture can cause structural neurophysiological changes has already been demonstrated in animal studies by Pomeranz, Mullen and Markus (Pomeranz, Mullen and Markus 1984).

Clearly acupuncture can be understood as a process of physiological relearning, where the current neurohumoral research demonstrates in principal only the immediate response. The shift observed in clinical practice toward healthier physiological behaviour may, in some cases, simply be a matter of activating the right trigger, but in most cases requires the persistent repetition of treatment. It appears that only under this constant encouragement do lasting changes occur. It is important to admit some concept of learned behaviour in order to link better the outcomes of research with clinical reality.

Many explanations have been offered to explain the mechanisms of acupuncture and these in turn have altered as awareness of acupuncture grew in the West. Each proposal usually had its weaknesses, which appeared after closer acquaintance with the practice of acupuncture and the breadth of its application. Although current neurophysiological understanding of acupuncture is very sophisticated and leaves no doubts as to the potential influence of acupuncture, even this theory needs to be refined.

Interestingly enough, the bioelectrical theory of action to which I have not yet made reference, is one that attempts to link the electromagnetic characteristics of the acupuncture points with the observed myoelectric currents during treatment and subsequent neurohumoral changes (Bensoussan, 1991). Despite some good foundation research on the electrical identity of the acupuncture points, and despite its enormous potential impact, this area has generated little interest or investigation by medical researchers.

Unquestionably, this ancient medical procedure does require more thorough explanation, yet this should not be a barrier to its adoption in the western health care system. Research, however, needs to be directed more clearly to define the limitations of the acupuncture techniques and produce guidelines that act more successfully as predictors of its efficacy, including its longterm benefits.

REFERENCES
Han, J.S., Ding, X.Z., Fan, S.G. (1986). CCK-8 antagonism to electroacupuncture and a possible role in electroacupuncture tolerance. *Pain* 27(1),101-115