The patient in front of us: from genes to environment

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In the current climate of professional insecurity and threatening market-place forces, it helps if physiotherapy can demonstrate to those who purchase its services that it is moving forward, keeping up to date, being cost effective and providing the public with a desirable service. The pressure is on. For example, in 1998 Cherkin and colleagues published the results of work that compared the outcomes for low back pain from chiropractic, McKenzie physical therapy, and an educational booklet. The outcomes need to be scrutinised in detail to be fair, but the publicised result of the research goes like this:

> Chiropractic and McKenzie treatments, which in this study cost about $235 more than the booklet, did not lead to decreased recurrences of back pain or to reductions in visits or costs of back care during the two years following treatment.
>
> Conclusions:
>
> …given the limited benefits and substantial costs of chiropractic manipulation and McKenzie physical therapy, treatments of this type should be used sparingly.

It is possible that the results will be generalised to all forms of therapy for back pain and sceptical referring practitioners will then take comfort in performing their usual speedy examination, giving a few words of reassurance and advice followed by handing out the latest back pain booklet, secure in the belief they are acting on 'the latest and most cost effective evidence'. They may have a point, but the complexity of factors that play a role in precipitating chronic pain and chronic disability are such that some at risk patients require thoughtful and time consuming assessment and management in the *early days* of their problem. This is the key time. Linton's (1998, 1999) work, has shown that identifying and addressing the known risk factors in early management of back pain can reduce chronic disability by 8 fold over 'treatment as usual'.

The interventions Linton (1998) used involved understanding and dealing with the anxieties and fears patients have about causing pain and causing structural damage with movement and activity, plus other psychosocial issues discussed at length in this book. What is evident from this work, is that alongside cognitive behavioural strategies that improve the patients' ability to cope, lies the fundamental issue of restoration of the patients' trust and confidence in their physical structure during activity. Hence the emphasis on incorporation into rehabilitation strategies of physical programmes aimed at providing a progressive restoration of confident physical function. Restoration of 'confidence', is about *proficient* examination, *helpful* education and *practical* experience. *This is a highly skilled area and one which is unique to the physiotherapy profession.* Guiding the patient into gradually more normal function, using practical tasks and exercises in ways where the patient always feel in control, feels safe, is a part of the decision making process, and can see where a particular exercise or movement is leading, are a few of the important issues.

The patient in front of us

Integrating psychological and social issues into practice is not an easy matter for professions that are linked historically to tissue/injury/pathology-based explanations and treatments for all pains. Overcoming a natural antipathy to integrate 'other' issues, concepts and explanations is a major step towards effective practice change.

The patient in front of us can have many problems, even one with such an apparently simple thing as a recently twisted ankle or a modestly sprained back. The more you enquire, the more information you seek, the more you tend to find. There may be loss of physical function and disability; there may be physical impairments—like losses of range of movement, tender areas, painful movements, or muscle imbalances; there may be anxieties and distress; there may be anger and unhelpful beliefs about the nature of the problem and about the effects of treatment; patients may have a significant fear of movement and harm; they may be under pressure from work and work colleagues, or may have financial problems and pressures; their standing in their social or work community may be under threat, and so forth. The term 'barriers to recovery' that Paul Watson uses, is so useful to think about when with a patient (see Chs 2 & 3). But perhaps a word of caution is needed: skilled therapists delve only to the depth of enquiry required for optimum outcome, and do so in a way that is quite comfortable for the patient. This skill is a product of high levels of knowledge, correct interpretation, and practised communication and handling.

Figure I.1 represents the traditional hierarchy of the sciences (see Rose 1997). This conventional perspective proceeds from the hard, reductionist and mechanistic lower levels that are most easily measured, controlled and analysed, to the upper softer, vaguer and more nebulous psychological and sociological levels. The disciplines at these upper levels have struggled to be accepted as scientific disciplines in their own right and still evoke general scepticism. Change in culture produces a change in attitude, and hypotheses

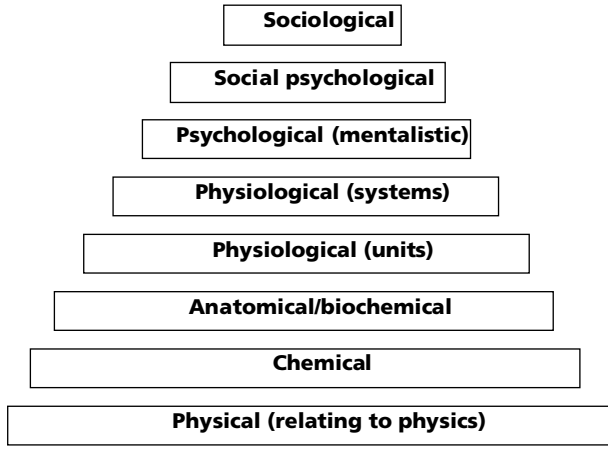

Fig. I.1 The traditional hierarchy of the sciences (adapted from Rose 1997)

and paradigms that were unacceptable and derided a few years ago may well offer pathways for the future. In this book we are dealing with the medical and physiotherapy culture related to patients in pain and their management and understanding. The plea is for integration of thinking and input from all levels of the scientific hierarchy.

From genes to environment

Scientists tend to operate within their own tightly knit communities. until recently it has been quite rare to find a scientific thinker and writer who seeks explanations and understanding from specialities beyond a specific discipline. Each level of the sciebntific 'hierarchy' may well have its own explanations and answers for a given phenomenon, and adherents often defend their position by openly and unproductively criticising those offered from competing disciplines. This is especially so in the field of pain science and pain therapy, where a plethora of explanations and treatments for pain and disability derive from the many different disciplines and clinicians involved. These include a spectrum reaching from the social scientists right down to the biochemists and geneticists, with treatment inputs coming via sociologists, clinical psychologists, rehabilitationists, manual therapists, alternative therapists right down to the pharmacologists and, now, gene manipulators. In general the overall tendency is to fund and seek explanations for pain from ever more reductionist and economy driven paradigms. Hence the current wave of enthusiasm for genetic understanding and eventual genetic manipulation by drug interventions in the world of pain science (for example, Iadarola et al 1997, Julius 1999, Woolf et al 1999), rather than for the increasingly evidenced-based practices more strongly linked to the upper tiers of the heirarchy—where industry driven profit motives are least likely to feature and which are far more difficult and time consuming to practise than the simple act of prescribing and taking a pill.

Figure I.2 represents a hierarchy of levels that may be used for explanations of pain and disability. It also indicates the type of therapists available at each level.

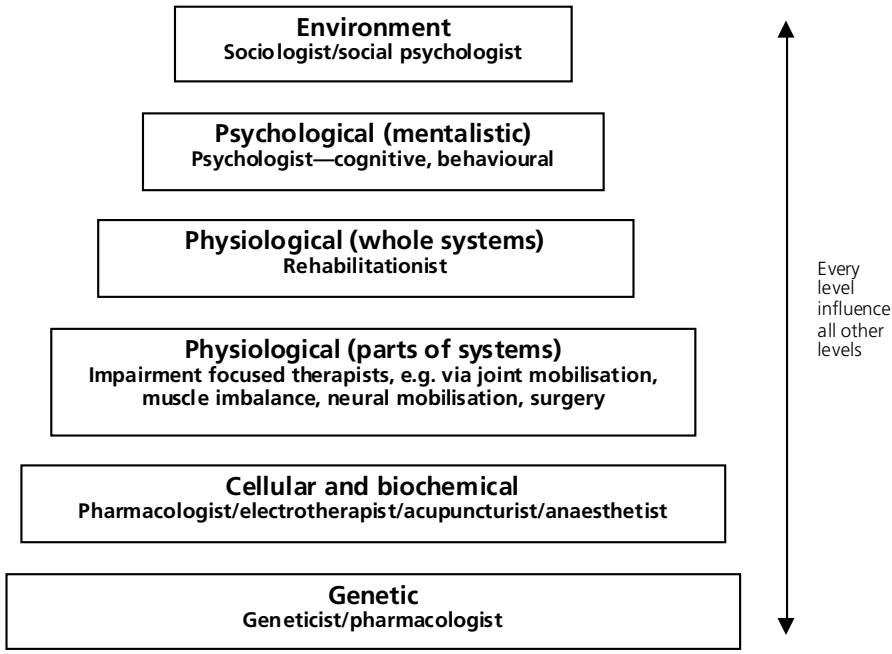

Fig. I.2 Hierarchy of explanations for pain and disability and related therapists

- At the top level is *environment.* Here, for example, chronic pain and disability may be linked to the patients' distress at work, to the way their family reacts to them or perhaps to some losses in their social life. Manipulate these and the patient may get better. Sociologists and social psychologists have a claim to pain treatments and management.
- At the *psychological* level, patients may have powerful beliefs that any physical movement is threatening to their weakened painful state and that rest is the best option for healing; or they may have such emotional turmoil that their interest in any form of healthy activity or life style is non-existent. Educate more healthy beliefs and demonstrate that their fears are unfounded, help them overcome their emotional turmoil, improve their coping strategies and reinforce more appropriate behaviour and patients may get better. Psychologists clearly have a role in pain.
- The *physiological: whole system* level relates to systems that may be considered to be faulty in some way, hence, temporarily or permanently altered function of the nervous, endocrine, musculoskeletal, locomotor, or visceral systems, and so forth. From a physical therapist's viewpoint this level may more easily relate to faulty or altered gross movement patterns and loss of function—it is here that research and therapy focus on ***disability.*** (In the

clinical reasoning literature the term *general physical dysfunction* has been used synonymously, see Gifford 1997, Gifford & Butler 1997, Butler 1998. Thus, the patient with back pain may be unable to bend and this affects ability to dress, to sit comfortably, to drive the car, and to sit at the desk for work. Treatment may focus on exercises to gradually improve flexion, to pace up sitting and bending tolerance. For the sprained ankle, treatment may focus on normal gait or on starting a gradual and progressive weight bearing programme. Rehabilitationists are central to this level of management.

- The *physiological: parts of systems* level can relate to more specific findings. For example, a joint under question might have modest restriction of accessory movement, ligaments, tendons, muscles, muscle groups, or a specific nerve may demonstrate increased mechanical sensitivity. Other issues might include loss of range, muscle imbalance, even loss of structural integrity or instability. This level relates to an ***impairment*** focus by the researcher or clinician. (In the clinical reasoning literature the term *specific physical dysfunction* has been used synonymously, see Gifford 1997, Gifford & Butler 1997, Butler 1998.) Altered function at this level might be addressed by manual therapists or surgeons.
- The *cellular and biochemical* level looks at pain from the perspective of changes in the tissue environment and changes in cells and pathways in the nervous system. Thus pain and disability may relate to changes in inflammatory chemicals in freshly injured muscle or ligament, to alterations in neuropeptides or receptor populations in nociceptors and nociceptor pathways subserving the injury, or to altered immune functions and altered neuroendocrine reactivity and so on. This paradigm for pain offers help via chemical manipulation of the tissue and pathways as well as the cellular environment—hence the pharmacological claims to the management and treatment of pain. Involvement at this level might be via pharmacology, electrotherapy, acupuncture or perhaps manual therapy.
- Currently, the lowest, most 'reductionist' level is the *genetic* level of research, thinking and intervention. This is worth discussing as it serves as a useful platform to relate to effects and interactions from other levels.

There are presently two schools of thinking with regard to genes and pain. The first view accepts that states like pain sensitivity, response to analgesics and susceptibility to painful pathologies are subject to great inter-individual variability (like all bio-physiological and bio-psychological phenomena), and that genetic factors have a role to play here (Mogil 1999). The bottom line is that some of us may be genetically 'programmed' or 'susceptible' to more lasting pain states, following the same injury or pathology, than are others. Environmental influences on gene 'expression' are of course acknowledged. Gene therapy, as it was originally conceived would be used to correct genetic defects by replacing or substituting the defective gene with a new, more appropriately functional copy (Iadarola et al 1997). In essence the idea for pain treatment using this approach to gene therapy is to implant functional

copies of new genes into appropriate sensory processing neurones (e.g. into nociceptors or nociceptor pathways) in order to confer new properties on them. Thus, the activity of the 'defective' gene is overridden and with the new gene's activity the cell changes its characteristics to become less sensitive. In genetic terms, the altered genotype changes the phenotype—the very structure and characteristics of the cell. A current research focus is targeting the spinal cord and dorsal root ganglion as potential sites of gene transfer (Iadarola et al 1997).

A second view seeks to alter gene 'expression' rather than actually change the gene for another one. At least this sounds more feasible! Appreciate that a specific gene is a unique series of amino acids on a molecule of DNA and that genes act as templates to build and produce relevant RNA molecules that go on to act as further templates for the construction of cellular proteins. When a gene 'expresses' it has to be switched on. A given gene produces or 'expresses' a protein specific to that gene. During the life of any given cell genes are continuously being switched on and off in order to manufacture, or stop the manufacture of, proteins needed/not needed by the cell to help it function and survive. The process of switching genes on and off is a fundamental part of cell homeostasis and very much a part of the normal day to day physiological processing for all active cells in all cellular organisms. For considerations with regard to pain and alterations in sensitivity we need to appreciate that the same mechanisms are operative. Genes are being switched on and off in response to injury and genes are being switched on and off in response to therapy. This needs closer scrutiny.

Electrical sensitivity and the ability to pass impulses via saltatory conduction is a characteristic of neurones that relies on the very rapid passage of Na^+, K^+ and Ca^{++} ions in and out of the cell through pores in the axoplasmic cell membrane (Shepherd 1994). These membrane pores are called 'ion channels' (Figs I.3 & I.4) and are capable of opening and closing in response to conditions locally (Kandel et al 1995, Tanner et al 1997). For example, some ion channels may be opened by nearby electrical activity—and are called 'voltage gated' channels; others may be opened by chemicals like adrenaline, noradrenaline, bradykinin, prostaglandins or hydrogen ions. Some open in response to mechanical stresses. Ion channels that are opened (or closed) by chemicals contain receptors and are termed 'ligand gated' ion channels. Ion channels, and their receptors if they have them, are protein molecules that are produced as a result of specific gene activity in the cell body of the neurone concerned. The more active ion channels and receptors that a given neurone has, the more sensitive it becomes. Further, the type of sensitivity characteristic of the cell is dependent on the type of receptor population present. Thus large populations of active mechanoreceptors signify a cell that is highly sensitive to touch and pressure—hence the clinical finding of mechanical allodynia/primary hyperalgesia (discussed in Gifford 1997, Gifford 1998a). Large numbers of adrenoreceptors signify a cell that is highly responsive to adrenaline and noradrenaline, and so forth.

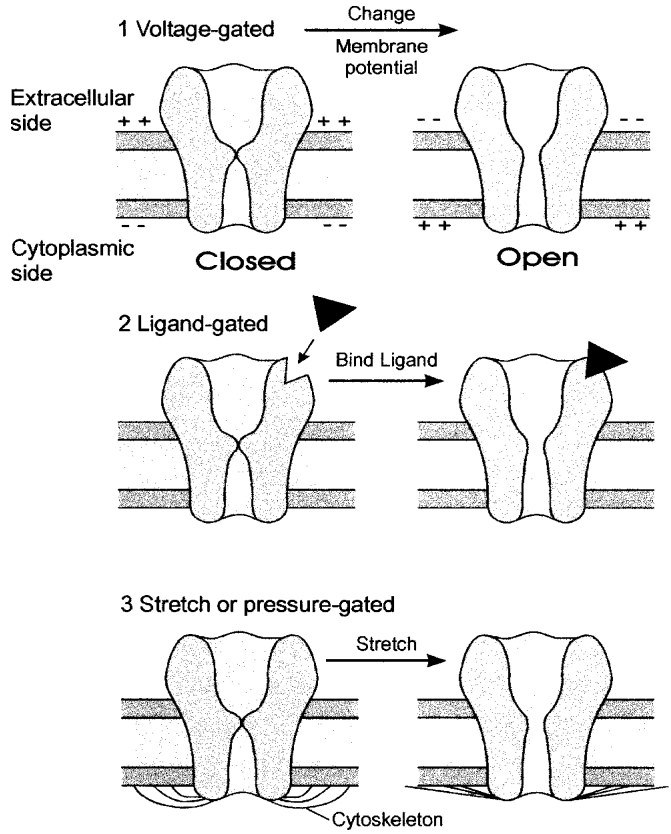

Fig. I.3 Ion channels in the cell membrane of sensory neurones:
1. Voltage gated. 2. Ligand gated. 3. Stretch or pressure gated channels.

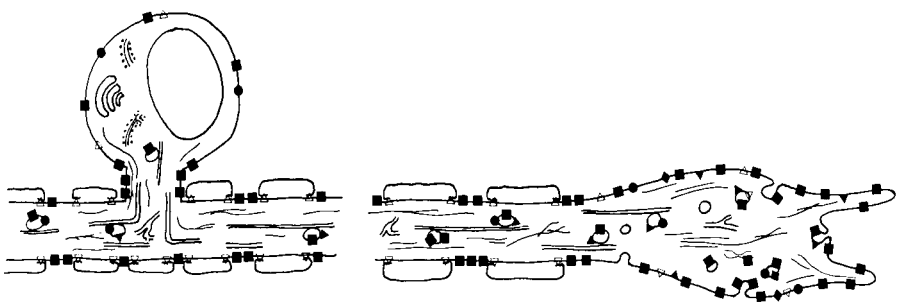

Fig. I.4 Schematic representation of a single sensory neurone highlighting ion channels and receptor proteins in the cell wall. Adapted from: Devor et al 1994
∇ K^+ channel ● Ca^{++} channel
■ Na^+ channel ▲ Adrenoreceptor = ligand gated ion channel sensitive to adrenaline.
◆ Mechaznoreceptor or Stretch activated receptor

When tissues are injured the nociceptive cells innervating that tissue begin to increase their sensitivity and start to fire more easily, some may even fire spontaneously. Increased sensitivity and spontaneous firing is a product of the availability of *active* ion channels and receptors and their relative numbers (Tanner et al 1997). Immediately after an injury many inactive or 'refractory' receptors in the membranes of the local nociceptors become activated. Hence the relatively rapid increase in sensitivity of the injury area. At the same time, chemicals which are produced by the injured tissues or immune cells in the injury area pass into the nociceptors and, via axoplasmic transport, eventually reach the cell body of the neurone. Once there they are known to stimulate specific gene activity and hence protein synthesis (McMahon et al 1997). This is a wonderful example of a cellular level '*sample, scrutinise* and *act'* process discussed in Chapter 2 of Volume 1 of Topical Issues in Pain (Gifford 1998). The nervous system chemically *samples* its target tissues; if they are damaged it detects the presence of injury related chemicals, *scrutinises* them and then mounts an appropriate *response*. Part of this response is to produce more ion channels and receptors so that the neurone can increase its sensitivity. The neurone may also 'upregulate' its production of inflammatory neuropeptides—needed in the tissues to produce inflammation and hence initiate the healing process (McMahon et al 1997).

New receptors that are produced and transported back to the peripheral terminals of the neurone become implanted in the cell membrane with the result that the cell further increases its sensitivity. This is clearly a process that takes a while. The message of importance behind these events, is that gene activity influences the sensitivity of the cell by ultimately altering its membrane structure. The inclusion of more ion channels and receptors changes the cell physically and changes its dynamic properties. This demonstrates the plasticity of the system that enables its adaptive response to the threat posed by tissue injury. At its core is the activation and expression of appropriate genes that act as templates in the process of protein synthesis. Importantly, what has just been described occurs not just in the periphery where it is most easily appreciated, researched and described, but also throughout the whole sensory, processing and response systems involved. Change in response means altered gene expression and altered morphology anatomy and responsiveness, all along the involved pathways.

At the heart of the geneticists' approach to pain is the 'regulation' of this expression. At the 1999 World Congress on Pain in Vienna there were a total of 16 poster presentations relating to the scientific manipulation of genes and gene expression for the treatment of pain. The manipulation on offer was wholly at the same reductionist level, in other words, by understanding the chemistry of sensitisation another chemical may be applied that can intervene and prevent or reverse it.

Thinkers might step back from this and reason that if this type of process is fundamental to pain and sensitivity it must also be influenced by all types of therapies that are successful. I would agree and it makes for quite thought provoking therapeutic philosophising.

A biological rationale for unity

No matter what you do to a patient, from whatever level you focus, changes in gene expression will occur if the patient makes some changes. That every practitioner is ultimately a gene therapist is a nice idea, is unifying, and is, as far as I can see, quite rational. Also, if you are a patient you can be your own gene manipulator if you get involved in self help. Every therapist *could* argue (and perhaps one day soon *should* argue) that fundamental to their 'technique' or 'input' is the modulation of gene expression. I might be no different in my influence as a physiotherapy practitioner from a healer, a medicine man, a magnetic or copper arm band with healing properties, a session of Reiki, a cranial manipulation, a grade II p-a on a zygapophyseal joint, a muscle rebalance session, a McKenzie extension exercise, an education session that changes the patient's perspective on their pain to a less fearful one, a successful rehabilitation session where a formerly feared movement is conquered, or a positively negotiated arrangement with a patient's employer that results in a comfortable stress free return to work (Fig. 2). Based on this type of logic it seems unwise to criticise therapies that you find unusual/different/unorthodox. If patients have improved in some way from a therapy, there must be a mechanism underlying that improvement. The suggestions here reduce therapeutic effects down to a common mechanism involving alterations in gene expression, changes in receptor populations and neural reactivity. In many ways this is a far more responsible explanation than the classic insult of labelling another's successes as mere placebo. The view here is that the placebo is a biological phenomenon that often takes quite remarkable therapist skills to access to its full potential.

The problems practitioners have in standing up for their particular brand of therapy is that they tend to isolate themselves at a particular mechanistic level. For example, some manual therapists might explain their success with a patient in terms of improved local joint function. This is the model of explanation that I was trained in and used for many years. For a psychologist the explanation might be in terms of altered thinking, coping and behaviour; for an acupuncturist in terms of altered yin and yang, or altered central nervous system endorphins, depending on the training. A pharmacologist might view the world of therapy in terms of targeted physiological changes; a Reiki therapist in terms of energy fields and so forth. Explanations for effect like these are naturally reductionist and unidimensional, confined to the theory underlying the discipline concerned, often inadequate, and may be part truths or even totally wrong because they are ignoring the *multidimensional nature of biological processing*. Once we learn to appreciate that a fundamental biological truth is that all levels in Figures I.1 and I.2 interact (see the arrow on Fig. I.2), we can begin to see a much more profound multilevel and multidimensional picture. Single level management and thinking is constrained, is unlikely to be as productive as it could be, and often leads to arguments and tension. Think of each level in Figure I.2 as a cave with many smaller caves within representing a particular method or therapy. Then consider that it might be well worth the practitioners within coming out of their particular caves and looking around

and into some of the others. For most practitioners it is relatively easy to take on the perspectives of those who are on adjacent levels. A herbalist can work in conjunction with an iridologist or a reflexologist but is unlikely to make much headway with an orthopaedic surgeon. Think about it in the terms suggested here and you realise that, philosophically, the entrance of the orthopaedic surgeon's cave lies quite close to the entrance to the caves where the alternative practitioners live; their philosophies are really all based on the identification of some form of impairment and its passive correction. Little is likely to be done by the majority of these practitioners in relation to promoting function or activities related to life and work, or active coping strategies, or decreasing fear about structural weakness or the nature of pain.

The argument here is for the emergence and appropriate integration of all levels because they all interact and interrelate biologically. For instance, change the way a patient thinks about a problem or a feared movement and you have the potential to change gene expression, sensitivity, pain response, muscle co-ordination and muscle strength, emotions and relationships. Add further potency by using a practical session whereby the patient is helped to find a way of actually starting to do the feared movement in a safe and controlled way. In some situations it may be appropriate to find a movement or even perform a passive technique on the patient that they find helpful in improving movement or reducing pain. Suggesting or asking for appropriate medication for pain control may be required, and so forth. The well established style of only doing 'one-technique-at-a-time', while occasionally necessary, may actually be missing a huge potential in terms of efficiency and cost effectiveness.

Treatments from professionals inputting at the bottom of the hierarchy can influence the top and vice versa. A particular message of this volume is that *some levels are more powerful than others* in influencing decline or wellbeing and recovery; these relate to the *environment, and the thoughts, feelings, beliefs, behaviours and functioning* of the patient—**the top three levels** in Figure I.2. If clinicians are to work efficiently to rehabilitate and prevent chronic incapacity then issues pertinent to these levels need their attention, understanding and integration into patient management. Those operating with models at lower levels need urgently to look upwards just as those above need to take an open minded look at those operating below. One day the well equipped therapist might be equally at ease using and integrating management skills derived from all levels. Let us hope, for the sake of the patient in front of us, that we are nearing a satisfying denouement underpinned by biological rationality. Perhaps we are about to witness the break-up of defensive boundaries with rigid enclosed thinking going quietly out of fashion?

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