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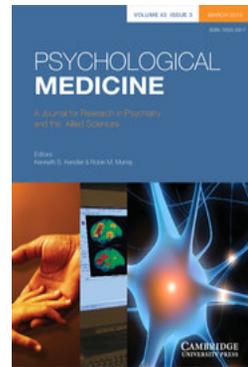
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# The placebo: from specificity to the non-specific and back<sup>1</sup>

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**SYNOPSIS** A brief historical outline is provided of the concept of specificity in biology and medicine. The advent of scientifically based therapeutics, and especially clinical pharmacology, has directed increasing attention to the role of non-specific factors in the field of mental disorders. The actions and effects of placebos are discussed in relation to the specific/non-specific dichotomy with particular reference to both pharmacological and psychological modes of treatment.

## INTRODUCTION

'The properties of placebos are said to be non-specific in that they are largely independent of the chemical substances of which they are composed and in that they are manifest in so wide a variety of disorders as to preclude explanation by a single mechanism' (Eisenberg, 1984). This serviceable definition, like most others, can be criticized according to the standpoint adopted but in common with the majority it includes a reference to the so-called 'non-specific' factors with which the placebo has been generally associated. The large literature on the concept and semantics of 'non-specificity', however, rarely takes cognizance of the still larger literature on specificity, principally because this has been primarily the concern of historians and practitioners of biological science and bio-medicine. A glance at the compendious volume *Placebo: Theory, Research and Mechanisms*, edited by White, Thursky and Schwartz (1985) and dominated by psychologists, illustrates the point. If, as I would maintain, it is logical to approach the matter by proceeding from the positive to the negative, priority should be given to specificity in its own right before proceeding to the domains of non-specificity within which the placebo concept is to be located.

In this context a brief historical outline of their development, primarily from the standpoint of clinical science, provides a background to current empirical and conceptual enquiry.

## BIOLOGICAL SPECIFICITY

The notion of specificity has been a constant pre-occupation among physicians since the time of ancient Greece. Essentially, as Owsei Temkin has pointed out, it is bound up with a fundamental dichotomy contrasting the Platonic or 'ontological' with the Hippocratic or 'physiological' view of disease (Temkin, 1963). The ontological notion of disease postulates an independent, self-sufficient entity with its own natural history; the 'physiological' emphasizes the individual biography of the patient. The distinction reflects the familiar contrast drawn between disease in man and man in disease.

Over the centuries the pendulum of opinion has oscillated between these two standpoints. Tracing its evolution, Galdston has observed that after centuries dominated by the thinking of Hippocrates and Galen the ontological concept of specificity came back into its own with the Renaissance, first through Paracelsus and then through the work of such men as William Harvey, Robert Boyle, François Boissier de Sauvages and, later, Morgagni, Bichat and Rokitansky (Galdston, 1941–2). All of them accepted the Cartesian model of the human body as a machine and, as Galdston remarks: 'Always we find that when the mechanistic

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viewpoint prevails in the biological sciences, medicine is specificistic in its nosology, aetiology and therapy'.

During the nineteenth century the physiological school produced a doughty champion in the person of Rudolf Virchow. In his forthright polemic, *Specifiker und Specifisches*, Virchow (1854) stated the case with characteristic directness. 'The destruction of the ontological conception of disease leads also to the destruction of ontological therapy, the School of the Specificists. Therapy is confronted not by diseases but by conditions; everywhere we deal only with alterations in the "life circumstances"'. By the end of the century, however, the specificists were back in the saddle with the arrival of the bacteriological era. Only slowly has the pendulum swung back during the twentieth century. In Britain the challenge was mounted in the name of social medicine (Ryle, 1944). In American medicine Richard Shryock (1969) has written perceptively on 'The Concept of the Specific', alluding to the influence of the stress concept with which psychosomatic medicine was so closely linked in its early days. At that time psychosomatics had to contend with its own 'specificity' theory when Franz Alexander, using a psychoanalytical framework, postulated specific unconscious and unresolved conflicts as being responsible for particular somatic diseases (Alexander & Szasz, 1952). These conflicts supposedly determined the nature of the emotion that is suppressed or unconscious, resulting in a state of chronicity. This hypothesis of a 'specific emotion' was related to Flanders Dunbar's concept of a specific personality and to Graham's notion of specific attitudes. Empirical research subsequently failed to support these notions, and Stewart Wolf (1961) summed up the situation some years ago in his paper 'Disease as a way of life: neural integration in systemic pathology', suggesting that 'physicians now consider most diseases to be distinct from one another insofar as they represent patterned responses or adaptations to noxious forces in the environment'. The currently fashionable biopsychosocial model of illness turns on the same paradigm.

This long-standing debate within medicine has been reflected by a corresponding trend within biological science since its inception. Indeed, Lester King (1978) has gone so far as to

argue that the history of physiology is synonymous with the search for specificity. Cellular specificity has been a basic concern of embryologists since the late nineteenth century, and Joseph Needham has drawn a direct parallel between medical and the biological thinking:

Is not the ontological-physiological antithesis in the philosophy of pathology a special case of the fully generalized biological situation of special stimulus on the one hand, and cell reactivity on the other? ... After the classical discovery of the embryonic organiser-region by Hans Spemann in the twenties, and the no less classical discovery ten years later that the active principle of the gastrula's dorsal blastopore lip was stable to boiling, a stream of research started which is yet far from exhausted. Some (including myself) have always been convinced that in normal development a specific chemical substance, a *Wirkstoff*, is primarily involved, but many biologists have preferred... to place most of the emphasis upon the reactivity of the overlying ectoderm, hence on the cell-proteins of this germ-layer, which must convert it into neural tissue as development goes on. In the end, Hippocrates must always be right - we cannot do without both of the factors, external and internal; the only problem is to know how they interact (Needham, 1963).

Nonetheless, the term 'specific' is so widely used in biological research that Peter and Jean Medawar have commented that:

If an estimate were to be made of the technical terms most frequently used in the professional writing and dialogue of biologists, we have little doubt that 'specificity' would come out way ahead. Specificity refers to the complementarity or matched opposite-ness in reactions between antigen and antibody, enzyme and substrate, and between stimulus and response in reflex action (Medawar & Medawar, 1985).

To underline the point mention may be made of three outstanding contributions that illustrate the variety of usages employed by biological scientists. First, Linus Pauling's fundamental work on molecular biology, which was founded on complementary action (Pauling, 1940). Secondly, Roger Sperry's work on the synapse in the visual system, which was directed at underpinning the specificity of cellular function within the central nervous system (Attardi & Sperry, 1963). Thirdly, R. A. Fisher's 'specific modulator', which played a large part in formulating modern notions of gene function (Fisher, 1930).

## PHARMACOLOGICAL SPECIFICITY

The biological domain with which we are most concerned, however, has to do with pharmacology because of its direct links with therapeutics. For proponents of the ontological view of disease the search for specific remedies has been a constant goal. The early work on colchicine or cathartics is primitive compared to modern chemotherapy, but the aims are identical (Temkin, 1972). In his monograph entitled *Of the Reconcilableness of Specific Medicines to the Corpuscular Philosophy*, published in 1685, Boyle even anticipated the standpoint of Ehrlich and the era of antibiotics (Boyle, 1685). Only in the recent past, however, has it been possible to identify some of the mechanisms involved. In the 1930s Clark proposed a general theory of antibiotic drug-mechanisms in terms of toxic action on nuclear processes (Clark, 1937), observing at the same time that whereas some substances, like colchicine, induced a selective toxic effect others, like phenol or formalin, induced what he called non-specific toxic effects by deranging the cellular protein structure. External influences like heat, oxidation or irradiation were also, he observed, best regarded as non-specific toxic agents acting on enzymes. Clark also extended his concept of the specificity of drug-action to the sphere of drug-antagonism. Here he distinguished chemical and physiological from specific forms of antagonism, reserving the latter term for cases in which one drug inhibits the action of another drug on living cells, though there is no drug-interaction *in vitro*.

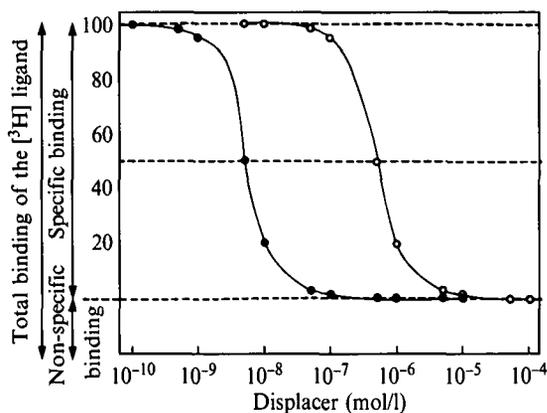


Fig. 1. Basic principles of receptor binding. (From Müller, 1987.)

With the identification of neurotransmitters came a more sophisticated view of specificity, derived originally from the actions of acetylcholine and well summarized by Sir John Eccles:

we assume that the post-synaptic membrane of the synapse has a highly developed specificity to the synaptic transmitter substance and its analogues. The relationship resembles that of lock and key. One of the major problems confronting neuropharmacology is to find the chemical keys for the synaptic locks. The more specific the keys, the more discriminate will be the pharmacological actions. However, on the other hand, there will also be value in having 'skeleton keys' that open closely related types of lock (Eccles, 1959).

Paradoxically, this pharmacological quest for the specific has served to highlight the biologically non-specific, nowhere more strikingly so than in the study of the benzodiazepine receptor, the highly specific benzodiazepine binding site in the central nervous system. Originally the receptor-mediated effects of drugs were examined indirectly by the use of specific or competitive antagonists. This method has been employed with benzodiazepine receptor antagonists like imidiazabenzodiazepinones, beta-carbolines and phenylpyrazoloquinolines, but with the advent of direct binding techniques tritiated benzodiazepines were used as radio-ligands. There is now extensive evidence supporting the view that the benzodiazepines act as GABA-mimetic substances and that receptor affinity represents the biochemical correlate of the therapeutic dose in man, GABA itself being an important inhibitory neurotransmitter of the mammalian central nervous system, while the benzodiazepine receptor is widely regarded as a modulatory unit of GABA-ergic neurotransmission. Yet, as Müller points out:

Unfortunately, practically all radio-ligands bind not only to their receptors, but also to different degrees to much less specific binding sites on the tissues investigated or even on the filters used for separating bound from free ligand. This unspecific or non-specific binding varies with the ligands and tissues used can account for less than 5% up to more than 90% of total binding ... receptor binding (also referred to as 'specific binding') and non-specific binding differ in some major aspects (Müller, 1987). (Fig. 1).

Even specific binding, it appears, is affected by many factors, e.g. ligand concentration, cerebral region, age, dosage, route of administration,

and the presence of other drugs (Garattini & Mennini, 1986). Further, there appear to be at least two subclasses of receptor, one of which binds ligands with more affinity than the other, and it still remains uncertain whether the benzodiazepine receptor has an independent physiological function and whether an endogenous ligand is involved. In addition, peripheral benzodiazepine binding sites have been established which are specific in respect of their binding capacity but are pharmacologically inactive.

### NON-SPECIFICITY AND THE PLACEBO

From this and comparable work with other neurotransmitters biological specificity emerges more as a metaphysical than a physical concept, to be viewed in 'more or less' rather than 'absolute' terms. The consequence most relevant to our present concerns has been drawn by S. Fisher:

There is no clear-cut agreement as to what, specifically, is meant by the phrase 'specificity of drug action'. And since the definition of 'specificity' is so vague, one cannot expect too much from its 'non-specific' corollary (Fisher, 1970).

The validity of this conclusion, based as it is on laboratory data, is greatly extended by the real-life human transaction of medical care in which a host of non-biological factors must be taken into account. Writing as a self-styled 'sociopsychopharmacologist', Joyce has listed some of the more important (Joyce, 1989) (Fig. 2).

Several of these psycho-social factors may, of course, be specific in their own right. The clinical notion of 'reactivity' implies the possibility of normalizing a morbid state if the *noxa* can be identified and reversed – as, for example, with hospitalism, transient personal loss or economic misfortune – and Harris and Brown have commented on the specificity of some life-events in provoking particular types of disorder (Harris & Brown, 1989). Nonetheless, the tendency to group most psycho-social factors together as non-specific has diminished scientific enquiry into their mode of action until recently, a trend that has been stimulated by the increasing attention paid to therapeutic specificity. Among

the fruits of this concern has been the notion of the placebo, literally 'I shall please', reifying a verb into a noun and introducing the element of subjectivity into the operational matrix.

In her brief historical survey Suzanne White (1985) has claimed that the first acknowledgement of the status of the placebo, which she calls 'medicine's humble humbug' is to be found in Oliver Pepper's 'A note on the placebo' published in the *American Journal of Pharmacology* in 1945 (Pepper, 1945) and pin-pointing the placebo as a biologically inactive form of medication. According to Pepper, its prescription demands 'a certain amount of skill'; it should have 'a Latin and polysyllabic name'; it should be given with 'some assurance and emphasis for psychotherapeutic effect'; and, above all, it must be seen as 'a part of what used to be called the art of medicine – the discredited sister of scientific medicine'. Since then the placebo has attracted the attention of workers from four disciplines in turn, namely pharmacology, psychology, philosophy and biochemistry. Their differences in outlook partly explain the confusion attending the semantics of the placebo which have been extensively discussed by Shapiro (1968), Brody (1977) and Grünbaum (1981).

Chronologically, the conferment of scientific respectability on the placebo in the post-war period was initiated principally by workers in the new field of clinical pharmacology. First came the studies of Beecher who demonstrated that the placebo-effect was therapeutically powerful and could be demonstrated in many morbid conditions (Beecher, 1955). Why this was so, however, remained obscure. Reviewing the subject in *Scientific American* in 1955 Lasagna remarked that '... most of these "principles" of the art of the placebo are based not on any systematic investigation of the facts but on impressions. Almost no controlled studies of them have been made' (Lasagna, 1955). Shortly afterwards he entered a plea for what he called the 'sociopsychology of therapeutics', commenting that

therapeutics has paid only lip service for so long to the importance of psychological and sociological variables. Too often we have had a sterile dichotomy between those individuals who tend to forget variability of response and the importance of non-drug variables, and those individuals so obsessed with the

A partial listing of non-specific influences of treatment.

*Environment* (milieu extérieur)

- Animate
  - Medical
  - Family
  - Friends
  - Casual contacts
- Inanimate
  - Physical
    - Temperature, etc.
    - Light/dark
  - Chemical
    - Pollutants
    - Diet

*Patient* (milieu intérieur)

- Physiological
  - Metabolism
  - Genetics
  - Structure
  - Aging
- Psychological
  - Experience
  - Expectations
  - Personality

*Drug*

- Size
- Shape
- Color
- Taste
- Route

FIG. 2. A partial listing of non-specific influences of treatment. (From Joyce, 1989.)

complexity of variables involved in drug responses that they are intellectually paralyzed (Lasagna, 1962).

Secondly, came the entry of the placebo into the field of experimental medicine via clinical therapeutics. Sir George Pickering asserted in 1949, Therapeutics is the branch of medicine that, by its very nature, should be experimental... Before concluding that the change for better or for worse in the patient is due to the specific treatment employed, we must ascertain whether the result can be repeated a significant number of times in similar patients, whether the result was merely due to the natural history of the disease or in other words to the lapse of time, or whether it was due to some other factor which was necessarily associated with the therapeutic measure in question (Pickering, 1949).

This passage is quoted with approval by Sir Austin Bradford Hill, the founder of the modern clinical trial, which has become one of the mainstays of modern medicine and which makes extensive use of the placebo or 'dummy'. Writing of the use of placebo treatment he says:

The object is twofold. On the one hand we hope to be able to discount any bias in patient or doctor in their judgements of the treatment under study. For

example, a new treatment is often given more favourable judgement that its value actually warrants. The effects of suggestibility, anticipation and so on must thus be allowed for. In addition, the placebo provides a vital control for the frequency of spontaneous changes that may take place in the course of a disease and are independent of the treatment under study.

In these two ways the placebo aids us to distinguish between (a) the pharmacological effect of a drug and (b) the psychological effects of treatment and the fortuitous changes that can take place in the course of time (Hill, 1971).

The point is illustrated by Fig. 3.

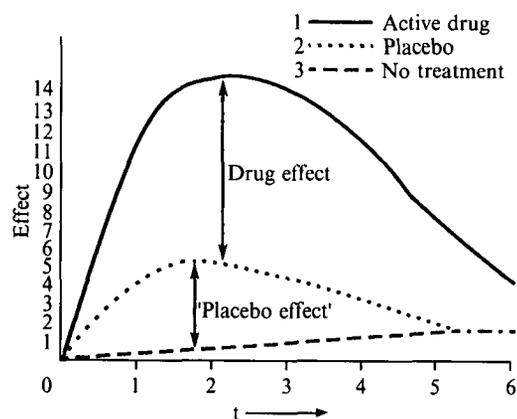


FIG. 3. Placebo and drug effects over time. (From Joyce, 1989.)

Accordingly, the central task of the pharmacologist becomes the search for specificity and, by the same token, the elimination of the 'non-specific'. This view has been the cornerstone of the various forms of clinical trial, the primary function of the placebo being to eliminate bias. However, valuable as this method of investigation has proved to be, it is not always recalled that the controlled trial is essentially an exercise in experimental epidemiology and as such has to do primarily with populations and hence with averages rather than with individuals. This point was made with some force by Lancelot Hogben (1954) for whom the aim of the assessment of remedies entailed 'the disclosure of a specific stimulus-response nexus', something that can never be attained by the study of groups. For the most part the data derived from clinical trials are stochastic. The establishment of biological specificity is therefore unattainable by the standard techniques associated with this method of evaluation. Hogben's own attempt to

achieve this goal within a therapeutic framework was via the self-controlled trial on a single individual but this, as he conceded, is limited to low-grade, reversible forms of morbidity (Hogben & Sim, 1953).

### THE PLACEBO EFFECT AND PSYCHOTROPIC DRUGS

Despite the manifest importance of the placebo effects a glance at most textbooks of clinical pharmacology shows that they were, and to some extent still are, largely ignored or minimized in discussing the treatment of physical illness. In part this reflects the emphasis on disorders with well-established aetiology and demonstrable response to rational treatment. Brody has observed 'that one of the most striking features of the placebo phenomenon is its ability to effect change in virtually any potentially reversible disease or disorder, while contemporary theories of pathophysiology and therapeutics lead us to expect a "specific" or characteristic remedy to be efficacious for only a small number of disorders. We anticipate that a "specific"/"characteristic" remedy has roughly a 75-95% probability of being efficacious for a very small number of disorders, while a placebo has a 30-40% probability of being efficacious for almost any disorder' (Brody, 1985). This being the case, it was to be expected that the pharmacotherapy of psychiatric and 'psycho-somatic' disorders would lend itself to a more productive study of the placebo. In this connection it may be recalled that the pioneering investigations of Emil Kraepelin in Wilhelm Wundt's psychological laboratory in the 1890s had resulted in studies of what he called pharmacopsychology and had led him to conclude that 'we might be able to learn from a specific drug or a specific symptom something about the true nature of this symptom' (Kraepelin, 1892).

The arrival of the new psychotropic drugs in the 1950s and the subsequent formation of psychopharmacology as an independent discipline enlarged the spectrum of phenomena under investigation by incorporating traditional psychological topics within the framework of enquiry. In particular, the newer techniques of behavioural pharmacology brought experimental psychology into play and the 'specific' -

'non-specific' dichotomy was given a new format in terms of reflex responses. Cook, for example, stated in 1959:

Animals which had their conditioned response blocked and still maintained unconditioned responses, were considered to have exhibited a specific block of the conditioned responses. Animals which had both conditioned and unconditioned responses blocked were considered to have exhibited a non-specific block (Cook, 1959).

The flush of therapeutic enthusiasm engendered by the new psychotropic drugs, however, tended to overshadow the attention drawn by Cheney & Drewry as early as 1938 to what they called the 'non-specific' factors influencing the response to deep insulin treatment of schizophrenia (Cheney & Drewry, 1938). These primarily psycho-social factors included staff attitudes, patient expectations, improved ward milieu, and changing social policies.

A striking example of this process was provided in the mid 1950s by the introduction of the first wave of psychotropic drugs. While pharmacologists speculated on their mode of action and clinicians on their modification of psychopathology the major impact was on the populations of mental hospitals. The movement towards 'deinstitutionalization' was initiated by claims that drug-treatment was making it possible to open the asylum-doors, nowhere advanced more firmly than in New York State by Brill and Patton (1955). In Britain there was a sharp public disagreement between two eminent leaders of the psychiatric fraternity. For one, a convinced somaticist, 'hospital administrative reforms would be crying in the wilderness if the so-called tranquillizing drugs had not appeared' (Mayer-Gross, 1959). For the other, representing a much more broadly based view, 'if we had to choose between abandoning the industrial rehabilitation centres and other social facilities available to us there would be no hesitation about the choice - the drugs would go' (Lewis, 1959).

How can a major issue of this kind be resolved? Most of the clinical trials were on too small scale to be conclusive, but we were able to carry out a detailed trend-analysis of mental hospital population statistics before and after the introduction of the psychotropic drugs (Shepherd *et al.* 1961). The hospital in question

had adopted a forward-looking policy long before the new drugs were available, and the data showed that the impact of medication on the movement of in-patients was relatively small.

This result was in line with Ødegaard's study of the variation between the hospital statistics of Norwegian institutions, demonstrating paradoxically that 'in hospitals with a favourable therapeutic situation the psychotropic drugs brought little, or no improvement in the rate of discharges. In hospitals with a low pre-drug discharge-rate, on the other hand, the improvement was considerable (Ødegaard, 1964)'. In other words, the non-specific placebo and milieu effects become most evident when the therapeutic situation is least favourable.

In the light of such findings it becomes patently inadequate to identify and evaluate non-specificity as no more than the residual obverse of specificity. The logic of this viewpoint has been cogently developed by Paul Meehl who analysed the part played by what he calls 'strong influences' which are not specifically causal (Meehl, 1977). Drawing on J. L. Mackie's account of causality, Meehl suggests that the modal type of causal explanation in the medical and social sciences is not biologically specific and is, indeed, fundamentally non-specific. Further, the use of the word 'cause' is legitimate even though the attributed cause is neither necessary nor sufficient in Koch's sense of the terms. What is sufficient is the entire complex of circumstances, and he summarizes the position in the following sentence: 'A causal factor *c* may be an insufficient but necessary part of a causal complex *C*, which complex is an unnecessary but sufficient condition for producing the effect'. Meehl calls this the INUS condition, the acronym INUS being formed by the initial letters of I (insufficient), N (Necessary), U (unnecessary) and S (sufficient) in the sentence given above. This view, it may be observed, highlights the importance of probabilistic and multiple determinants in non-specific aetiology. Applying this mode of reasoning to the factors bearing on deinstitutionalization, the drugs may be seen as constituting an insufficient but necessary part of just one causal complex that was responsible for the massive programme of patient discharge. This particular complex is sufficient for the purpose, but that it is unnecessary is shown by the fact that another,

drug-free complex of circumstances can produce the same effect.

## THE PLACEBO AND PSYCHOTHERAPY

In this case the components of Meehl's INUS, his 'complex of circumstances', would presumably include a variety of psychosocial factors favouring discharge from hospital. Many attempts to account for such non-specific phenomena have been couched in terms of descriptive or 'folk' psychological concepts like 'faith', 'expectation', 'hope', 'anticipation' and 'suggestibility'. All healing, as Thomas Sebeok remarks, is accompanied by the healer's 'verbal patter' and 'strings of non-verbal signs' which have been recognized, often implicitly, as potent since the dawn of medicine (Sebeok, 1983). Understandably, therefore, such phenomena have attracted the interest of workers attempting to unravel the nature of psychotherapy because they contain so many of the elements associated with psychotherapy itself. As Downing and Rickels maintain, in the sphere of mental disorders the more intense the doctor-patient relationship, the less likely is one to obtain a significant difference between drug and placebo (Downing & Rickels, 1978). In addition, the doctor-patient nexus is readily available for experimental manipulation.

Empirically, one of the most thoroughgoing attempts to investigate the issues to date is the large-scale NIMH Treatment of Depression Collaborative Research Program (TDSCR), whose major purpose has been to assess the effectiveness of two forms of brief psychotherapy, compared with a reference form of pharmacotherapy and a placebo for a defined group of depressed out-patients (Elkin *et al.* 1988*a*). The study raises a number of conceptual and methodological issues which the authors have explored in some detail. As they comment:

A comparative study of psychotherapy and pharmacotherapy may be conceived as a 'horse race' to determine which of the treatments is more effective or, alternatively, as an attempt to address more differentiated and ultimately more meaningful questions regarding which patients may be helped more by each of these approaches and in what ways (Elkin *et al.* 1988*b*).

In their view answers to these questions turn on the assumption that the basic differences

between the treatments reside in the contrast between their active ingredients and in the mechanisms by which they effect change. Anti-depressant drug treatment is assumed to operate mainly through biological mechanisms, psychotherapy through psychological mechanisms that are initiated by various aspects of the interaction between therapist and patient. However, as they admit:

a design including both a pill placebo and a psychotherapy placebo is not easy to execute, largely because of the difficulty of devising an adequate psychotherapy control condition. A major methodological advantage of psychopharmacological outcome research has been the availability of inert pill placebos that produce no physiological effects related to the treatment of the disorder and can thus control for the non-active components in the drug condition. The task of developing a 'placebo' condition for psychotherapy is far more complex, largely because of the problems in articulating what the active ingredients actually are in any form of psychotherapy (Elkin *et al.* 1988 *c*).

To circumvent this obstacle the authors aimed at a less ambitious goal, preferring to study particular factors that may exercise an effect on outcome, either independently or through interaction with a specific treatment approach. In so doing they admit to entering the area of 'non-specific' factors which operate in every form of therapeutic intervention. They conclude that in psychotherapy any comparison is between not just specific techniques of intervention but between 'different treatment packages' each of which is made up of a particular treatment approach and a particular therapist and in which the patient's expectations and preferences play a significant role. Shades of Meehl's INUS!

This view runs counter to the many evaluative studies of psychotherapy that have been based on the assumption that it is sufficiently specific to be compared with placebo controls of the type included by Prioleau *et al.* (1983) in their meta-analytical study, e.g. pills, play-reading, group activities, film-watching, relaxation training, music, personal hygiene, etc. It is more in line with the second of Jerome Frank's postulated two components of all treatments, the first aimed at correcting the specific pathological processes underlying a particular morbid state, and the second at counteracting the non-specific demoralizing impact of all illnesses (Frank,

1989). Both placebo and psychotherapy counteract demoralization, he argues, by a combination of 4 circumstances: (1) an emotionally charged, confiding relationship with a helping person; (2) a healing setting; (3) a rational, conceptual scheme or myth; and (4) a ritual. On this basis he concludes that as a symbolic communication that combats demoralization by inspiring the patient's hopes for relief, administration of a placebo is a form of psychotherapy (Frank, 1983).

## MEANINGS AND MECHANISMS

This whole process reflects what Frank calls 'the transformation of meanings' (Frank, 1986), a phrase that echoes Adolf Meyer's 'symbolization' as a basic function of human consciousness. It also introduces a hermeneutic dimension into the placebo-effect which is to be detected among the opinions of other workers. According to Howard Brody's 'meaning model', for example, a positive placebo effect is most likely when (a) the meaning of the illness is altered in a positive manner, given the patient's pre-existing belief system and world view, (b) the patient is supported by a caring group, and (c) the patient's sense of mastery and control over the illness is restored or enhanced (Brody & Waters, 1980). Kleinman's anthropological approach brings 'meaning' into line with 'expectation' and the 'cultural dimension' (Hahn & Kleinman, 1983), and Jerome Bruner has made a strong case for re-introducing what he calls 'meaning-making' as a core activity in modern psychology: '... culture and the quest for meaning within culture', he claims, 'are the proper cause of human action. The biological substrate, the so-called universals of human nature, is not a cause of action but, at most, a *constraint* upon it or a *condition* for it' (Bruner, 1990).

Overtones of the old body-mind issue are sounded by this extension of the specific-non-specific dichotomy. Clarification may eventually be obtained, at least in part, by research into the mechanisms of the placebo effect. As Fisher observed 20 years ago:

the phrase 'non-specific factors' is frequently used almost as a wastebasket category. We search for obvious physiologic or pharmacologic variables to account for our observed differences and if we cannot find satisfactory explanations within this domain, we

then invoke the concept of 'non-specific', 'non-drug' causal factors... many of the non-drug factors may eventually turn out to be typical conventional pharmacologic variables in disguised form (Fisher, 1970).

This notion is illustrated by many ongoing studies of the endorphins, hormones, immunological mechanisms and conditioned responses and Wickramasekera, for example, has incorporated current thinking on the placebo-response in his general definition of it as a 'composite of patterned interacting verbal-subjective, motor, neuro-endocrine, and neuro-immunological response systems that can attenuate or potentiate both the underlying mechanisms of pathophysiology and overt clinical symptoms' (Wickramasekera, 1985).

Perhaps the most far-reaching extension of this standpoint has come from the perspective of molecular biology. Thus Ivor Black, who adopts a weak reductionist position, goes so far as to maintain that information processing within the nervous system involves the postulate that symbols are actually physical structures that constitute a neural language representing the physical world (Black, 1991). This is rendered possible because some molecules have multiple functions, acting simultaneously as physiological signals and as symbols that carry environmental information. On the basis of laboratory experiment Black is prepared to suggest that the neurobiology of the brain can be changed by the alteration of mental imagery that evokes attention, hypervigilance and anxiety. The high-level software, he asserts, is capable of modifying the low-level hardware of the brain. Here is an approach to placebo action as a key element of the non-biological environment, which has still to be explored by empirical research. It may be that the 'humble humbug' may help define the boundaries between specific and non-specific, body and mind, soma and psyche.

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