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William Cullen and a missing mind-body link in the early history of placebos

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Introduction

Until the late 18th century, the term 'placebo' was used in a religious rather than a medical context: an early Latin translation of the Hebrew Bible, Psalm 116, verse 9, was rendered as *Placebo Domine* – 'I will please the Lord'. In the medieval Catholic Church, 'placebo' was the term used to refer to a funeral rite – Vespers for the Dead – which employed Psalm 116.¹ By the 13th century, the term had taken on a disparaging, secular meaning: mourners paid to attend a funeral to 'flatter' the dead, were said to 'sing placebos' of false and easy praise. Indeed, in the 14th century, in the *Canterbury Tales*, Chaucer named his obsequious, flattering courtier Placebo.²

How did the word 'placebo' come to mean a medical treatment intended to please a patient? The term appears to have entered common usage sometime in the late 18th century. The 1775 edition of George Motherby's *New Medical Dictionary* contains no listing on the subject, while the 1785 edition defines 'placebo' as 'a commonplace method or medicine'.³ Arthur Shapiro, a distinguished historian of the placebo, has expressed puzzlement over the changing meaning of 'placebo', suggesting 'the reasons for the introduction of the word placebo into medicine in 1785 are largely unknown'.¹

The transition from religious to medical meanings of the word 'placebo' can be enlightened by an analysis of the writings of William Cullen (1710–1790), dubbed by one historian 'the leading British physician of the 18th century'.⁴ Cullen was the most prestigious and thus influential medical educator of his day, holding chairs in chemistry, theory of medicine and practice of medicine at the University of Edinburgh. Over his

lifetime, his famous lectures were attended by thousands of pupils from throughout the Anglo-American world, including many of the early leading figures in American medicine. Thousands of patients consulted Cullen by post and in person at the Edinburgh clinic, including such luminaries as his friend Adam Smith, the famous economist.⁵

In his historical account of Scottish medicine, Risse⁶ noted that Cullen 'employed regular drugs as placebos, although at lower doses'. We have examined the manuscripts of Cullen's clinical lectures,⁷ which are held in the Historical Library of the Royal College of Physicians of Edinburgh. They offer a valuable insight on how notions of placebo pertaining to religious ritual and flattery became a term referring to a method for pleasing difficult or incurable patients. The Cullen lectures also reveal the medical and social context of placebo use in actual medical practice in the late 18th Century.

'Placebo' in William Cullen's 1772 lectures

Cullen employed the term 'placebo' at least twice in his series of lectures given in 1772. In the first instance, he described giving a placebo treatment to a Mr Gilchrist, whom he regarded as 'absolutely incurable' and 'hastening fast to his fate'. Indeed, as Cullen remarked to his students, his motivation for taking the case was more for scientific than for clinical reasons ('I took him in hope of making some observations upon his case & even of learning something by his death'). Because Cullen had no hope that treatment could cure Mr Gilchrist, he decided to employ a placebo treatment to comfort or please his patient. Notably, he decided to use what we would now call an 'active placebo', as distinct from an 'inactive' substance which he knew to be physiologically inert (for example,

a bread or sugar pill). Cullen described his prescribing principle as follows:

'I prescribed therefore in pure placebo, but I make it a rule even in employing placebos to give what would have a tendency to be of use to the patient.'

From this passage it is clear that Cullen's definition of placebo treatment related not so much to the actual substance being prescribed, but to the intention with which it was being prescribed. He regarded a 'placebo' treatment as one given to please, but without any curative intent or hope. It is less clear what Cullen meant by his selection of a placebo that 'would have a tendency to be of use to the patient.'

A later passage reveals Cullen's thinking about the use of active placebos more clearly. He describes a patient for whom he prescribed mustard, an active treatment whose 'stimulant power... might be useful in paralytic affections'; but, notably, the drug was prescribed without any curative intent:

'I own that I did not trust much to it, but I gave it because it is necessary to give a medicine, and as what I call a placebo. If I had thought of any internal medicine it would have been a dose of the Dover's powders.'

For Cullen, either mustard, an external treatment, or Dover's powder, an internal treatment (made up of Ipecac and opium) could serve the purpose of being prescribed when a given situation makes it 'necessary to give a medicine' – even when the clinician himself does 'not trust much to' the actual curative activity of the particular medicine being offered. In this case, Cullen illustrates his general principle of prescribing placebos that might be 'of use' to the patient: he uses his knowledge of botany and materia medica to offer active compounds that might 'have a tendency' to be useful to the patient, even though they are offered without specific hope for a cure.

To summarize: Cullen's use of placebo was informed by two ideas:

- (1) Placebo treatment is defined more by the physician's lack of curative intention than the actual physiological make-up of the compound being prescribed;
- (2) When prescribing placebo, physicians should choose, in low doses presumably, active compounds that will tend to work against the disease in question, and in concert with the patient's general constitution.

William Cullen: clinical scientist of the Scottish Enlightenment

To understand Cullen's theory of placebo, one must consider his role as an original and important Scottish Enlightenment thinker in two domains: the functions of the nervous system, and medicinal chemistry and materia medica. Along with other thinkers of the period, including the economist Adam Smith and the philosopher David Hume,⁵ Cullen developed a theory of 'sympathy' which informed his ideas about clinical medicine. For Cullen, sympathy was a mind-body function, a kind of 'vital force' that animated the human body, coordinated function, and transmitted sensation to target organs.⁸ Cullen's theory of sympathy underpinned his description of the functions of the nervous system, which made up two-thirds of his lectures on medical physiology.⁹ As a theorist of sympathy and 'vitalism', he thus propounded a psychosomatic theory of illness and mind-body therapeutics.

Cullen was also an important chemist, however, and his ideas about medicinal chemistry and materia medica were highly influential in Anglo-American medical and scientific circles. He was one first in the British Isles to offer a regular course of lectures on chemistry¹⁰ and to introduce and teach a system of chemical notation that was disseminated and published by several of his pupils. Importantly for medicine, his *Materia Medica* was the first to use a Linnaean system of classification, providing a rational taxonomy of therapeutic substances such as plants and minerals.¹¹ In the introduction to an early (1761) edition of his lectures on *Materia Medica* (which was collected and published without his permission), Cullen criticizes past attempts at classification as having been based on whimsical or irrational categories. Praising Linnaeus' systematic method, he writes:

'The sensible Qualities alone are not to be trusted, the colour is fallacious, the smell more to be depended on, the taste more certain but less extensive. We shall consider their sensible Qualities and along with them give their chemical Analysis, but not in the ordinary way, which is to little Purpose, but such an analysis as separates the parts without altering the Qualities, and gives those separate in which the medical virtues are suppos'd to reside, such as Gums, Resins &c. The End of our operations on these substances is to gain their more efficacious parts and to reject such as are useless and Poisonous.'^{11[87]}

We can see here Cullen's role as a forerunner of modern pharmacology and as one of the first analytical medical chemists. He was one of the first to argue for analysis of a complex substance to discover the substance's active component, and to discard inactive or toxic components. Cullen's principle of prescribing an active placebo with chemical components which would be 'of use' to the patient was thus built on a scaffold of analytical chemistry influential at that time.

At the same time, perhaps paradoxically, Cullen's study of the objective science of analytical chemistry was counterbalanced by his sense that the patient's subjective, psychosomatic or 'sympathetic constitution' determined his reaction to a prescribed therapeutic substance. A distinguishing characteristic of Cullen's pathology is that almost all diseases are viewed as consequences of disorders of the nervous system. In the preface to his *First Lines in the Practice of Physick*, Cullen asserts that 'almost all diseases considered on a certain point of view could be considered nervous'.¹² Indeed, Cullen coined the term 'neurosis' to mean a disturbance in a patient's sympathies, and he was one of the first to use the terms 'hysteria' and 'hypochondriasis' to describe recognizably modern, nervous, psychosomatic disorders.¹³ In Cullen's view, the role of the physician was to be a gentle, sympathetic listener, who could interpret the patient's sympathetic disorder and select the proper remedy to treat it, whether by prescribing placebos to please the patient, or medicine to cure the patient's disorder.

William Cullen's sophisticated use of placebos to please patients is clearly discontinuous with early medieval and religious uses of the term. His theory and practice of active placebo may constitute a distinct early modern understanding of prescribing medicine that was based on objective, analytical chemistry and a consideration of the patient's nervous, sympathetic propensities. His use of placebo appears to be motivated by his philosophical and scientific commitment to Scottish Enlightenment thought in two forms: rational empiricism of scientific chemistry, and psychological inquiry into patients' nervous constitution (in an early form of what would later be called psychosomatic medicine).

Cullen's commitment as a physician attuned to a patient's sympathetic constitution may also explain his neutral use of a term that had previously, pejoratively, referred to flattery and fraud. The pursuit of a rational sympathetic medicine by Cullen and his Edinburgh colleagues reflects the broader 18th century Enlightenment

rejection of antiquarian, scholastic doctrines based on invisible, unverifiable metaphysical entities, such as humours or astrology.¹⁴ In place of invisible metaphysics, rationalists like Cullen focused on the doctor's empirical role as the interpreter of the patient's nervous sympathies.¹⁵ In this view, pleasing the patient was neither flattery nor fraud, but a real therapeutic objective. Cullen's neutral secular use of what had been a negative religious term can also be seen as his recognition that an empirically grounded medicine needed to take into account the present-moment emotional states of patients.

A final historical note

William Cullen's medical use of the term 'placebo' is the earliest of which we are aware. His lecture notes reveal a sophisticated clinical understanding of mind-body interaction,^{13,16} centred on a physician's therapeutic intentions and his attunement to patient sympathy. This finely calibrated, rational use of active placebo treatment, in which the physician dispensed a weak, physiologically active substance in order to please and calm the patient rather than to cure the patient's underlying disorder, was a product of the rational scientific culture of the 18th century Scottish Enlightenment and its embrace of a grounded, empirical approach to medicine.

The idea of placebo as a diluted but active substance persisted into the 19th century¹⁷ but the term also came to mean a physiologically inert substance – bread or lactose, for example.^{18,19} Inert substances began to be used in comparative clinical trials during the first half of the 19th century,²⁰ but this latter meaning of the term was given particular impetus at the end of the 19th century and the beginning of the 20th century, when inert substances were used as controls in pharmacological experiments.²¹ This shift in meaning may have reflected the rise of a new emphasis (or even metaphysics) in medicine, in which the molecular make up of an active drug assumed central importance, and any other positive benefits were seen as non-specific, placebo effects.

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