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Review

Physiological regulation through learnt control of appetites by contingencies among signals from external and internal environments

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Abstract

As reviewed by Cooper (2008), Claude Bernard's idea of stabilisation of bodily states, as realised in Walter B. Cannon's conception of homeostasis, took mathematical form during the 1940s in the principle that externally originating disturbance of a physiological parameter can feed an informative signal around the brain to trigger counteractive processes – a corrective mechanism known as negative feedback, in practice reliant on feedforward. Three decades later, enough was known of the physiology and psychology of eating and drinking for calculations to show how experimentally demonstrated mechanisms of feedforward that had been learnt from negative feedback combine to regulate exchanges of water and energy between the body and the surroundings. Subsequent systemic physiology, molecular neuroscience and experimental psychology, however, have been traduced by a misconception that learnt controls of intake are 'non-homeostatic', the myth of biological 'set points' and an historic failure to address evidence for the ingestion-adapting information-processing mechanisms on which an operationally integrative theory of eating and drinking relies.

Keywords: homeostasis; negative feedback; signals as information; quantitative systems theory; learnt identities of foods; learnt sating of appetite for food.

Regulatory physiology of drinking and eating since Cannon

The physiological research field

Claude Bernard took it for granted that consumption of food and drink delivers nutrients to digestion for circulation to the liver and other tissues, but Walter Cannon gave eating and drinking an explicit role in stabilising vital functions (Cooper, 2008). Thanks in part to E.F. Adolph (1943; 1964; 1980), the role in physiological regulation of this (literal) incorporation of environmental materials became a substantial area of research by the 1960s among medical, biological and psychological scientists around the world. Much of this new field of research concerned the 'managerial' role of the brain argued by Bernard and investigated by Cannon via the digestive tract and other parts of the body.

Measuring the disappearance of nutritious materials into the mouth became respectable in physiology beyond all doubt in 1977 when the *American Journal of Physiology* (edited by Cannon in its early years, as noted by Cooper, 2008) was divided into sections that included one called *Regulatory, Integrative and Comparative Physiology* -- moreover, separate from *Gastrointestinal and Liver Physiology*.

Meetings on regulatory intake

In 1962, the International Union of Physiological Sciences (IUPS) approved a new satellite to their then-quadrennial Congress, the International Conference on Regulation of Food and Fluid Intake. The theoretical term 'Regulation'[1] was later replaced by the discipline's name 'Physiology' but the thenceforth ICPFFI kept a primary focus on mechanisms that regulate bodily states by influencing the amounts ingested of solid or liquid mixtures that provide energy to metabolism and contain other nutrients, including sodium salts and water.

Throughout the time of ICPFFI, individuals around the world who were prominent in the research field hosted an additional meeting between IUPS Congresses (which became triennial). This tradition was consolidated in the USA in 1987 by the founding of the Society for the Study of Ingestive Behavior (SSIB) to run an open meeting annually, aiming to include biological, psychological and social aspects of the appetite(s) for food and drink. SSIB merged their annual meeting with ICPFFI when the IUPS Congress was near enough for workers in North America. So, when IUPS stopped approving Satellites, around the north Atlantic at least there was little effect on research into the physiology of intake, especially as SSIB's meetings have in practice centred on the neuroscience of amounts consumed at test meals.

Publications on regulatory intake

A key event in the 1960s was the appearance of a book on application of the engineers' concept of negative feedback to the physiology of balances of heat, carbon compounds and water (Yamamoto & Brobeck, 1965). John R. Brobeck worked on the volume with colleagues as Chair of the Department of Physiology, to celebrate the 200 years of the School of Medicine at the University of Pennsylvania. Starting with Brobeck's own overview, the chapters mapped out mathematical possibilities for the control of exchanges between a body and its surroundings -- including inanimate objects and plants as well as animals, similarly to Bernard and his contemporaries (Cooper, 2008).

Over the subsequent decade, such transfer of engineering control theory into physiological, psychological and some clinical and social research on drinking and eating came to fruition in calculations combining known mechanisms into self-regulatory animal systems. Keith Oatley and Frederick Toates built computed physiological control theories of water exchange in the rat (Oatley, 1967; Toates & Oatley, 1970). Their work inspired analogous efforts for the exchange of energy with the environment by both rats and people (Booth & Toates, 1974; Booth, Toates & Platts, 1975; Toates & Booth, 1974), which were detailed in full by several reviews in books and journals over the subsequent decade (e.g., Booth, 1976,[2] 1978, 1980, 1988a). In this quantitative modelling of the physiology of eating, both physiological and psychological details were 'lumped' by the use of data on emptying of the stomach and the partition of energy metabolites between lean and fat body masses. The computer model therefore remained realistic when particular mechanisms were 'unpacked', such as insulin's control of glucose uptake (Campfield, Smith & Fung, 1982).[3]

Psychologists in research on regulatory intake

Cannon was responsible for some rapprochement between physiology and psychology in the study of emotion (Cooper, 2008). Emotion in food consumption became an important area of socio-psychological research. However, the involvement of psychologists in the physiology of eating and drinking took a different direction.

Some psychologists working with laboratory animals began to turn to the systemic physiology (i.e. 'blood and guts') of hunger and thirst, either out of a direct

interest in signals to the brain from the digestive tract or the liver through neural pathways or the blood, or because of problems with the scheme of hypothalamic 'centres' of hunger and its satiety (e.g. lateral - Booth, 1967a; Ungerstedt, 1970; ventromedial – Booth *et al*., 1976; Duggan & Booth, 1986). Neuroscience by itself is incapable of explaining the control of ingestion, because the internal and external systems are what the brain is required to organise. So the body cannot be ignored as it was by the 'centralists' of the mid-20th century and still is by their successors, the neuro-reductionists and the neo-phrenological users of brain imaging (e.g. of 'palatability' or of 'satiety').

Furthermore, regulatory intake in generalists such as primates and rodents cannot be achieved by innate predispositions alone, genetically expressed in broad-brush structuring of neuronal connections. Learnt associations among events in the external and internal environments are required in addition. Systemic physiologists had difficulty in dealing with phenomena of learning but psychology is based on them. Acquired dispositions turned out to be essential to homeostatically effective feed-forward from previous negative feedback (Booth *et al*., 1976).

In addition, a tradition had grown in experimental psychology of approaching the mind as a problem in engineering science. As a result, it was psychologists who carried out the first integrative calculations of physiological influences on the consumption of water and of metabolic energy, once enough was known of the relevant digestive, circulatory and cellular systems.

Nevertheless a far more fundamental exchange between physiology and psychology is required in order to exploit fully Cannon's advance beyond Bernard.

A physiological signal is a mental mechanism

Engineered and natural communication

As pointed out by Cooper (2008) and Brobeck (1965), negative feedback is a concept from the theory of communication of signals through engineered systems, first developed by Norbert Wiener who had indirect contact with Cannon. The fundamental scientific point of the present review is that Wiener's concept of a signal was not of any particular material process, such as transmission of light or movement of electrons. A signal in engineering is a physically indeterminate process that serves a social culture by communicating (*sic*) well specified information between sites within a functional system including both internal and external *milieux*, such as the direction of the firing of a gun and the extent to which the shot missed the human operator's target. Therefore the idea of a signal of hunger, thirst or satiety going through the brain and influencing intake of food or drink imported a radically new theoretical proposition into physiology - that meaningful messages are transmitted through a material system that has roles in a societal system.

Signalling within a well adapted system requires the input of some interpretable information, the transmission of that interpretation around the system in various forms and some meaningful output as a result. These requirements are identical to those for a mental process in psychological science. The individual takes in observable patterns of information from the environment and transforms them into patterns of information put out observably into the environment. Much processing of information within the human mind is unconscious or subconscious but, whether in awareness or not, this mentation can be measured by the input/output performance of the individual, successfully transforming social, sensory and somatic stimulation into physical or symbolic actions or reactions -- in the case of ingestive appetite, the rated or actual selection of a mouthful of a material to be swallowed.

The neural processing involved does not specify the information conveyed. Just as in communication engineering, so also in psychology and in neuroscience and indeed messages within a society, a signal's meaning is independent of the physical medium that carries the signal. Engineered examples of material systems processing information that has meaning in human society began to appear after the time of Cannon and indeed of Wiener. The running of a program on a general computer is a 'virtual machine' having its own sort of reality, as also do a culture's language and political process, or again your and my achievements of thinking, feeling and talking sense. Yet these autonomous types of causation all operate within a unitary biosocial cognitive world of developed persons that is neither solely physical nor primarily subjective in construction.

Thus the Cannon/Wiener idea of a signal from a bodily disturbance to a behavioural remedy is a special case of a causal process between what psychologists have called a stimulus (or percept) and a response (or intention). In biological or social life, as in communications engineering, each discrete type of signal is transmitted over its own channel. Within the body, a signal is transmitted from receptor generator potentials through the peripheral and central nervous systems to muscle endplate potentials. Outside the body, a message is conveyed through social systems such as the market, politics, mass media and conversations between individuals.

The psychology of physiological signals of appetite

Failure to recognise this incorporation into physiology of the information-processing basis of psychology has led to serious confusions about bodily signals of ingestive appetites or their sating. These errors are encapsulated in statements such as "satiety is a subjective fulness" or is neural activity from receptors in the wall of the digestive tract, and "thirst is a central sensation" (criticised for instance in Booth, 1976, 1991, respectively).

Instead, the relevant physiological events are, for satiety, the stimulation of (e.g.) stretch receptors in the wall of the stomach that are made more sensitive by hormones from lower in the digestive tract, generating neural and/or circulatory activity registered in the brain or, for thirst, the stimulation of osmoreceptors in the brain and of pressure receptors in the wall of the large vein to the heart. The relevant mental events are a disposition to cease or avoid eating or to start drinking that is influenced by such stimulation, often unconsciously but sometimes with a sensation of fulness of the upper abdomen or of a dryness in the mouth. These dispositions are expressed in action by no longer taking mouthfuls of the available foods and equally objectively in words such as "I'd like a drink."

The psychological nature of the physiological signals in behaviour such as eating and drinking (or verbal expressions of dispositions to ingest) is poorly recognised also outside physiology. Yet some of the most important issues in psychology itself, and in philosophy of mind and applied behavioural sciences, are best handled in terms of signals -- for example, controversies over unconscious influences on action.

Social signals. For instance, we can be influenced to help a person in distress by someone else moving to help and yet remember our move as having been at our own initiative: it is likely that the social signalling is masked in recall by our theory of ourselves as spontaneously helpful (Nisbett & Bellows, 1977). Some of the influences on eating or alcohol consumption from others present or from prior acculturation might also be best investigated as discrete social signals picked up by the medium of sight or hearing and then measured for level of awareness.

Sensory signals. An example of a subconscious sensory signal is the observation that some people prefer to taste a particular amount of caffeine in their coffee without being able to tell the difference in bitterness between that level of the gustatory signal and less liked levels (Booth, Conner & Gibson, 1989; Conner, Sharpe & Booth, submitted).

Somatic signals. We may rate ourselves as too full to continue a meal in everyday life or decide to end a test meal in the laboratory without being aware of any signals from the stomach (Booth, 1976; Kissileff, Booth, Thornton *et al*., 2008). Yet unconscious physiological signals may be crucial to the control of eating that appears to be entirely social (Booth, Mather & Fuller, 1982; Gibson, Wainwright & Booth, 1995).

Strength of a control as discriminative sensitivity of the effector to the signal

Unfortunately, psychologists as well as physiologists have missed a key implication of the fact that negative feedback operative through eating and drinking is an informational processes. Indeed, in psychology the concept of negative feedback is widely regarded as of little use. This is largely because psychologists have neglected implications of classic work by Fechner, Weber and Thurstone on the performance of signal-transmitting channels through the mind, known as psychophysics.

These early psychological scientists obscured their subjects' (and their own) achievements by the fallacy of introspectionism (e.g., "just-noticeable difference [in sensation]", JND) that still afflicts many people's thinking about the mind. Nonetheless, the data that they collected on sensory performance clearly showed that the size of the effect of a signal on output was proportional to ratios (logarithmic differences) of the measurement of the material state being signalled, while for symbolised states the effect was proportional to simple differences in quantity (Booth & Freeman, 1993).

The strength of a physiological control mechanism can therefore be measured as the output's acuity to disparities of input. This has been called the 'suprasthrehold' sensitivity of that signal's channel. Its best established measure (that used for the JND: Booth, Thompson & Shahedian, 1983) is halfway from perfect (100%) discrimination between levels of the stimulus towards complete failure to discriminate (0%). For appetite control, this is the disparity between values of a signal that is 50%-discriminated by the short-term intake or rated appetite of an individual in the context of a particular ingestive episode (Conner *et al*., 1988; Booth, Earl & Mobini, 2003). The half-discriminated disparity (HDD) is a fully generic measure of the strength of a sensory factor in food or drink preference, a somatic factor in the initiation or termination of a meal, or a social factor in choice or amount of what is consumed.

Initially, though, the communication engineers' concept of a signal was taken down a blind alley, measuring merely the amount of information being transmitted by a channel. This approach cannot deal with the structure or content of what is being communicated.

Later, attention switched to measuring the output's detection of the presence of an input signal at its lowest levels, as it emerges above the noise in that channel. Although detection is still widely studied in psychology, in engineering and biology it is relevant only to the first warning of an emergency. Despite this limitation, signal detection theory provided one important updating of Cannon's work. Stunkard and Fox (1971) used the mathematics of detection to extend Cannon's efforts to relate gastric motility to the epigastric pangs that many people associate with the rise of the desire to eat.

However, the physiology of eating shifted in focus during the late 1960s from hunger signals to satiety signals (cp. Le Magnen & Tallon, 1966). This left little room for work on detection because that addresses only a start in the rise of satiety, not the substantial level of satiety at which eating stops or is prevented from restarting. Hence the signal discrimination measure is needed for quantitative investigation of sources of influence on eating. It has been applied to the sensing of materials (Booth *et al*., 1983; Conner *et al*., 1988; Booth *et al*., 2003) and cultural attributions (such as believed calories: Freeman *et al*., 1993), as well as somatic influences such as gastric distension (Kissileff *et al*., 2008). This psychophysical measure from Bernard's contemporaries in experimental psychology is also beginning to be used in neuroscience (Ernst, 2007; Deco & Rolls, 2006).

Further steps are needed for regulatory theory to become realistic to the eating of multiple foods in varied social contexts, with choices among foods being made from before the start to after the end of a meal or snack. To characterise the mental interactions among contextualised signals, each signal needs to be separately manipulated in a disconfounded design and the signal values zeroed on the normal context.

Sensory, somatic and social signals to ingestive appetite

The body or the culture?

The early 1970s saw a rush of experimental evidence that rats' choices among foods and amounts of them to eat under normal conditions were controlled by signals from all three categories of stimulation, the oronasal senses (Booth & Simson, 1971; Booth, Lovett & McSherry, 1972; Booth, Stoloff & Nicholls, 1974), ingested food before and after digestion and absorption (Booth 1972a; Booth & Jarman 1976) and conspecifics (Galef & Clark, 1972).

Biological psychologists pursued somatic factors and social and clinical psychologists pursued social factors. This could have been productive but unwarrantedly exclusive postures were adopted. Also, both sides ignored sensory signals. Worse, instead of identifying the actual signals, research was diverted into attributing somatic effects to the food's satiating powers, sensory effects to the food's palatability or appetising nature, and social effects to the food's undeconstructed conventional role. This was as helpful as attributing effects of barbiturates to their dormative essence.

For example, it was soon claimed, and still remains widely believed, that physiological states such as gastric distension or blood levels of glucose or of insulin play no role in normal human eating. This view, however, is a *non sequitur* from showing the importance of cultural controls or interpersonal influences in food intake. Such social cues are likely to be confounded with gastric fill (Booth & Mather, 1978) and so the demonstration of controls that are not physiological provides no evidence either way. Indeed, there has long been clear evidence that the sating of appetite is influenced by physiological signals, from experiments testing people's normal eating for combined gastric and sensory influences by disconfounding them and minimising effects of the social environment (Booth *et al*., 1976, 1982, 1994).

Physiologists are partly to blame for lack of evidence for visceral control of appetite, because of designs that isolate a particular signal from its normal context. (The same error has crippled the contribution of perceptual psychology to sensory evaluation of foods and drinks.) When gastric fill, small-intestinal chemostimulation and information from the culture are independently manipulated within a familiar context of eating, then each signal can be seen to have an effect on appetite (Cecil, Francis & Read, 1998). Nevertheless this ingenious design has severe limitations.

Comparison of only two experimental conditions allows no quantitative analysis of the signal. Grouping of raw data prevents characterisation of the interactions among signals within each individual that may differ qualitatively between people.

Signal levels in context

Full measurement of a contextualised appetite signal is remarkably straightforward but did not begin until the 1980s. Quantitative data have been published but not used to calculate the discrimination acuity or the comparison norm.

Sensory signals. Booth *et al.* (1972) showed that control of intake in rats was learned for a particular level of sweetness, in contrast to the unlearnt greater liking for greater sweetness. Considerably later, this was also shown for the salt in a familiar food in human infants (Harris & Booth, 1987) and adults (Booth *et al*., 1983). The first discrimination measurements of control of momentary appetite by the learnt signal of amount of deviation from a particular level of stimulation were reported for the tastes of sodium chloride or sucrose in each food or drink, with values that varied both among the ingestates and among individuals (Conner & Booth, 1988; Conner *et al.*, 1988).

Social signals. Social manipulations liable to affect the eater's belief about the calories in a portion of food have been much investigated in qualitative, two-condition designs (Wooley Wooley & Dunham, 1972; Booth *et al*., 1982). Freeman *et al*. (1993) partly quantified this signal but results from discrimination scaling have yet to be published.

There is considerable evidence that people eat more and for a longer time in proportion to the number of others present. Yet there has been remarkably little study of what are the social signals that increase intake. Unpublished expertiments indicate that the effect can come in part at least from facilitatory feedforward as the combined social and sensory signal of the offering of a second helping

Somatic signals. The osmotic signal to rated thirst has been quantified (Robertson, 1991). Sensory and/or social facilitation or inhibition of eating can be dependent on somatic state then being signalled (Booth *et al*., 1982; Booth & Toase, 1983). Such results also indicate why somatic signals are 'hidden': their effect depends on the sensory signal and so the effect on appetite is attributed to the foods having those sensory properties, e.g. dessert foods or even their levels of sweetness are regarded as appropriate to end a meal.

Integration of signals

In order to understand the interactions of different signals and their integration as ingestive appetite, it is essential to manipulate and/or to monitor each particular somatic, sensory and social signal quantitatively. At the very least, graded signals within or between these categories should be disconfounded.

However, there is an even less well understood prerequisite for understanding influences on eating and drinking. Appetite and its sating are states of the moment. The level of any signal is liable to change with the setting that makes food or drink available, as each combination of items is taken for consumption and is swallowed, digested and assimilated, and when the physical and social context shifts.

Hence the amount eaten during a bout of ingestion is useless as a measure of appetite, especially when tested at arbitrary times after previous ingestion, unless facilitatory and inhibitory signals have been dissociated (Booth, 1972) and preferably different levels of each signal are compared within a sufficient brief time for no appreciable change to have occurred in any other signals (Booth & Davis, 1973).

Defeat of science by word games

Sad to say, this search for signals of appetite for food and drink had hardly begun when it was largely abandoned in favour of deployment of mere 'concepts.' Different test intakes or appetite ratings were assigned different names without any evidence as to which particular signal or combination of signals was influencing the momentary disposition to eat or to drink.

Each wording of rated appetite was assumed to measure a different mental state, not only without any psychophysical evidence as to the signals being processed but also in the face of psychometric evidence to the contrary whenever examined – namely, all the wordings gave ratings that were highly correlated with each other.

The sizes of some meals were labelled a measure of "satiation" and other meal sizes as "satiety," merely because of the way the investigators were thinking of the meal. Yet whole meals are useless to measure the processes that satisfy the appetite for food, since they vary greatly between the start and finish of a session of eating. Worse, the terminology is a solecism: satiation is merely the process of going from a state of less satiety to a state of more satiety. The scientific issue is which facilitatory signals are declining and/or inhibitory signals intensifying.

As a result, magical properties are attributed to foodstuffs, such as sensory cues to the nutrients in them ("macronutrient selection"; Booth & Thibault, 2001), a fixed hierarchy of palatabilities or satiating powers (Booth, 1981b, 1990) and effects on body weight regardless of the way the foods are used (Booth, 1988b), the idea that individuals' food preferences should be attributable to their family genes and environment, and so on. Drugs and neurotransmitters are claimed to affect appetite or satiety without considering which signals they are modulating (cp. Matthews, Gibson & Booth, 1985; Booth, Gibson & Baker, 1986). Health claims about satiety would be as deceptive to consumers wanting to lose weight as the disclaimer that a product is useful only in a "calorie-controlled diet." Behavioural phenotypes have no meaning without identifying both the genotype and the particular habit that biases the regulation of adipose energy (Peck, 1978). Daily fat intake, for example, is an artefact of many and varied choices and amounts of foods, each action being controlled by an integrated set of signals at momentary levels.

This neglect of the mechanisms of appetite has had a devastating impact on fundamental and applied research. Such misdirection of academic work cannot have helped to slow the rise of obesity or to characterise the epidemiologists' one-third dietary causation of cardiovascular diseases and cancer, having contributed to the dearth of evidence on which to base public health nutrition and commercial food marketing (Booth, 1988b; Booth *et al.,* 2007).

Regulatory learnt mechanisms of eating

Learning of signals facilitating or inhibiting momentary appetite

The case from theoretical integration of the evidence is that the metabolic regulation conceived by Claude Bernard works only because onset and offset of a bout of ingestion are subject to feedforward learnt from negative feedback. All signals have to be adapted to the individual's internal and external *milieux*, especially in an omnivore capable of exploiting and indeed creating a great variety of niches.

Homeostasis in energy and nitrogen exchanges (at least) is critically dependent on effects of particular learnt levels of current signals from sensing of consumable materials and of the cultural, interpersonal and physical context of eating and drinking, as well as of states of innervated tissues. Combinations of signals at specific levels have gained the power through learning to facilitate or to inhibit the central pattern generators (CPGs) of the movements that transfer samples of food and drink from the front to the back of the mouth and trigger swallowing. Such neural 'drive' in

a learnt preference is what I. P. Pavlov called a conditioned response centre. Acquisition of fine orosensory control of a CPG is what followers of B.F. Skinner called the shaping of the operant response.

The study of learnt signals

Disregard of the learning in signals controlling eating has therefore greatly retarded scientific development of the understanding and exploitation of physiological regulation through controls of ingestion.

Part of the reason is that it can be technically complex to characterise the ways in which past experience can influence present performance. Hence the experimental situations may seem artificial and the necessary terminology can be daunting. The learning of goal-directed actions has proved to be so flexible that testable theory is hard to construct. Early work on the capture of unlearnt movement patterns by cues predicting biologically important consequences was described in a pseudo-neurological jargon in an effort to be consistent with dialectical materialism. So perhaps it is unsurprising that Cannon neglected the scientific study of the processes of learning that flowered in his time (G.P. Smith, 2008).

The only objective way to identify the learnt information held in a memory is by effectively designed psychological experiments. These have to measure the effects of an organism's exposure to cue-consequence contingencies among sensory, somatic and/or social signals on that individual's subsequent performance on recurrence of the cuing signal(s). Historic experiments of this sort include Le Magnen (1956), Booth and Simson (1971), Booth *et al*. (1972), Booth and Davis (1973), Holman (1975), Sclafani and Nissenbaum (1988) and E.L. Gibson and Booth (1989).[4]

Neuroscience alone cannot measure what the organism has learnt. There is no hope of identifying these specific memories because myriads of synapses between nerve cells within any particular small region of the brain adapt their transmissivity to contingent signals. The proposal of such synaptic changes by Donald Hebb in 1949 (Cooper, 2005) had become a truism in psychology by the 1960s.[5] Physiologists recording the electrical activity of single cells in the brain increasingly recognised that the transmission characteristics of a substantial proportion of synapses were altered by concurrent pre- and post-synaptic activity. Such adaptations encode into their locations in the brain's circuitry (Booth, 1967b) whatever contingencies (Dickinson, 1981) occur among perceived affordances by the environment (J.J. Gibson, 1979) or between intended or reactive patterns of movement and their sensed impact on the environment (Powers, 1974). Experimental psychological analysis of learnt performance is the prerequisite to working out how the acquired signalling is structured in the material medium.

Learnt sensory facilitation and inhibition of ingestion

Those sensory, social and somatic signals at particular levels that are followed by delivery of glucose or essential amino acids to tissues become highly facilitatory of eating when the combination of signal levels is restored. Infant rats (Booth *et al*., 1974) and human beings (Beauchamp & Moran, 1982; Harris & Booth, 1987) learn to like whatever flavour and texture delivers glucose or amino acids to the small intestine. Indeed, learning is the only explanation that can be given for generalist feeders' ability to distinguish edible from inedible materials, without which intake of many nutritious materials would not occur. The physiologists of thirst have been scandalised by the suggestion that even the recognition of water has to be learnt (Booth, 1979, 1991).

Such associative conditioning of sensory preferences thus provides a feedforward mechanism that is much more efficient than indiscriminate eating driven

by extreme need. An even more efficiently regulatory feedforward has recently been demonstrated: the sensory signal guides avoidance of the hunger it predicts by increases in the amount eaten (Jarvandi, Booth & Thibault, 2007).

Learnt sensory inhibition also has a homeostatic role of the emergency sort: aversions to tastes and odours are associatively conditioned by signals of potentially dangerous consequences, such as nausea or an unfamiliar sensation.[4]

Contextualised facilitation: learnt appetites

Learning from past repair of deficits provides direct facilitation of ingestion of foods by sensory and social signals. The learnt somatic facilitation, e.g. by GI distress such as the epigastric pangs studied by Cannon, may however be indirect. The gastrointestinal signal may arise from conditioned central facilitation of the motor migratory complex seen in the postabsorptive state (Booth, 1980). F. Smith and Campfield (1993) made a similar suggestion about central control of the shifts between tissue uptake and mobilisation that produce a blood glucose dip predictive of meal onset.

Contextualised inhibition or de-facilitation: learnt satieties

Le Magnen (1956) argued that food-specific learning to stop eating was necessary in order to account for control of intake at a meal by the physiological consequences of digestion and absorption of that meal. Such associatively conditioned sensory-somatic satiety was first distinguished from learnt sensory aversion by an acquired reduction in sensory acceptance that was specific to the physiological state towards the end of the meal, with no such inhibition at the start of the meal (Booth, 1972b) or, more clearly, substantial initial facilitation (Booth & Davis, 1973).

Contingencies serving homeostasis

Thus each individual has a large set of learnt normal levels of sensed, cultured and embodied facilitators or inhibitors of eating or drinking. The remembered 'norm' may be the most familiar situation or the most preferred or appetising (or aversive or sating) version. Differences between habituated stimuli, conditioned stimuli, discriminative stimuli, personal habits and subcultural norms are theoretically important but empirically very difficult to pin down – partly because these differently acquired set points often coincide in value. Such a norm is the nearest to a reference value that exists in the control of exchanges of energy, nitrogen, salt and water.

Hence the first simulation of the control of patterns of meals in the laboratory rat only became fully realistic physiologically when a recently discovered mechanism for learnt sensory-somatic control of meal size was added (Booth *et al*., 1976). Moreover, the published models of rats and of a human being deal with only a single 'diet' and so unpublished programming of the control of selection among available foods by learnt state-dependent preferences would have to be added in order to simulate the composition of meals in free-living individuals. That is, quantitative physiological theory of bouts of food intake only works if the facilitation of ingestive movements sufficient to start a meal and learnt inhibition sufficient to terminate sipping, biting and chewing are both postulated to have been acquired.

The myth of a homeostat's pre-set target value

Opposing negative feedbacks

Engineers' systems often compare the current value of the signal that is fed back to the central controller with a fixed value relating to the target and drive the corrective effect by the difference of feedback from that reference value or set point. This is indeed the simplest design for gunnery control, guided missiles and

thermostatically controlled heaters or coolers. It is good design too when the target object, place or temperature needs to be adjustable by human intervention.

Nevertheless, identical performance with respect to a fixed value can be obtained by inversely relating the correction to the feedback with appropriately shaped mathematical functions (Booth, 1980). Two opposing negative feedback functions without a set point will defend the system from excursions in either direction. Biology is full of such untargetted corrective processes operating without central control, whereas it is hard to conceive the neurogenetics of a circuit that computes and imposes a particular value of a sensed state.

Thus there is no scientific reason to doubt that physiological and behavioural activities that defend the state of the body against external disturbances are all part of negative feedback mechanisms distributed around the body that operate without a reference value, whether fixed, sliding or adjustable. The excursion-correcting power, its triggering and its rate of rise are all built into the feedback, not controlled by the extent of current deviation from the setting of a genetically programmed 'dial' in the hypothalamus or anywhere else in the brain.

The set-point is not a useful metaphor, nor a simplifying heuristic. It is a myth that has the malign effect of diverting research from the real task faced of identifying each homeostatic feedback signal and any feedforward mechanisms and then characterising their mathematical equations and how they interact quantitatively. Persistence of this damaging error is one of the worst failures to use the quantitative model of hunger and its sating to bridge between ideas and experiment.

The early collapse of physiological set-point theory

One strategy for managing the implausibility of a "set point" is to pose it as a purely hypothetical variable. This approach is scientifically invalid, however, since the hypothesis is both mathematically redundant and empirically false.

In Yamamoto and Brobeck (1965), Yamamoto based his mathematical account of (hypothalamic) temperature regulation on "set points" but as soon as he got down to plausible neuronal mechanisms that pre-set fixed value disappeared. J.D. Hardy (Yamamoto & Brobeck, 1965, Chapter 6) ended detailed analysis of temperature regulation with explicit conclusion that "… the system performs 'as if' it were a set-point system, but it could also be a combination of two balanced dynamic systems…" Indeed, Hardy's title and final sentences condemn the term by enclosing it in quotation marks. The point is that research needs to identify the equations for the dynamic control processes, not to search for the source of a reference value or to spend time puzzling about what is regulated whenever a negative feedback mechanism is discovered.

A decade later, for regulatory eating, Booth *et al.* (1975) and Peck (1978) showed that opposing negative feedback functions were mathematically equivalent to the same system with a set point added. Wirtschafter and Davis (1977) showed that a simple equilibrium function produced a "settling point" If the parameters of one or other direction of reaction were altered (e.g. by hormonal action), then the system retained its regulatory properties but equilibrated at a different value. The equilibrium is also shifted when an external bias is imposed, such as increased fatness in children or adults trapped in motorised vehicles or in front of TV without precautionary eating controls.

Evidence for precise stabilisation without reference value

In addition to the logical redundancy of set points and the implausibility of their location in the brain, there is simply no evidence for preset reference values or thresholds in the system's performance and its known mechanisms.

Heat. Human beings have a supremely accurate thermoregulatory system (compared with chimps) for working in the heat of sun (Adair, Mylacraine & Allen, 2003). The overall management of sources of thermal comfort and distress, i.e. effortless reactions and effortful skills that compete for attention, are presumably learnt.

CO_2. Haldane's work on human respiration (Cooper, 2008) showed exquisite control of the rate and depth of breathing by the signal from carbon dioxide in the blood. Furthermore, control of oxygen uptake near sea level is exerted by blowing off CO_2.

Salt. Learning facilitates sodium intake by the preferred taste of some foods including its usual level of saltiness (Conner *et al*., 1986). Rats have an innate salt appetite but it is made more finely regulatory by learning to recognise sources of salt. Aversions to the taste of salt are not generally acquired. Hence regulation of salt balance has to be achieved by excretion. An abundance of salt-containing foods provides repeated challenges to blood volume regulation, the homeostatic response generating an unhealthily chronic rise in blood pressure.

Water. Similarly, water intake is facilitated by osmotic and perhaps volaemic signals of water deficit. It is generally thought that this facilitation is innate but the sensory signalling required for this has not been adequately considered. Indeed, it was for this reason that it was suggested that thirst is learnt (Booth, 1991).

Fat mass. Energy flow from unstimulated turnover of adipose triglycerides is sufficient negative feedback to account of defence of human body fat content but this control works very slowly and so can be overwhelmed by environmental facilitation of intake (Booth, 1988a). In the simulation, this feedback operates entirely through the learnt control of meal size, i.e. an acquired feedforward loop. Furthermore the learnt signal is a combination of sensory and somatic signals, e.g. a distinctive flavour of a foodstuff and a particular level of gastric distension. This learnt norm can be established experimentally by the immediate effects of rapidly digested starch (Booth & Davis, 1973; Booth *et al.*, 2004).

Human engineering versus natural selection

Cooperation of the kidneys with the lungs is crucial for water/salt balance. Metabolic energy is cycled among the digestive tract, muscles and liver (and kidneys too) with central efferent control. A blood-based 'glucostatic' theory flies in the face of Bernard's basic point against the chemists, picked up by Haldane against Henderson (Cooper, 2008), that chemical equilibrium is a single entity (such as a buffered solution) whereas physiological regulation is (as we say nowadays) 'distributed' over the organs of the body. The passage of carbohydrates and glucogenic amino acids down the digestive tract, the integration of glucose and fatty acid metabolism by the liver and the autonomic and hormonal signalling between brain, liver and adipose tissue are all integral parts of the mechanisms with orbitofrontal cortex, the diencephalon and the brainstem. It makes no sense to search just within the brain for the control of appetite, let alone for set-point cells or circuits.

Finally, the broadest argument against set points is that they are unnatural. The notion of a target value has been transferred from human-designed controls to the mechanisms for biological stabilisation. All that is needed to explain the observed defence of a physiological parameter is distributed feedback functions that oppose each other. This would be complex to engineer but readily emerges in animal species that have prospered in challenging circumstances from "the fixity of the *milieu intérieur* which is the condition of a free and independent life" conceived by Claude Bernard (Cooper 2008).

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Footnotes

[1] "Regulation" is of course an ambiguous term, most often used for a rule that an organisation is required to follow by government with the backing of the legislature. More importantly in this context, "regulation of intake" is an erroneous concept, as emphasised by authorities such as John Brobeck (1965) in the USA and Jacques Le Magnen *et al*. (1973) at the Collège de France (where Bernard had worked). Unfortunately this fundamental error continues to be widespread. What is regulated is a physiological parameter, not intake. Body fat, say, or liver glycogen or blood osmolarity may be regulated through control of intake (that is, by one or more influences on eating or drinking) but then (that aspect of) the intake is regulat*ory*, not regulat*ed*.

[2] This conference-book on 'Appetite and Food Intake' was the second in the multidisciplinary Dahlem Life Sciences series (later published by Springer), which was the origin of the UK-based series of annual meetings later re-named BFDG and a major inspiration for the founding of the journal *Appetite* by Academic Press in 1980.

[3] This extension of the computer model was consistent with the implication that the VMH inhibits gastric emptying autonomically and does not mediate signals of satiety. The release of emptying by VMH lesions causes immediate overeating by a decrease in time between meals (Duggan & Booth, 1986) and the increased absorption could induce greater secretion of insulin – a possibility not excluded by subsequent work on the early hyperinsulinaemia in VMH rats.

[4] A personal account of the development of evidence and theory on roles of learning in eating and drinking has recently been placed online at http://www.ctalearning.com (November 2007).

[5] For some years, Steve Cooper and I shared an undergraduate lecture course that included molecular bases of the changes in neuronal connectivity constituting memory. I particularly remember the superb diagrams he drew for his visual aids (cp. Higgs, 2008).