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Current dilemmas in defining the boundaries of disease

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Abstract

Boorse's biostatistical theory states that diseases should be defined in ways that reflect disturbances of biological function and that are objective and value-free. We use three examples from contemporary medicine that demonstrate the complex issues that arise when defining the boundaries of disease: polycystic ovary syndrome, chronic kidney disease and myocardial infarction. We argue that the biostatistical theory fails to provide sufficient guidance on where the boundaries of disease should be drawn, contains ambiguities relating to choice of reference class, and is out of step with medical processes for identifying disease boundaries. Although proponents of the biostatistical theory might regard these practical issues as irrelevant to the aim of providing a theoretical account of disease, we take them to indicate the need for a theoretical account that is adequate for current needs -- including limiting new forms of medicalisation that are driven by the identification of disease based upon dysfunction. Our processes for determining the boundaries for disease need to recognise that there is no value-free method for making these decisions.

Introduction

Since Boorse published his seminal paper on "Health as a theoretical concept" (Boorse 1977), philosophical discussion about defining disease has been dominated largely by the evaluation of naturalist versus normative approaches. Three related questions arise in these discussions. The first is what is meant by the term 'disease', in opposition to the term 'health'? The second is which particular conditions can be considered diseases, for example 'Is alcoholism a disease'? And the third is to do with how well our definitions of diseases function in delineating the boundaries of specific diseases. For example, if we accept that there is a disease 'liver failure', what criteria accurately map the contours of the disease liver failure so that we can distinguish cases from either healthy livers or other ailments?[1]

[1] Question one concerns the intension of the term 'disease', while questions two and three refer to its extension.

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Both the second and third questions relate to issues of defining the boundaries of the concept 'disease': the second concerns whether a condition of type X falls under the concept or not; the third concerns what states will count as instances of a specific disease, and in virtue of doing so will fall under the general concept 'disease'. Much of the criticism of Boorse's theory has focused on how well the theory is able to answer the first and second questions, with less focus on the third (Hausman 2014). There has been some discussion of issues relating to the third kind of question, primarily in relation to 'spectral' diseases, the diagnosis of which relies on identifying a threshold point on a variable that is continuously distributed in the population (see, e.g., Schwartz 2007). Schwartz's paper focuses on several other issues in defining the boundaries of specific diseases, and what these issues imply for accounts of the general concept of disease. We take these issues to show the need to recognise values and contingencies that affect disease definition, and argue that lack of such recognition is a limitation on the usefulness of naturalistic theories of disease.

We begin by reviewing Boorse's statements regarding disease boundaries and the biostatistical theory (BST). We then give three detailed examples of specific diseases to illustrate several challenges relating to disease boundaries for Boorse's theory. In relation to dysfunction as a necessary criterion for disease, we analyse the condition of polycystic ovary syndrome, showing the difficulty of identifying the relevant dysfunction in this disease. Regarding reference classes, we discuss chronic kidney disease, a disease whose boundaries are particularly sensitive to any changes in the reference class. Finally, we consider the advent of extremely sensitive biomarkers used for diagnosing myocardial infarction to show how previously unproblematic disease definitions fail in the face of biomarkers that can detect almost literally 'one dead cell'.

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We take these three examples, grounded in contemporary medical practice, as evidence that Boorse's BST is not sufficient to delineate disease boundaries. Further, these examples show that actual medical processes of disease definition are imbued with values, thereby throwing doubt upon the possibility of a purely naturalist definition of specific diseases based upon objective biological criteria. Finally, we argue that given the serious problems related to the lack of definitive boundaries in many diseases, and the serious consequences these can have for individuals diagnosed with disease, we need theories of disease that are transparent about the values at stake, and that can be used to prevent problems that arise from indistinct boundaries. Although a proponent of the BST might reply that these are practical problems, to be dealt with by appeal to concepts other than the theoretical one it offers, we argue that these sorts of problems reveal important limitations on the usefulness of any such value-free, theoretical notion. An important motivation for the BST was to resist political misuse of concepts of health and disease, such as pernicious forms of medicalisation in psychiatry, by insisting that for disease, some identifiable dysfunction must be present. But today, the identification of disease with dysfunction can actually drive new forms of medicalisation, which expand the boundaries of disease in ways that are problematic. Focusing on the possibility of naturalistic disease definition becomes problematic where it obscures the ways in which values come into play in real-world practices of defining disease.

The BST's approach to determining the boundary between disease and normality

In this section, we highlight features of Boorse's account that are challenged by the examples to follow. Boorse states that disease is a "state of statistically species-subnormal biological part-functional ability, relative to sex and age" (Boorse 2014, 684). This definition takes any state that impairs health to be disease. Health is defined as "normal functional ability", where normality is statistical, and function is biological. Boorse provides an analysis of biological

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function as contribution to goals that considers an organ, or physiological system, to be functioning normally when it makes its normal or 'species-typical' contribution to the organism's goals (Boorse 1976b). Biological goals are arranged hierarchically: for instance, the function of the stomach is its contribution to digestion, in which it is part of the larger digestive system, whose function is to contribute to higher-order goals of nutrition and energy distribution, which in turn contribute to further higher-order goals. At the top of the hierarchy, as a matter of descriptive fact, are survival or reproduction. At each level, 'species-typical' contribution is defined statistically, and is to be considered relative to reference class, that is, an age-group of a sex of the species, in order to acknowledge that our functional abilities vary with age and sex (Boorse 1976a). Thus, to impair health is to reduce one or more functional abilities below typical efficiency (Boorse 2014, 684).

One critique made of the BST is that it can seem to include too much as disease. For instance, the 'one dead cell' objection to the BST, first made by Nordenfelt (1987), is that the BST seems to imply that disease is present where there is just one dead cell, since that cell is failing to make its species-typical contribution to the biological goals of the organism, even if there is no noticeable change in overall functioning. While Boorse accepts that no one is ideally healthy (1987, 365, cited in Wakefield 2014, 656), the additional criterion that the dysfunction be statistically atypical also limits what dysfunctions count as diseases.

Another important question raised for the BST in relation to the boundaries of specific diseases is how far below typical efficiency a functional ability must fall before it counts as dysfunctional. In some cases, a particular organ or organ system can cease to function altogether, so that cases of total blindness, for example, will count as a disease. But in most cases, measures of biological function will be on a continuum from poor function to high

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function. As Geoffrey Rose has said, "there is no disease that you either have or don't have - except perhaps sudden death and rabies. All other diseases you either have a little or a lot of" (Rose 1992, 72). Nonetheless, we need some kind of threshold to indicate what level of dysfunction counts as a disease state. Whilst Boorse states that a condition counts as a dysfunction when it "falls more than a certain distance below the population mean" (Boorse 1977, 559), he also thinks the exact level below the population mean at which we have disease "can only be conventionally chosen" (1977, 559), and the BST does not provide guidance on how a threshold is to be chosen. This is a specific problem for 'spectral' diseases with diagnostic definitions that locate a threshold point on a measure of some continuous biological variable, such as type 2 diabetes or osteoporosis. We do not focus on this issue further in this paper, since it has been discussed in detail elsewhere (Schwartz 2007), though it arises in some of the examples discussed below.

Several criticisms have also been raised regarding what should guide the choice of reference class, given that this will affect what is taken to be normal function for particular individuals. The BST does seem to need to acknowledge that statistical abnormality is relative to reference class, since normal function differs quite considerably between adults and children, men and women. Boorse also states there may be a need to relativise normality to race (Boorse 2014, 702). Some have argued that choosing a reference class necessarily involves values, thereby undermining the objectivity of the BST. Kingma (2007), for example, argues that whether a state counts as normal or not may depend on the choice of reference class, that is, the choice of the group we take to be indicative of normality, against which any particular instance is to be judged.[2] But there are no empirical facts that can direct our choice of

[2] See also Cooper (2005).

reference class. Boorse's reply is that even if the choice of reference class were directed by some evaluative factor this would not show that disease was evaluative on the BST, since none of the components of his analysis (including age and sex) are themselves normative categories.

Further, Boorse states that the age group and sex of a species or subspecies is a biologically natural choice of reference class: "the BST's reference class is just one morphological type in the smallest taxon to which an organism belongs" (Boorse 2014, 695). Boorse claims to be following in biological tradition regarding reference classes: "When biologists describe and classify organisms, they sort them into species or subspecies, separate them by sex in sexual species, and distinguish immature from adult forms. The BST departs from this only in making old age as well as youth count for classification" (2014, 695). Elsewhere, he states that reference classes relevant for medical applications seem "to be an age group of a sex of a species, e.g., human male neonates or, say, 7-9 year old girls" (1977, 588), although he does not provide specifics on how a reference class would be chosen.[3] In relation to a criticism raised by Schwartz that some diseases are statistically prevalent, Boorse has recently considered regarding all adults of the same a sex as one reference class (Boorse 2014, 714). We take up this point further below.

Boorse states that his view is value-free in the sense that "none of its component ideas requires value judgements" (Boorse 2014, 684). He intends this definition of disease to capture the concept as used in theoretical medical science (specifically pathology) and is very clear that this concept will differ from practical or clinical concepts of disease. These, he

[3] We thank an anonymous reviewer for this latter point.

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states, are inescapably normative. Practical or clinical notions of disease also need to fall under the theoretical concept, so that they are limited by it, but may need to meet other, evaluative criteria, in addition to the value-free criteria of the BST. Boorse develops several notions, first discussing 'illness' and later diagnostic normality, therapeutic normality, and several other practical options (1997, 12-13). The theoretical notion of disease he explicitly detaches from any imperative to intervene, or any value-judgements about states categorised as disease.

Despite aiming at a value-free definition of disease, the BST was developed, in part, for a particular purpose: resisting political misuse of the term 'disease'. Boorse insists on the presence of dysfunction for disease, in part, to resist what he takes to be various kinds of problematic medicalisation, such as having the term applied to conditions regarded as socially undesirable, or as a means of stigmatising some behaviours (Schramme 2007, Boorse 1976a, 68-75, 1997, 99-100, Agich 1983). Insisting on the presence of dysfunction as necessary for disease might help to prevent expansions of the concept to conditions where there is no identifiable dysfunction. We agree that this expansion of the use of the concept 'disease' and the associated medicalisation is problematic. As we discuss below however, our concern is that the BST alone cannot achieve this goal, and that, paradoxically, finding ever smaller degrees of dysfunction which will be included as diseases in accordance with the BST is now leading to increasing rates of medicalisation and overdiagnosis (Rogers and Mintzker, 2016). That is, the value-free, naturalistic account of disease itself has a practical purpose – but it is not clear that this kind of account is, any longer, the best way to meet this purpose.

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Example 1. Which function: Polycystic Ovary Syndrome

The BST does not deal in any detail with the challenge of identifying which functions are the relevant ones in particular diseases. Boorse might consider such identifications a matter for nosology, distinct from his project of analysing the distinction between normality and pathology. Yet it is problematic to leave this matter aside, as it is only through a detailed attempt to identify relevant disease-making functions that we discover that the boundary between normality and pathology shifts, depending upon which function we take to be pathognomic for any particular disease. Our example here concerns polycystic ovary syndrome (PCOS), a condition affecting adult ovaries. The function of the ovaries is to regularly (roughly monthly, in the years between menarche and menopause) respond to hormonal signals in order to trigger the release of mature eggs with the capacity to be fertilised. Along with egg maturation, ovaries also play a role in the regulation of female sex hormones. In 1935, Stein and Leventhal described a series of women with polycystic ovaries associated with amenorrhoea (Stein and Leventhal 1935); that is, they initially characterised the disease of PCOS as involving pathology of the ovaries (presence of cysts), disruption to the usual menstrual cycle (amenorrhoea), and lack of release of mature eggs (infertility). Later studies showed that PCOS is associated with high levels of circulating androgens.

However, over time, the diagnostic criteria for this condition have shifted. Diagnostic criteria are the measures which are taken to identify the presence or absence of the relevant dysfunctions for particular diseases. That is, high levels of thyroid hormone are one of the diagnostic criteria for the disease hyperthyroidism, while an x-ray showing segmental opacity in a lobe of the lungs is one of the diagnostic criteria for the disease pneumonia. Diagnostic criteria may act as necessary or sufficient criteria for the identification of instances of specific diseases, thus setting the boundary of those diseases. Changing diagnostic criteria may reflect

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the advent of new tests, or a changed understanding of the underlying disease. However, changing diagnostic criteria may also reflect lack of medical agreement over the nature of the underlying disease, such as the key function, disruption of which indicates the presence of that disease.

There are currently two main competing criteria for PCOS (Lujan, Chizen, and Pierson 2008), one developed at a conference sponsored by the National Institute of Health (NIH) in 1990, and one developed by the European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine in 2003, called the Rotterdam criteria (see Table 1). The NIH criteria are based on abnormalities of two factors: 1) clinical and/or biochemical signs of high androgen levels; and 2) measures of anovulation.[4] Interestingly, this set of diagnostic criteria does not include the presence of polycystic ovaries in the definition. The Rotterdam criteria include polycystic ovaries as a criterion, with patients meeting the conditions for diagnosis if they have abnormalities in two of the three criteria. Comparison of these two methods of diagnosis in a birth cohort of women aged 27 to 34 showed that 9% of women met the NIH criteria for PCOS, whereas approximately 18% of women met the Rotterdam criteria (March et al. 2009). Of the women meeting the NIH criteria, 68% were "undiagnosed". Of the women who had previously been diagnosed with PCOS, 51% did not meet the NIH criteria and 34% did not meet the Rotterdam criteria.

(Insert Table 1 around here)

[4] Both definitions exclude other causes for the disorder, such as Cushing's syndrome.

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Part of the difficulty in the current diagnostic criteria for PCOS, and hence our understanding and definition of the disease, arises because the syndrome involves measurement of three different variables associated with the healthy function or otherwise of the ovaries: circulating androgen levels, regularity of ovulation, and presence of cysts in the ovaries. Each of these variables can be measured in a multitude of ways. For example, the presence of cysts can be measured using the number of cysts in the overall ovary, the number of cysts in a single cross section or the total ovarian volume. Similarly, anovulation can be measured using number of cycles per year or days between cycles or mid-luteal progesterone levels. Each of these variables has a continuous distribution in the population. Menstrual irregularity, symptoms of hyper-androgenisation (such as acne) and the presence of ovarian cysts are each common, particularly in younger women, with no discrete cut-off between measures that indicate normal, and those that indicate abnormal functioning. More than two thirds of "healthy" young women will have multiple cysts in their ovaries that meet the Rotterdam criteria (Duijkers and Klipping, 2010). It is clear that abnormalities in the three measures are clustered within populations, but at the individual level there are significant variations in the clinical symptoms and signs of the disease, including in the same woman over time (which is one explanation for the number of women with a previous diagnosis of PCOS who no longer met the criteria in the birth cohort study).

This detailed discussion of PCOS demonstrates how difficult it is to know how to assess the dysfunction that is definitive of any particular disease. All three measures (circulating androgen levels, regularity of ovulation and presence of cysts in the ovaries) tell us something about the overall capacity of the ovaries to perform their function – i.e., to produce mature eggs. Yet it is not at all obvious how we should assess this function, given that the various proposed measures assess different aspects of that overall function; and give us

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different answers as to whether or not PCOS is present. We may be able to appeal to hierarchies of function by breaking down the function of the ovary into various sub-functions (processes or mechanisms), such as the production of and sensitivity to sex hormones. But as well as being cumbersome this would leave it unclear as to which level in any hierarchy of function (cellular, tissue, organ, organism) should be determinative of disease, as well as raising difficult questions about how diseases map on to dysfunctions at different levels. Not only is there a question of choice regarding which functions are the relevant ones for defining the disease, each of the three postulated variables reflecting different aspects of ovarian function occurs on a spectrum requiring further choices about thresholds. What choices are made about the criteria and the thresholds, can affect whether or not particular women are healthy or diseased with regard to PCOS.

It is quite possible that there is no 'best' way to distinguish between women with the variety of disorders that cluster under the current label of PCOS and 'normal' patients. While groups struggling with these definitions have emphasised the need for scientific evidence that could guide these decisions, there are no currently accepted criteria for how this should be done. The three variables, reflecting different aspects of ovarian function associated with PCOS overlap but how and whether they should be considered together or not is contentious. The claim of the BST that normal functional ability is "the readiness of each internal part to perform all its normal functions on typical occasions with at least typical efficiency" (1977, 555) seems unworkable in the face of these complex overlapping functions. Our way of determining whether or not a particular case is a state of disease depends on determination of the relevant function, a matter Boorse appears to consider only relevant to questions of nosology.

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A Boorsian might respond that since dysfunction of any part, no matter how small, counts as pathological on the BST, atypical measures on any of these criteria should be considered pathological (whether or not the woman concerned is considered to have PCOS). But (in addition to the threshold problems this raises) it is implausible that menstrual irregularity, and even the presence of cysts, be considered pathological. As such, a woman might meet one or more of the criteria for PCOS without actually being a candidate for PCOS – or any pathology.

There is no easy solution to this problem. Physiological functions frequently cluster and trying to map diseases to single disturbances of functions will create highly complex diagnostic variations that are likely to be unworkable in clinical practice. The BST offers insufficient and unintuitive guidance for determining whether function should be assessed at the level of the cell, organ, system or whole organism; which of the competing variables should be taken to reflect function, nor how the chosen variable should be measured.

Example 2. Chronic kidney disease

As discussed above, according to the BST, function is assessed relative to a subset of the species, known as a reference class, which is "a natural class of organisms of uniform functional design; specifically, an age group of a sex of a species" (Boorse 1997, 7-8). In responding to his critics Boorse states that the BST does not need to provide further justification of its chosen reference classes "unless there are actual examples of medical disputes about whether something is pathological which turn on choice of reference class" (Boorse 2014, 695). As we discuss, chronic kidney disease (CKD) provides just such an example of a medical dispute based upon choosing an appropriate reference class for determining the boundary between normal function and pathology.

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Until recently, there was considerable overlap and inconsistency in the terms used to describe disorders of kidney function. In 2002, the United States Kidney Foundation released a set of guidelines, in part to reduce these inconsistencies and standardise the terms used to describe kidney disease (National Kidney Foundation 2002). The new classifications for CKD use a combination of two measures of kidney function, the glomerular filtration rate (GFR) and the presence of albumin in urine (albuminuria) (see Table 2). The thresholds are based on where the risk of cardiovascular disease and end stage renal failure begin to rise in association with these two measures based on population cohort studies of more than 2 million individuals, including all ages and sexes and a wide range of ethnic groups (Hallan et al. 2012).

The threshold used to delineate "mild chronic kidney disease" includes patients with a glomerular filtration rate < 60 ml/min/1.73m^2. This threshold identifies around half of people aged over 75 as having chronic kidney disease (Moynihan, Glassock, and Doust 2013) as there is a natural age-related decline in renal function as measured by the glomerular filtration rate. Advocates for the current threshold argue that the threshold should lie where the risk of cardiovascular disease and end stage kidney disease rises above the population level of risk, and point to evidence from the large international collaborative study to ground the claim that the risk of cardiovascular disease does indeed begin to rise at this level.

Critics of the current boundaries argue that the risks of both end stage kidney disease and cardiovascular disease for patients in this category are very small. In the United Kingdom, there are approximately 1.8 million people over the age of 75 labelled as having mild to severe chronic kidney disease by the current definition. Of these, only 1700 are on dialysis (Stevens et al. 2007). For the vast majority of patients labeled with CKD, their risk of

succumbing to an alternative disease is far greater than their risk of end stage kidney failure. Similarly, the risk of cardiovascular disease attributable to CKD after adjusting for traditional risk factors such as blood pressure is very small. Large numbers of people are needlessly labelled with a disease for very little benefit (Spence 2010). Conversely, young patients with reduced glomerular filtration rates such as < 75 ml/min/1.73m^2 are not defined as having disease using this classification, although their probability of proceeding to serious renal disease is similar to those who are elderly with mild CKD (Hallan et al. 2012).

This example illustrates there are cases where considerable controversy exists as to whether a measurement is deemed pathological or not depending on the choice of the reference class. Some functions vary so much with age, that having a wide reference class (e.g., 'adults'), results in a significant proportion of elderly individuals being labelled with disease because of the normal changes of ageing. That is, the judgements yielded by this definition seem medically wrong in some cases because of the lack of recognition that this particular function will, normally, decline with age.

This could be a reason to resist the recent change considered by Boorse of regarding all adults (of the same sex and perhaps race) to be in the same reference class (2014, 714), and perhaps even to introduce a series of more fine-grained reference classes. But there seems no clear way to make choices about these reference classes without appeal to some other criteria, such as risk of harm. And Boorse has made it clear that he would resist any such refinement of reference classes. Indeed, he has recently investigated dealing with the problem of some diseases of aging being 'typical' for those reference classes by considering all adults as a reference class irrespective of age (Boorse 2014, 714), thereby accepting that elderly people are inevitably diseased. Though Boorse indicates that this idea needs further exploration, it

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would seem to endorse the results of applying this contentious definition of CKD, with its inability to isolate a sense of 'normality' against which dysfunctions can be identified as disease.

Of course, since Boorse detaches his concept of disease from practical or evaluative criteria, including the imperative to intervene, he might respond by saying that a high proportion of older people do have CKD, but have cases that are unlikely to need treatment, or to be symptomatic for them. Since the BST analyses a theoretical and value-free concept of disease, this implication is not problematic. But we might also take this to demonstrate, not only that the theoretical notion of disease is practically unhelpful, and that a non-theoretical notion of disease deserves more attention, but that the theoretical notion could actually contribute to unhelpful expansions of disease boundaries and negative forms of medicalisation.

The example also illustrates another key point regarding the boundaries of disease. *Pace* Boorse, pathologists are not the arbiters of disease and neither do they have the final word. Rather, many diseases are defined by panels of specialists who gather to determine whether or not current diagnostic criteria for particular diseases are acceptable or need revising. As already alluded to in the examples of PCOS and CKD, this process may be driven by many concerns, such as early identification of treatable disease, to bring consistency to diagnosis for research and treatment purposes and so forth. This process seems inimical to the BST, which if correct, would stipulate the boundaries of disease once and for all. Instead, the experts gather, weigh up the evidence one way and another, and more likely than not, change the boundaries of the disease in question. A recent review showed that most guideline writers widened the boundaries of the disease they were considering (Moynihan et al. 2013). This

process undermines the BST's claim to provide an account of disease consistent with medical/pathological practices. Concerningly, the panels that determine changes in the boundaries of disease often include members with considerable financial conflicts of interest, interests that are benefitted by changes that increase rates of diagnosis and hence numbers of patients requiring treatment. More subtle conflicts can also exist, such as an academic career in a particular disease area that can be boosted by a rapid increase in affected patients secondary to redrawing the boundaries of that disease. Thus our current methods for defining disease are far from value-free, and the experts who are involved in these processes do not have a unique or even reliable insight into where these boundaries should lie.

Example 3. Myocardial infarction

Our final example involves heart attacks – myocardial infarction (MI), the understanding of which has been challenged by increasingly sensitive modern diagnostic tests. These tests undermine the previous disease concept of MI, while their results occur on a spectrum, raising the question as to where on this spectrum dysfunction occurs, and revealing a tension in how the BST understands functions and goals. The example demonstrates another way in which the BST will sometimes expand disease boundaries.

Prior to the 1920s, it was only possible to make the diagnosis of myocardial infarction (MI) post-mortem, and it was assumed that the formation of a cardiac thrombus (or blood clot in the arteries of the heart) was a fatal event. The development of the electrocardiogram, white cell counts and erythrocyte sedimentation rate in the 1920s, however, led to increasing numbers of patients being diagnosed with non-fatal MI (Faergeman 2001). Over the course of the 20th century, there was a dramatic increase in the incidence of MI in industrialised countries, peaking in the 1960s. In part this was due to changes in environmental factors,

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such as industrialisation and increased rates of smoking, but the ability to detect MI also contributed to the increase, as doctors were able to differentiate MI from other causes of chest pain or discomfort.

In 1979, the World Health Organisation developed a new definition of MI to standardise monitoring of the incidence and prevalence of the disease and to enable consistent diagnoses for treatment and research purposes (Gillum et al. 1984). There have been several subsequent revisions to that definition, the latest being the Third Universal Definition of Myocardial Infarction in 2012 (Thygesen et al. 2012). These revisions have incorporated new and more sensitive diagnostic tests, such as the biomarkers troponin and high sensitivity troponin.

Each of the task forces has started from the pathological definition of MI as "any degree of myocardial necrosis in the presence of ischaemia" (Thygesen et al. 2012), a definition compatible with Boorse's statement that "any premature cell death is pathological – including even clinically undetectable liver necrosis, as in mild poisoning" (Boorse 2014, 706). However, the increasing ability to detect smaller and smaller degrees of necrosis has led to many more people being labelled as having an MI than would be diagnosed using older diagnostic techniques (Langorgen et al. 2014). The more sensitive tests have not only reduced the proportion of patients with MI who were missed by previous diagnostic methods, but have also increased the proportion of patients presenting with chest pain who are diagnosed as having MI, with estimates of the increase being up to 64% (Sandoval, Smith, and Apple 2016). Using the BST to define disease, which includes patients with "one dead cell" in the definition, results in a large expansion in the proportion of patients who are labelled with myocardial infarction.

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The use of increasingly sensitive markers of necrosis that can be detected in vivo leads us back to questions about hierarchies of function and which functions are critical in determining disease. Our current diagnostic technologies can detect minute levels of myocardial necrosis. In keeping with the BST, this is disease – the function of those myocardial cells is to contract and they no longer contract because they have died. And Boorse is in general happy to acknowledge trivial disease. But this creates a tension regarding the relationship between functions and goals. Minute amounts of myocardial necrosis may not impair overall cardiac contractility, as the affected individual's heart continues to pump blood at average capacity. Thus for us to know whether or not disease is present, we need to know if the relevant function is cellular (in which case disease is present as cells are dead), or whether it is at the level of the organ. An added complication is that such minute amounts of cardiac necrosis may be statistically common, in which case, there is no disease. Thus on the theoretical account of disease, it is unclear as to whether or not troponin-detected MI is a disease or not.

As well as this theoretical consideration, there are important clinical questions. Should such patients be categorised as having an MI, in keeping with the initial conception of the pathology of MI? Has the incorporation of the more sensitive biomarkers with the subsequent increase in numbers of those caught in the diagnostic net revealed a disease categorisation that is ill suited on both theoretical and practical grounds? Certainly we might be able to specify that troponin-detected MI is a disease on theoretical grounds, and that it may not reveal disease of sufficient severity to require treatment, but this determination is of little use for determining treatment options and for providing prognostic information and an understanding of the disease process for patients and other decision makers.

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This example highlights the difficulties of categorising and sub-categorising patients within classes of diseases. Endless divisions of patients based upon highly sensitive biomarkers reduce our ability to determine effective treatments. On the other hand, divisions that are too broad, such as occurs with chronic kidney disease, group patients who are so heterogeneous as to not provide useful diagnostic categories for recommendations about treatment or accurate prognoses. The example also further demonstrates how a theoretical notion of disease such the BST can contribute to unhelpful expansions of disease boundaries.

Conclusion

It has become apparent relatively recently that threshold setting is a problem across the medical spectrum. Initiatives such as the "Too Much Medicine" series in the *BMJ* and the "Less is More" series in the *Archives of Internal Medicine* highlight numerous examples where the expansion of disease categories leads to overdiagnosis and problematic medicalisation. Alongside the problems of too much medicine lies the fear of missing serious disease. Here medicine looks to philosophy for clarity: "How do we know that we are not throwing the baby with the bath water when we can't articulate the criteria by which a condition can properly be called a disease?" (Accad 2016)

Considerable controversy exists regarding the boundaries that should be placed around breast cancer, thyroid cancer, multiple sclerosis, gestational diabetes, pulmonary embolism and numerous other conditions. Conditions without objective measures and that consist of constellations of symptoms, such as overactive bladder or restless legs are even more controversial, as are the psychiatric disorders. As new and more sensitive diagnostic tests have been introduced, finer gradations of dysfunction have been identified, leading to the diagnosis of disease in people who have very mild levels of dysfunction. This increased

diagnostic acuity has been coupled with a risk-aversive approach to disease definition and shifts in perceptions about the benefits and harms of treatment. The result is widened definitions of disease, making more and more of the population "diseased" and increasing problems of overdiagnosis (Carter et al. 2015). Such changes are not trivial or marginal. Patients are at increasing risk of serious harms, including from treatments where the harms outweigh benefits. There are also social consequences, as all governments struggle to find ways to contain health care costs. These problems will only increase with the development of new measures of function, including genetic testing.

The above examples show that the BST fails to offer the assistance sought by Accad and others who seek a firm foundation in a definition of disease that can rebut claims that trivial levels of dysfunction are disease. The theory does not provide a principled way to identify what levels of dysfunction indicate disease other than by appeal to the level below the population mean that is "conventionally" accepted; contains ambiguities about reference classes reflecting difficulties in identifying normality; and is out of step with medical processes of identifying dysfunction. The BST's limitations in these regards arise from a lack of clear lines in nature, such that in order to define the boundaries of disease, we need to make reference to values and practical consequences. Such an appeal is not necessarily a problem for the BST, if we consider the disease boundaries to be practical or convenient rather than reflections of natural boundaries, since it is consistent with Boorse's aim to analyse the theoretical and not the practical notion of disease. But that the lack of clear boundaries does cause real problems and controversies in medicine belies Boorse's apparent understanding of these issues as merely academic (as he states (1977, 559) in relation to choosing thresholds for statistical abnormality).

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As shown by the examples above, most of the shifts in the boundaries of disease are determined by specialty interest groups. Boorse's statement that "Neither individuals nor societies have any power to decide what is a theoretically healthy human being" (2014, 702) is not reflected in how contemporary disease is defined. Boorse might reply to these kinds of examples that they do not challenge his statement because the decisions made about disease boundaries only impact on what counts as a 'healthy human being' clinically or practically speaking. But such an answer would just show that the BST, in focusing on theoretical health, makes itself irrelevant to dealing with these sorts of problems. Even if it is the case that these boundaries might be derived in an objective and value-free way in some theoretical sense, this is certainly not a practical possibility, nor anything like what goes on in the real world. In addition, if dysfunction of any part is to be taken to indicate disease, then boundaries set by appeal to a theoretical notion of health may be far too broad to be of use. We need to acknowledge that judgements about disease boundaries are inherently driven by values and by various contingencies, as this is the only means of working towards these judgements being informed by the values and interests of all relevant groups. The focus on a theoretical possibility of an objective and value-free way to determine disease boundaries can prevent us from acknowledging this and responding to the problems that it raises.

Naturalistic theories such as the BST seem to be either irrelevant for this purpose, insofar as they are limited in their capacity to identify disease; or actually unhelpful in encouraging expansive definitions of disease which include dysfunctions that are not harmful. Our processes for determining the boundaries for disease need to recognise that there is no value-free method making these decisions. Moreover, decisions need to more closely reflect the wider values of the community, rather than single interest groups.

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Table 1. Diagnostic Criteria for PCOS (Bachanek M, Abdalla N, Cendrowski K, et al. 2015)

NIH Diagnostic Criteria (1990)	**Rotterdam Diagnostic Criteria (2003)**
Both: 1) Oligo- or anovulation; and 2) Clinical and/ or biochemical signs of hyperandrogenism And exclusion of other aetiologies	Two of the following: 1. Oligo- or anovulation 2. Clinical and/or biochemical signs of hyperandrogenism 3. Polycystic ovaries And exclusion of other aetiologies

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Table 2. Classification of chronic kidney disease (adapted from (Hallan et al. 2012)

Stages of Chronic Kidney disease				**Persistent albuminuria categories (mg/mmol)**		
				A1	**A2**	**A3**
				Normal to mildly increased	Moderately increased	Severely increased
				Male < 2.5 Female < 3.5	Male 2.5-25 Female 3.5-35	Male > 25 Female > 35
GFR categories (ml/mini/1.73m2) Description and usage	G1	Normal or high	≥90	Not CKD unless haematuria, structural or pathological abnormalities present	Mild	Severe
	G2	Mildly decreased	60-89		Mild	Severe
	G3a	Mildly to moderately decreased	45-59	Mild	Moderate	Severe
	G3b	Moderately to severely decreased	30-44	Moderate	Moderate	Severe
	G4	Severely decreased	15-29	Severe	Severe	Severe
	G5	Kidney failure	<15	Severe	Severe	Severe